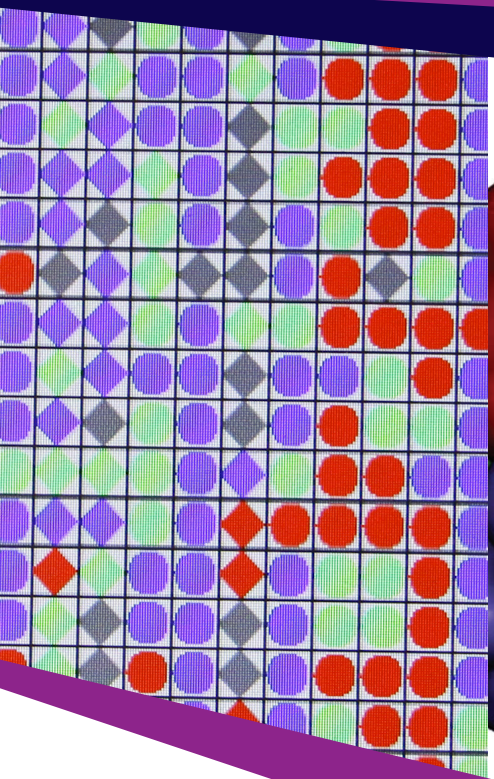
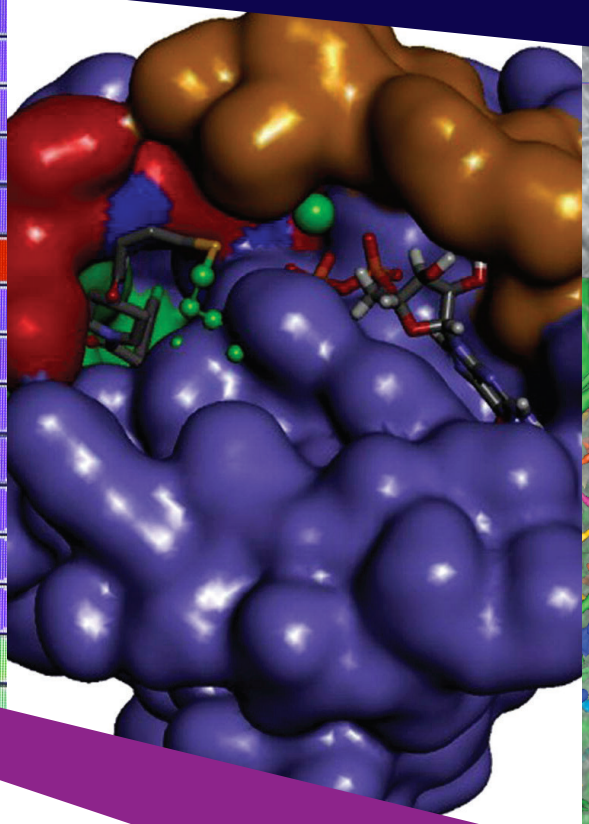
Leidos Biomedical Research, Inc.

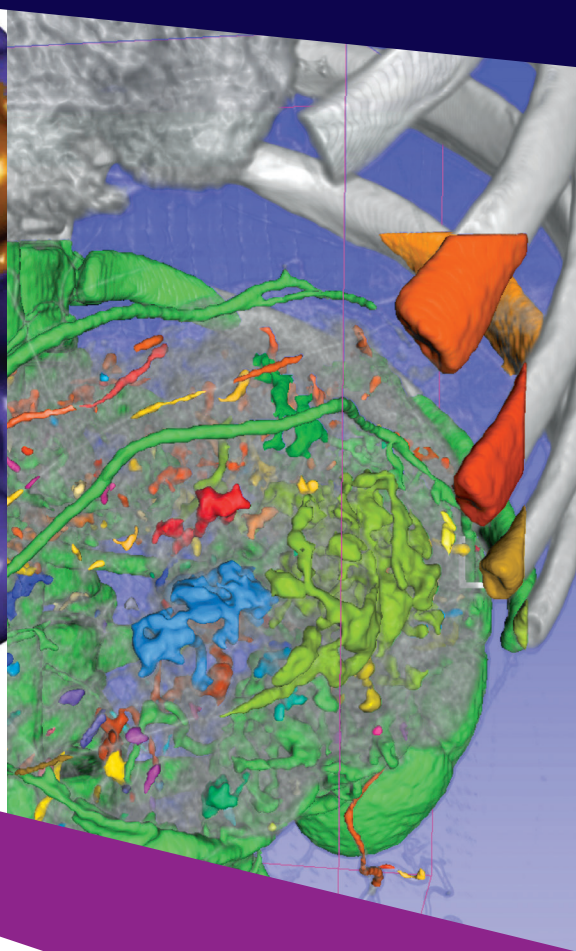
Frederick National Laboratory for Cancer Research

2014–2015

ANNUAL REPORT







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Leidos Biomedical Research, Inc.

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Operations and Technical Support Contractor for the Frederick National Laboratory for Cancer Research

2014–2015 Annual Report

Leidos Biomedical Research, Inc., operates for the National Cancer Institute under Contract No. HHSN261200800001E.
P. O. Box B, Frederick, Maryland 21702-1201

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2014–2015 Annual Report

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Contract Year 7
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Executive Summary

Leidos Biomedical Research, Inc. (Leidos Biomed) is pleased to submit this annual report for the Frederick National Laboratory for Cancer Research (FNLCR) Operations and Technical Support (OTS) Contract, for the period of September 26, 2014, to September 25, 2015.

FNLCR is a Federally Funded Research and Development Center (FFRDC) sponsored by the National Cancer Institute (NCI). It is the only FFRDC dedicated to biomedical research. Through its status as an FFRDC, FNLCR provides NCI and others with a unique national resource to accelerate the development and delivery of effective preventive, diagnostic, and therapeutic products to people living with cancer and HIV/AIDS.

The following annual report documents the extensive breadth of activities performed by Leidos Biomed in support of NCI's mission. These activities span the research and development spectrum, including investigator-initiated, hypothesis-driven research into cancer and AIDS; advanced technology programs focused on genetics and genomics, proteins and proteomics, imaging, nanotechnology, bioinformatics, and laboratory animal sciences; clinical operations in support of NCI– and National Institute of Allergy and Infectious Diseases (NIAID)–sponsored clinical trials, as well as NCI drug discovery and development efforts; and management and operations of biopharmaceutical development and manufacturing programs under current Good Manufacturing Practices conditions for NCI and NIAID. Administrative, financial, safety, and facilities support is provided to these research and development activities through state-of-the-art business processes.

National Resource

To more effectively portray the scope of activities conducted at FNLCR, the annual report is structured to align with the institutes and agencies that FNLCR supports, as well as national mission research projects that NCI assigns to FNLCR. The breadth of activities conducted in support of its customers underscores FNLCR's role as a national resource.

FNLCR Customers

FNLCR provides direct program support to numerous divisions, offices, and centers within NCI. These include:

- **Center for Strategic Scientific Initiatives** – creates and implements exploratory programs focused on emerging scientific discoveries and innovative technologies to accelerate the pace of cancer research and the translation of research results into new therapies, diagnostics, and preventive agents.
- **Center for Cancer Genomics** – unifies NCI's activities in cancer genomics by aiming to synthesize research in different fields of cancer genomics—structural, functional, and computational—in order to improve patient outcomes.
- **Center for Global Health** – provides assistance and guidance to nations as they develop and implement cancer control plans; trains international investigators; and strengthens U.S. national, regional, multilateral, and bilateral collaboration in health research, cancer research, and cancer control to advance global cancer research, build expertise, and reduce cancer deaths worldwide.
- **Center for Biomedical Informatics and Information Technology** – collaborates across NCI to plan, provide, and coordinate technology, standards, and scientific computing in support of the NCI mission to speed discovery, facilitate open science, and progress towards precision treatment in cancer care and a learning health care system.
- **Coordinating Center for Clinical Trials** – facilitates efforts across NCI to enhance the effectiveness of NCI's clinical trials enterprise through collaboration and harmonization among NCI programs and extramural stakeholder communities.
- **Center for Cancer Research** – a productive community of NCI intramural basic researchers, clinicians, and translational scientists who integrate basic and clinical research discovery to develop novel therapeutic interventions that better treat adults and children living with cancer or HIV/AIDS.
- **Division of Cancer Epidemiology and Genetics** – conducts population and multidisciplinary research to discover the genetic and environmental causes of cancer and ways to prevent it.
- **Division of Cancer Biology** – encourages and facilitates continued support of basic research in all areas of cancer biology to provide the research foundation that enables improved understanding of the disease and may lead to new approaches for prevention, diagnosis, and treatment.

- **Division of Cancer Prevention –** conducts and supports research to find ways to prevent and detect cancer, and to prevent or relieve symptoms from cancer and its treatments.
- **Division of Cancer Treatment and Diagnosis** – supports the translation of promising research into clinical applications to improve the diagnosis and treatment of cancer in areas of unmet need that are often too risky or difficult for industry or academia to develop alone.
- **Division of Cancer Control and Population Sciences** – supports an integrated program of genetic, epidemiologic, behavioral, social, applied, and surveillance cancer research to reduce risk, incidence, and death from cancer, as well as to enhance the quality of life for cancer survivors.

FNLCR also provides significant support within the OTS Contract to NIAID. Support is provided to the following NIAID divisions/centers:

- **Division of Intramural Research** – conducts basic and clinical research in a wide range of disciplines related to immunology, allergies, and infectious diseases.
- **Division of Clinical Research** – provides multidisciplinary trans-NIAID services for facilitating clinical research and managing special projects as directed by NIAID leadership.
- **Division of Acquired Immunodeficiency Syndrome** – supports a global research portfolio on HIV/AIDS, and its related co-infections and co-morbidities.
- **Vaccine Research Center** – conducts research that facilitates the development of effective vaccines for human disease.

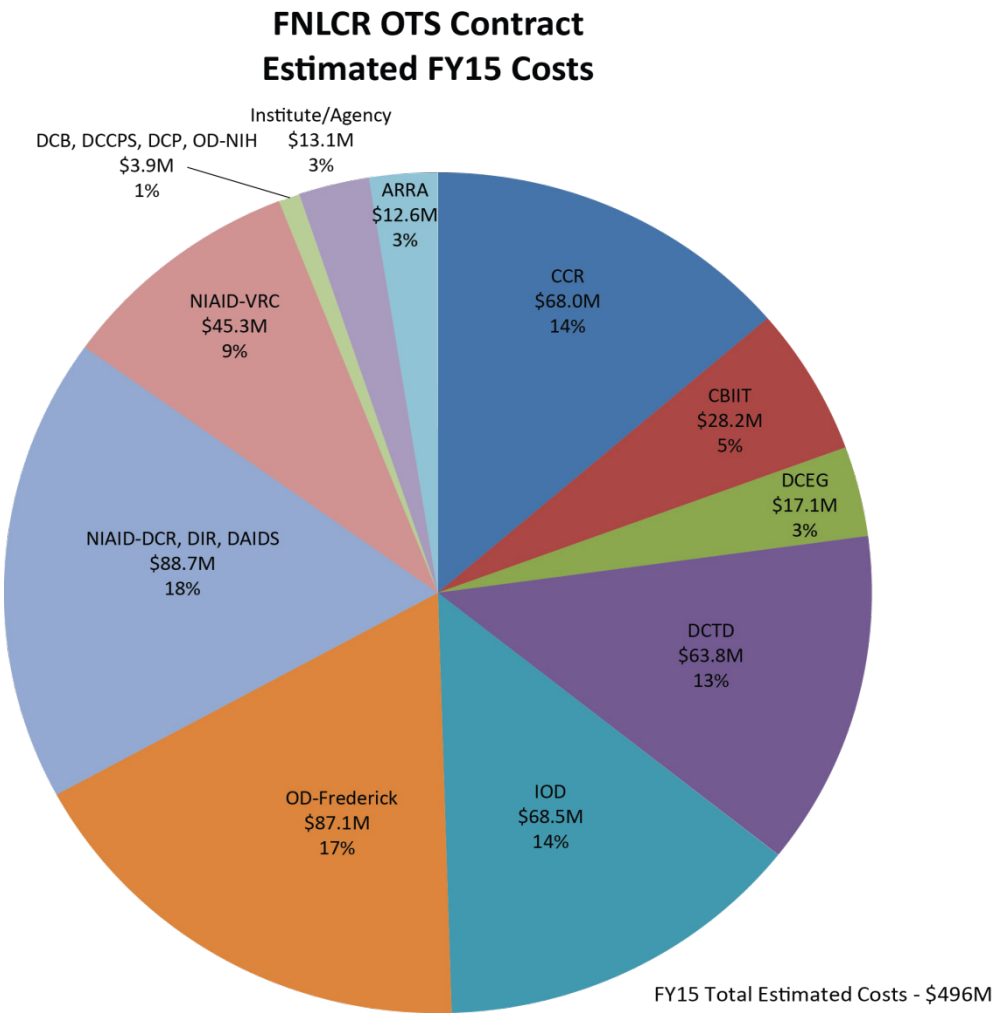
Support is also provided to approximately 15 other institutes within the National Institutes of Health (NIH) and other federal agencies.

FNLCR Customer Funding

The estimated fiscal year (FY) 2015 cost for the OTS Contract is approximately $496.2 million, which includes approximately $12.6 million in costs associated with programs funded through the American Recovery and Reinvestment Act of 2009 (ARRA). As represented in the pie chart, 67 percent of the costs are associated with NCI programs, 27 percent are associated with NIAID programs, 3 percent are associated with ARRA programs, and 3 percent are associated with other institutes and agencies. The overall estimate for FY2015 represents a reduction of $13.8 million or 2.7 percent, with the largest decrease for the ARRA program. FY2015 will represent the final year of ARRA programs, which is the main reason for the decrease.

Excluding ARRA, the FY2015 estimate is approximately $28.9 million higher, or an increase of 6.4 percent compared with FY2014. NIAID represents the largest of this increase with $24.3 million, or 22 percent of the FY2015 estimate.

Since FY2013, the OTS Contract has increased overall by 2.8 percent in annual costs; NCI programs have increased 16.4 percent, NIAID programs have increased 25.3 percent, ARRA funding has decreased 81.9 percent, and other institutes and agencies have decreased 24.6 percent, as represented in the pie graph below.



FNLCR National Mission

FNLCR is an integral part of an aggressive national initiative to further scientific understanding of cancers driven by mutations of the *RAS* family of genes. Established by NCI, the RAS Initiative seeks to facilitate connections between and among researchers, bringing new ideas and technologies to bear on RAS.

FNLCR serves as the research hub that connects RAS researchers, nationally and internationally, through collaborations and several spoke projects. RAS Initiative hub research areas include Structural Biology and Biochemistry, RAS Assays, Biology of Mutant KRAS Cell Lines, Pathway Analysis, Cell Surface Analysis, and RAS Reference Reagents.

FNLCR Organization

President's Office: David Heimbrook, Ph.D., President, Leidos Biomedical Research, Inc., and Laboratory Director, FNLCR

The three Leidos Biomed key staff report to Dr. David Heimbrook, and are each responsible for leading one of the three operating groups within the OTS Contract. Within the groups there are 15 directorates, each of which has either a primary technology focus or is aligned with a primary customer. Support to the federal customers and performance of the RAS national mission are accomplished through the collaboration of these 15 directorates.

Science and Technology Group: David Heimbrook, Ph.D., Chief Science Officer, Interim

The Science and Technology Group (STG) provides scientific expertise and support for basic and applied research and data management. STG comprises the following five directorates:

- **AIDS and Cancer Virus Program (ACVP)** – pursues studies that have direct or potential relevance to the overall goal of developing an effective vaccine or other approaches for the prevention or treatment of HIV infection and AIDS, and to the study of viruses involved in cancer.
- **Basic Science Program (BSP)** – covers a wide spectrum of research activities, with a focus on

immunology and genetics in support of the Center for Cancer Research.

- **Cancer Research Technology Program (CRTP)** – serves as the program hub for the RAS Initiative, and provides expertise in genomics, proteomics, imaging, informatics, and nanotechnology to NCI and external partners.
- **Laboratory Animal Sciences Program (LASP)** – provides an integrated portfolio of research animal programs, including the development of genetically engineered mouse models, cryopreservation and assisted reproduction, pathology and histotechnology, small animal imaging, molecular diagnostics, and animal husbandry.
- **Data Science and Information Technology Program (DSITP)** – develops and maintains an enterprise approach to IT infrastructure support at FNLCR, and operates the Advanced Biomedical Computing Center.

Clinical Group: Barry Gause, M.D., Chief Medical Officer

The Clinical Group is composed of four directorates at the clinical end of the research spectrum that are directly involved with patients. This group includes the following directorates:

- **Clinical Research Directorate (CRD)** – provides clinical research management, regulatory, and pharmacovigilance support to NCI, NIAID, and other NIH clinical programs, and provides quality assurance for the Biopharmaceutical Development Program and the Vaccine Clinical Materials Program.
- **Applied and Developmental Research Directorate (ADRD)** – provides clinical and biological monitoring, regulatory support, biospecimen processing and storage, assay development, and project management support to NCI and NIAID clinical programs.
- **Vaccine Clinical Materials Program (VCMP)** – manufactures and provides biological agents used in NIAID-sponsored clinical trials.
- **Biopharmaceutical Development Program (BDP)** – manufactures and provides biological agents used in NCI clinical trials.

Operations and Financial Group: David Bufter, MBA, Chief Operating Officer, Interim

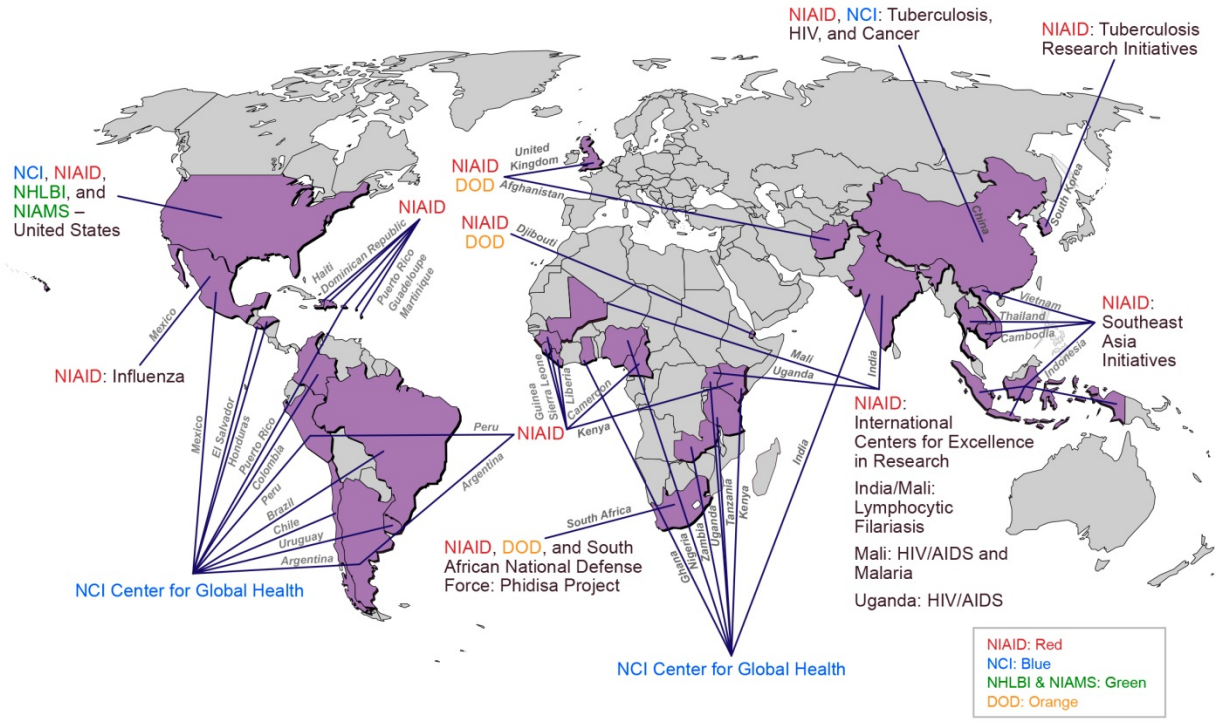
The Operations and Financial Group provides the administrative, financial, and facility operations resources required to support the myriad of research activities conducted at FNLCR. The group includes the following directorates:

- Management Support Directorate
- Contracts and Acquisitions Directorate
- Human Resources Directorate
- Facilities Maintenance and Engineering Directorate
- Environment, Health, and Safety Directorate
- Financial Operations Directorate

Collectively, these directorates continued to direct significant effort during the past year to support ARRA/stimulus projects assigned to FNLCR and to ensure accountability for government funds.

Global Impact

Through its direct support of clinical trials, FNLCR activities are not limited to national programs. Clinical trials management support to NCI, NIAID, the National Heart, Lung, and Blood Institute, the NIH Clinical Center, the National Institute of Arthritis and Musculoskeletal and Skin Diseases, the National Institute of Mental Health, the National Institute for Neurological Disorders and Stroke, and the National Center for Advancing Translational Sciences comprises more than 400 domestic and international studies related to cancer; influenza, HIV, other infectious diseases (such as hepatitis C, tuberculosis, and malaria), and viral hemorrhagic fevers, Ebola virus, and chikungunya virus; heart, lung, and blood diseases and conditions; parasitic infections; and rheumatic and inflammatory diseases. FNLCR provides medical and clinical research professionals to support numerous NIH clinics. Support provided to the NCI Center for Global Health and NIAID's Southeast Asia Influenza Clinical Research Network allows the efforts of FNLCR to have a global impact.



Community Involvement

FNLCR is dedicated to biomedical research on a national and global level, and it approaches local community involvement with a similar passion. As an organization, Leidos Biomed is actively involved in nurturing the community in which its employees live and work. The company monetarily supports a wide cross-section of nonprofit organizations and charity fundraisers. Leidos Biomed representatives serve leadership and supporting roles in advancing local business and economic development, and are committed to being actively involved at the city, county, and state levels. FNLCR sponsors a series of educational programs supporting students from grade school through grad school, including outreach to local elementary schools, scholarship support to high school students interested in science, technology, engineering, and mathematics (STEM) careers, and advisory support to local higher education institutions.

Leidos Biomed employees are equally generous, through participation in a company program in which they make charitable contributions and provide hands-on volunteering at local organizations such as Habitat for Humanity and the Frederick Rescue Mission.

Whether through local involvement or support of international clinical trials, the staff of Leidos Biomed is committed to promoting FNLCR and helping NCI prevent, diagnose, and treat cancer and HIV/AIDS. It is a privilege to serve as NCI's FFRDC contractor in support of this important mission.

Scientific Program Support

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Leidos Biomedical Research, Inc.

SCIENTIFIC PROGRAM SUPPORT

NCI OFFICE OF THE DIRECTOR

Frederick National Laboratory

RAS Program

Support Provided by the Cancer Research Technology Program

Structural and biophysical characterization of KRAS (Project 1)

The initial goal of RAS structural biology efforts is to provide detailed structural insights of wild-type (WT) and oncogenic mutants of KRAS4b in active (GTP-bound) and inactive (GDP-bound) states. The long-term goal of our efforts is to provide a molecular basis of KRAS' interaction with various effectors, regulatory proteins, and trafficking proteins. The structural information obtained from these studies will not only improve our understanding of how KRAS interacts with these proteins, but also could act as a blueprint for structure-based drug design.

Last year, the structure of full-length WT KRAS4b (2-188) in complex with GDP was solved. This structure showed an extended conformation for switch-I that has not been previously observed. Further analysis of this structure suggested the possibility that this conformation of switch-I could also exist in solution. To examine the presence of such an extended conformation of the switch-I region in KRAS, collaborative studies were initiated with the National Magnetic Resonance Facility at Madison (NMRFAM) to carry out the dynamics of the switch-I region in the KRAS–GDP complex, and with Dr. Hans Robert Kalbitzer (University of Rosenberg, Germany) to use high-pressure nuclear magnetic resonance (NMR) studies to see if a similar switch-I conformation exists in solution. Since this KRAS–GDP structure contains a groove at the base of the extended switch-I region, a collaboration with Dr. Brian Schoichet's group at the University of California, San Francisco (UCSF), was initiated to carry out virtual compound screening to see if any compound can fit in the groove. His group recently completed in silico screening for compounds/fragments that dock in the switch-I pocket of the KRAS–GDP complex structure. The group's data suggested that we test the top 20 compounds/fragments for possible binding, followed by co-crystallization or soaking in KRAS crystals with extended switch-I conformation. Dr. Schoichet's group also carried out docking of two KRAS (with extended switch-I conformation) monomers to see if any of the loops present in KRAS can bind in the groove of another KRAS molecule. Based on interaction energy criteria, the group found a penta-peptide region, Glu63-Tyr64-Ser65-Ala66-Met67, that fits reasonably well in this groove. A contractor Collaborative Research and Development Agreement (cCRADA) with UCSF (Brian Schoichet's group) is in the final stages of approval. Once the cCRADA is approved, execution studies will begin in order to measure the binding of these fragments/ compounds and peptides to the KRAS–GDP complex.

A subcontract with Beryllium (a crystallography contract research organization) to solve the structures of KRAS mutants in complex with the GTP analog GppNHp is still in place. Beryllium has obtained the structures of truncated (2-166) WT KRAS, $KRAS^{G12C}$, and $KRAS^{Q61L}$ mutants in complex with GppNHp. Overall, structures of $KRAS^{G12C}$ and $KRAS^{Q61L}$ mutants in complex with GppNHp resemble the WT KRAS-GppNHp structure where the switch-I region interacts with the nucleotide-binding pocket. In the $KRAS^{G12C}$ structure, the side chain of Cys12 points away from the gamma-phosphate, whereas, in the $KRAS^{Q61L}$ structure, Leu61 points in the same direction as Gln61 in the WT KRAS structure. In these structures of KRAS (WT, G12C, and Q61L), in complex with GppNHp, no Mg was observed in the nucleotide-binding pocket. Since Mg likely plays a key role in the structural rearrangement of the switch-I region upon GTP binding, efforts are under way to capture both GppNHp and Mg with other KRAS-mutant structures (G12D, G12V, G13D, and Q61R) using higher concentrations of Mg in the final buffer.

Significant progress has been made towards obtaining structural information of KRAS in complex with known protein-binding partners PDEδ and calmodulin.

- **KRAS4b-FME-PDEδ complex:** One characteristic of processed KRAS4b is that it should specifically interact with the farnesyl-binding protein PDEδ. Analysis of recombinant processed KRAS4b binding to PDEδ by size-exclusion chromatography (SEC) and SDS-PAGE indicates that these proteins bind as a 1:1 stoichiometric complex. Additional experiments, including analytical ultracentrifugation and surface plasmon resonance (SPR) spectroscopy, provided additional evidence of equimolar binding. Recently we crystallized and solved structures of processed KRAS (farnesylated and methylated), in complex with PDEδ, in three different crystal forms at a resolution of 2.0, 3.0, and 3.8 Angstroms (Ang). The 2.0-Ang structure provides the molecular basis of recognizing the farnesyl group present in the hypervariable region (HVR) of processed KRAS by PDEδ. In the 3.0-Ang structure obtained in a different crystal form, we can see electron density for all the residues present in the HVR. In both of these structures, the G-domain of KRAS4b does not interact with PDEδ. These structures are currently being analyzed. After this analysis, structure-based functional studies will occur.
- **KRAS4b–calmodulin complex:** Previous studies have shown that calmodulin binds to KRAS in GTP-bound (or GTP analog–bound) form mainly by

interacting with its hypervariable region. To determine the structural basis of the interaction between KRAS and calmodulin, two orthogonal approaches are being employed—NMR and crystallography—through collaboration with the University of Maryland, Baltimore, and Dr. Carla Mattos (Northeastern University), respectively. At the Frederick National Laboratory for Cancer Research (FNLCR), alternative approaches to crystallizing calmodulin with the HVR of KRAS4b are being attempted. For crystallization purposes, two fusion constructs were designed with calmodulin and the HVR peptide of KRAS connected by a six or twelve amino acid–long linker. Both of these constructs yielded soluble protein, and crystals of calmodulin fused to the HVR peptide by a six amino acid–long linker were obtained. Crystallographic data collected on this crystal showed no electron density for the HVR and linker regions. Current efforts are focused on the crystallization of a fusion construct that has a farnesylated and methylated HVR peptide (HVR-FME) fused to calmodulin, as HVR-FME has been shown to have a 20-fold higher affinity for calmodulin than unmodified HVR.

KRAS is localized at the inner leaf of the plasma membrane through a farnesylated and methylated terminal cysteine residue, and is only competent in signal transduction when bound to a membrane. Structural determination of KRAS4b alone or bound with effector molecules at the membrane may provide novel opportunities for structure-based drug design. A combination of NMR, high-resolution cryo–electron microscopy (EM), and crystallography will be used to achieve this. To accomplish this goal, significant improvements have been made in the recombinant production in insect cells of farnesylated and methylated KRAS4b (KRAS4b-FME); specifically, engineering a single baculovirus with both subunits of the farnesyl-transferase enzyme, along with MBP-KRAS4b and the use of Trichoplusia ni (Hi5) insect cells, resulted in yields of 7 mg/L of purified KRAS4b-FME. This protein has been extensively characterized and demonstrated to be predominantly monomeric by analytical ultra-centrifugation and dynamic light scattering, and contains a similar secondary structure to non-processed KRAS, as determined by circular dichroism.

In order to analyze the binding of KRAS4b-FME to membranes, a collaboration with Dr. Stephen Sligar from the University of Illinois at Urbana-Champaign was established. Dr. Sligar invented lipid nanodiscs, which are lipid bilayers stabilized by two amphipathic belt proteins organized as small 10 x 5–nm discs. Nanodiscs are extremely amenable to biophysical analysis of protein–membrane interactions. In this collaboration, Dr. Sligar's laboratory provided nanodiscs with variable lipid composition and also shared protocols to enable FNLCR to prepare nanodiscs. The binding of KRAS4b-FME to nanodiscs composed of variable amounts of phosphatidylserine was evaluated using SPR spectroscopy. These studies demonstrated the binding affinity of KRAS4b-FME to nanodiscs decreases with increasing phosphatidylserine concentration. This interaction required the presence of the farnesyl and methyl group, and non-processed KRAS4b did not bind to nanodiscs irrespective of the phosphatidylserine concentration. Once binding conditions were established for KRAS4b-FME to nanodiscs, the GTPase activity of KRAS4b-FME when bound to a nanodisc was measured and found to be comparable to that of non-processed KRAS. Finally, using a combination of analytical ultracentrifugation and SPR, the farnesyl group in KRAS4b-FME was available to bind to the farnesyl-binding protein PDEδ. No binding to PDEδ was observed with non-processed KRAS4b. The extensive characterization of KRAS4b-FME confirms that this reagent would be amenable for biophysical and structural analysis. The following collaborations have been established to probe the structural and biophysical aspects of KRAS4b-FME–membrane interactions.

- Dr. Jay Groves (University of California, Berkeley). Objective: Investigate KRAS4b-FME dimer and effector interactions using single-molecule fluorescence measurements on tethered lipid bilayers. Preliminary results indicate that KRAS4b-FME dimerizes on tethered lipid bilayers that contain phosphatidylserine, and, in the absence of phosphatidylserine, KRAS4b-FME is present only as a monomer.
- Dr. Marco Toneli (NMRFAM). Objective: Determine if the conformation of KRAS4b-FME when bound to a nanodisc is different than the conformation of KRAS4b-FME when in solution using NMR. NMRFAM has completed NMR analysis of 15N-labeled, non-processed KRAS4b. 15N-labeled KRAS4b-FME in insect cells has been optimized, and the isolation of the KRAS4b-FME–nanodisc complex is complete. Analysis of these samples by NMRFAM began in mid-September.
- Dr. Frank Heinrich (Carnegie Mellon University/ National Institute of Standards and Technology [NIST]). Objective: use neutron reflectivity to determine the orientation and depth of insertion of KRAS4b-FME on tethered lipid bilayers. Data from the NIST neutron reflectivity group showed that KRAS4b-FME binds to tethered lipid bilayers in a phosphatidylserine-dependent manner, as measured by SPR spectroscopy. Neutron reflectivity measurements were performed in mid-August.

Identify compounds that inhibit KRAS-driven tumors (Project 2)

RAS Project 2 is an effort by several groups within the Cancer Research Technology Program (CRTP) to establish cell-based, high-throughput screening assays to identify candidates for therapeutic development against KRAS-driven tumors. The short-term objective is to qualify the cell-based assays within FNLCR, and then

transition them to collaborators with chemical libraries and automation for the execution of screening campaigns. Hits derived from these screens will be evaluated within the laboratories at FNLCR and, when warranted, advanced to chemical optimization programs with our screening partners or additional collaborating laboratories.

During fiscal year (FY) 2015, we established the project and engaged approximately three full-time equivalents (FTEs) of effort in the process of developing cell line reagents, testing conditions for cell-based assays in a high-throughput format, establishing relationships with external screening partners, developing a screening pipeline, and validating primary hits from pilot screening efforts with collaborators. The initial effort has focused on the development of specific model systems using mouse embryonic fibroblast (MEF) cell lines developed in the laboratory of Dr. Mariano Barbacid. These lines are generated from fibroblasts derived from mice that are null for HRAS and NRAS, and contain a floxed allele of KRAS. The cells are strictly dependent on KRAS activity for growth, as evidenced by the cessation of proliferation when the KRAS allele is removed using Cre recombinase. The growth phenotype can be restored by the addition of an active RAS protein. Thus, the model system can be reconstituted with specific forms of RAS and used in cellular assays to evaluate compounds that impact RAS-driven proliferation.

Progress to date: MEF cell lines have been generated in Dr. Rachel Bagni's laboratory within FNLCR. Cell pools were treated with Cre recombinase to remove the endogenous murine KRAS locus and have been rescued with exogenous WT HRAS or mutant KRAS4B transgene using lentiviral transduction. Multiple clonal isolates were then derived for each pool of transduced cells, and each line was evaluated for comparable growth rates, genetic drift and homogeneity, response to tool compounds, expression of the RAS transgene, and activation of the canonical RAS signaling pathways.

Genetic analysis of multiple HRAS and KRAS 4bG12D MEF lines has revealed several cell lines harboring additional cancer-relevant mutations in Trp53. Because genetic mutations that alter P53 activity may compromise dependence on the RAS transgene, each cell line generated has undergone full-exome capture and illumina sequencing to identify any additional P53, MAPK, or cancer-relevant mutations, and we now have several unique clonal MEF isolates expressing WT HRAS, KRAS 4bG12D, KRAS 4bG12V, or WT KRAS, but they lack any additional cancer-relevant mutations. As a final control, dependence on the transgene for growth will be confirmed by shRNA knock down in the lines to be used for compound screening.

Compound screening will be done in collaboration with external partners, including the National Center for Advancing Translational Sciences (NCATS). Initial efforts with NCATS have been focused on identifying molecular targets that specifically inhibit growth of KRAS 4bG12D–dependent growth using a well-characterized library of approximately 2,000 tool compounds and U.S. Food and Drug Administration (FDA)–approved drugs with known cellular targets. Wild-type HRAS, KRAS 4bG12D, KRAS 4bG12V, KRAS 4bG12C, and wild-type KRAS 4b MEFs were screened using the NCATS library, and known HRAS-specific compounds, including a farnesyl transferase inhibitor (tipifarnib) and broad-spectrum receptor tyrosine kinase inhibitors, selectively inhibited growth of wild-type HRAS MEFs. As predicted, no class of compounds or targets was identified as selective inhibitors of mutated KRAS-dependent growth.

Several Cooperative Research and Development Agreements (CRADAs) have been proposed with pharmaceutical companies for screening collaborations using the panel of MEF lines. One proposal is designed to identify novel compounds that inhibit the growth of a KRAS 4bG12D MEF and then use wild-type HRAS as a negative control to identify selective inhibitors of KRAS 4bG12D–dependent growth. Initial pilot and primary screening will be performed externally, and screening hits will be validated and characterized at FNLCR.

Two other CRADAs have been proposed to use the RAS-dependent MEFs to characterize lead compounds developed by pharmaceutical companies. We plan to verify the mechanism of action and identify off-target effects of putative KRAS inhibitors. Selective inhibitors of mutated KRAS should be relatively ineffective in BRAF- or HRAS-driven MEF lines, yet should potently inhibit proliferation of mutated KRAS-driven MEF lines.

Characterize and disrupt KRAS complexes and probe the nature of KRAS dimerization (Project 3)

RAS Project 3 focuses on developing assays and imaging approaches for characterizing KRAS complexes in the context of membranes and cells. Emerging evidence suggests that RAS molecules form dimers at the plasma membrane and that dimer formation may be a prerequisite for signaling downstream through hierarchical, RAS-dependent effector cascades. It follows that if oncogenic KRAS does indeed form dimers, disrupting the dimer interface may represent a new target space. Advanced imaging techniques, such as single-molecule tracking, step photobleaching, and fluorescence fluctuation microcopy, offer new lines of attack for studying both the spatial and temporal behavior of RAS molecules in both reconstituted artificial membrane systems and cells. However, no assays exist to quantitatively measure KRAS dimerization in cells or to detect KRAS dimerization in a format amenable to high-throughput compound screening. Protein–protein interaction assays such as the bioluminescence resonance energy transfer (BRET) assay can be used to interrogate this interaction in intact cells and serve as platforms for screening campaigns. Finally, high-content imaging can be used to interrogate the spatial localization of KRAS and downstream signaling molecules in cells, and is an assay platform amenable to small-molecule screening. The goal is to share the screening assays with interested partners

from Pharma and academic institutions, and to use the assays and imaging technologies here to support further biological characterization of KRAS as a drug target.

Over the last year of the project, we have been working on three major approaches to interrogate and disrupt KRAS complexes:

1. Developed a primary high-content imaging assay that would be capable of identifying small molecules that disrupt the membrane localization of fluorescently tagged, full-length KRAS molecules in cells.
2. Developed a BRET assay suitable for high-throughput screening to target KRAS/KRAS complexes in the membranes of live cells.
3. Developed single-molecule approaches for characterizing KRAS molecules and protein complexes in cells, and to probe the nature of KRAS dimerization.

High-content screening assay for identifying small molecules that disrupt KRAS localization and/or signaling. All RAS isoforms, including the oncogenic variants, must localize to the plasma membrane (PM) to initiate downstream signaling. H-RAS, N-RAS, and the KRAS splice variant, KRAS4a, all transit to the PM through the golgi, and rely on cycles of reversible palmitoylation on one or two cysteines in the HVR to regulate exchange on and off the PM. In contrast, the KRAS4b HVR contains a series of positively charged lysine residues, which target KRAS4b to regions of the PM rich in negatively charged phospholipids. Though the details have not been fully worked out, evidence suggests that KRAS4b trafficking to and from the PM is mediated by chaperones such as PDE6δ and smgGDS. Since its path to the PM is distinct, and since membrane localization is a requirement for downstream signaling, perturbing the spatial organization of KRAS4b may uncover new molecular targets for KRAS-dependent cancers.

To this end, we developed a high-content assay and image analysis pipeline to screen for molecules that disrupt the PM localization of KRAS4b. The assay is based on a doxycycline-inducible green fluorescent protein (GFP)–$KRAS^{G12V}$-expressing HeLa cell line, and uses confocal microcopy to automatically image cells at sub-micron resolution in multi-well glass-bottom plates. To specifically counterstain the PM compartment and nucleus, we use fluorescently labelled Concanavalin A (ConA) and Hoechst (a DNA-specific dye), respectively. An image analysis pipeline was developed to segment and quantitate the levels of GFP-$KRAS^{G12V}$ in the PM compartment. The pipeline includes a supervised machine-learning algorithm to convert the gray-scale intensity values of the PM channel (ConA) to the probability that the ConA signal belongs to the PM. These probability values are subsequently used to segment the cell boundary and PM using a graph-cut method and a thresholding technique. We use the nuclear channel to eliminate any segmented boundaries that do not belong to a cell. Calculated Z' factors using the mean values per well of membrane-localized GFP-$KRAS^{G12V}$ in doxycycline-treated and -untreated cells show acceptable values (0.7) for high-content screening. Reference compounds, such as the dual farnesyl transferase and geranlygeranly transferase inhibitor L778123, disrupt GFP-$KRAS^{G12V}$ membrane localization in a dose-dependent manner (Figure 1).

In collaboration with Krishna Kota from the Molecular and Translational Sciences group at United States Army Medical Research Institute of Infectious Diseases (USAMRIID), we screened a small library (222 compounds) of biologically active molecules and FDA-approved drugs to test the performance of the assay. We determined that the assay has excellent reproducibility and a 2-percent hit rate when a cut-off of 50-percent inhibition of KRAS membrane localization is used.

Milestones:

1. Installed the high-content assay and image analysis pipeline.
2. Validated the assay with a pilot screen of 222 compounds.
3. Developed a counter screen assay to identify compounds that selectively disrupt KRAS4b localization.

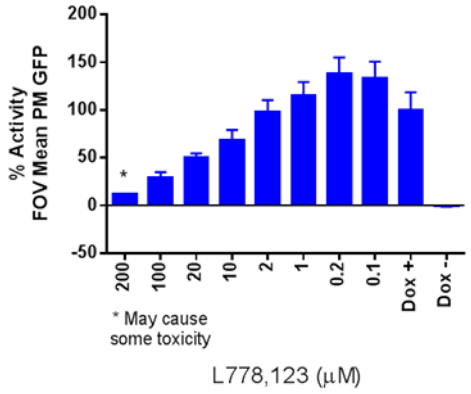


Figure 1. *Disruption of GFP-HRAS membrane localization and GFP-KRAS membrane localization. Increasing concentrations of L778123, a prenylation inhibitor, quantitatively disrupts the localization of GFP-$KRAS4b^{G12V}$ to the membrane.*

Multimerization assay. To fully test the hypothesis that KRAS dimers are critical for initiating or igniting the oncogenic signaling cascade, and to identify new drug leads, we developed a cell-based dimerization assay for identifying small-molecule disruptors and modulators of KRAS multimerization. Our primary objective is to develop an assay that will be useful as a primary screen for small molecules that target oligomerization of KRAS, and that secondarily will also serve to more fully characterize this interaction. BRET uses a natural phenomenon observed in marine organisms where a luminescent protein transfers energy to a fluorescent protein acceptor, which then emits light at a longer wavelength. This transfer of energy can only occur when the donor and acceptor molecules are within 10 nm of

each other, and so can serve as a tool for measuring protein–protein interactions. By tagging KRAS4b molecules with the luciferase donor and fluorescent acceptor, we have developed a highly sensitive assay for measuring interactions of KRAS4b molecules in the membrane of live cells. The specificity of this interaction has been determined by showing that the donor signal can be saturated by increasing concentrations of the acceptor (Figure 2, blue curve). We also showed that the interaction could be displaced by an untagged KRAS4b molecule (Figure 2, red curve), and that a CAAX-box mutant, KRAS4b^{C185S} acceptor, which fails to localize to the membrane, does not generate a BRET signal with the membrane-localized donor (Figure 2, green curve).

In addition to establishing the specificity of the interaction of KRAS/KRAS molecules in cell membranes, we have optimized the assay for screening. Parameters such as optimal seeding density and time course have been determined. Current efforts are to use a small library of chemically diverse molecules obtained from the National Cancer Institute (NCI) Developmental Therapeutics Program to measure assay performance under screening conditions and to potentially identify tool compounds.

Milestones:

1. Optimized the BRET assay in HEK293 cells with nanoBRET (Promega), showing specific KRAS/KRAS interactions.
2. Optimized assay conditions and developed a protocol for assay-ready cells (cells are transfected and then frozen down to be used at any time).

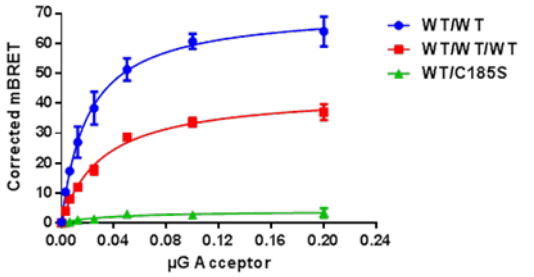


Figure 2. *The mBRET signal is saturable. Increasing concentrations of the acceptor eventually saturate the ability of the donor to exchange energy, and results in a characteristic sigmoidal curve (blue). This signal can be competed with unlabeled KRAS (red). The CAAX box mutant C185S does not interact with the nanoLuc-KRAS donor in the membrane, so there is no energy exchanged (green).*

Single molecule imaging. Sensitive detection with advanced cameras combined with total internal reflection fluorescence (TIRF) microcopy and newly developed fluorescent dyes that are exceptionally bright and photostable have afforded an outstanding opportunity to study KRAS molecules at nanoscopic spatial and millisecond time scales in the membrane of live and fixed cells. Using these techniques, we are testing the hypothesis that KRAS4b forms dimers or higher-order complexes in the membranes of cells. A better understanding of this biology could lead to improved targeting of RAS in cancer cells; furthermore, the biophysical measurements will support mechanistic studies of lead molecules identified in the various screening assays being developed within the RAS Initiative.

To characterize KRAS4b complexes, we are using fluorescent dyes from the lab of Luke Lavis at Janelia Farms. These dyes are cell permeable and label genetically expressed tags such as HaloTag. We combined these exceptionally bright dyes with TIRF to reduce signal background. Using these dyes and TIRF, we are able to achieve a 10-ms frame rate on our camera, and observe the lateral mobility of fluorescent KRAS4b molecules at the single-molecule level in the membrane of cells. Time-lapse images of these mobile molecules are then processed and analyzed. Trajectories (Figure 3) can be used to calculate the two-dimensional diffusion and extract other useful parameters, such as the probability of molecules switching from a fast- to a slow-diffusing state. The brightness of the individual molecules retains other information as well; specifically, the oligomerization state of the molecule. By using a technique called step-photobleaching, we are able to count the number of fluorophores in a sub-diffraction-limited spot by the number of steps in takes to photobleach the molecule (Figure 4).

To support these efforts, RAS Project Z developed RASless MEFS that express HaloTag-KRAS4b. The HaloTagged construct was able to rescue the growth of the MEFS after removal of the endogenous *KRAS* gene, providing an important reagent to study KRAS4b in a truly physiological context. These cells are being used presently to carry out the measurements described above. An advantage is that we can use serum starvation, EGF stimulation, and small-molecule treatments to perturb the system and observe the consequences on RAS behavior.

Milestones:

1. Optimized image acquisition and cell culture conditions for single-molecule measurements.
2. Developed an image analysis pipeline for computing the mobility and oligomerization state of RAS molecules in live and fixed cells.
3. Used HaloTag-KRAS4b^{wt}-rescued RASless MEFS to acquire physiologically relevant data.
4. Developed a counter screen assay to identify compounds that selectively disrupt KRAS4b localization.

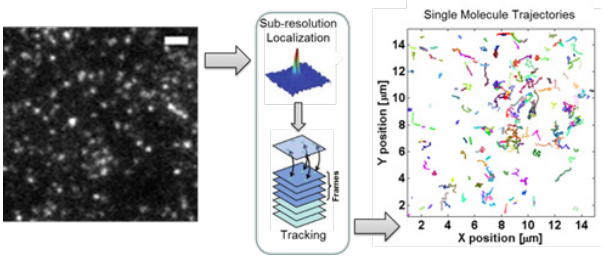


Figure 3. *Single-molecule tracking experiments can be used to trace the trajectories of individual molecules at a 10-ms time scale. These trajectories can be computationally analyzed and lateral mobility measured.*

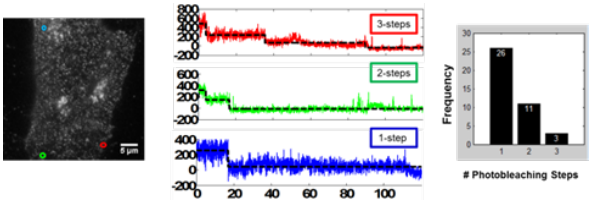


Figure 4. *Step-photobleaching data shows the number of fluorescent molecules in each spot and is a measure of the distribution of oligomers.*

Cell surface mapping (Project 4)

The aim of the cell surface mapping project is to investigate the possibility of either unique or overexpressed proteins in KRAS tumors as compared to normal tissue. This has been performed using mass spectrometry interrogation of cell surface protein-enhanced preparations of cell lines progressing to tumor tissue.

The initial experiments were done using MCF10a cells that contained either an empty vector or a KRAS G12V insert. During the past year, a method of cell surface protein enhancement was devised that would work in both cell lines and tumor tissue. The results of a comparison in cell lines with published methods showed equivalence in results. The method was used to catalog the cell surface proteins in several KRAS-mutant cell lines (H2122, H2444, A549, SW620, and KP3) as well as tumor tissue obtained from Dr. Mariano Barbacid. Proteins were considered significant if they were identified with high confidence and in high concentration as judged by spectral count. A list of 31 exclusively expressed and 19 highly overexpressed proteins has been provided to Dr. Jim Wells at UCSF. These were all manually confirmed as having high-quality spectra. Dr. Mariano Barbacid has selected an initial 18 targets for generation of human Fabs using two approaches for biopanning from a large library of candidates. Currently, two Fabs have been generated with several more in production. We have completed a Material Transfer Agreement (MTA) and will receive these materials for use to further confirm both presence and location in the cell lines.

One of the cell lines tested in the above Project 4 studies (A549) has been used to generate tumor tissue in mice. This tumor tissue will be used for testing biological replicates (which was not possible in the samples from Dr. Barbacid due to tissue quantity), as well as comparing the cell culture and the in vivo environment.

We are currently in the process of preparing manuscripts on the protein enhancement method applicable in tumors and cells based on initial data presented at both the American Association of Cancer Research (AACR) and American Society for Mass Spectrometry (ASMS) meetings, and are in the planning stages for a manuscript, in collaboration with Dr. Wells' lab, describing the selection of targets and the generation of affinity-binding reagents.

Synthetic lethal screens (Project 5)

The Synthetic Lethality workshop hosted by the NCI RAS Initiative on January 6 and 7, 2014, resulted in a Funding Opportunity Announcement (FOA), PAR-14-314, issued August 7, 2014. The FOA expired July 9, 2015, and review dates are November 2015 (scientific merit) and January 2016 (advisory council).

Project 5 has evolved to include websites and tracking of interactions between the RAS Initiative and extramural and intramural collaborators. The primary website, http://cancer.gov/RAS, was launched September 23, 2014. The NCI Office of Communications and Public Liaison manages the infrastructure of the site, which contains information on the origins of the program, its oversight, and its scientific organization, goals, tools, and leadership. The "RAS Central" section of the site features essays and observations about RAS biology, links to recorded seminars, dates for upcoming events, and reagents and resources available to the community.

A new, highly interactive website, the RAS Lab discussion group, was established in the spring of 2015 and was made available to the larger community on August 5, 2015. The goal of RAS Lab is to foster rapid, informal exchanges of information, questions, observations, and ideas. Accordingly, RAS Lab is based on a third-party platform, and allows all members to post questions and comments and upload supporting documents. All posts are published immediately and are moderated post-hoc.

Subsequent to the RAS Structures workshop at the Advanced Technology Research Facility (ATRF) on July 21 and 22, 2015, participants expressed a desire to remain in contact. A new website, RAS Structures and Biophysics, was launched July 31, 2015, on the same third-party platform as the RAS Lab website, to facilitate ongoing interactions among the workshop participants and RAS Initiative staff.

Outreach to the RAS community has been extensive. Four workshops (Synthetic Lethality, RAS Pathways, Cell Surfaces, RAS Structures) have been held, and two more (RAS Immunotherapy and an open RAS Symposium) are scheduled before the end of 2015. A session at the AACR

Annual Meeting was devoted to describing the RAS Initiative, and featured talks by two postdocs funded by the Pancreatic Cancer Action Network and chosen by RAS Initiative leadership. More than 20 outside speakers have visited the RAS Initiative and given talks that were either RAS-centric or described novel technologies that could be applied to the goals of the initiative. Currently, RAS Initiative scientists are collaborating with more than two dozen outside investigators, institutes, or companies, as well as half a dozen National Institutes of Health (NIH) researchers.

RAS reference reagents (Project 6)

The RAS Reference Reagents Project (RRR) has the two-fold goal of (1) generating reagents to support the other projects in the FNLCR RAS Initiative and (2) producing reagents that will assist external RAS scientists with their research. The team consists of 2.5 FTEs within the Protein Expression Laboratory (PEL), whose focus is on the generation of new DNA clones and the development of reagent collections. In FY2015, the RRR program generated over 900 individual new DNA clones in support of FNLCR RAS projects and external collaborators. Almost all of the cloning and subcloning was done using Gateway recombinational cloning on our in-house developed combinatorial cloning platform (CCP).

- RAS Initiative support: In total, 501 new constructs were generated in FY2015 in support of RAS Initiative efforts. Sixty-five constructs were produced in support of Project Zero, including constructs for lentiviral delivery of RAS to MEFs and genome engineering constructs using the clustered, regularly interspaced, short palindromic repeat (CRISPR). An additional 125 constructs were produced to support assay development, including protein expression constructs for alpha screen development, protein localization constructs for Project 3, and 57 constructs for development of BRET assays. The majority of RRR efforts in support of the RAS Initiative were the production of 254 clones for protein expression in support of biochemistry, biophysics, and structural biology of RAS and RAS effector proteins. This work included the development of engineered baculoviruses to permit the facile high-yield production of processed KRAS in insect cells, as well as a number of additional reagents for the generation of high-value structural targets, including NF1, PDE6D, and RAF kinase.
- Support of intramural and external collaborators: More than 75 DNA constructs were generated in support of collaborations with Center for Cancer Research (CCR) investigators, as well as external collaborators and scientists. Among these were 35 clones generated for the laboratory of Dr. Deborah Morrison in CCR for co-development of NanoBRET assays. Additional lentiviral and Escherichia coli (E. coli) clones were made in collaborations with researchers at the University of Maryland, UCSF, and University of California, San Diego. In a number of cases, investigators from universities contacted the RRR for support in obtaining various constructs that had previously been generated for the RAS Initiative.
- RAS clone collections: The two currently available clone collections (KRAS entry clones and RAS pathway clones) were distributed to 11 investigators through a Technical Services Agreement. These samples were sent to diverse locations, including the Center for Applied Medical Research in Spain, the Fred Hutchinson Cancer Research Center, the Massachusetts Institute of Technology, Stanford University, Johns Hopkins University, Cancer Research UK, and Turku University in Finland.
- RAS Pathway Collection v2.0 (R777): A significant effort was put forth in FY2015 to generate a large clone set consisting of the 180 genes in the new version 2.0 of the RAS pathway. These genes were cloned in two formats (stop and nostop) in fully validated Gateway entry clones. A major bioinformatic effort was launched to identify the major isoforms of these genes expressed in cancer cells, and the discovery was made that at least 30 percent of these specific transcript isoforms were not available in commercial clones without mutations. Template cDNAs were obtained commercially where possible, and additional clones were generated by combinations of mutagenesis, overlap PCR, and synthetic approaches to obtain all needed templates. As of August 1st, 98 percent of the clones have been validated, and work is ongoing on the remaining samples. The collection is undergoing quality control, and final clones will be sent to Addgene for distribution to the community.
- Cancer Toolkit v2.0: In a collaboration with Dr. Kris Wood at Duke University, the RRR group has generated 18 test clones based on Dr. Wood's original Cancer Toolkit clone set published recently in Science Signalling. The new library uses a new barcoding scheme and better cloning strategies to improve the utility of the clones. This set will be validated by Dr. Wood in his assay, and if it works, we will continue the collaboration in FY2016 to generate a large library of mutant oncogenes and tumor suppressors to enhance the value of the toolkit.

In the second year of a cCRADA with Biogen Idec, PEL collaborated on the production of high-value reagents for early stage drug development in the Molecular Discovery group at Biogen. Work in FY2015 focused on production of c9orf72 and MLKL1 proteins, and included a dozen small-scale protein production scouting projects and pilot-scale growths of over half a gram of c9orf72. These proteins have been successfully used by Biogen for biochemical and structural work, as well as in assay development for drug screening.

Target Biology Unit–Calmodulin

Biochemical KRAS-RAF assay

Detection of KRAS-RAF binding using BiaCore has been described in the literature, and immune-precipitation results and even a co-crystal structure have been published for RAP (a RAS homologue), in complex with the RAS-binding domain of CRAF. However, there are no publications describing a RAS-RAF-binding assay that is amenable to high-throughput screening. In an effort to develop such an assay, PEL expressed and purified the recombinant WT Avi-tagged KRAS protein for use in KRAS-effector binding studies. Active KRAS complexes were subsequently assembled by loading the recombinant KRAS protein with GDP, GTP, or GTP analogues to study conformation-specific KRAS interactions with the RAS-binding domain (RBD) of RAF kinase fused to GST (GST-RBD). Binding was measured by a proximity-based reaction (AlphaScreen technology, Perkin Elmer) coupled to the biotinylated KRAS and GST-labeled RBD. Binding specificity in the assay is highly GTP dependent.

A CRADA has been established with Daiichi-Sankyo to identify compounds that inhibit KRAS–RAF interactions using the assays developed at FNLCR. The KRAS-RBD AlphaScreen assay was optimized for high-throughput screening, and primary screening was conducted using the full library of 20,000 compounds. In order to differentiate potential non-specific inhibitors from specific KRAS-RBD protein–protein interaction inhibitors, the active compounds will also be tested in an unrelated AlphaScreen proximity-based assay to identify compounds that may interfere with the chemistry of the detection system, rather than compounds that specifically interfere with KRAS-RBD binding. Positive screening hits will then be derivatized by chemists at Daiichi-Sankyo in an effort to establish a compound structure–activity relationship.

Biochemical nanodisc-KRAS-RAF assay

Optimization of the KRAS-RBD-binding reactions continues in an effort to incorporate more physiological KRAS–effector interactions. Variations of the biochemical assays have been developed to include the use of farnesylated and lipid-associated KRAS. By using the proximity-based AlphaLisa technology coupled to affinity tags on the RBD (GST tag) and on the amphipathic belt protein of a nanodisc bilayer, we have demonstrated GTP-dependent binding of CRAF-RBD to membrane-associated KRAS. We are currently optimizing conditions to assess the feasibility of using such an assay in a large-scale high-throughput screening effort. In addition to membrane-associated KRAS, the assays are well suited for incorporating full-length CRAF (as opposed to only incorporating the RBD domain), as well as adding scaffolding proteins, such as KSR, or other proteins, such as GAP and GEF, that directly interact with KRAS proteins.

Cellular KRAS-RAF-binding assay

In addition to measuring the binding of recombinant KRAS–effector interactions in a purified system, a second assay is currently under development to measure the same interaction in a cellular context. To do so, we are evaluating a technology developed by Promega. This technology uses a version of luciferase (nano-luciferase) that has been truncated into two non-functional domains, which, when brought into proximity, will recombine to form an active luciferase enzyme. By fusing each domain either to KRAS or CRAF, we are able to express these constructs in mammalian cells and quantify KRAS-CRAF binding by measuring luciferase activity. The assay components have been generated and tested, and are now being assessed for feasibility in drug discovery and lead compound optimization efforts.

Validation of KRAS as a target (Project Zero)

The RAS Target Validation Unit was developed as an additional project/group to (1) pursue the validation of KRAS and/or effectors as targets for therapeutic intervention, and (2) consolidate and standardize cell line development support to the overall RAS Initiative.

Significant effort and resources were put towards completing comprehensive and systematic analysis of the effects of KRAS and downstream effector node ablation in a panel of 70 mutant and wild-type KRAS pancreatic and colorectal cell lines to identify novel vulnerabilities. In collaboration with Dr. Tina Yuan (formally UCSF, currently Broad Institute), who analyzed 40 lung cell lines, a multi-parameter flow cytometry–based assay was used to measure changes in viability, proliferation, reactive oxygen species, apoptosis, and cell size after node ablation (simultaneous knock-down of a down-stream KRAS complete signaling node: e.g., RAF: ARAF, RAF:BRAF, and RAF:RAF1, or MEK:MEK1 and MEK:MEK2, or ERK:ERK1 and ERK:ERK2). The cell lines were selected from the 1,000 Cell Line Collection (Cyril Benes, Massachusetts General Hospital (MGH)/Harvard), and have gene expression, genomic, and drug sensitivity data available for integration with the results of the current effort.

- This assay uses the percentage of eGFP-positive cells as a read-out for node dependence. Derivative cell lines stably expressing eGFP were generated, and transfection conditions were optimized.
- Cell line testing in the assay was completed at the end of November 2014. Preliminary analysis identified the need for some repeated testing, which was completed in January of 2015.
- Integrating the current data sets with existing gene-expression and genomic data using novel analysis tools is ongoing between our lab, the RAS Informatics Group, and Cyril Benes' group at MGH/Harvard.

- The assay and preliminary results were presented in two separate sessions, including the NCI-sponsored RAS Initiative session at the 2015 AACR meeting in Philadelphia.
- A manuscript is in preparation with a target submission date of fall 2015.

Cell line development continued to be a priority in year two for use in drug screening efforts within the RAS Initiative. The workhorse cell background includes the use of RAS-dependent MEFs (developed by Dr. Mariano Barbacid) for proliferation-based screens. These cells are HRAS-/-, NRAS-/-, and KRASfl/fl. The removal of KRAS by Cre recombinase results in G1 arrest (proliferation), but not cell death. Proliferation can be rescued by the transduction and expression of a WT RAS or a mutant RAS allele. This cell platform provides a unique opportunity to study aspects of (K)RAS signaling and biology as a single isoform in an isogenic system.

- This year, the focus shifted from pooled cell lines to clonal derivations from the rescued pools. Greater than 60 clonal lines have been generated. A subset of these lines have been transferred to the cell-based assay screening group (Project 2) for further analysis/inclusion in compound library screening efforts.
- A quality control (QC) pipeline has been established to monitor cell line development and exclude cell lines that do not meet QC criteria before transfer to the cell-based assay screening group (Project 2). The QC pipeline includes the following activities:
  - Exome sequencing to confirm the absence of compensatory mutations in known oncogenes.
  - Confirming clonality using integration analysis.
  - Calculating growth rates.
  - Detecting stable expression of (RAS) transgene.
  - Detecting the loss of endogenous KRAS.
  - Detecting the activation of canonical signaling pathways (MAPK, PI3K, EGFR).
  - Confirming dependence on the exogenous allele.
- A priority panel of WT and mutant KRAS cell lines (G12C, G12D, G12V, and G13D), and a BRAF V600E cell line have been re-derived and cloned. Characterization and validation using the new QC pipeline are under way.
- Additional KRAS-mutant cell lines have been derived and are in various stages of cloning/validation: KRAS 4B G12A, G13C, A146V, R68S, A146T, G12R, G12S, and K117N.
- Pools of rescued RAS-dependent MEFs have been generated and will proceed to cloning at a future date, depending on project needs: KRAS 4B S181A, K104A, K104Q, K147L, K147Q, and M188L.
- In support of imaging and localization studies, clonal HRAS WT and KRAS 4B G12D DOX-inducible HEK, HELA, MCF-7 and PANC-1 cell lines have been developed. HELA- and PANC-1-derivative lines were selected for further assay development within the imaging/Project 3 group.

Scientific mission coordination – RAS Initiative bioinformatics

As presented in last year's report, the RAS/CRTP bioinformatics team provides focused bioinformatics support to the NCI RAS Initiative. The support is concentrated in three primary areas:

1. Developing and maintaining a centralized database system to collect, organize, and share the data collected across the different projects throughout the RAS Initiative.
2. Providing direct support to specific projects requiring development of novel analysis work flows and/or significant and ongoing informatics analysis.
3. Data mining of publicly available genomics data sources in the context of the RAS pathway to inform and guide RAS-driven research, and validate results from the individual program projects.

Each of these areas will be discussed in more detail in the sections that follow.

Data Mining

Following the recommendation of the Frederick National Laboratory Advisory Committee (FNLAC) sub-committee last year, the bioinformatics team has established a collaboration with the Broad Institute/The Cancer Genomic Atlas (TCGA) data analysis team. This collaboration brings together the FNLCR bioinformatics teams' focus on the RAS pathway and the Broad team's extensive expertise and experience in working with the complex and diverse data types available through TCGA. The collaborative teams, including Dr. Frank McCormick, hold biweekly teleconferences to communicate progress and discuss next steps. The teams have applied many of the tools developed to systematically analyze each tumor type within TCGA for common/driver mutations, gene expression, and copy-number analysis, and to place these results in the context of the RAS pathway. As expected, many genes within the RAS pathway are involved across a broad spectrum of tumor types at the copy-number variation, mutation, and expression-change levels. The teams are now developing an outline for a first manuscript describing many of these results, and we anticipate that this information will be well received by the scientific community. The manuscript will provide details regarding genes that are most and least differentially expressed across both normal and tumor samples, and between tumor types, and also how this information is reflected in the redundant nodes of the consensus RAS pathway.

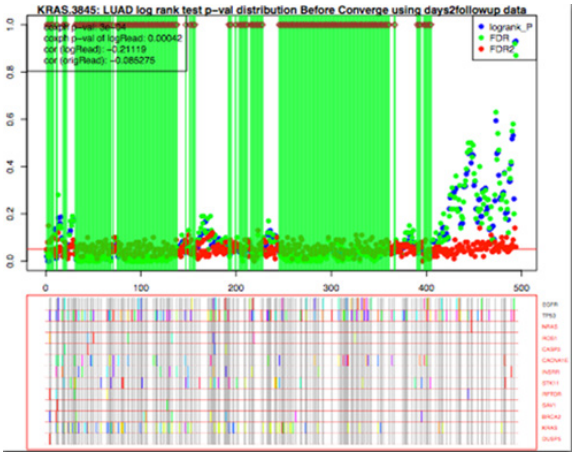
In addition to the efforts with the collaborative team, the internal team continues to mine these data extensively and to pursue the open questions reported in last year's report. One such question is to try to distinguish between

different mutant KRAS alleles in terms of accompanying mutations or co-expression-specific signatures. As the number of samples available in each of the individual sources is somewhat limiting in terms of the numbers of samples of each mutant allele, we are using the approach of combining multiple data sets, each with limiting numbers, to try to gather additional statistical power. This effort now includes a collaboration with Dr. Udo Rudloff, a CCR investigator with NCI who is focused on the KRAS G12R–mutant allele that shows particularly poor prognosis in pancreatic cancers.

Another question we have been pursuing is to try to identify specific attributes of the KRAS 4A and 4B isoforms. This study has been limited by the fact that, while the expression levels of the 4A isoform are quite variable, the levels of expression of the 4B isoform are relatively constant and far outweigh the 4A isoform. We have collected expression information across all of the different tumor types within TCGA and are now able to get this same data for Cancer Cell Line Encyclopedia (CCLE) cell lines after we internally derived the transcript isoform expression information using the available raw data. We have been able to show some correlation between the levels of KRAS 4A expression and survival in limited tumor types, but in these cases overall, KRAS and KRAS 4B show the same correlation. In addition, we have shown that there is a subset of genes that are more commonly mutated among the highest KRAS 4A–expressing samples, and we are further investigating the roles these genes may play in RAS biology.

It is our hope that we will be able to move this analysis forward now that we have cell lines available from RAS Project Zero where only a single KRAS isoform is expressed. Using these cells that lack endogenous *RAS* genes, which were originally developed by Dr. Barbacid's laboratory (see MEF description in Project 2), and expression analysis, we hope to be able to develop KRAS 4A– and 4B–specific signatures that we can then evaluate in the context of TCGA data. In addition, Dr. Rudloff (see above) has derived a series of cell lines expressing the G12R mutant of KRAS, and has RNA expression data for these cells when they are grown in two and three dimensions over a time course that we hope will show some changes in the levels or ratio of 4A and 4B. Experiments to test this are under way.

In the process of these continuing analyses, we have developed pathway-centric analysis tools that facilitate systematic pathway assessment across a variety of dimensions. First, we developed a tool for survival analysis using continuous variables such as gene expression. For review, conventional survival analysis approaches typically use a discontinuous variable, such as a gene's mutational status, to distinguish classes. In our method, the samples are arranged in increasing order of expression, for example, and each subsequent class division is tested for survival significance. Using random sampling from the actual data, we are able to derive statistical significance estimates from these comparisons. This approach has been applied in the demonstration of expression correlation with survival for HRAS, NRAS, and KRAS across a variety of tumor types. Interestingly, the analysis shows a negative correlation between HRAS expression levels and survival times, so that high expression levels correlate with longer survival times, whereas both KRAS and NRAS show the inverse correlation—low expression levels correlate with longer survival. The survival tool, written in the R language, produces textual and graphical outputs. The graphical output shows a combination of the per-sample survival analysis and a panel of mutational information for the samples, integrating the expression and mutation data into a single view as shown below.

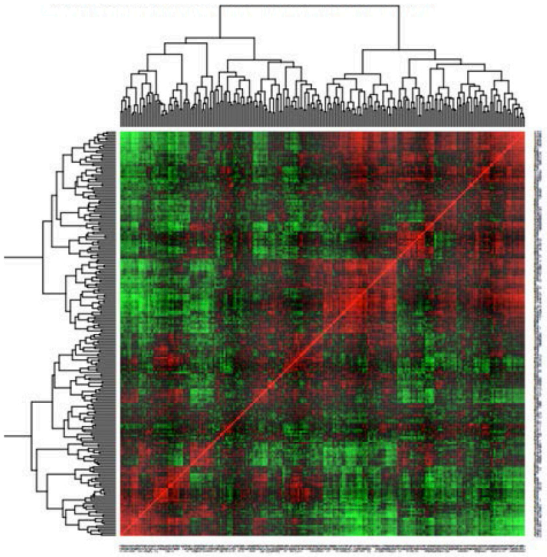


Several additional tools have been developed that scan across all of the tumor types within TCGA to produce gene-specific, pathway-specific analyses. For example, one tool takes an input set of genes representing a node in the pathway and then generates a Venn diagram that correlates with each gene in the node's expression. These lists can then be compared to identify features shared by different tissue and tumor types, and also those that are unique to a particular tumor type. This analysis has revealed that each specific tissue possesses a unique signature of gene-gene correlations. As a result of this fact, coupled with the observation that the gene expression of the genes in the RAS pathway for distinct expression clusters, it comes as no surprise that large differences can be observed when examining the RAS-pathway readouts between different tissues, and reaffirms the large role of tissue context in experimental outputs.

Another tool derives pathway heat maps for expression and/or mutation across each tumor type. The common goal of these tools, which remains to be realized, is to be able to produce a context-specific pathway view for each tumor type or even specific samples. This is a long-sought goal of the precision medicine era, and these tools will aid in reaching that goal.

The application of these tools has revealed a complex network of gene–gene correlations that exists in normal cell samples. When compared with their matched tumor samples, many of these correlations are lost and many of the genes expressed in the pathway are altered. Still, most

tumor samples cluster with their normal counterparts, with the exception of the squamous tumor samples from the lungs, and head and neck, which cluster together. A snapshot of this complexity is shown in the figure below, where we show the correlations across all RAS pathway genes in normal lung samples. In the image, the red color corresponds to genes in the network a showing positive correlation, and the green represents genes that are negatively correlated. In the matching tumor samples (not shown), many of these correlations are much more subdued or absent altogether.



Infrastructure and support

This year, we have focused our efforts on expanding the data repository for the data produced by all of the collective projects within the RAS Initiative. We requested a partition (5 TB) for storage of all of the internally generated RAS data, and that data is now directly accessible to our scientists via a folder on their desktop, through a defined file location on our batch cluster, and also through our filemaker databases. This is an important step towards unifying all of our data generated in-house so that, for example, all of the information pertaining to a particular KRAS-mutant sample prep can be brought together, from the protein purification and intact mass spectrometry measurements to crystallization experiments.

In addition to the internally generated data, we continue to expand our collection of publicly available data. We have recently begun to convert much of our internal MySQL database infrastructure to Oracle with the assistance of the Data Science and Information Technology Program (DSITP). We anticipate that this will provide a much-needed large boost to the performance of the databases that now house all of our TCGA, International Cancer Genome Consort (ICGC), CCLE, and other data sources.

Data collection, organization, and accessibility in the RAS Knowledgebase

The RAS projects have continued to expand their needs for data storage, management, and informatics. The database system put in place last year continues to grow and evolve along with those needs. As mentioned in last year's report, each project has been assessed both individually and from the perspective of the aggregate that the collective represents. The projects are storing raw data files, images, analyzed data, sample information, and electronic lab "notebooks" in the RAS database system.

The system to house, organize, analyze, and make accessible these data, called the RAS Knowledgebase, is built to allow controlled access through either the file system, the database, or web interfaces, so that this information can be made accessible to collaborators worldwide. The system also has the ability to both upload and download files to further enhance sharing capabilities and file transfers between different groups.

The RAS Knowledgebase currently warehouses 55 GB of data in the database system itself. This includes information about 17,000 samples resulting from cell line development and protein production, as well as 3,000 image and experimental results files, and over 1,800 "lab notebook" entries. The project also has access to over 1.0 PB of centralized storage for backups, data files, lab use, etc. The approach being used to organize the RAS Initiative data and make it accessible applies all available IT best practices. The best practices are primarily the centralization of the data around a common set of data elements, described as attribute-value pairs, in combination with a flexible system that allows for information to be accessed seamlessly, whether it is stored physically within our centralized relational database or as a linked entity on an external file system. Because many of the projects and labs share both the same samples and attributes, the integration of data from across the projects is dramatically simplified. The cross-project access afforded by the database system is allowing team members to share data about samples, experiments, and results seamlessly, and this facilitates team efforts, increases communication about results, and reduces misinformation about samples and results. Integration with other data sources, such as TCGA and public data sources (e.g., the National Center for Biotechnology Information) continues.

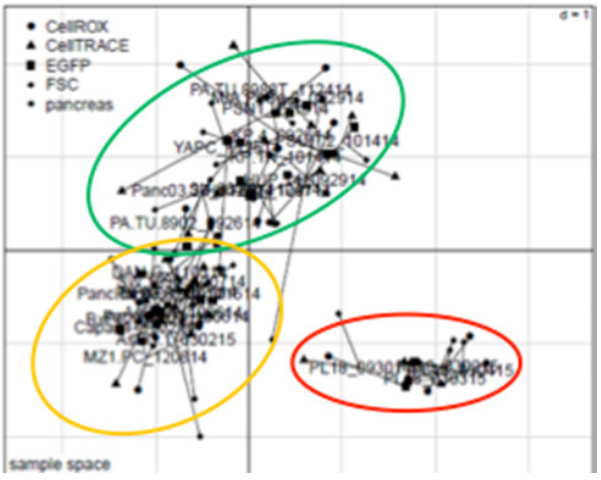
It is envisioned that the evolution of our data architecture and interface will continue over time as refinements and additional data types or concepts are introduced through experimental approaches, and the flexibility being applied will facilitate the ability of the emerging system to accommodate these improvements with relatively little impact.

Direct project support

SiREN data analysis

The silencing RNA knockdown of effector nodes (SiREN) project (see Project Zero) evaluates the perturbation of multiple RAS-pathway signaling nodes using siRNAs to determine the down-expression of the multiple genes representing each of the many nodes in the pathway. We have been working closely with the Project Zero team and collaborators to develop an automated protocol for normalizing and standardizing the raw data, permitting node–node and sample–sample comparisons across the 90 or so cell lines that have been screened in the assay. The approach involves subtracting a negative-control sample from each sample and generating bins that represent the maximally knocked-down proportion of the approximately 30,000 cell samples in each condition. These cell subsets are then used to derive a single metric (area-under-curve) that can be compared across the different nodes and cell lines in the heat map format. The results from this procedure are currently being incorporated into a manuscript. In addition to the preliminary data processing, the team (spearheaded by Ming Yi) has also adapted a method (A multivariate approach to the integration of multi-omics datasets.

Meng C, Kuster B, Culhane AC, Gholami AM. *BMC Bioinformatics*. 2014 May 29;15:162. doi: 10.1186/1471-2105-15-162. PMID: 24884486) that takes the input matrix and projects the multi-dimensional data into different planes representing the different dimensions of the data. The advantage of this approach is that it allows the multiple channels of data collected in the SiREN experiment to be used in a manner similar to principal component analysis so that those data elements that do not significantly contribute to the discrimination do not interfere with those that do. In the image below, the subset of pancreatic cell lines can be seen as separating into three relatively distinct groups. This separation can then be aligned with the genomic features to determine what distinguishes the cell lines in each of these classes, and those experiments are now under way.



Project 2 support

We have worked closely with the Project 2 team to optimize the curve-fitting procedures that are being applied to the raw screening data obtained from the team's collaboration with NCATS (see Project 2). These approaches have refined the curve fitting so that multiple outputs are generated, including area under the curve, IC10, and IC50, and the methods developed can now be applied to the data generated in-house or externally through our collaborations with pharmaceutical organizations.

Project 3 support

The Project 3 team has developed a RAS localization assay (see Project 3) that produces a large data set containing quantitative image analysis information produced by an analysis work flow developed by the Project 3 team. These data are then normalized using positive- and negative-control data so that drugs/ compounds that reduce the plasma membrane–associated signal by a given percent of signal can be identified. The procedure collects data across a number of fields of view and then shows results for the individual fields and for an aggregated view. The procedure can easily be extended as additional constraints are added to the analysis.

Project 4 support

In the last year, the database used for searching by mass spectroscopy data has been modified to incorporate the ability to detect proteins with known mutations as identified through the uniprot resource. This feature permits, for the first time, the ability to identify peptides corresponding to mutated RAS, for example, and, therefore, represents an important extension to the existing capabilities.

Conclusions

The year has been very productive for the informatics team. Each of the individual projects within the RAS Initiative are now generating large and complex data sets that require development of detailed analysis work flows. The team is well immersed in the development of these new analysis approaches and work flows. We are anticipating the first publication of these efforts with the SiREN analysis to be published by the end of the calendar year. The informatics team is also anticipating publication of a joint publication with the Broad Institute team as a result of that collaboration. In addition, we hope to be able to publish some of our own internal analysis results from TCGA data regarding the gene correlation network analysis and systemic gene dysregulation.

cCRADAS

Support Provided by the Applied and Developmental Research Directorate

10014-13: Building a Vaccine Strategy to Prevent Oral Cancers in Men (Moffitt Cancer Center) – Applied and Developmental Research Directorate. This contractor Collaborative Research and Development Agreement (cCRADA) involved the evaluation of antibody responses to the HPV quadrivalent vaccine at the oral cavity of healthy mid-adult males, in comparison to responses induced systemically. The laboratory concluded activities under this cCRADA and is in the process of executing a second agreement to follow up on findings, and address questions on antibody longevity at the oral cavity and other B cell functional responses.

NCI at Frederick Office of Scientific Operations

Support Provided by the AIDS and Cancer Virus Program

Research Support Cores

Quantitative Molecular Diagnostics Core

The Quantitative Molecular Diagnostics Core (QMDC) provides state-of-the-art quantitative molecular analyses to measure specific nucleic acid sequences in provided specimens, meeting evolving changes in demand for targets, samples, and analyses, to support studies within AIDS and Cancer Virus Program (ACVP), intramural National Institutes of Health (NIH) laboratories, and in the extramural community. The QMDC performs testing for simian immunodeficiency virus (SIV) and related viruses, determining viral loads in specimens from nonhuman primate (NHP) models for AIDS, including plasma viral loads, cell-associated viral loads, and tissue-associated viral loads.

For FY2015, at the current level of throughput, the QMDC will have handled more than 15,000 plasma samples and more than 1,000 isolated cell samples; and significantly assayed approximately 6,000 tissue and biopsy samples with an ultrasensitive, hybrid real-time/digital nested polymerase chain reaction (PCR) assay format. The latter PCR testing format and associated customized processing methods were developed by the QMDC to be able to accurately determine viral loads in necropsy tissues from which the recovery of RNA and DNA with varying levels of contaminants inhibitory to PCR were anticipated. Also responding to the demands for an ever-more-sensitive determination of viral loads from limited amounts of samples, the QMDC has applied the hybrid real-time/digital PCR testing format to other types of specimens, including isolated cells and cell-free fluids. In FY2015, in addition to supporting ACVP internal studies, the QMDC also provided key enabling collaborative support to multiple high-profile studies by extramural investigators involving vaccines (Barouch DH, et al, *Science*. 2015, 349:320; Adnan, et al, *PLoS Pathog*. 2015, 11:e1004633), nonvaccine prophylaxis approaches (Gardner et al, *Nature*. 201, 519:87), and pathogenesis (Fukazawa, et al, *Nat. Med.* 2015, 21:132).

HIV Molecular Monitoring Core

The HIV Molecular Monitoring Core (HMMC), established in FY2011 performs specialty services, including ultrasensitive HIV-1 plasma, cell and tissue viral load testing, and single-genome sequencing and analysis. The HMMC originated in response to investigator requests for expanded access to these specialty services initially developed by the Virology Core of the HIV Drug Resistance Program, (DRP; Center for Cancer Research [CCR]/NCI). Services are provided for specimens from qualified government-supported studies, allowing the DRP Virology Core to focus on the development of alternative assays, potentially to be transferred to the HMMC when appropriate, and on research support services for the DRP investigators. Since its inception, the core has been housed in temporary laboratory space, and in February 2015, the quantitation activities and operations were relocated to permanent renovated space in Building 432. The single-genome sequencing activities of the HMMC are resident with the Viral Evolution Core of the ACVP in Building 535 under the direction of Dr. Brandon Keele. The quantitation activities of the HMMC makes use of its established multiplexed, hybrid real-time/digital assay format that interrogates multiple sequence regions in HIV-1 DNA or RNA isolated from plasma, cell, or tissue samples. In a head-to-head comparison with the Roche COBAS Taqman assay using a panel of 76 patient isolates from the NIH AIDS Reagent Program comprised of clades A, B, C, D, E, F, and G, the original gag single-copy assay (gSCA from the DRP) detected only 45 percent of the viruses within 10-fold of COBAS results, whereas the HMMC gag assay detected 96 percent of the viruses within 10-fold of COBAS results (at least 25,000 copies assayed). HMMC gag detected 80 percent HIV-1 clade A virions, whereas gSCA detected 0 percent of the viruses within 10-fold of COBAS results with this panel. Clade C detections were similar, with HMMC gag detecting 100 percent and gSCA detecting 43 percent of the viruses within 10-fold of COBAS results with these clades in the panel. HMMC has made significant progress in the development of multiplexed, ultrasensitive HIV assays for plasma, cell, and tissue samples, with improved sensitivity and coverage of HIV-1 subtypes over the protocol transferred from the DRP, addressing the evolving needs of the HIV-1 research community and expanding the services offered. The HMMC quantitation group has successfully applied these revised assays and formats to the testing of more than 1,000 plasma samples, approximately 100 cerebrospinal fluid (CSF) samples, and approximately 90 cell samples this past year, including, an RV254 plasma study set in

collaboration with Dr. Jintanat Ananworanich (U.S. Military HIV Research Program [USMHRP]), and an opportunistic infection plasma/sorted CD4 cell study set in collaboration with Dr. Irini Sereti (National Institute of Allergy and Infectious Diseases [NIAID]), both containing non-B subtype HIVs that were not detected by the original gSCA assay, but were detected with the new HMMC gag assay. Additional study sets are currently in process.

The sequencing group within the HMMC has supported three extramural research studies to determine the genetic composition of HIV-1 following ex vivo induction of cell-associated (CA) RNA, DNA, and vRNA (Dr. John Mellors, University of Pittsburgh), and two structured treatment interruption studies in fully suppressed HIV-1-infected subjects (Dr. Timothy Schacker, University of Minnesota, and Dr. Jonathan Li, Harvard). For the ex vivo induction analyses, sequencing of ex vivo induced or spontaneous expression of vRNA in resting CD4+ T cells versus total integrated DNA provides insight into which viral lineages are capable of reigniting viremia if treatment interruption occurs. The entire viral genome is amplified in overlapping halves, and the entire proteome is compared between groups, asking the following questions: Is the genome intact? Do expressed viruses match proviral sequences in resting cells? How many proviruses are expressed spontaneously or induced by specific ex vivo treatments? What proportion of the total proviral DNA can be induced to express virus? Are there clonally expanded cell populations that can produce progeny virus? Currently we are performing a prospective assessment of inducible reservoirs (total and infectious) from resting CD4+ T cells in 10 patients.

The HMMC also provided sequencing support for two treatment interruption studies. In the first study, with Drs. Schacker and Haase (University of Minnesota), 14 patients on suppressive therapy with viral load below 50 copies/ml were taken off therapy and monitored frequently for viral rebound. Once rebound occurred, blood and biopsy (lymph node and colon) were obtained. All but one patient had detectable rebounding viremia, with evidence of virus in multiple tissues. The sequencing group of the HMMC sequenced over 300 envelope genomes and was able to determine the number of unique rebounding/founder genomes. We found genetic evidence of multiple variants re-igniting infection, providing a useful indicator of the number of genomes capable of contributing to rebound viremia, while underscoring the challenges in eradicating these viral reservoirs (Rothenberger et al. *PNAS* 2015). In a second collaborative treatment interruption study, this time with Dr. Li and Mary Kearny (DRP/NCI), 10 patients were sampled pre–antiretroviral therapy (ART), on-ART (CA-RNA/DNA), and at two time points post-treatment interruption. The HMMC sequenced over 1,100 single genome amplification (SGA)–derived amplicons representing 1,180 bases of the Pol gene, including viral protease (PRO) and reverse transcriptase (RT), and then phylogenetically compared the pre-, on-, and post- therapy sequences per patient. Interestingly, viral sequence diversity was highest in the cellular HIV DNA and RNA populations during suppressive ART. Furthermore, we identified expanded clonal populations of cellular HIV DNA, which we found could give rise to rebounding virus after treatment interruption, but most of the time, rebounding virus was most similar to that found in the pre-ART plasma population. Importantly, the viral populations with increased diversity measures during the on-ART phase do not appear to contribute to rebounding viremia and likely represent nonviable or replication-deficient genomes that are increasing in proportion as the viable/protein-producing genomes are being eliminated. These data were presented at the Conference on Retroviruses and Opportunistic Infections (CROI) 2015 and are being prepared for publication.

Biological Products Core

The ACVP capabilities include the production and provision by the Biological Products Core (BPC) of highly cost-effective antigen capture immunoassay kits for determination of HIV virus levels in samples from in vitro experiments. During the current year, the BPC provided more than 340 antigen capture kits to 14 intramural and extramural laboratories under the Technical Services Agreement (TSA) system; since these kits are designed and produced for analysis of in vitro samples rather than clinical specimens, and are provided to requesting investigators at the cost of manufacture, they are significantly less expensive than commercially available kits. Providing these kits resulted in an estimated savings to the research community in excess of $92,000, which is particularly important during a sustained period of tight research funding. Beginning in 2015, NCI permitted the BPC to convert from providing complete kits under the TSA system to providing the key reagents to AIDS research laboratories at no cost, using a simple material transfer agreement (MTA). These reagents, all produced by the BPC, include purified capture monoclonal antibody against HIV-1 p24, HIV-1 p24 standard, and the primary anti-HIV-1 polyclonal antibody. These reagents allow recipient laboratories to set up their own kits using the simple instructions provided. Reagents equivalent to 1,140 kits and valued at an estimated $342,000 were provided to 17 AIDS research investigators.

The BPC has extensive expertise and experience in the production of purified retrovirus preparations at multiple scales, and provides them in either infectious or chemically inactivated form. It provided over 376 mg of highly purified and concentrated retrovirus preparations and related control reagents to 18 qualified requesting intramural and extramural laboratories. This service represents an estimated cost savings to the requesting investigators of approximately $170,000, compared with a conservative estimate based on $1,000/ml for commercially sourced purified virus; however, all of the materials provided by BPC were unique reagents that are not available from commercial sources at any cost. In keeping with the mission of a national laboratory, over 98 percent

of these materials were provided to extramural investigators. Another key function of the BPC is the small-scale purification of HIV or SIV from new, productively infected cell lines/cell clones under development or from samples submitted by other laboratories for analysis to assess the quantity and quality of the virus in these samples. The aim is either to identify the best cell lines/cell clones for use in future large-scale virus production/purification projects, or to assess some compositional element of the virus. Depending on planned analyses, the virus was sometimes chemically inactivated prior to purification. During this period, over 100 preparations were made from nearly 10 liters of cell culture supernatant. All were analyzed by the Retroviral Protein Chemistry Core (RPCC; Dr. Elena Chertova, head), and selected ones were further analyzed by cryo-EM (Dr. Sriram Subramaniam, NCI). Finally, the BPC optimized the transfection conditions for and prepared a 3,000 x 1 ml aliquot infectious stock of simian human immunodeficiency virus SHIV "C5" at the request of Dr. Alan Schultz (NIAID) for use as an international reference stock. Expert analysis of this stock was provided by other groups within ACVP, including the Retroviral Protein Chemistry Core (Dr. Elena Chertova), Retroviral Pathogenesis Section (Dr. Greg DelPrete), and Quantitative Molecular Diagnostics Core (Dr. Jeff Lifson).

The BPC, in collaboration with the RPCC, developed an automated fast protein liquid chromatography (FPLC)-based anion exchange chromatographic method for the partial purification of rhesus IL-7 from rmIL-7 293H/A6292 CL.54 culture supernatant. A total of approximately 75 mg of rhesus IL-7 was processed in 10 purifications. This material was transferred to Dr. Elena Chertova (ACVP Retroviral Protein Chemistry Core Laboratory) for final purification and analysis. This work is part of a collaboration between the ACVP and the laboratory of Dr. George Pavlakis (NCI).

Cellular Immunity Core

The Cellular Immunity Core (CIC) provides ACVP investigators and collaborators with quantitative multi-parametric cellular analysis and cell separation using advanced flow cytometry methods and instrumentation. Given its infrastructure and enhanced safety protocols, the CIC is the only group in the Frederick National Laboratory for Cancer Research (FNLCR) that is approved by the Institutional Biosafety Committee to perform fluorescence-activated cell sorting of infectious specimens. In addition, the CIC devises and applies polychromatic flow cytometry methods to monitor phenotypic and functional immune changes associated with disease, clinical parameters, and other study events, in support of internal and collaborative NHP studies.

In utilizing its state-of-the-art resources and technical expertise, the CIC has made many important contributions to HIV, AIDS, and NHP research over the last year, by providing immune response monitoring, subset phenotyping, cell sorting and separation analysis, novel assay and reagent development for NHP studies, technical assistance, flow cytometry and immunology consultation and training, assay and instrument troubleshooting, and multiparameter data analysis for many laboratories. Laboratories and internal NHP studies supported within the ACVP include the Retroviral Immunology Section (RIS; Ohlen, Trivett, Ayala, Jain); Retroviral Pathogenesis Section (RPS; Lifson, Schneider, Del Prete); Tissue Analysis Core/Retroviral Immunopathology Section (TAC/RIPS; Estes, Deleage); Viral Evolution Core/Retroviral Evolution Section (VEC/RES; Keele, O'Brien, Camus); BPC (Bess, Schaden-Ireland, Smith); Viral Oncology Section (VOS; Whitby, Rashon, Labo, McClain, Marshall); Specimen Support Core (SSC; Del Prete, Coalter); and Retrovirus-Cell Interaction Section (RCIS; Ott, Barsov). The CIC provides these groups with key data for multiple publications and presentations at scientific conferences. Intramural laboratories include the FNLCR Laboratory of Experimental Immunology (Carrington, Apps) and Laboratory of Cancer Biology and Genetics (Merlino, Day, Kozlov), and the NIAID Vaccine Research Center (Mascola), Laboratory of Immunoregulation (Connors, Migueles, Mendoza), and Emerging Viral Pathogens Section (Jahrling, Johnson, Cornish). Extramural laboratories include the University of Minnesota (Schacker); University of California Davis Infectious Diseases Unit (Luciw, Adamson); Yerkes National Primate Research Center (Tiwari); Tulane University (Veazey, Ling, Johnson); Aaron Diamond AIDS Research Center (Hatziioannou, Bieniasz); University of Massachusetts Medical School (Reimann); Merck Research Laboratories (Tan, Rizk); University of Pennsylvania (O'Doherty, Hoxie, Riley, Scholz); and University of North Carolina (Garcia-Martinez).

Some key publications and conferences include: Del Prete, et al. Effect of suberoylanilide hydroxamic acid (SAHA) administration on the residual virus pool in a model of combination antiretroviral therapy-mediated suppression in SIVmac239-infected Indian rhesus macaques. *Antimicrob. Agents Chemother.* 2014. 58:6790-6806; Ling, et al. Effects of treatment with suppressive combination antiretroviral drug therapy and the histone deacetylase inhibitor suberoylanilide hydroxamic acid (SAHA) on SIV-infected Chinese rhesus macaques. *PLoS One*. 2014. 9(7):e102795; Estes et al. Antifibrotic therapy in simian immunodeficiency virus infection preserves CD4+ T-cell populations and improves immune reconstitution with antiretroviral therapy. *J. Infect. Dis*. 2015. 211:744-754; *Nat. Commun.* 6, no. 8020, doi:10.1038/ncomms9020; Apps, et al. Relative expression levels of the HLA class-I proteins in normal and HIV-infected cells. *J. Immunol*. 2015. 194:3594-3600; 32nd Annual Symposium on NHP Models for AIDS; CROI 2015; and 2015 Keystone HIV Vaccines and Immune Activation in HIV Infection symposia.

Over the last year, the CIC has evaluated and developed essential reagents and immunological assays to further

our understanding of NHP systems and HIV/SIV research endeavors, and provided support to fulfill ACVP and collaborative project research goals. Some key examples include developing and optimizing polychromatic antibody panels and flow assays to directly quantitate B cell and DC subsets in NHP whole blood, which now allows us to define and concomitantly monitor NK, B, T, M/M, DC and memory cell subsets, giving us a more comprehensive picture of the absolute cell number changes that occur in NHP as a result of infection and treatment. In addition, we can now use flow cytometry to concurrently detect and monitor viral RNA transcripts and surface/intracellular markers at the single-cell level; this should prove to be a very useful assay for future studies. The CIC has also performed NHP cross-reactivity analysis on many antibodies directed against human surface and intracellular proteins, in conjunction with laboratories specializing in human research, other NHP laboratories specializing in NHP models for research, and companies with mutual interests in determining the applicability of reagents for use in NHP studies; and it provided this information to the HIV research community.

Over the review period, the CIC performed the following assays on whole NHP blood, peripheral blood, lymph node, gut- and rectal-associated lymph node tissue, bronchiolar lavage cells and cell lines: 2,500 samples in 6- to 8-color absolute cell counting assays; 14,000 samples in 6- to 12-color phenotyping and immune function assays; and sorted/separated 400 samples.

Retroviral Protein Chemistry Core

The Retroviral Protein Chemistry Core (RPCC) provides protein chemistry support to the ACVP and collaborating investigators, analyzing purified virus preparations and providing expertise in the purification and characterization of proteins, including recombinant proteins.

The RPCC continues to characterize purified preparations of retroviruses of interest generated either within ACVP or by our collaborators, with analyses that include assessment of the state and amount of surface (SU) and transmembrane (TM) envelope glycoproteins and gag proteins; application of a spectrum of methods, including gel-based calibrated fluorescent staining analysis and immunoblot analysis; and HPLC fractionation and quantitative amino acid analysis and mass spectroscopy, as well as more intensive interventional analyses involving enzymatic digestions or covalent modifications. Different preparations (viral samples for analysis, cell lysate samples, plus samples of monkey sera) were analyzed during the period; 120 gels and 100 immunoblots (most with multiple re-probes) were performed with densitometric and other analyses of those when appropriate; the majority of this material was provided by extramural investigators. Over the same time period, the RPCC performed quantitative amino acid analysis on 96 samples (both for ACVP and external requests). The RPCC developed HPLC quantitation of AT-2 solutions used in the inactivation of HIV and SIV preparations, which is necessary for safe shipping of the virus to other institutions. RPCC also monitor by using HPLC quantitation of antiretroviral drug solutions used in the therapeutic treatment of SIV infections.

The RPCC, in collaboration with J. Bess (BPC), purified the simian form of IL-15 and IL-15 receptor alpha as a biologically active heterodimer from a supernatant provided by the George Pavlakis laboratory (CCR/NCI) using Capto Q anion exchange chromatography, and further processed the simian IL-15 and IL-15 receptor alpha proteins by reverse-phase HPLC to a high degree of purity. The biologically active heterodimer was reconstituted by mixing the two proteins together at a nonacid pH. Approximately 30 mg of biologically active simian heterodimer complex (with 14 mg of IL-15) was aliquoted into 250 microvials for use in the continuation of in vivo macaque studies.

The RPCC has continued to assist Dr. Pavlakis (CCR/NCI) by characterizing human IL-15/IL-15Rα complexes from engineered overproducing human cell lines. IL-15 is a growth, mobilization, and activation factor for NK cells, CD8+ T cells, and intraepithelial T lymphocytes. IL-15 activates target cells via a heterodimeric receptor consisting of a beta subunit (CD122) and a gamma chain (CD132) common to the IL-2 receptor. Recently, we demonstrated that, in vivo in both mice and humans, IL-15 circulates as a heterodimeric cytokine in a noncovalently associated 1:1 complex with a soluble processed form of the IL-15 receptor alpha subunit (IL-15Ra). These findings suggest that the IL-15 heterodimer is the natural, biologically relevant form of the cytokine in vivo. The RPCC, using reverse-phase HPLC, assayed the purity of human IL-15 and IL-15 receptor alpha heterodimer preparations produced by the Xcellerex company, providing direct support for a successfully filed investigational new drug (IND) application for first-in-human clinical evaluation of this novel form of IL-15, with clinical testing slated at the NIH Clinical Center for the summer of 2015. The RPCC, along with M. Thaysen-Andersen (Glycoproteomics and Analytical Glycobiology Department, Chemistry and Biomolecular Sciences, Macquarie University, Sydney, Australia), helped perform glycosylation analysis of biologically active heterodimeric IL-15 purified from human cells. Purified recombinant IL-15 and IL-15Ra were used to study *N*- and *O*-glycosylation sites and composition using mass spectrometry. HPLC-purified IL-15 and IL-15Ra showed highly reproducible glycoprofiles from multiple preclinical- and clinical-grade samples that demonstrated uniform and robust manufacturing and purification of hetIL-15, including its *N*- and *O*-glycosylation, which are key molecular features for the therapeutic characteristics of the hetIL-15 complex. These identified properties of heterodimeric IL-15 provide a strong rationale for the evaluation of this molecule for clinical applications.

The RPCC with O. Chertov and A. Stephen, Protein Chemistry Laboratory (PCL), Leidos Biomedical Research, Frederick, MD, developed quantitation of standards and methods for calibration of recombinant Ras proteins in support of the NCI/FNLCR Ras Initiative.

Tissue Analysis Core

The Tissue Analysis Core (TAC) utilizes state-of-the-art tissue-based methods; combining immunohistochemistry (IHC), immunofluorescence analysis (IFA), in situ hybridization (ISH), and laser capture microdissection (LCM) to better understand HIV/SIV mucosal transmission, pathogenesis, and therapeutic intervention strategies. In addition, the TAC developed a new next-generation ISH approach that, for the first time, allows for the detection of vDNA in tissue sections, as well as a multiplexing capability to detect vRNA and vDNA on the same tissue section. This new approach provides a powerful tool to identify and characterize viral reservoirs in situ for the first time. The supports numerous collaborative ACVP, extramural, and intramural scientific research projects aimed at better understanding HIV/SIV mucosal transmission, pathogenesis, reservoir establishment and persistence, and the development of novel lentiviral animal models. During FY2015, the TAC continued to handle, process, and perform IHC, IFA, ISH, and LCM experiments on tissue samples in support of all ACVP NHP studies as well as numerous collaborations with both intramural and extramural scientists that have resulted in 15 publications during this period in high-tier journals (i.e., *AIDS, Clin Immunol., J. Infect. Dis., J. Virol., Mucosal Immunol., Nat. Med., Nat. Commun., PLoS Pathog., Proc. Natl. Acad. Sci.,* and *Retrovirology*). Furthermore, during FY2015, the TAC executed/completed two large TSAs (University of California, San Francisco [UCSF] and Emory University), completed one cCRADA with the University of Minnesota, and executed another cCRADA with UCSF.

Significant Achievements

TAC accomplishments for FY2015 include key contributions to ACVP, intramural and extramural studies. Highlights of TAC work include: (i) Demonstrating that SIV-induced translocation of bacterial products in the liver mobilizes immune cells that are associated with liver damage (*J. Infect. Dis*. 2015 Aug 3. pii: jiv404); (ii) Determining the differential impact of in vivo CD8+ T lymphocyte depletion in SIV-infected controllers versus progressors rhesus macaques (*J. Virol*. 2015 Sep 1;89(17):8677-86); (iii) Demonstrating that T-cell depletion occurs in the colonic mucosa as well as the blood of patients with a rare idiopathic CD4+ lymphopenia (*J Infect Dis*. 2015 May 20. pii: jiv282); (iv) Determining that a large number of rebounding/founder HIV variants emerge from multifocal infection in lymphatic tissues after treatment interruption (*Proc. Natl. Acad. Sci. U.S.A*. 2015 Mar 10;112(10):E1126-34); (v) Showing that a B-cell follicle sanctuary permits persistent productive SIV infection in elite controller rhesus macaques (*Nat. Med*. 2015 Feb;21(2):132-9); (vi) Using novel LCM techniques, demonstrating that dysbiotic bacteria translocate in progressive SIV infection (*Mucosal Immunol*. 2015 Jan 14); (vii) Using the novel RV254 cohort in Thailand, helping to determine that initiation of ART during early acute HIV infection preserves mucosal Th17 function and reverses HIV-related immune activation (*PLoS Pathog*. 2014 Dec 11;10(12):e1004543); (viii) Demonstrating that gut epithelial barrier and systemic inflammation persists during chronic HIV infection, even in the face of combination antiretroviral therapy (cART) (*AIDS* 2015 Jan 2;29(1):43-51); (ix) Demonstrating that CD4-depletion in rhesus macaques results in macrophage and microglia infection with rapid turnover of infected cells (*PLoS Pathog*. 2014 Oct 30;10(10):e1004467); and (x) Demonstrating that antifibrotic therapy in SIV infection preserves CD4+ T-cell populations and improves immune reconstitution with antiretroviral therapy (*J. Infect. Dis*. 2015 Mar 1;211(5):744-54).

Viral Evolution Core

The mission of the Viral Evolution Core (VEC) is to provide expertise in specialized sequencing techniques, molecular cloning, and viral evolution analyses to support the ACVP, NCI, NIH, and extramural investigators in order to increase our overall understanding of viral transmission and early diversification, viral immune and drug evasion, reservoir establishment and maintenance, preclinical vaccine efficacy including genetic sieve analyses, and species-specific adaptation with a major focus on exploiting the unique advantages afforded by utilizing SIV infection in NHP models. The VEC has established crucial infrastructure and essential personnel providing key genetic insights of viral evolution to a diverse group of scientists that lack the capability and expertise to perform such analyses in their individual laboratories. The VEC supports a number of diverse scientific research objectives including preclinical vaccine evaluations in NHPs, transmission studies, animal model development, and basic viral evolution studies. VEC's services can be categorized into four research areas: (1) preclinical vaccine, (2) viral transmission, (3) NHP model development, and (4) general viral evolution studies.

The VEC spends considerable time and effort in support of collaborative preclinical NHP vaccine studies. This year the VEC contributed sequencing and analysis in support of a study with Dr. Preston Marx (Tulane) in which the transmitted/founder virus was examined following prime boost of vesicular stomatitis virus (VSV) expressing SIV Gag-Env proteins (*PLoS One* 2014). We also completed and published a study with Dr. Franchini (NCI) wherein human papillomavirus pseudovirions were used as a gene-delivery system directly within the vaginal compartment. Although there was no protection from acquisition or a reduction in the number of transmitted/

founder variants, there was a vaccine effect on viral load. We have also begun a study with Dr. Picker (Oregon Health & Science University) to determine the number of variants establishing infection using our molecularly tagged SIVmac239X virus. The model is based on the notion that one can save time and resources by sequencing a small amplicon surrounding several genetically modified synonymous mutations. This virus has been generated and titered in vivo and is in use in several collaborative studies.

The VEC continues to support transmission studies within the ACVP. We have completed both a vaginal and a rectal transmission/early viral dynamics study which are currently in preparation. These studies identified the number of genomes within each anatomic foci of infection, the routes and timing of viral dissemination, and the effects of antiviral innate responses to infection. In addition, the VEC is currently collaborating with Drs. Nikki Klatt (University of Washington) and Keith Reeves (Harvard) to support research projects designed to understand the role of NK cells in transmission and acute SIV infection. Previously, this group, with Drs. Keele and Estes, described the rapid loss of NKp44+ cells in all mucosa as early as day 6 post-infection (Li et al *PLoS Path*. 2014). Follow-up experiments with both the Klatt and Reeves labs are currently under way. Dr. Reeves is seeking to determine the differences in TF genomes following NKp44+ cell depletion (NIH R21/R33 grant recently funded). We also have a collaborative study in place with Dr. Klatt to determine the kinetic changes in neutrophils following intrarectal infection with SIVmac239X. Specifically, the VEC will determine the number of variants establishing infection in this model. We hope that, as the usefulness of this viral model becomes more widely known, the VEC will be able to further contribute to studies seeking to enhance our knowledge of viral transmission. Finally, we have worked with Dr. Qingsheng Li (University of Nebraska) to identify genetic bottlenecks during rectal transmission (manuscript in preparation).

To support novel NHP model development, the VEC has continued its long-term evolutionary analysis of a minimally chimeric HIV/SIV infection in pigtail macaques with Drs. Lifson (ACVP), Vineet KewalRamani (NCI), and Theodora Hatziioannou and Paul Bieniasz (Aaron Diamond Research Center). The initial publication of this work, which included significant contributions from the VEC, was recently published in *Science* (Hatziioannou et al. 2014). Additionally, in two separate studies recently published involving NIH researchers Drs. Richard Koup (VRC), Mal Martin (NIAID), John Mascola (VRC), and Robert Seder (VRC), the VEC has provided sequence and evolutionary analysis support in Env SHIV longitudinal studies. Both studies describe the evolutionary adaptation of a virus in conjunction with host antibody responses. Animals who generated significant antiviral antibodies forced significant viral adaptation, which in turn, acting as a self-reinforcing feedback loop, providing additional variation for new antibodies responses (Francica et al. *Nat. Commun*. 2015, and Yamamoto et al. *Sci. Transl. Med*. 2015).

The VEC also continues to support basic evolutionary analyses in vivo and in vitro. Here we have collaborated with Drs. Pathak and Wei-Shau to quantify the number of recombination events that occurred between two subtype A viruses (Nikolaitchik et al. *Virology* 2015) and between several APOBEC-mutated genomes (manuscript in preparation). We also built upon a long-standing collaboration with Drs. Jim Hoxie (University of Pennsylvania) and Andrew Lackner (Tulane) to genetically characterize an SIV lacking a gp41 trafficking motif within pigtail macaques (Breed et al. *J. Virology* 2015).

ACVP Principal Investigator Research Sections

Retrovirus-Cell Interaction Section

The goal of the Retrovirus-Cell Interaction Section (RCIS) is to study the interactions between HIV-1/SIV and their host cells to address important biological questions, emphasizing T-cell-mediated antiviral immunity and mechanisms for T-cell resistance to HIV/SIV infection.

Significant Achievements

Preferential targeting of $CD8^+$ T cells to B-cell follicles by CXCR5 transduction: The RCIS redirected the in vivo trafficking of $CD8^+$ T cells into B-cell follicles in rhesus macaques by engineering the cells to ectopically express the CXCR5 homing receptor. Normally, effector $CD8^+$ T cells are excluded from B-cell follicles. In AIDS virus–infected individuals, B-cell follicles also harbor significant levels of infected $CD4^+$ T cells. Since a primary mechanism for AIDS virus control is clearance of infected cells by cytotoxic $CD8^+$ T cells, B-cell follicles represent a sanctuary for virus infected $CD4^+$ T cells to escape the action of antiviral $CD8^+$ T cells. Indeed, in rare individuals who are able to spontaneously control the AIDS virus infection, infected cells are readily detectable within B-cell follicles. Virus from infected cells in B-cell follicles can also persist despite cART. Thus, placing effective antiviral $CD8^+$ T cells into this viral sanctuary could facilitate targeting of this persistent viral reservoir. As a first step to placing antiviral $CD8^+$ T cells into B-cell follicles, the RCIS retrovirally transduced $CD8^+$ T cells with the B-cell follicle homing protein CXCR5, then used these cells in adoptive transfer studies in rhesus macaques. After infusion of equal amounts of engineered $CXCR5^+$ and control $CXCR5^-$ $CD8^+$ T cells into rhesus macaques, the CXCR5-expressing cells were predominantly found in B-cell follicles of lymph nodes and spleen, while the untransduced control cells were essentially absent from these structures. Thus, this homing study demonstrates that CXCR5 is necessary and sufficient to allow $CD8^+$ T cells entry into B-cell follicles. Current work focuses on placing CXCR5 on anti-SIV $CD8^+$ T cells and infusing infected, yet viral, controlling

rhesus macaques to redirect them into B-cell follicles to suppress this source of residual virus hiding in these sanctuaries. This approach also has the potential to be translated into an anti-HIV therapy for the elimination of residual virus in otherwise controlling AIDS patients.

Biology of TRIM5α-mediated restriction of HIV-1 and SIV: The RCIS extended its prior study of Tripartite motif protein 5-alpha (TRIM5α)/AIDS virus biology. The RCIS found that ectopic expression of African green monkey TRIM5α (AgmTRIM5α) could provide strong restriction of both HIV-1 and SIV_{mac} in transformed $CD4^+$ human T-cell lines (*Retrovirology*. 2015;12:11. doi: 10.1186/s12977-015-0137-9). The observed restriction was considerably more robust and effective than restriction mediated by other TRIM5α proteins. Overall, these data show that AgmTRIM5α is the most effective in restricting TRIM5α species observed to date. The RCIS used this strong restriction to counteract a severe limitation of studying primary rhesus macaque antiviral $CD4^+$ T-cell clones in vitro. The RICS currently studies the contribution of antiviral cytotoxic $CD4^+$ T cells to the control of AIDS viruses by examining the ability of anti-SIV $CD4^+$ T cells to suppress viral replication in vitro. One confounding issue for these studies is that antiviral $CD4^+$ T cells are also targets for infection and virus-mediated death, thus reducing their life span and effectiveness. To overcome this vulnerability, the RCIS utilized the robust AgmTRIM5α-meditated restriction to protect antiviral $CD4^+$ T cells from SIV_{mac} infection. Ectopic expression of AgmTRIM5α in anti-SIV $CD4^+$ T cells transferred resistance to infection and increased their ability to suppress SIV_{mac} replication in mixed $CD4^+$ T-cell cultures by preventing their infection and subsequent virally induced cytopathology (*J. Virol*. 2015 Apr;89:4449. doi: 10.1128/JVI.03598-14). This approach now allows for better analysis of primary antiviral $CD4^+$ T-cell clones using the SIV_{mac}/rhesus macaque system.

High-efficiency production of retroviral T-cell receptor transfer vectors: The RCIS developed a novel approach to simultaneously isolate, clone, and construct retroviral T-cell receptor (TCR) transfer vectors using a one-step cloning approach (*Biotechniques*. 2015; 58:135. doi: 10.2144/000114265). Part of the RCIS research effort is to use retroviral vector transduction to engineer virus-specific T cells for both in vitro and in vivo studies. This innovation streamlines the production of vectors, eliminating unneeded steps and reducing vector production time by two-thirds. Furthermore, the reduced number of PCR steps greatly reduces the risk of PCR errors. This system has allowed for the successful construction of TCR transfer vectors that were unable to be attained by conventional methods. The RCIS has produced both human and rhesus macaque versions of this system that are being used for its own studies as well as collaborative studies with Dr. Whitby's Viral Oncology Section.

Retroviral Immunology Section

In early February 2015, Dr. Claes Ohlen, head of the Retroviral Immunology Section (RIS) unexpectedly passed away. Dr. David Ott, his long-time close collaborator assumed responsibility for Dr. Ohlen's personnel and projects, folding the RIS into the Retrovirus-Cell Interaction Section (RCIS). This report covers the first four months of the contract year of the RIS with continuing effort reported in the RCIS report.

The RIS studies the role of cellular immune responses in the prevention and control of primate immuno-deficiency virus infections, emphasizing in vitro and in vivo studies in NHP systems using a variety of approaches, including adoptive transfer studies.

The approach considers that, while many vaccine protocols have successfully generated functional anti-SIV cytotoxic T-cell lymphocyte (CTL) immunity with measureable efficacy in controlling viremia and decline of $CD4^+$ T cells in NHP models, these responses generally have been unable to provide sterilizing immunity and prevent infection upon challenge with highly pathogenic virus strains. Therefore, a fundamental question is whether the lack of sterilizing immunity in these studies is due to failure to achieve sufficient frequency of primed virus-specific CTL in the host before challenge (a quantitative failure) or to an intrinsic failure of the CTL response to prevent establishment of infection (a qualitative failure). The overall aim of the RIS is to employ multiple approaches, including in vivo adoptive T-cell transfer, to studying the basis of effective cellular immune responses to AIDS viruses using the SIV/rhesus macaque system. Using its ability to isolate and maintain SIV-specific T cells in vitro for prolonged periods, the RIS has developed and uses in vitro assays to assess functional suppression of SIV replication by CTL clones, in part mimicking in vivo host/virus immune interactions, allowing direct and reproducible comparisons of efficacy between SIV-specific T-cell clones with different effector function in a system that closely matches the conditions in vivo. Insights obtained from these studies should lead to increased understanding of HIV/SIV immunobiology and immunopathology, and to novel approaches for vaccine development.

Significant Achievements

Chimeric Antigen Receptor (CAR)–expressing T cells suppress AIDS virus replication: CAR-expressing T cells have shown very encouraging efficacy when tested against certain malignancies in recent clinical trials. Previously, our section produced T cells expressing an engineered CAR produced by fusing a single-chain HIV Env-specific antibody to a CD3 signaling domain. These CAR-engineered primary rhesus $CD8^+$ T cells suppress SHIV replication in vitro and lyse HIV-infected cells. In a pilot experiment, adoptive transfer of CAR-expressing T cells into SHIV-infected animals found that these cells were well tolerated and homed to appropriate lymphoid

organs, opening the way for further antiviral studies using the HIV/SHIV CAR approach.

Cellular immune response to Kaposi's sarcoma–associated herpesvirus (KSHV): Working closely with the Viral Oncology Section (VOS), the RIS has isolated KSHV-specific T cells from healthy seropositive donors. These are now being studied in both the VOS and the RCIS. The ability to bring together the immunology expertise of the RIS (now combined with the RCIS), the KSHV virology expertise of the VOS, and the molecular immunology/engineering of the RCIS now allows for detailed and thorough identification and characterization of T-cell immune responses to KSHV.

Retroviral Pathogenesis Section

The Retroviral Pathogenesis Section (RPS) studies interactions of primate lentiviruses with their hosts to better understand the mechanisms by which these viruses cause disease, in order to more effectively prevent and treat such infections and their consequences.

Significant Achievements

In Vitro Studies: In collaborative studies with Sriram Subramaniam, the RPS used advanced electron microscopy methods on specimens prepared in the ACVP laboratories to provide new insights into maturation of the HIV core structure (*Nat. Commun*. 2015 Jan 8;6:5854) and into the structure and function of virological synapses (Do T et al., *J. Virol*. 2014, 88:10327).

Improved SHIV/NHP models: Chimeric viruses containing HIV-1 Env sequences in an SIV backbone, designated SHIVs, are a mainstay of research on Env-targeted prophylactic and therapeutic interventions, including vaccines, antibodies, and other approaches, but existing SHIVs in the field are not representative of current, clinically transmitted viruses that are the intended target of these interventions. In collaboration with Drs. Paul Bieniasz and Theodora Hatziioannou (Rockefeller University/Aaron Diamond AIDS Research Center), the RPS developed a strategy for generating and evaluating novel SHIVs that embody a range of clinically relevant features, including R5 tropism, the use of actual transmitted Env sequences, and tier 2 neutralization phenotypes. We have used this approach to generate two novel SHIVs and demonstrated mucosal transmission, robust in vivo replication and pathogenesis, and passive immunoprophylaxis with the broadly neutralizing monoclonal antibody PGT-121 (Del Prete et al., *Cell Host Microbe*, 2014, 16:412).

Viral "reservoirs" and "HIV Cure" research in NHP models: Characterizing and devising definitive interventions to target the residual virus that persists in the face of cART is one of the frontier areas of AIDS research. The RPS has pioneered the development of NHP models for studies relevant to this challenge. This group continues to lead the development and application of novel, effective, and sustainable cART regimens for use in NHP (Del Prete, et al., *AIDS Res. Hum. Retrovir.*, 2015, in press), including using long-acting/sustained release nanoformulations of antiretroviral drugs. We continue to use the model of cART suppression in SIV-infected NHP to study interventions targeting residual virus that persists despite cART, including histone deacetylase inhibitors (Del Prete, et al., *Antimicrob. Agents Chemother.*, 2014 58:6790), toll-like receptor ligands, and therapeutic vaccination.

Viral Oncology Section

The overall aim of the Viral Oncology Section (VOS) is to study the role of viruses in cancer. Studies are focused in three major areas: KSHV epidemiology and transmission, KSHV immunity and pathogenesis, and viral and host genetics in KSHV infection and disease.

Significant Achievements

KSHV Epidemiology and Transmission: We have continued our KSHV research program in Uganda in collaboration with Uganda Virus Research Institute (UVRI) in Entebbe, Uganda. A manuscript was published describing a case-control study nested within the Ugandan General Population Cohort (GPC) showing elevated antibody titers to the KSHV K8.1 antigen years prior to KS in KS cases compared to controls. Trends in KSHV antibodies prior to the development of HIV-associated KS: a nested case-control study. Wakeham K, Johnston WT, Nalwoga A, Webb EL, Mayanja BN, Miley W, Elliott AM, Whitby D, Newton R. *Int. J. Cancer*. 2015 Jun 15;136(12):2822-30. Another manuscript was published that extended our studies of KSHV risk and malaria: Association between malaria exposure and Kaposi's sarcoma-associated herpes virus seropositivity in Uganda. Nalwoga A, Cose S, Wakeham K, Miley W, Ndibazza J, Drakeley C, Elliott A, Whitby D, Newton R. *Trop Med Int Health*. 2015 May; 20(5):665-672. An analysis of KSHV viral load in the saliva of KSHV-infected mothers and children in Uganda was completed, and an oral presentation of the data was made at the KSHV meeting. A manuscript is in preparation. Analysis is ongoing of the KSHV serological testing of approximately 10,000 samples from the GPC. In addition to a remarkably high prevalence, we observed elevated antibody levels to K8.1 in this population. In order to further understand this observation, a subset of 1,000 samples was titrated in both K8.1 and ORF 73 assays. An additional 4,500 samples from a later round were tested to extend this study.

Further studies related to the Cameroon KS case-control studies are ongoing, including DNA extraction from saliva and blood, and analysis of risk factors associated with KSHV infection and detectable viral load.

Analysis of the KSHV testing of approximately 9,500 samples from the AIDS Clinical Trials Group Longitudinal Linked Randomized Trials (ACTG ALLRT) study of 13,000 samples of U.S. highly active anti-retroviral therapy (HAART) users has been completed, and a manuscript on the epidemiology of KSHV in

U.S. subjects initiating cART has been published: Epidemiology of Kaposi's sarcoma-associated herpesvirus in HIV-1-infected U.S. persons in the era of combination antiretroviral therapy. Labo N, Miley W, Benson CA, Campbell TB, Whitby D. *AIDS*. 2015 Jun 19;29(10):1217-25. Parallel analysis of approximately 2,300 samples from the international component of ALLRT is ongoing.

KSHV Immunity and Pathogenesis: The VOS has extended its ambitious project to systematically investigate the immunogenicity of the KSHV proteome. Major progress has been made on the development of an enzyme-linked immunospot (ELISPOT) assay to detect cellular immune responses to KSHV, using overlapping pooled peptides for the entire KSHV genome. KSHV responses in healthy KSHV seropositive donors and patients with KSHV-related diseases have been mapped. A project to make and characterize T-cell clones from subjects with positive responses is ongoing in collaboration with Drs. Ohlen and Ott. Two manuscripts are in preparation, and a poster was presented at the International Herpesvirus Workshop (IHW). The VOS had previously reported genetic variation in the KSHV microRNA encoding region in cell lines and clinical samples. Studies are ongoing to determine the microRNA profiles of KS biopsies from South African and U.S. subjects whose microRNA region sequence we also determined. These studies, using a combination of array and real-time PCR approaches, will enable us to demonstrate the effect of sequence variation on microRNA expression in clinical KS. A poster describing this work was presented at the 18th International Workshop on KSHV and Related Agents meeting, and a manuscript is in preparation. The VOS obtained Clinical Laboratory Improvement Amendments (CLIA) certification and has continued to collaborate with the HIV and AIDS Malignancy Branch on clinical projects to understand basic KSHV pathology and also to evaluate novel therapeutic approaches for KSHV-related disease. Two publications have resulted from these studies this year: 18F-fluorodeoxyglucose positron emission tomography in Kaposi sarcoma herpesvirus-associated multicentric Castleman disease: Correlation with activity, severity, inflammatory and virologic parameters. Polizzotto MN, Millo C, Uldrick TS, Aleman K, Whatley M, Wyvill KM, O'Mahony D, Marshall V, Whitby D, Maass-Moreno R, Steinberg SM, Little RF, Yarchoan R. J. Infect. Dis. 2015 Mar 31; Rituximab plus liposomal doxorubicin in HIV-infected patients with KSHV-associated multicentric Castleman disease. Uldrick TS, Polizzotto MN, Aleman K, Wyvill KM, Marshall V, Whitby D, Wang V, Pittaluga S, O'Mahony D, Steinberg SM, Little RF, Yarchoan R. *Blood*. 2014 Dec 4;124(24):3544-52.

Viral and Host Genetics in KSHV Infection and Disease: Using KS cases and KSHV-positive controls from the Cameroon case-control study, a project is ongoing to determine host and viral genetic factors that play a role in KSHV transmission and KS pathogenesis. A panel of host immune and viral receptor genes has been selected for targeted exome sequencing and a Sureselect probe set designed. Sequencing has been completed for 112 cases and is ongoing for HLA-matched controls. In conjunction with this study, we are determining HLA and KIR sequence diversity in collaboration with Mary Carrington, in order to determine whether these central adaptive/innate immune molecules influence KSHV transmission and/or disease pathogenesis. We have used next-generation sequencing to determine entire KSHV genome sequences from clinical and epidemiological samples. Shotgun Illumina sequencing has been used to derive whole KSHV genomes from 15 pleural effusion samples with extremely high KSHV viral loads. This work was presented at the IHW, and a manuscript is in preparation.

Retroviral Immunopathology Section

The Retroviral Immunopathology Section (RIPS is a new section that was established in March 2012. The mission of the RIPS is to determine the causative processes and pathological consequences of chronic inflammation/immune activation in AIDS virus infections, with the goal to develop and assess adjunctive therapeutic strategies that can ameliorate these pathological processes. The RIPS seeks to achieve this mission through two main research projects: Project I seeks to understand the pathological consequences of inflammation and immune activation; Project II seeks to determine viral establishment and persistence in vivo.

Significant Achievements

During FY2015, we have made significant progress in both of our primary areas of research interest. We are finalizing the data analysis and beginning to write up reports on studies initiated by Dr. Estes in his role as a principal investigator (PI) aimed at determining the barriers and early events leading to vaginal and rectal transmission, in order to understand the process of viral establishment (collaboration with Drs. Keele [RES] and Lifson [RPS]). In addition, we recently published work demonstrating the benefits of an antifibrotic therapy using the drug pirfenidone, which inhibited lymphoid tissue fibrotic damage when started at the time of infection. Furthermore, antifibrotic therapy, in combination with antiretroviral therapy, partially reversed fibrosis in chronic infection and was associated with significantly more CD4+ T cells in peripheral blood and lymphoid tissues, as compared with antiretroviral therapy alone, demonstrating the potential therapeutic benefit of adjunctive antifibrotic therapy in association with antiretroviral therapy in HIV-infected patients (*J. Infect. Dis*. 2015 Mar 1;211(5):744-54.). In addition, we also recently published a manuscript in *Nature Communications* (in press) describing the first NHP model of experimentally induced colitis that shows direct links between gastrointestinal (GI) tract epithelial damage and local and systemic microbial translocation and inflammation/immune activation. Furthermore, in

collaboration with the NCI Molecular Imaging Program, we described a novel, clinically relevant, and applicable noninvasive magnetic resonance imaging (MRI) approach to track, monitor, and quantify the extent of inflammation in the GI tract in our NHP model of colitis. Finally, in additional work with the NCI Molecular Imaging Program, we have developed novel techniques to quantitatively measure the impact of progressive SIV-induced lymph node fibrotic damage on antigen uptake, distribution, and clearance, demonstrating how lymph node fibrosis adversely affects the function of secondary lymphoid tissues in vivo.

Retroviral Evolution Section

The Retroviral Evolution Section (RES) was highly productive, with the start of several new PI-initiated research projects and the preparation of final publications on previous projects, including collaborative studies. The RES is dedicated to addressing essential research questions surrounding viral transmission and viral evolution in an effort to interdict transmission, systemic spread, and adaptation to host responses. The RES uses novel approaches, technologies, and NHPs to provide a fundamental understanding of how the virus is successful in the fight against the host.

Significant Achievements

The first project for the RES is built upon the hypothesis that the greatest opportunity for inhibiting viral growth occurs during the transmission process, when the viral population is significantly reduced to one or a few variants. This genetic bottleneck highlights a significant weakness of the viral life cycle. However, the mechanisms and details surrounding the transmission process and early viral replication dynamics are poorly understood. The RES has developed various viruses, models, and assays to specifically identify the mechanisms of the transmission bottleneck, with the hopes of augmenting the host's ability to repel new infections and prevent systemic dissemination from the site of entry. The RES initiated two serial euthanasia studies in rhesus macaques aimed at identifying the genetic bottleneck following vaginal and rectal exposure to SIV. We have identified the route of systemic infection, enumerated the number of variants within the sites of viral exposure, and determined a variable timing to dissemination. We have adapted MiSeq sequencing and a molecularly tagged virus, providing an unprecedented view into the transmission processes. Both the vaginal and rectal studies are completed and are currently being written for publication.

We found significant variability of time to systemic dissemination between animals challenged intravaginally with SIVmac239X. We therefore looked for potential explanations within the host and within the virus. While we tried to limit host differences by synchronizing menstrual cycles, variability within the host (e.g., preexisting inflammation, target cell density, disparate vaginal flora, and innate immune function) likely contributes to the delay in the time to dissemination. We also sought a viral explanation for this delay. We noted published reports of four nucleotides within the SIVmac239 genome with the potential to increase variability during primary infection. These four suboptimal nucleotides in SIVmac239 were identified over a decade ago and are presumed to be lab-generated errors originating during the cloning process or minor variants found at the terminal stages of disease in the animal from which SIVmac239 was derived. The mutations are found in the primer binding site, Pol (RT and Int), and Env (overlapping with second exon of Tat and Rev). Importantly, the primer binding site mutation results in a mismatch to tRNA3Lys, potentially reducing efficient binding of the tRNA primer. Using site-directed mutagenesis of the full-length/nef-open SIVmac239 clone, we reverted all four nucleotides to the consensus/optimal base and subsequently compared the resulting virus, designated SIVmac239Opt, with parental SIVmac239 for infectivity and replicative capacity in vitro and in vivo. In cultures of primary cells and cell lines, we observed that the optimized virus displayed consistent, but not statistically significant, increases in replicative kinetics as compared with wild type (WT). In vivo, SIVmac239Opt replicated to high peak titers, with an average of $1.2x10^8$ viral RNA copies/ml at day 12 following intrarectal challenge, reaching set-point viremia of $1.2x10^6$ viral RNA copies/ml by day 28. Although the peak and set-point viremia means were not statistically different from WT SIVmac239, viral load variation at set-point was greater for SIVmac239WT than for SIVmac239Opt ($p=0.0015$), demonstrating a more consistent infection model. Our results demonstrate that SIVmac239Opt has marginally faster replication dynamics than WT but is unlikely to cause the disparity in time to systemic dissemination seen in our mucosal infection studies (Fennessey et al. *Retrovirology*. 2015 Jun 16;12(1):49. doi: 10.1186/s12977-015-0175-3. PMID: 26076651).

Another project for the RES seeks to answer key scientific questions of reservoir biology by utilizing cART regimens developed by Dr. Lifson and a novel sequence-tagged virus system designed by the RES to track individual viral reservoirs. We developed, characterized, and validated the barcoded virus approach in both untreated and cART-treated cohorts. We determined that our SIVmac239M stock contains 10,000 unique genomes distinguishable by sequence analysis. In addition to our manuscript describing our approach (manuscript in preparation), we have initiated two NHP studies to examine the effects of the timing of cART initiation on reservoir size and a third study to determine whether CD4-depleting antibodies can reduce or eliminate the latent reservoir. We are also expanding our research of CD4 T cells to determine whether macrophages and follicular dendritic cells are also long-lived viral reservoirs. This project has the potential to provide significant understanding of the establishment and maintenance of viral reservoirs, and will provide a model for testing anti-reservoir therapies.

Support Provided by the Laboratory Animal Sciences Program

Animal Research Facilities Oversight

National Cancer Institute (NCI) at Frederick and NCI-Bethesda are among 750 organizations, institutions, and companies in 29 countries that are accredited by the Association for Assessment and Accreditation of Laboratory Animal Care (AAALAC) International.

The Laboratory Animal Sciences Program (LASP) manages 27 animal research facilities, 22 of which are located in Frederick and five in Bethesda. Collectively, the facilities on both campuses support 206 investigators (95 in Frederick and 111 in Bethesda) and 551 active Animal Study Proposals (ASPs) (198 in Frederick and 353 in Bethesda), and are currently maintaining 133,400 animals (91,891 in Frederick and 41,509 in Bethesda) occupying 49,228 cages. The animal support areas of LASP include: NCI animal facilities, the Animal Health Diagnostic Laboratory (AHDL), Receiving and Quarantine (R&Q), and Laboratory Animal Medicine (LAM). LASP serves primarily as a resource for animal-based research for the NCI scientific community. Additionally, LASP provides significant levels of support to other institutes and entities, including the National Institute of Allergy and Infectious Diseases (NIAID), Leidos Biomedical Research, Inc. programs, and other agencies approved by NCI. In addition to facility operations, LASP provides a wide array of support services in a number of areas, including colony management, technical support on an as-needed basis, requested dedicated technical support; and performance of, as well as training in, advanced surgical procedures. The current animal population is distributed as follows:

Species	Animals
Mice	132,433
Rats	460
Frogs	200
Nonhuman Primates	132
Fish	175
Total	**133,400**

Significant Achievements – Bethesda

LASP effectively managed the impact of severe weather-induced facility damages in Building 14DS, a building-wide flood in Building 37, and HVAC failures in Buildings 37, 41, and 14DS, such that no research animals were harmed and no research experiments were compromised.

In spite of vacancies in two primate veterinary positions, LASP effectively supported all ongoing nonhuman primate research programs with no delays in research endeavors until the two new senior veterinarians were on board. LASP received accolades regarding the level of LASP veterinary care and research support.

LASP developed an in-house aseptic surgery technique training program for NCI research staff, and has successfully conducted well-received training on a monthly basis since June.

LASP successfully initiated an Assistant Laboratory Animal Technician (ALAT) training course that resulted in eight LASP staff members who attended the course achieving eligibility to take the certification examination.

LASP enhanced daily health-status communication with research staff through the use of iPads in LASP-managed rodent facilities.

LASP successfully managed the adverse impact on facility-wide animal husbandry operations during the two-month repair of the walk-in autoclave in the Clinical Research Center (CRC) vivarium. Through exceptional coordination, all animal cages were transported, cleaned, and autoclaved in other LASP-managed facilities, and returned to the CRC such that no animal health status was compromised.

LASP streamlined and improved the animal study proposal pre-review process such that the formal animal care and use committee (ACUC) review process time is greatly reduced.

Dr. Robert Hoyt was reappointed as an adjunct professor at the Virginia-Maryland College of Veterinary Medicine.

Significant Achievements – Frederick

In a continuing extramural collaboration with Therapeutics for Rare and Neglected Diseases (TRND), a program within the National Center for Advancing Translational Sciences (NCATS), LASP is currently conducting a large-scale preclinical efficacy study of candidate pharmaceutical agents utilizing two genetically engineered mouse models of LEOPARD syndrome, the focus of which is the development of therapies for hypertrophic cardiomyopathy. LASP has characterized the two mouse models, involving the collective efforts of the Small Animal Imaging Program and the Pathology/Histotechnology Laboratory.

In addition, LASP conducted several preclinical studies for the NCI Invention Development Fund (IDF), a pilot program designed to give intramural researchers resources to move their inventions to the next decision gate in translational medicine.

LASP has established a gnotobiotic facility in Building 550 for housing germfree animals to support research efforts focused on the role microbiota has in inflammation, pathogenesis, and antitumor response. Three LASP staff members (Mark Shrader, Simone Difilippantonio, and Raja Sriperumbudur) attended a four-day training session at the germfree mouse facility operated by Dr. Sarkis Mazmanian's lab at the California Institute of Technology (Caltech), which provided instruction in husbandry and rederivation procedures relevant to the operation of a large gnotobiotic facility. The training was very productive and resulted in the adaptation of several practices from Caltech, which has

improved the success of the LASP operation. LASP has successfully rederived several mouse strains and is gearing up to offer germfree rederivation as a regular service to investigators. LASP has also successfully completed several studies in support of the Cancer and Inflammation Program (CIP), and is expanding its operations to breed the C57Bl6 mouse strain obtained from Taconic to provide experimental animals to CIP and other Center for Cancer Research (CCR) investigators. Once the operations expand to include the second floor of the facility, animals can be offered to other NCI investigators. As part of facility infrastructure modifications to accommodate the germfree operations, a new generator was recently installed to ensure the entire building has an uninterrupted power supply.

Facility upgrades initiated and successfully conducted by LASP in Frederick include the following:

- Renovations in Buildings 1032 and 1038 were completed to provide isolator production facilities for the Division of Cancer Treatment and Diagnosis (DCTD) that were formerly supplied by Charles River Laboratories in Frederick.
- Carbon dioxide euthanasia chambers in all animal facilities and laboratories were modified for compliance with the 2013 American Veterinary Medical Association (AVMA) euthanasia guidelines, and were retrofitted with nonadjustable flow meters compatible with euthanasia regulations.
- Repaving of deteriorating asphalt surfaces was completed in the former animal production facility areas.
- A large autoclave was replaced in Building 539-2.
- Installation of a new emergency generator was completed to service Building 550.
- Air-flow alarms were installed on isolators in Buildings 1032 and 1038.

Facility upgrades that are in progress include the following:

- New biosafety cabinets are being installed in laboratories 261 and 265 in Building 539-2.
- Blender hoods are being removed and new biosafety cabinets will be installed to create a surgical suite in laboratories 193 and 194 in Building 539-1CC.
- Animal room pneumatic controls are being replaced in Building 567.
- The air handling unit is being replaced in the office and AHDL laboratory areas of Building 429.
- The autoclave is being replaced in Building 1046.
- The façade is being replaced in Building 571.

Animal Health Diagnostic Laboratory

The AHDL is responsible for monitoring the health of all rodents at the NCI at Frederick and Bethesda animal facilities, and it provides diagnostic resources to several other NIH facilities. The major focuses of the diagnostic services include microbiology, parasitology, serology, and health-monitoring necropsies. AHDL has been a consistent resource to the scientific community for more than forty years.

Significant Achievements – Frederick

- AHDL performed 2,175 necropsies; 72,533 serological tests; 10,661 bacteriological tests; 16,997 ectoparasite tests; and 24,900 endoparasite tests as part of its routine health monitoring function.
- Due to a report from Taconic regarding the detection of *Syphacia obvelata* in Taconic Barrier 506 at the Cambridge City, Indiana facility, AHDL rigorously screened a group of animals that was received from this facility. After conducting several rounds of follow-up testing, it was determined that the mice were negative for *Syphacia obvelata*.
- AHDL is providing environmental monitoring of the isolators and supplies for the germfree facility, which often requires rapid turnaround of test results.
- AHDL assisted NCI-LASP-Bethesda with health monitoring of an outgoing shipment of animals housed in Building 14C to the University of Southern California (USC) Department of Animal Resources.
- AHDL performed intensified health monitoring in support of the consolidation of Center for Advanced Preclinical Research (CAPR) mouse colonies from several animal facilities to the second floor of Building 539. These efforts enabled the timely transfer of the mouse colonies between facilities.
- With the termination of the NCI animal production contract, AHDL provided substantial diagnostic support for the orderly transfer of numerous isolator-maintained strains to NCI-DCTD facilities located at the Frederick National Laboratory for Cancer Research (FNLCR). AHDL is also providing monthly diagnostic support for routine health monitoring associated with these isolator colonies.
- AHDL is assisting NCI-LASP-Bethesda with diagnostic support for the experimental autoimmune encephalomyelitis (EAE) study in which the investigator is experiencing unexpected experimental variations. The supplemental diagnostic testing may show the variations are due to adventitious biological agents that do not normally cause fluctuations in non-genetically engineered mice (non-GEM).

Receiving and Quarantine Program

The Receiving and Quarantine (R&Q) Program is a vital, gate-keeping facility that is charged with safeguarding and protecting the health status of the FNLCR and NCI-Bethesda rodent colonies. R&Q is responsible for the quarantine of imported animals that may harbor unwanted viral and microbial agents, and for coordination of animal shipments.

Significant Achievements

Approximately 177 animal importations were processed, of which 20 were animals from approved sources, 16 were from modified-approved sources, and 141 were from non-approved sources.

Laboratory Animal Medicine Program

The LAM program is organized to: (1) provide research support to NCI investigators, (2) ensure the welfare of NCI animals, and (3) ensure compliance with all local, state, and federal regulations that govern the ethical use of animals in biomedical research, with the continuing objective of maintaining full compliance with AAALAC International.

LAM provides a wide array of support services to NCI investigators, including assisting with the development, submission, and modification of Animal Study Proposals (ASPs); consulting and training on surgical procedures, anesthesia, analgesia, endpoints, and various technical procedures; and developing, performing, and refining research, surgical, and diagnostic techniques for animal models.

LAM also provides a comprehensive array of support services to NCI animal programs, including provision of high-quality medical, surgical, and behavioral support; oversight of biosecurity, animal procurement, and sentinel programs; establishment of policies, practices, and operating procedures to ensure regulatory compliance; and acquisition of supplies requiring veterinary prescriptions.

LAM provides support and guidance to two institutional ACUCs; oversees NCI animals housed in shared facilities, both on the NIH main campus and at Poolesville; and organizes the American Association for Laboratory Animal Science (AALAS) training courses for technicians.

Significant Achievements

A new employee training course on animal handling techniques targeting new postdoctoral fellows and scientists is being offered by LAM after a request was received from the ACUC to address multiple accidents and off-protocol incidents. The course has been well-received by investigators.

Gillian Braden, V.M.D., began employment with LASP as an animal program veterinarian on July 27, 2015.

LAM staff successfully trained LASP and NCI technical staff on a survival collection of cerebrospinal fluid in mice.

AALAS certification training and preparation facilitated by LAM resulted in one laboratory animal technician (LAT) and three assistant laboratory animal technician (ALAT) certifications in Frederick; and one laboratory animal technologist (LATG) and one ALAT certification in Bethesda.

LAM personnel, Julie Bullock and Dr. Raja Sriperumbudur, completed the first part of the aseptic techniques in rodent surgery course taught by Dr. Robert Hoyt.

Scientific Support Programs

Transgenic Mouse Model Laboratory

Management of the Transgenic Mouse Model (TMM) and Cryopreservation laboratories was consolidated under the Mouse Model Core Technologies Laboratory.

The primary role of the TMM Laboratory is the production of genetically engineered mice by gene transfer into developing embryos (pronuclear microinjection), which has been instrumental in the study of in vivo gene function through the use of genetically engineered mice to model human diseases. TMMs have specifically been essential for investigating gene functions and their role in cancer biology. The TMM Laboratory offers a complete array of services aimed at successfully generating transgenic and gene-targeted mice. For production of transgenic mice, the services include consultation with the investigator regarding transgenic design; purification of the DNA fragment to be microinjected; pronuclear microinjection of DNA into fertilized mouse oocytes; and genotypic evaluation of the resulting animals by Southern blot analysis. The gene-targeting component of TMM is a comprehensive service that involves advising the requesting investigator on design of the targeting vector, targeting the mouse embryonic stem cells (mESC) by electroporation, selecting the correctly targeted mESC clones by Southern blot hybridization, and generating chimeras by microinjection of karyotypically normal targeted embryonic stem (ES) cells, which is followed by confirmation of germline transmission of the targeted mutation. The TMM Laboratory also performs microinjection of mutant ES cells obtained from repositories such as the European Conditional Mouse Mutagenesis Program (EUCOMM) and the microRNA (miRNA) Resource available through the NCI Mouse Repository. Chimeras generated will be transferred to the requesting investigator for further characterization.

Significant Achievements

The TMM Laboratory has successfully completed 62 construct-based transgenic, knock-out, conditional knock-out, and knock-in mouse models, in support of 20 principal investigators; this is an increase from the 45 projects completed in FY2014. In addition to NCI, TMM provides services for other institutes within NIH outlined in the table below. Included are 10 projects that have utilized the newly implemented CRISPR/Cas9 technology (Clustered Regularly Interspaced Short Palindromic Repeats), in support of Drs. R. Hodes, NCI (8 projects), A. Bhandoola, NCI (1 project), and F. Gonzalez, NCI (1 project).

Principal Investigators Who Used Transgenic Mouse Models
September 26, 2014 through September 25, 2015

Principal Investigator	Laboratory	Number of Constructs
Dr. H. Cai	Laboratory of Neurogenetics, NIA	9
Dr. R. Casellas	Molecular Immunology and Inflammation Branch, NIAMS	6
Dr. F. Flomerfelt	Laboratory of Metabolism, CCR, NCI	1
Dr. L. Gattinoni	Experimental Transplantation & Immunology Branch, CCR, NCI	1
Dr. F. Gonazalez	Laboratory of Metabolism, CCR, NCI	2
Dr. B. Graham	Viral Pathogenesis Laboratory, NIAID	5
Dr. J. Green	Laboratory Cancer Biology and Genetics, CCR, NCI	1
Dr. R. Hodes	Experimental Immunology Branch, CCR, NCI	8
Dr. M. Kelley	Section on Developmental Neurosciences, NIDCD	1
Dr. S. Kozlov	Center for Advanced Preclinical Research, Leidos Biomedical, Inc.	1
Dr. K. Natarajan	Laboratory of Immunology, NIAID	1
Dr. A. Nussenzweig	Laboratory of Genome Intergrity, CCR, NCI	2
Dr. H. Park	Experimental Immunology Branch, CCR, NCI	3
Dr. L. Pobezinskiy	Lymphocyte Development Section, CCR, NCI	1
Dr. R. Sen	Laboratory of Molecular Biology and Immunology, NIA	1
Dr. A. Singer	Experimental Immunology Branch, CCR, NCI	8
Dr. D. Singer	Division of Cancer Biology, CCR, NCI	4
Dr. F. Van Laethem	Experimental Immunology Branch, CCR, NCI	5
Dr. T. Waldmann	Lymphoid Malignancies Branch, CCR, NCI	1
Dr. A. Bhandoola	Laboratory of Genome Integrity, CCR, NCI	1
Total		62

Among the projects listed above, 19 requests were for microinjection of genetically engineered ES cells on various parental backgrounds (KH2, JM8.N4, E14 Tg2A.4, and C57BL/6NCr). TMM has continued to successfully complete four comprehensive gene targeting projects, three utilizing the germline-competent ES cell lines on C57BL/6 NCr background, generated within the TMM Laboratory, and one project using the commercially available E14 Tg2A.4 parental cells. This work was performed in support of Drs. L. Pobezinsky (NCI), R. Sen (NIA), A. Singer (NCI), and L. Gattinoni (NCI).

Cell Culture Laboratory

This laboratory has processed 39 tumor cell lines during the past year in support of projects for NCI investigators, which are detailed in the following table:

Investigator	Cell Line	Cell Type
Dr. C. Redon/ Dr. U Weyemi	HCT116 Sh control	Epithelial, colon carcinoma
Dr. C. Redon/ Dr. U Weyemi	HCT116 ShH2AX	Epithelial, colon carcinoma
Dr. P. Steeg	4T1-Br5 vector	Breast cancer
Dr. P. Steeg	4T1-Br5 RAD51	Breast cancer
Dr. P. Steeg	4T1-Br5 2v	Breast cancer
Dr. P. Steeg	4T1-Br5 '79'	Breast cancer
Dr. P. Steeg	4T1-Br5 BARD1	Breast cancer
Dr. E. Jagoda	MKN-45	Gastric cancer
Dr. L. Wakefield	D2A1	Mammary carcinoma
Dr. L. Wakefield	Met-1	Mammary carcinoma
Dr. C. Redon/ Dr. U Weyemi	HCT 116 WT Luc	Epithelial, colon carcinoma
Dr. C. Redon/ Dr. U Weyemi	HCT 116 H2AX KO	Epithelial, colon carcinoma
Dr. C. Redon/ Dr. U Weyemi	HCT 116 H2AX Revertant	Epithelial, colon carcinoma
Dr. G. Whitely	A549	Lung carcinoma
Dr. J. Beutler	SA673	Ewing sarcoma
Dr. P. Steeg	4T1-Luc2	Mammary tumor/adenocarcinoma
Dr. M. Schnermann	MDA-MB-231	Breast cancer
Dr. M. Schnermann	MDA-MB-468	Breast cancer
Dr. P. Steeg	231 Br-eGFP	Mammary metastatic tumor
Dr. P. Steeg	SKOV3	Ovary, adenocarcinoma
Dr. P. Steeg	MDA-231T	Breast, adenocarcinoma
Dr. P. Steeg	OVCAR5	Ovary, adenocarcinoma
Dr. P. Choyke	MB49	Urothelial carcinoma
Dr. P. Choyke	PancO2	Pancreas cancer
Dr. L. Neckers	22Rv1	Prostate cancer
Dr. B. Gril	SUM190 BR3	Inflammatory breast carcinoma
Dr. G. Whitely	H2122	Lung carcinoma
Dr. J. Beutler	UOK 262	Renal cell carcinoma
Dr. S. Y. Cheng	2C4	Hybridoma
Dr. S. Y. Cheng	C4-A	Hybridoma
Dr. S. Y. Cheng	C4-L	Hybridoma
Dr. P. Steeg	SUM190 BR3	Inflammatory breast carcinoma
Dr. J. Green	D2.OR pLLuc	Mouse/mouse hybridoma
Dr. P. Choyke	DMS 114	Lung carcinoma
Dr. P. Choyke	MDA MB 361	Metastatic breast cancer
Dr. P. Choyke	HT 29	Colon carcinoma
Dr. P. Choyke	NCI H69	Lung carcinoma
Dr. P. Steeg	E0771 BR2	Metastatic breast cancer
Dr. P. Steeg	JIMT-1 BR3 Luc/GFP	Breast cancer

Cryopreservation Laboratory

Cryopreservation of valuable GEM is an essential service provided to the NIH community and its collaborators by the Cryopreservation Laboratory. It is critical that these unique mouse models are protected against genetic drift or loss due to unforeseen events, including natural disasters. This laboratory offers an array of services, including assisted reproduction techniques such as in vitro fertilization (IVF), as a means to rescue a given mouse line on the verge of being lost due to breeding deficiencies, or for expansion of a colony to produce a large cohort for experiments. The Cryopreservation Laboratory has the expertise to freeze both sperm and embryos, and the modality is recommended to the requesting investigator based on the genetics of the strain, the complexity of its genotype, as well as natural reproductive characteristics of the strain. This laboratory is also responsible for rederivation of mice that require this service if they test positive for pathogens and microorganisms that are excluded from animal facilities on the Frederick or Bethesda campus.

Significant Achievements

In the last year, Cryopreservation services were fulfilled for the following institutes: NCI, National Institute on Aging (NIA), NIAID, National Institute of Child Health and Human Development (NICHD), U.S. Food and Drug Administration (FDA), Animal Production Program, and the NCI Mouse Repository. The Cryopreservation Laboratory completed the embryo cryopreservation of 26 strains; this is a decrease from the 32 strains completed in FY2014. The program is expected to bank 60 mouse strains via sperm cryopreservation by September 2015, representing no change from FY2014. The laboratory reconstituted nine strains from cryo-preserved sperm samples utilizing IVF in comparison with 14 in FY2014, while 22 strains were reconstituted from cryopreserved embryos, an increase from 18 of such procedures performed the previous year. Live offspring resulting from the reconstitution procedure were shipped to animal facilities designated by the requesting investigators. Since October 2014, the Cryopreservation Laboratory has rescued two valuable mouse lines in support of CCR investigators (Drs. H. Park and T. Waldmann) and generated large cohorts of male mutant mice for one knock-in mouse model for LEOPARD syndrome in support of a project from NCATS. Rederivation by the conventional embryo transfer method was performed for 4 strains, and 4 lines were rederived by IVF for importation into the NCI animal facilities at the Frederick or Bethesda campuses.

In addition, cryopreserved materials comprising 10 shipments of embryos were sent to scientific institutions throughout the world in support of the NCI Mouse Repository.

Animal Molecular Diagnostic Laboratory

The Animal Molecular Diagnostic Laboratory (AMDL) performs nucleic acid–based diagnostics using polymerase chain reaction (PCR) technology as part of the LASP animal health surveillance program. AMDL also serves as the genetic quality control laboratory for the NCI Mouse Repository and LASP's Cryopreservation Program. In addition, the laboratory conducts mycoplasma assays for NIH investigators.

Significant Achievements

- AMDL processed and tested 21,696 diagnostic, tail biopsy, and cell culture samples. AMDL performed 9,312 molecular diagnostic tests for animal health monitoring; 8,670 PCR assays for 510 cell line molecular testing of biological materials (MTBM) tests; 16,895 mouse genotyping; and 431 mycoplasma assays for the NCI Mouse Repository and NIH investigators.
- AMDL launched an in-house pinworm PCR assay as part of routine health monitoring. The assay is highly sensitive and able to detect a potential infection earlier.
- AMDL worked with AHDL in providing environmental monitoring of the isolators and supplies for the germfree animal facility. Using the universal 16S RNA gene amplification assay, the laboratory provided essential tools to assess the sterility status of these isolators, which ensured the timely processing of required supplies to support germ-free isolator operations.

Speed Congenics Service

The LASP Speed Congenics Service, which includes genetic testing and colony management, derives congenic strains of mice for NIH intramural investigators using marker-assisted backcrossing. Through analysis of polymorphic microsatellite markers and a selection of optimal breeders, congenic mice can usually be obtained in 12 months, whereas they may take as long as 2.5 years to produce by conventional backcrossing.

Significant Achievements

Five new projects have been initiated. Six genomic scans were performed in support of five investigators. The supported projects are detailed in the table below.

Principal Investigator	Affiliation	Number of Projects	Status
Dr. Charles Vinson	NCI, CCR	1	Genome scan
Dr. Yun Ji	NCI, CCR	1	Genome scan
Dr. Li Lin	NIA	2	Genome scan
Robin Winkler-Pickett	NCI, CCR	1	Genome scan
Dr. Zoe Ohler	NCI, CCR	1	Genome scan

Small Animal Imaging Program

The Small Animal Imaging Program (SAIP) provides a state-of-the-art in vivo imaging facility for studying intact biological systems for researchers at NCI's CCR, DCTD, the Center for Strategic Scientific Initiatives (CSSI), the NCI at Frederick Office of the Director (OD) and Office of Scientific Operations (OSO), and NCATS/NIH.

The function of the SAIP is to assist investigators in developing mouse models, determining new targets for early detection and therapy, and testing potential new therapies without sacrificing the animal. Another core function of SAIP is to assist the CSSI Nanotechnology Characterization Laboratory (NCL) in analyzing nanoplatforms. In addition to these core functions, SAIP's multifaceted mission is to assist DCTD initiatives in developing standards in small animal imaging and integrating imaging into drug development.

The noninvasive in vivo imaging facility (greater than 7,500 square feet) incorporates a clinical 3T magnetic resonance imaging (MRI) machine utilizing specially designed rodent coils, nuclear scanners (positron emission tomography/computed tomography [PET/CT] and single-photon emission computed tomography/computed tomography [SPECT/CT]), optical scanners (bioluminescence, fluorescence, and tomographic fluorescence), high-frequency (40 MHz) rodent ultrasound and photoacoustic scanners, a high-spatial resolution autoradiography system, a gamma-well counter, and several high-end image processing workstations.

Significant Achievements

SAIP developed and/or administered new imaging techniques and enhanced several existing ones to assist investigators, as follows:

- Implemented a new MRI probe (Eovist) for enhanced imaging of liver metastasis. SAIP collaborated with Dr. James Tatum (Cancer Imaging Program, DCTD) to enhance the visualization of liver metastasis in a patient-derived xenografts (PDX) bladder cancer mouse model.
- Implemented a new MRI coil for imaging large rats. SAIP developed new SOPs and imaging parameters for a new MRI coil for the imaging of large rats (greater than 700 gm).
- Conducted training of CCR investigators for self-service bioluminescence imaging. CCR requested that SAIP conduct training sessions for its investigators and postdoctoral fellows so that they can perform bioluminescence imaging independently to enhance career development and reduce budgetary costs. SAIP instituted SOPs and training documents for CCR investigators to conduct bioluminescence imaging, including safe entry and operations within an animal facility (i.e. animal preparation, equipment and area decontamination, and image acquisition and analysis).
- SAIP conducted 48 imaging projects in support of the following programs/divisions:
  - CCR/NCI (39 studies)
    - Basic Research Laboratory (1 project)
    - CAPR (9 projects)
    - CAPR-Internal (5 projects)
    - CAPR (TSA) (4 projects)
    - Chemical Biology Laboratory (1 project)
    - Developmental Therapeutics Branch (4 projects)
    - Laboratory of Cancer Biology and Genetics (2 projects)
    - Laboratory of Cell and Developmental Signaling (1 project)
    - Laboratory of Experimental Immunology (1 project)
    - Laboratory of Genome Integrity (2 projects)
    - Laboratory of Immune Cell Biology (1 project)
    - Laboratory of Protein Dynamics and Signaling (1 project)
    - Mouse Cancer Genetics Program (4 projects)
    - Molecular Imaging Program (2 projects)
    - Urologic Oncology Branch (5 projects)
    - Women's Malignancies Branch (3 projects)
    - Technology Transfer Center Invention Development Fund (2 projects)
  - CSSI/NCI
    - Nanotechnology Characterization Laboratory (2 projects)
  - DCTD/NCI
    - Cancer Imaging Program (3 projects)
  - NCATS/NIH
    - Leopard Syndrome (YT) (1 project; 2 animal models)
  - FNLCR
    - RAS Program, (2 projects)

Infrastructure and Operational Enhancements

Small Animal Imaging DICOM committee (NEMA/DICOM: WG30)

The function of the Digital Imaging and Communications in Medicine (DICOM) Small Animal Imaging Working Group (WG30) is to address the issue of non-standard image formats for small animal imaging, encourage the adoption of the DICOM format for exchange of all forms of small animal imaging and results of image-related research, as well as to extend DICOM to describe the animal-specific aspects of the acquisition (physiological waveforms, animal model, route of injection, and the labeling and location of each mouse in a multimouse acquisition), and to new objects that describe

modalities that are not yet standardized (e.g., photo-acoustics). The WG30 group collaboration is composed of the DICOM international committee, the National Cancer Informatics Program/CBIIT, the Division of Cancer Biology, the Cancer Imaging Program/DCTD, and external investigators (academic and industry). Dr. Joseph Kalen serves as co-chair of this body.

Large Cohort Translational Research Projects

SAIP collaborated with the Pathology/Histotechnology Laboratory (PHL) and LASP technical support to conduct large-scale drug efficacy studies for the National Center for Advancing Translational Sciences, a NIH institute, on two genetically engineered mouse models of cardiac LEOPARD syndrome; and with LASP/CAPR industrial partnerships on genetically engineered mouse models (pancreas and non-small cell lung models).

Patient-Derived Xenograft Models, DCTD

The SAIP conducted several large imaging studies to characterize a bladder cancer PDX mouse model in a drug study for DCTD, which included MRI (contrast-Eovist), ultrasound (3D volumes, microbubbles for tumor perfusion, photoacoustics for oxygen saturation, and cardiac function), [^{18}F]FDG PET/CT for glucose metabolism, and [^{18}F]FLT PET/CT for cell proliferation.

Molecular Imaging Probe Characterization, CCR

The SAIP conducted imaging probe characterization (validation imaging and biodistribution) studies (^{89}Zr-PDL1 and ^{124}I-TEMP4) for the Molecular Imaging Program, CCR. The Molecular Imaging Program provides pertinent mouse models developed by CCR investigators to test imaging probes developed by the Imaging Probe Development Center, NIH. These studies are conducted in collaboration with SAIP and LASP technical support.

Pathology/Histotechnology Laboratory

The PHL provides specialized research support for FNLCR/NIH, including animal health monitoring, disease model expertise, phenotyping of genetically engineered mice, preclinical toxicity studies, and support for molecular profiling of tumors. Interactions with investigators are a constant emphasis. A veterinary pathology section (VPS) provides experimental design consulting, development of necropsy and trim protocols, and comprehensive pathology evaluation. Additionally, the full-service Histotechnology Laboratory (HL) offers powerful tools for rodent experimental studies, including blood chemistry, hematology, complex necropsy support, OCT (frozen) and paraffin block production, microtomy, cryotomy, and a full range of histological stains. The HL also offers a range of molecular histology services, including Western blotting, immunohistochemistry (IHC) for more than 600 validated targets, chromogenic in situ hybridization (CISH), RNAScope™ CISH, and nucleic acid isolation from human research specimens via hand/macro-dissection, laser capture micro-dissection (LCM), and laser cutting (LC). PHL also offers Leica bright field and fluorescent digital whole-slide scanning with image annotation capabilities and digital image analyses options, and has banked a wide range of reagents used to facilitate research and develop novel assays.

Infrastructure and Operational Enhancements

RNAScope ISH Assay Support

PHL has begun testing a significantly improved RNA in situ hybridization assay that shifts the considerable time and money required for novel assay development to a commercial vendor.

Cryo Microtome Procurement

PHL replaced a nonserviceable cryostat with a state-of-the-art automated model that also includes rapid decontamination.

WebEx Digital Slide Conferencing

PHL replaced poorly performing digital slide conferencing software with an improved workflow that incorporates WebEx remote desktop sharing allowing secure and controlled collaboration with anyone with an internet connection.

Significant Achievements

- **PLCO Biospecimen Working Group DCEG, NCI:** PHL completed digital analysis of IHC staining in a large tissue microarray (TMA) project consisting of 1,000 subjects each of whom have two distinct normal prostate cores and four distinct prostate cancer cores (6,000 unique cores) stained and scored for four distinct markers (24,000 total).
- **Laboratory of Pathology, Pathogenetics Unit, Advanced Technology Center, CCR, NCI:** PHL provided LCM support for a large-scale human prostate cancer project by developing an optimized method of DNA retrieval from LCM targets on archival tissue slides for Sanger sequencing analysis.
- **National Clinical Target Validation Laboratory and Pharmacodynamic Assay Section:** Expanded support that includes hematoxylin and eosin (H&E), immunofluorescent staining, and image capture on biopsies from human and canine patients in research clinical trials.
- **Biological Testing Branch (BTB), DTP:** Expanded support for histology, digital imaging, and histopathology evaluation from PDX in NSG mice.
- **Drs. Doroshow and Hollingshead, NCI, DCTD, DTP, BTB:** Expanded support for examinations of protein expression in cancer TMAs as well as in vivo testing of chemotherapeutic agents on urinary bladder cancer that included digital quantification of IHC of p53/RAF mutant xenografts.

- **Drs. Howard Young and Julio Valencia NCI, CCR, LEI:** Continued their support for studying the role of interferon gamma (IFN-gamma) in oncogenesis, metastasis, and drug resistance in melanoma.
- **Dr. Mary Barcus, Biorepository and Biospecimen Research Branch, BBRB:** Provided LCM project support on 1,500 Genotype-Tissue Expression (GTEX) tissues stabilized in PAXgene molecular fixative. The resultant RNA sequencing data support that a novel bimodal gene pattern in stomach reported previously is likely due to variable sampling of mucosa versus muscularis rather than a biological event.
- **Dr. Peter Johnson, NCI, CCR, MCGP:** Provided support for studies involving effects of Cebp-β mutations on cancer development and progression.
- **PLCO Biospecimen Working Group DCEG, NCI:** Completed the final of three challenging projects whose collective goal is to develop unique TMA of human cancers and harvest corresponding paraffin tissue-core sets for use in biomarker identification/validation.
- **Dr. Vanja Lazarevic:** Working together with Bethesda animal program veterinarians and animal facility staff, PHL provided histopathology support to investigate unexpected experimental variations in mouse models of experimental autoimmune encephalomyelitis (EAE).
- **Drs. Mary Ernst and Jeff Strathern, NCI, CCR, GRCBL:** Set up necropsy/histology protocols for an RNA polymerase error study in mice using yellow fluorescent protein (YFP).
- **Nanotechnology Characterization Lab, NCI/OD:** Continue to provide necropsy and histopathology support for several efficacy, toxicity, toxicokinetics, and imaging studies.
- **Dr. Brad StCroix, NCI, CCR, MCGP:** Pathology support for studies with treated and untreated TEM8 mutant mice.
- **Dr. Daniel McVicar, NCI, CCR, CIP, LEI, and Dr. Oberdoerffer, NCI, CCR, LRBGE:** Set up new protocols and provided pathology evaluation of GEM on various studies.

High-Throughput Animal Genotyping Laboratory

High-Throughput Animal Genotyping Laboratory (HTAGL) provides genotyping in high-throughput format using ABI TaqMan technology (as formerly offered by the Laboratory of Molecular Technology) and end point PCR using the LabChip as the detection platform. Enhanced workflows in conjunction with a laboratory information management system (LIMS) are used to automate the entire genotyping process from sample submission to final reports.

Significant Achievements

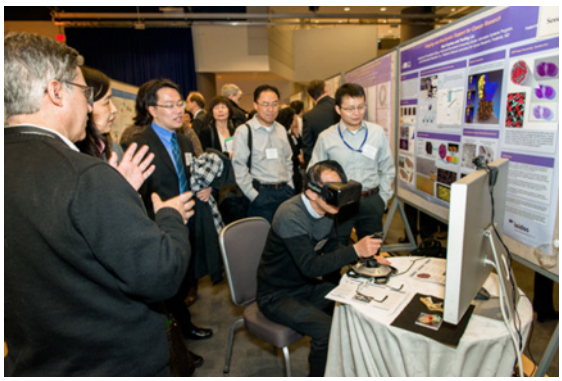
- HTAGL has more than doubled the number of assays performed from approximately 20,000 genotypes evaluated in 2014 to 41,700 genotypes in 2015. HTAGL largely supports NCI's CAPR, but is actively exploring support to additional NCI investigators.
- Data Management Services completed an improved LIM system that supports additional assay formats, clients, reports, and the billing process.

Support Provided by the Data Science and Information Technology Program

Advanced Biomedical Computing Center

Scientific Project Support

Visual Analytics in Bioinformatics for Cancer Research. The complexity in large cross-disciplinary bioinformatics data sets has created new challenges in short-turnaround knowledge mining and hypothesis validation. The large number of data points and heterogeneous characteristics in such data sets make manual examination and trend analysis virtually impractical. New interface and visualization technologies are needed to fully utilize high-bandwidth human visual perception to accelerate knowledge extraction and reasoning on such data sets. The Advanced Biomedical Computing Center's (ABCC's) Image and Visualization Group (IVG) works to leverage open-source data analysis and visualization techniques and new human–computer interfaces, including zSpace virtual holographic display, Oculus Rift immersive display, and Kinect and LeapMotion tracking devices, to develop a web-centric visual analytics framework in order to meet the evolving needs for highly interactive and flexible data analysis and visualization on large, cross-disciplinary bioinformatics data sets. The goals are to enhance information visualization and visual analytics capabilities, to develop core visual analytic frameworks to meet informatics requirements from different NCI labs and facilities, and to reduce development costs and time.



New 3D visualization technologies, such as the Oculus Rift device, draw wide interest at the 2015 NCI Intramural Scientific Investigators Retreat. The ABCC IVG works with data and 3D models and structures.

Information Visualization, Analysis, and Navigation (IVAaN) Framework. This software framework helps researchers quickly understand significant trends within complex heterogeneous bioinformatics data sets. ABCC scientists and developers develop data analysis workflows based on the IVAaN framework. Partnering with the Small Animal Imaging Program, ABCC is developing a novel pipeline to extract information from vendor software–produced data files and save data in NoSQL MongoDB database for flexible viewing, comparison, and report generation. The new pipeline saves technicians and investigators from tedious manual data extraction from hundreds of files per single experiment. ABCC is working on standardizing the pipeline and making it available campus wide.

Nanoparticle Informatics and Imaging. ***Imaging Techniques for Nanomaterials Analyses—High-Dynamic-Range Imaging for Nanoparticle Tracking Analysis and Nanoparticle Genotoxicity:*** Optical imaging methods for nanoparticle tracking are a powerful set of techniques for the rapid characterization of polydisperse nanomaterials. Nanoparticle tracking analysis (NTA) platforms rely on a laser illumination system coupled with an optical magnification path allowing the rapid and accurate tracking of single-particle positions in liquid suspensions. Traditionally, the particle tracking information is then used to estimate the particle hydrodynamic radii and other properties of interest. However, more information may be present in the signal if appropriate contrast and signal-to-noise enhancements can be realized. We utilized high dynamic range (HDR) photography as a relatively inexpensive way to obtain additional information in settings where high-contrast information may be lost due to over-/underexposure of image or data acquisition time constraints.

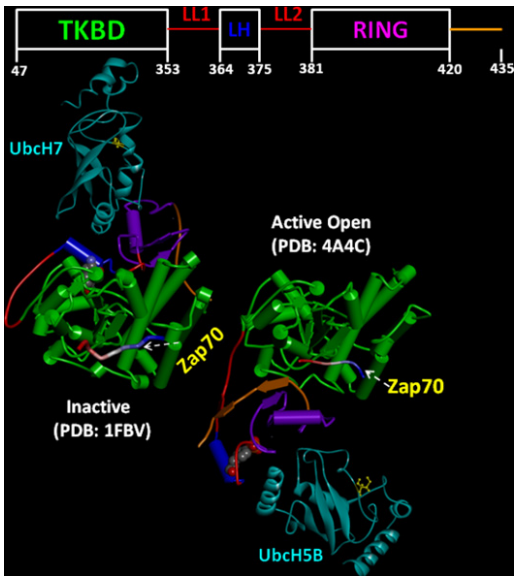
We developed algorithms that allow the use of NTA data obtained from multiple virtual cameras (HDR-NTA). Among the advantages of using multiple camera settings in NTA are the increase in total tracking time per particle and the ability to collect nonsaturated images of bright spots. The increased tracking time can be used to gather more data to generate meaningful statistics. The enhanced dynamic range can also be used to quantify the particle flickering, which may offer new ways to characterize particle shape fingerprints using NTA platforms. Additional advantages of HDR-NTA approaches include the possible increase in accuracy in the evaluation of particle concentrations and the ability to extend the method to larger particles or aggregates. Similar high-dynamic-range imaging (HDRI) techniques were also used to improve the characterization of metal oxide nanoparticles in support of efforts by the Laboratory of Cancer Biology and Genetics, Carcinogen-DNA Interactions Section, NCI, Center for Cancer Research (CCR; Ofelia Olivero) for the characterization of nanoparticle genotoxicity.

Genotoxicity is defined as a deleterious action on a cell's genetic material (i.e., performed by a xenobiotic or some external agent, such as radiation, nanoparticles, etc.) that affects the cell integrity. Genotoxicity assays include animal and non-animal tests. Non-animal tests are preferable as prescreens, especially when characterizing new materials (i.e., nanoparticles). Several in vitro genotoxicity tests have been widely adopted and standardized (in the European Union and the U.S.). Recent studies by members of the Laboratory of Cancer Biology and Genetics, Carcinogen-DNA Interactions Section, NCI, CCR (Ofelia A. Olivero) support the growing indication that the in vitro micronuclei assays may be more appropriate than the Ames test for evaluating the genotoxicity of engineered nanoparticles (T. D. Palacios-Hernandez et al., Effect of surface modification of metal oxide nanoparticles upon cell viability and genotoxicity of epithelial breast cells. *Society of Toxicology*, PS1777, March 2013). The lack of a fully automated, high-throughput, procedure for micronuclei image acquisition and annotation has limited its use. We developed a combined micronulcei assay image acquisition and analysis tool (GeNanoTox) based on HDRI that may aid in understanding the mechanisms of interaction of nanoparticles with the genetic material. Upon completion of the first prototype of GeNanoTox, it become evident the value of the tool far exceeded its use in the context of the micronuclei assay, and a more general approach is being developed with application to a larger target audience, such as the characterization of exosomes (Vanesa Sanchez, Laboratory of Cancer Biology and Genetics). The improved algorithms for the processing of microscopic images developed for GeNanoTox will be applicable to tumor cells in general and will facilitate the identification and quantification of many molecular markers in cells previously omitted. The development of this capability will in turn benefit better recognition of cell morphologies and better quantification of nanoparticle genotoxicity. The main limitation for this effort has been the access to extensive libraries of images, which we have solved by (a) acquiring a large data set of blood cell samples used to characterize cell patterns in children with acute lymphoblastic leukemia, and (b) generating extensive data sets of lymphoblast images collected in-house at the ABCC. We expect the new version of GeNanoTox to be available for testing before December 2015.

Improved Electron Microscopy (EM) Methods for Soft Nanoparticle Characterization. Peptide-based nanocapsules are a promising platform for biomedical applications. The characterization of these materials by transmission electron microscopy (TEM) presents a number of challenges when standard instruments are used. Low voltage electron microscopes (LVEMs) operate at a lower voltage (5–35 KeV), resulting in a large increase in contrast. This makes LVEM particularly suitable for the characterization of soft materials (polymers, cellulosic materials, unstained biomolecular aggregates, etc.) We used LVEM data to characterize peptide-based nanocapsules in support of efforts by the Cancer and Inflammation Program, Synthetic Biologics Core, NCI, CCR (Nadya I. Tarasova). The narrow polydispersion and polymorphisms of peptide nanocapsules made them uniquely suited to three-dimensional (3D) reconstruction. We explored this problem using a single projection reconstruction technique and a structure docking procedure. These efforts, combined with the recent development within the ABCC of a platform (QMRx) for the refinement of large macromolecular models using QM methods (Firas Fadel, Yuguang Zhao, Raul Cachau, et. al.). New insights in the enzymatic mechanism of human chitotriosidase (CHIT1) catalytic domain by atomic resolution X-ray diffraction and hybrid QM/MM. *Acta Crystallographica Section D*, 2015) resulted in predictions and models that were experimentally verified within Dr. Tarasova's lab.

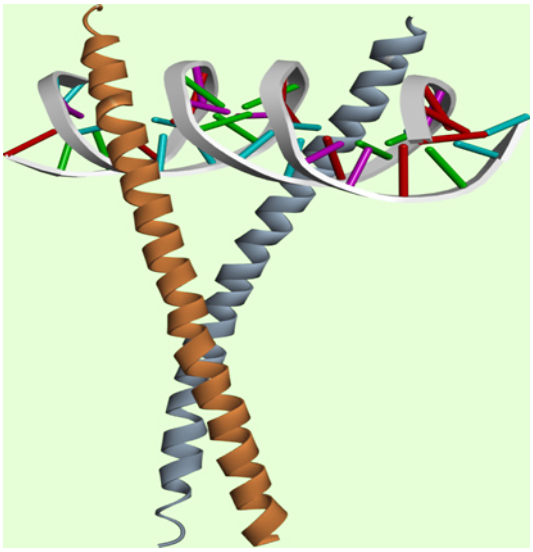
Simulation, Analysis, and Mathematical Modeling. The Simulation, Analysis, and Mathematical Modeling group performs mathematical and statistical analyses, determining the effect of mutations on protein function, and performing high-level quantum chemical calculations to understand biochemical processes affecting drug molecules.

Effect of a CBL Mutation in Juvenile Myelomonocytic Leukemia: Juvenile myelomonocytic leukemia (JMML) is a type of blood cancer that often targets younger children. Using exome sequencing, Drs. Anand Pathak and Douglas R. Stewart (NCI/Division of Cancer Epidemiology and Genetics [DCEG]) identified a germline mutation (p.Y371C) in a protein called Casitas B-lineage lymphoma proto-oncogene (CBL). Using extensive family history and genomic data based on in silico analysis, along with structure-based modeling, we have been able to identify an association between the Y371C mutation and JMML. This study was the first of its kind (400 person-years of follow-up over four decades) that helped clarify several key factors, such as partial penetrance (30 percent), and the functional impact for JMML patients with this variation. This work was recently published in the high impact journal, *Human Genetics* (134:775-87, 2015).



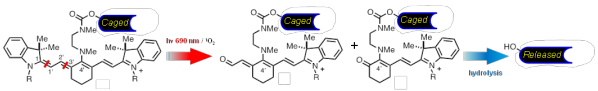
Functional (phosphorylation) impact of Y371C mutation and the resulting conformational mobility are highlighted by comparing the inactive and active forms of CBL. Note the location of Y371 is marked in yellow.

Mutations of C/EBP alpha in Familial Acute Myeloid Leukemia: Drs. Douglas R. Stewart and Lynn Goldin (NCI, Division of Cancer Epidemiology and Genetics) and their collaborators, with assistance from the simulation, analysis and modeling group, performed a 45-year follow-up of a large family with familial acute myeloid leukemia (AML). Using exome sequencing technology, they identified a novel germline mutation in a gene called CEBPA. This study shows that there is an association between the variation (not explicitly identified in this report because this work is currently being reviewed by a prestigious journal) and AML. The protein product (C/EBP alpha) of CEBPA is a transcription factor and binds to DNA at a specific motif as a homodimer and controls expression of certain genes. C/EBP alpha also acts as a tumor suppressor. Any mutation(s) to this gene that leads to a nonfunctional protein can lead to uncontrolled expression. The study presents extensive experimental, in silico analysis and molecular modeling simulations to identify the association between the mutation and AML.



Crystal structure (PDB ID 1NWQ) of C/EBP alpha-DNA complex.

Design of Near-Infrared Light-Induced Optical Tools Based on Cyanine Photochemistry: Cyanines are important fluorophores that find extensive use across a range of modern biological procedures. Particularly useful are the heptamethine cyanines, which contain a 7 carbons-linker connecting two indolenine heterocycles. The emission and absorbance maxima of these molecules are generally around 800 nm, occupying the center of the near-infrared (IR) window where tissue penetration is maximized. One example, indocyanine green, is a U.S. Food and Drug Administration (FDA)–approved diagnostic agent used in numerous clinical contexts. The Chemical Biology Laboratory is currently researching the development and clinical application of next-generation near-IR optical tools for diagnostic and therapeutic applications. The following figure shows the molecular strategy, based on heptamethine cyanines, that the Chemical Biology Laboratory is pursuing for near-IR light-activated uncaging approaches.



Light-activated uncaging (release) process based on heptamethine cyanines. Near-IR light irradiation indirectly causes production of reactive oxygen species (ROS), which fragments the cyanine system at two locations. Subsequent hydrolysis causes the caged molecule to release.

We are assisting the Chemical Biology Laboratory in its goals by using computational chemistry to probe important aspects of this process that are extremely difficult to investigate experimentally, such as:

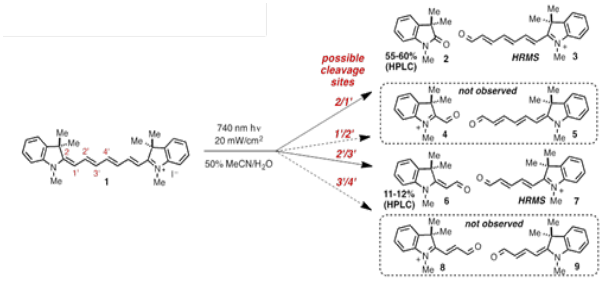
a) How can the system be modified to activate at tailored wavelengths?

b) Why does fragmentation occur only at two sites when four seem equivalent in nature?

c) What is the exact reaction mechanism that guides this process, i.e., how is the ROS fragmenting the molecule?

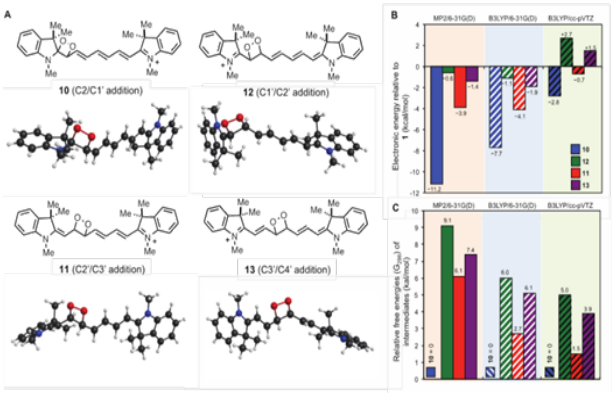
Computing answers to the above unknowns will enable the design of more efficient and useful uncaging developments, such as near-IR light-targeted drug delivery approaches.

While current work is focused on all three of the aforementioned areas, significant progress has been made on the second mystery. A rigorous collaborative computational/experimental investigation was employed to study the puzzling regioselectivity during the oxidative cleavage process. As a first step, experiments were conducted on the model heptamethine cyanine, and results showed that only two of four seemingly equivalent fragmentation pathways occurred.



Photoproducts observed by high-resolution mass spectroscopy upon 740 nm light irradiation of 1.

Quantum chemistry methods were then employed to probe the intermediate reaction steps that occur between the reactants and fragmentation products. We discovered that there were short-lived, stable dioxetane intermediates that exist just prior to decomposition.

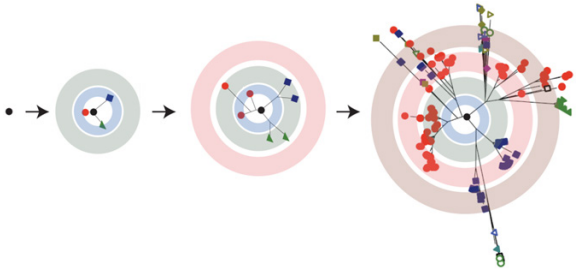


Computed structures of the short-lived dioxetane intermediates (A) and calculated stabilities relative to (B) reactants and (C) each other.

Furthermore, at our best level of theory we computed that only two of these (10 and 11) were stable relative to the reactants. These results indicate that fragmentation reactions can proceed only via these two intermediates, thus matching exactly the two reaction pathways that were observed in the experiments. Of more consequence, the theoretically predicted ratio of products matched almost exactly the experimentally measured yields. A

manuscript describing this work has been submitted for publication to *Chemical Science*, a Royal Society journal. This investigation is an excellent example of how computational chemistry can provide insights into chemical reactions and molecular properties that are unable to be discovered experimentally.

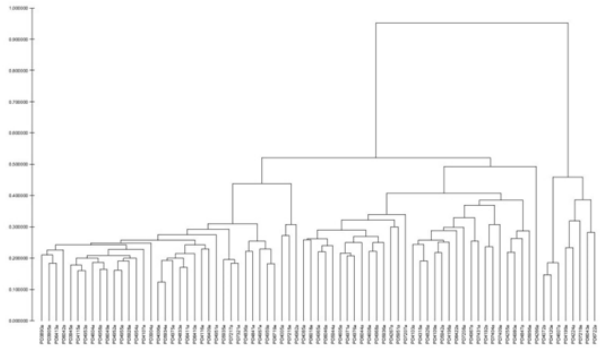
PacBio Sequencing of HIV Quasispecies: The difficulty of developing effective HIV therapeutics and vaccines is due largely to the extraordinary mutation rate of HIV, which enables the virus to rapidly evade the selective pressures imposed by antiretroviral medications and potential vaccines by generating a large and genetically diverse population through mutagenesis.



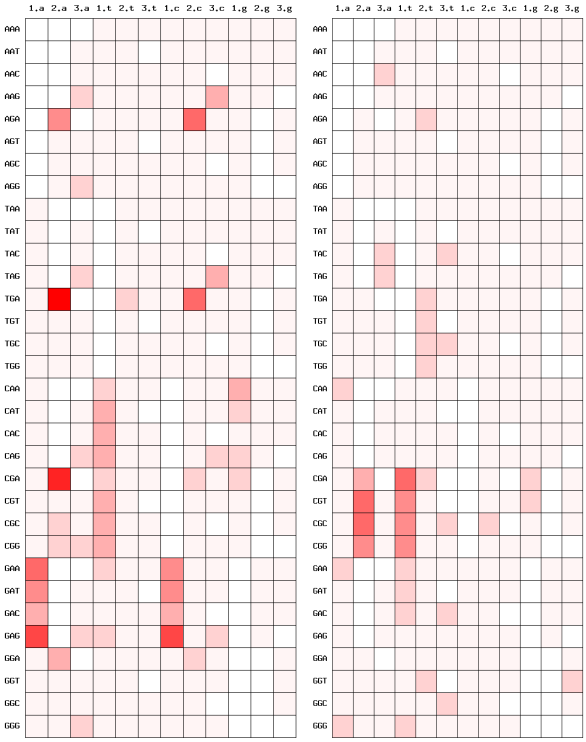
A comprehensive knowledge of the genetic diversity characteristic of HIV populations in infected individuals—what have been termed viral quasispecies—is therefore essential for the discovery and delivery of effective HIV medications and vaccines.

We used PacBio, the third-generation sequencing technology, capable to perform single-molecule, real-time DNA sequencing (SMRT technology), to sequence the full length of HIV quasispecies. The difficulty of sequencing HIV quasispecies was the rare strains (< 20 percent) in a patient and the haplotypes of the mutations. Our goal is to use PacBio to sequence approximately 1,000 naive HIV patient samples in clinical trial in order to improve this problem. The aim is to obtain approximately1.3 kb of highly accurate HIV circular consensus sequences (CCS sequences) with haplotype information, using PacBio.

The Somatic Autosomal Mutation Matrix in Cancer Genomes: DNA damage in somatic cells originates from both environmental and endogenous sources, giving rise to mutations through multiple mechanisms. When these mutations affect the function of critical genes, cancer may ensue. Although identifying genomic subsets of mutated genes may inform therapeutic options, a systematic survey of tumor mutational spectra is required to improve our understanding of the underlying mechanisms of mutagenesis involved in cancer etiology. A somatic autosomal mutation matrix (SAMM) was constructed from tumor-specific mutations derived from each of 909 individual cancer genomes harboring 10,681,843 single-base substitutions. In addition, mechanistic template mutation matrices (MTMMs) representing oxidative DNA damage, ultraviolet-induced DNA damage, ^{5m}CpG deamination, and APOBEC-mediated cytosine mutation, are presented. MTMMs were mapped to the individual tumor SAMMs to determine the maximum contribution of each mutational mechanism to the overall mutation pattern. We show that cancer-tissue preference exists for each MTMM (lung for oxidative damage, skin for photo-damage, pancreatic cancer for ^{5m}CpG deamination, and breast cancer for APOBEC activity). When a distance-dependent 6-nearest neighbor classifier was used, 10.4 percent of the SAMMs had an undetermined tissue of origin, and 92.2 percent of the remaining SAMMs were assigned to the correct tissue of origin. Thus, although tumors from different tissues may have similar mutation patterns, their SAMMs often display signatures that are characteristic of specific tissues.



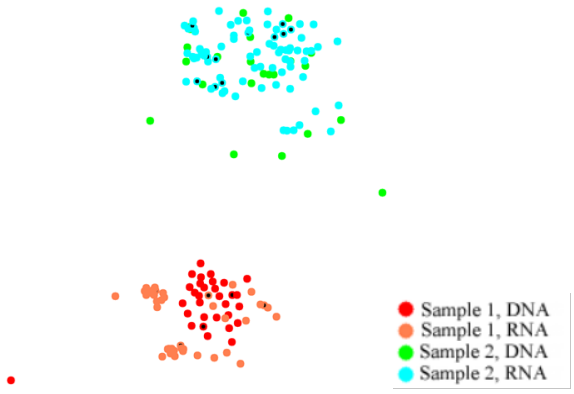
Average linkage hierarchical clustering results for the 77 breast cancer SAMMs obtained from Sanger show definite subclusters that may represent different underlying mutational mechanisms.



Heat maps of the SAMMs for two breast cancer samples from Sanger show very different overall mutational patterns.

Mathematical and Statistical Support for NCI Research: Mathematical and statistical support is provided for a wide range of NCI research. Much of this support involves the analysis of mass spectrometry data to determine differential expression of proteins. For data representing mass spectra peak intensities, an in-house program using three overlapping Poisson distributions was developed. If, instead, peptide counts were used, the analysis was based on a binomial distribution.

The HIV Dynamics and Replication Program is examining the variation in HIV sequences obtained from both DNA and RNA sequencing and is interested in the difference in sequences within a given infected individual and between two individuals. We have explored using nonlinear projections to graphically display the distance between each sequence, from which the distance between individuals can be determined in a more obvious way.



Nonlinear projection of DNA and RNA samples from two individuals infected with HIV. The black dot means that these samples are observed more than once (known as clonal expansion).

Infrastructure Support

In order to make the infrastructure more available and applicable to the research community, the Core Infrastructure and Systems Biology Group (CISB) continues to develop data mining and integration applications. CISB strives to provide multiple access methods for gaining maximum usage, and therefore most of these applications are available through (i) command line—for access to internal bioinformatics analysis pipelines run on the MOAB compute cluster; (ii) web interface—simplified access to scientific users across the globe; and (iii) web services—programmatic access for bioinformaticians and computational biologists across the globe. These applications also allow integration into other bioinformatics tools.

Biological DataBase Network: A new version of the Biological DataBase Network (bioDBnet) with the dbAnnot and dbOrtho functionality was released towards the end of fiscal year 2014 (FY2014). There has been no significant development on this application in the past year; however, CISB continues to monitor and maintain production databases, answer user queries, add new databases, debug IT administrative issues, and resolve any bugs associated with the existing features in bioDBnet. The flexibility of the application, and wide variety of databases and conversion features continue to bring in a wide variety of users across the world, and in fact, the number of users in FY2015 has increased by 25 percent compared with the same period in FY2014.

Overview of bioDBnet usage statistics from October 1, 2014 to July 25, 2015.

bioDBnet also saw increased adoption and advertising from the external bioinformatics environment, where it is either directly or indirectly integrated into multiple modules and applications, including GEWorkbench (http://wiki.c2b2.columbia.edu/workbench), GASOLINE (http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4197741/), Python bioservices module, (https://pythonhosted.org/bioservices/), and the human cancer secretome database (http://cancersecretome.org).

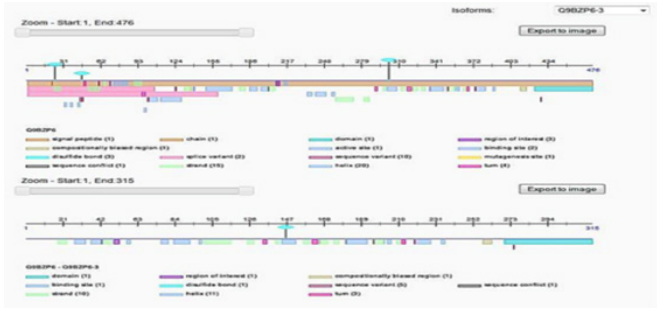
In addition, bioDBnet also continues to be referenced in the bioinformatics and computational biology courses, and is included in course lectures at universities such as George Mason (http://binf.gmu.edu/vaisman/binf630/lec04s15.pdf), University of Toronto (http://steipe.biochemistry.utoronto.ca/abc/index.php/Computational_Systems_Biology_Main_Page), and Saint Louis University (biochem.slu.edu/bchm628/notes/bchm628_lect4_15.pptx).

Annotation, Visualization, and Impact Analysis: The application for Annotation, Visualization, and Impact Analysis (AVIA) saw many feature improvements to support custom requests from user. A new summary page prioritizing the variants by impact has been added, and several visualization features to provide functional insights have been customized. AVIA now supports multiple VCF files and variant lists in the range of millions.

AVIA 2.0 showing the prioritization of variants and probable functional impact by overlaying variant details on KEGG pathways.

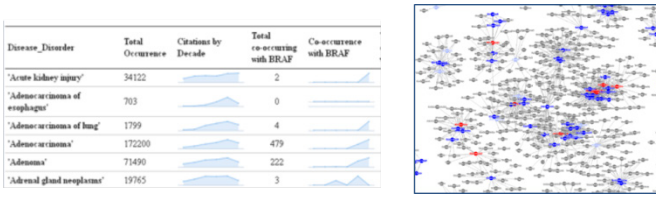
This new version was recently published in *Bioinformatics*. (Vuong H, Che A, Ravichandran S, Luke BT, Collins JR, Mudunuri US. AVIA v2.0: annotation, visualization and impact analysis of genomic variants and genes. *Bioinformatics*. 2015 Apr 9.)

Protein features: CISB developed a web application for accessing and querying protein features available in the downloadable XML files from UniProt. These features can be queried using gene/protein identifiers or by specific protein positions. The results are displayed in a table format and, most importantly, the protein features can be visualized using BioJS. The application also offers researchers custom visualization, enabling them to add details from their research and generate publishable figures integrating the lab-generated results with known position-specific protein features. An additional advantage of the application is the ability to visualize these protein features on both the canonical protein and all its known isoforms, thereby providing the ability of deducing impact on any of these isoforms. In addition, representational state transfer (REST) application programming interfaces (APIs) are available for accessing the results and the protein images programmatically.



Screen shots from the UniProt mining application showing isoform visualization and impact on protein features.

Mining Medline: An application to query Medline using simple text-based searches was developed, and many features not available through any other publicly available application have been added. This application uses the indexing and faceting features provided by Apache Solr. In the past year, we have seamlessly integrated several features offered through bioDBnet, thereby enabling the user to query using gene symbols and any associated interaction, pathway, drug, or disease information. The results are presented in separate categories and allow further filtering. In addition, several complex queries to create author and biological term networks have been created. The results from these queries not only allow easy visualization of co-authors in a specific field of research but are interactive and provide links to articles showing pairwise relations. We have also recently added charts to display trends and pairwise relations across the years.



Screen shots from the Medline mining application showing co-author networks and trends by disease and gene co-occurrence.

Support is also provided for a number of bioinformatics applications and databases used by NCI and larger biomedical communities.

- More than 100 bioinformatics software programs are supported for high-throughput analysis performed by multiple groups within ABCC and NCI at Frederick. In addition, training and custom user support are provided to all bioinformatics analysts, thereby reducing the time to debug problems related to software usage.
- Nearly 80 biological databases are being automatically updated and made available through multiple mechanisms to the analysts and researchers accessing the MOAB compute cluster.
- Oracle databases are created and administered in support of multiple projects and applications, including bioDBnet, SysBioCube, DAVID, caHUB, developmental therapeutics database (DTP), Pathway Studio, and Open Clinica. The current production server supports 20 production databases and 2.5 TB of data, while the development server houses 18 database instances with 4.7 TB of data.

Scientific Web Programming Group

The ABCC's Scientific Web-Application Programming Group (SWPG) enables and supports NCI science by providing innovative web application and tool development to assist groups and researchers with managing and tracking data, and interacting with data and scientific applications through web interfaces.

The Data Science and Information Technology Program (DSITP) profile website is currently in transition from the previous (Information Systems Program [ISP]) branding to support the new DSITP and is expected to be

completed by early fall FY2015. The site supports Frederick National Laboratory for Cancer Research (FNLCR) as well as DSITP and its groups by offering applications and tools to assist in data management. Supporting an open-source content management system, WordPress allows authorized users to manage site structure, content, and services. Users have the ability to manage their content and determine access requirements to their content, requiring NIH Active Directory authentication prior to allowing viewing privileges and restricting specific pages to authorized users only.

The ABCC has continued to support FNLCR groups through the Leidos Biomedical Research publications application (https://publications-abcc.ncifcrf.gov). This enterprise-level application supports Leidos Biomedical Research/FNLCR by recording and tracking all publications, manuscripts, inventions, and journals created by FNLCR employees for reporting to FNLCR and NCI management. Continued user support and feature enhancement are the majority of current efforts for this operational project, and the ABCC has provided continued support by participating in numerous presentations and tutorials throughout the year. Future enhancements for this project include adding a "widget" to allow users to share and post their publications as content by adding a small block of code to their associated site. This content would update in real-time to provide labs and researchers a more communicative tool to promote their achievements.

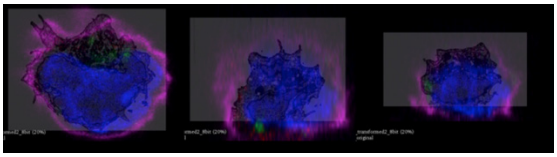
Technology Development and Enhancement Projects

Project Tracker: ABCC/SWPG developers continue to support the Office of Scientific Operations (OSO), NCI at Frederick, while building a project management tool that will assist the ABCC with managing and tracking projects and tasks, and assist NCI in review, approval, managing, and prioritizing the technology development portfolio as well as other ABCC projects. Recent accomplishments include adding multiple user interface controls to capture essential project data for reporting purposes. Also included are mechanisms to report accomplishments, issues, and risks. Currently, reporting features are being built out that will allow external users access to project information such as status updates, overall progress, and project histories.

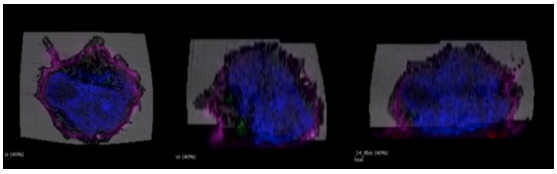
Linguamatics: ABCC acquired a pilot license to evaluate the I2E software from Linguamatics Inc., for mining several text documents including literature, clinical trials, and pathology reports. Several use cases were developed through interactions with different NCI groups, and CISB is creating queries to address each of the use cases. In the process of this evaluation, CISB has not only installed and indexed the required documents but has also made great progress by creating unique pathway ontologies and developing new methods for addressing the use cases.

FedCentric Collaboration: ABCC entered into a collaborative agreement with FedCentric Technologies to evaluate the applicability of graph databases for variant-related information. As part of this collaboration, a graph model to support genomic location–based variant and gene relations is developed. Efforts are currently under way to create complex queries for mining the variant details at individual and population levels.

Automatic Registration of 3D Electron and Light Microscopy Image Volumes for Feature Correlation and Discovery: Partnering with the Center for Molecular Microscopy (CMM), ABCC scientists are developing an automatic registration pipeline to correlate EM and light microscopy (LM) image volumes. Automatic registration of confocal and EM image volumes further enhances the study of many cellular processes, such as virus–cell and cell–cell interactions. The images below demonstrate the preliminary result of the ABCC-developed registration pipeline.



Before registration



After registration

Images showing preliminary registration results. Top row: Three different views showing misalignment between the colored confocal image and grayscale EM image. Bottom row: Same views showing properly aligned results. Data provided by Dr. Kedar Narayan, CMM.

Support Provided by the Clinical Monitoring Research Program

CMRP Program Management Office

The Clinical Monitoring Research Program (CMRP) continues to provide high-quality program management and administrative support to the regulatory, clinical, and programmatic efforts being provided to National Cancer Institute (NCI), National Institute of Allergy and Infectious Diseases (NIAID), Clinical Center, National Heart, Lung, and Blood Institute (NHLBI), National Institute for Arthritis and Musculoskeletal and Skin Diseases (NIAMS), National Institute of Mental Health (NIMH), National Center for Advancing Translational Sciences (NCATS), and National Institute of Neurological Disorders and Stroke (NINDS) initiatives. The ability to provide rapid responses

and high-quality solutions, and to recruit and retain diverse subject matter experts (SMEs) is evidence of CMRP's continued success.

CMRP's programmatic management support was launched to offer a complete approach to clinical support services. The CMRP Program Management Office contributes to the various institutes' clinical research activities by providing centralized administrative and management support services that facilitate high-quality clinical research through program guidance and support, strategic planning and direction, program/project management, technical direction, learning and professional development (coordination of approximately 10 training requirements), and general assistance to various government entities. The Program Management Office consists of a program manager, a clinical program administrator, two senior program coordinators, an administrative coordinator, an administrative assistant, and a secretary.

The Program Management Office is actively involved and works closely with CMRP hiring managers and the Leidos Biomedical Research, Inc., Human Resources (HR) Recruitment Office to recruit and hire qualified candidates for the numerous medical, clinical research management, regulatory, information technology (IT), program/project management, and administrative positions within CMRP. The Program Management Office serves as a valuable resource for existing and new employees, providing the New Employee Orientation (NEO) and logistical support to new hires while communicating and coordinating critical information pertaining to their upcoming activities and responsibilities. During the reporting period, the Program Management Office scheduled 206 interviews (including phone and face-to-face meetings) for 111 different positions, ranging from administrative support to high-level medical/clinical experts. From those 206 interviews, 92 positions were successfully filled. The Program Management Office is currently actively recruiting for 26 open positions.

In addition to recruitment activities, the Program Management Office also prepared and submitted 20 credentialing packages to the NIH/NIAID Credentialing Office, including two physician packages, five nurse practitioner/physician's assistant packages, one thoracic surgeon package, and 12 registered nurse packages.

Policy and procedure updates are provided to all CMRP staff members to ensure that the program operates under the most current guidelines and requirements, and that any changes and revisions are clearly identified.

Under the direction of the CMRP director, the Program Management Office also works closely with the HR Compensation Department to coordinate the necessary performance management activities throughout the year.

A signature block audit was conducted on CMRP employees (e.g., desktop, mobile device, laptop, and webmail) to ensure 100 percent compliance with Leidos Biomedical Research Signature Block Guidelines. Due to telework policy changes, the Program Management Office evaluated CMRP needs and expected coverage during unscheduled closures, as well as confirmed existing approved telework agreements.

CMRP Project Management Office

The CMRP Project Management Office provides project management and operational support to all overarching CMRP initiatives, as well as several external high-profile projects. The Project Management Office comprises two clinical project managers, one medical writer, and one documentation specialist. Additional team members providing support to the Project Management Office, but who were also assigned to support other specific initiatives within institutes, include one clinical project manager (NCI), one senior special projects administrator (NIAID), one additional medical writer (NIAID), and one secretary (NIAID).

Working in conjunction with the Program Management Office and other CMRP functional groups, the Project Management Office manages the Yellow Task (YT) system workflow, including development of task responses, facilitation of budget preparation and approval, and tracking of process metrics for CMRP, and, as of fiscal year 2015 (FY2015), Clinical Research Directorate (CRD) support to the Clinical Proteomic Tumor Analysis Consortium (CPTAC) and the CRD Biospecimen Research Group (BRG). The average YT turnaround time is five days for response to YTs requesting work that is new to CMRP and two days for revisions to existing YTs. Notably, YTs concerning the NIAID Division of Clinical Research (DCR) and Vaccine Research Center (VRC) Ebola efforts are expedited to meet the high expectations of these projects while ensuring efficiency. This requires close collaboration between the CMRP Project Management Office, Program Management Office, and the Financial Management Group.

In addition, Project Management Office staff is responsible for coordinating the submission of numerous annual and biannual reports throughout the contract year. These reports include the CMRP section of the larger Leidos Biomedical Research Annual Report, the fall and spring Contract Performance Status Reports, monthly goals and objective reporting, and the CMRP Report of Activities. For these reports, as well as others, the Project Management Office staff is responsible for all aspects of preparation, coordination, review, and submission.

The Project Management Office provides overall project management support for internal CMRP initiatives, as well as external, high-profile projects, including the HIV/AIDS collaboration between NIH and the Washington, D.C., Department of Health, and a neurocognitive initiative. In addition, the Project Management Office provides oversight to the NCI Division of Cancer Control and Population Sciences (DCCPS) Behavioral Research Program Network on Biobehavioral Pathways in Cancer, managing several research subcontracts, including, but not limited to, the following

projects: a Tel Aviv University Clinical Research Protocol, titled Aiming to Reduce Long-Term Breast Cancer Recurrence and Metastasis by Targeting Excess Perioperative Catecholamines and Prostaglandins; a University of California, Los Angeles, fMRI Probe Optimization Study of Social Support; the Affective Science and Palliative Care pilot project; and the Systematic Reviews to Inform Research and Treatment of Multi-Morbidities project. Furthermore, the Project Management Office manages the subcontracting efforts for the NCI Center for Cancer Research's (CCR's) Protocol Re-engineering and Laboratory of Pathology strategic planning projects with Dilts Partners, LLC, and NIAID's Development of Program Performance Measures in the DCR. In addition, the Project Management Office provides oversight to NIAID DCR research subcontracts that are not associated with any of the larger DCR initiatives, but require project management support. Many of these initiatives fall under the NIAID Clinical Consulting and Support (CCS) section of this report.

The Project Management Office provides background research for projects, and assists with creating and editing presentations. Supporting the CMRP director, the Project Management Office provides medical writing services to prepare presentations, edit statements of work (SOWs), review job requisitions, generate and distribute meeting minutes, write internal procedures, and review and edit protocols, informed consents, and research plans. In addition, the Project Management Office provides medical writing assistance to CMRP technical project managers for Source Evaluation Group meetings and other meetings as necessary.

Project Management Office staff continues to upload documents associated with multiple projects to the CMRP Administration and Management Site (CAMS) and presents a portion of the NEO presentation, which provides an overview of CMRP support to all newly hired staff.

Of critical importance within CMRP is the requirement for all staff to be appropriately trained in the protection of personally identifiable information and protected health information. In FY2012, a compliance policy, a guide, and associated training materials were developed. These materials are updated on an annual basis. Project Management Office staff is currently working with the Regulatory Compliance and Human Subjects Protection Program (RCHSPP) Clinical Trials Management (CTM) and Learning and Professional Development (L&PD) teams to develop an internal, computer-based training on the Health Information Portability and Accountability Act (HIPAA) and the Health Information Technology for Economic and Clinical Health (HITECH) Act that will be required for all new hires, and eventually for all CMRP staff on a regular basis. The CMRP Project and Program Management Offices are in the process of comparing and contrasting three existing training presentations and developing a gap analysis to ensure that the new training is comprehensive and contains the most current information related to HIPAA/HITECH.

During the reporting period, the Project Management Office took the lead in coordinating CMRP research subcontracting efforts, including defining workflow processes and establishing procedures and training for technical project managers to ensure consistent communication to all technical project managers and provide assistance to technical project managers across CMRP. In addition, the Project Management Office serves as a resource to mentor new technical project managers. The Project Management Office also assists multiple CMRP programs in establishing research subcontracts and agreements, including assisting in the preparation of SOWs, shepherding subcontract documents through the research subcontracts process, and performing a critical review of proposals and budgets. During this reporting period, the Project Management Office coordinated the dissemination of subcontract policies, guidelines, and processes to CMRP technical project managers to enhance communication and improve the CMRP subcontracting processes.

During FY2015, the Project Management Office collaborated with the CMRP IT group to make extensive updates to the Project Management Office SharePoint site, which uses a workflow platform to automatically distribute, track, and manage all sections of CMRP's Annual Report. The site eliminates tasks that historically were performed manually, including e-mailing individual report sections to the appropriate staff, tracking document version history, and tracking the status of documents to ensure timely movement through the workflow, which allows staff members involved in the reporting process to concentrate on their individual tasks of preparing and reviewing report sections, conducting technical reviews, and approving the final draft of the report.

In May 2015, a survey was created and administered to CMRP staff to determine usage of the CMRP public website and intranet site and to determine unmet needs. This information is being used by a working group consisting of IT and Project Management Office staff to determine if the intranet will continue to be utilized, and if so, what changes and updates will be needed. The feedback received from this survey also guided possible updates to be discussed by the working group for the public CMRP website.

Obtaining quality information on significant accomplishments for CMRP's annual and biannual reports remains a challenge, as the definition of what work activities may be considered significant is interpreted differently by the individuals tasked with reporting this information. This year, in an effort to standardize the definitions of significant accomplishments, the Project Management Office medical writer significantly updated the report section templates—a tool used by CMRP to collect consistent report information; it contains detailed instructions for preparers and reviewers of report sections—and created a training presentation focused on CMRP's annual and biannual contractual reporting responsibilities. This training presentation was provided on three separate occasions to accommodate

staff involved in preparing and reviewing report sections. The training session provided a detailed overview of all CMRP reporting timelines for FY2015, the information requested for each report, the role and responsibilities of section preparers, reviewers, and technical reviewers, an in-depth look at the report section template and significant accomplishments (e.g., definitions were provided to better explain significant accomplishments and the types of activities that would be deemed significant), and contacts for questions. The training sessions were well received and deemed highly educational by those in attendance.

During FY2015, the Project Management Office medical writer took on a new role in report-related responsibilities to ensure that all programs falling under the CRD are fulfilling their contractual reporting responsibilities on an annual and biannual basis. The Project Management Office has taken the lead in training these CRD groups in these responsibilities, which includes sharing best practices pertaining to CMRP's internal process for facilitating the preparation, collection, review, and submission of all report information. In this capacity, the Project Management Office medical writer will serve as a resource to CRD groups requesting assistance in developing their own processes for annual and biannual reporting or choosing to adopt certain aspects of CMRP's processes and will be the overall CRD contact for all report-related submissions to the Leidos Biomedical Research Quality Management Office (QMO) and the dissemination of information from the QMO to programs and groups within CRD. The Project Management Office developed a PowerPoint presentation and a 34-page informational manual, which was shared with the QMO and used to facilitate the July 1, 2015 CRD group training session. The session was recorded using GoTo Meeting, which enables those who were unable to attend to follow along by listening to the recording and seeing the presentation visually on screen. After the training session, the medical writer forwarded the recording to CRD staff members who were invited to the training session and mailed copies of the informational manual to those who attended remotely or were unable to attend. To ensure CRD staff within BRG, the Molecular Characterization (MoCha) Laboratory, the Therapeutics for Rare and Neglected Diseases (TRND) program, and CPTAC were beginning preparations for the Leidos Biomedical Research Annual Report and Contract Performance Status Report, the medical writer followed up via e-mail, outlining the specific steps that were needed to begin report preparations and supplying these staff members with the tools they needed to get started, including report section tracking spreadsheets, report section templates to gather report information, language for e-mails requesting report information, etc. The medical writer continues to maintain communication with CRD staff to field questions and help these programs become accustomed to the reporting requirements.

During FY2015, there has been a critical need for medical writer support to the NIAID DCR RCHSPP Clinical Safety Office (CSO). While the RCHSPP CSO recruits to fill its vacant medical writer position, the Project Management Office medical writer and the NIAID medical writer have assumed all responsibilities for NIAID protocol reviews, as well as duties for note taking at CSO meetings, and presenting the CSO medical writer section of the NEO presentation on a biweekly basis. The review of protocols has been a challenging and labor-intensive effort, considering the frequency with which protocols and associated documentation are sent to the CSO by principal investigators (PIs) and the designated two-day review time allowed for the medical writer portion of review. Both medical writers are working together to share this additional work and have maintained open communication and transparency with the CSO in order to conduct their reviews within a realistic timeframe when they are unable to meet the two-day deadline. Most recently, a third medical writer, who supports the National Institute of Mental Health (NIMH), has also been enlisted to provide minimal support to the Project Management Office and NIAID medical writers for this effort, should they need it.

The establishment of biweekly Project Management Office and Program Management Office meetings has helped foster an atmosphere of teamwork and collaboration between both offices. Key staff members from each group attend this meeting to discuss directorate challenges and issues that affect not only both offices, but also CMRP staff. Discussions often lead to solutions, which are then carried out and monitored by both groups. Due to the nature of the services provided by CMRP, it is vital to foster positive team dynamics in a high-energy, fast-moving work environment. This collaboration between offices provides another layer of transparency that encourages this type of interaction and communication.

CMRP Document Control

CMRP Document Control comprises one documentation specialist, who coordinates, compiles, and tracks all program documents, and maintains the CMRP master documentation file and archive. The document specialist creates progress report templates to assist technical project managers with managing subcontractor progress reporting. Additionally, the documentation specialist provides administrative and clerical support related to CMRP program initiatives.

To simplify the process for collecting and storing data used to track employee publications, CMRP uses the Publications site, a web-based document management software system, to gather and summarize publication data, ensuring that program reports are in compliance with NIH requirements. Internal audits are performed by a medical writer to verify that all CMRP publication data are entered and to affirm the software is correctly pulling reports from the entered data. Publication reporting results from the site have been successfully used to prepare all publication sections of reports from FY2013 to the current FY2015 reports.

During the reporting period, CMRP electronic file data storage was reviewed monthly to ensure that new information was deposited appropriately, thus maintaining a simplified navigation of the folders and files held within the internal CMRP shared drive.

The documentation specialist: assisted in the maintenance of a CMRP research subcontracts database by uploading the appropriate documentation into a Microsoft SharePoint library, and tracking and loading financial updates into the library; maintained a subcontract spreadsheet for 35 research agreements; managed a spreadsheet to track historical YT data, and assisted with subcontract renewals.

The documentation specialist continues to draft and update sections of the CMRP Report Handbook to define the staff's roles and responsibilities in writing, reviewing, and submitting program reports. The processes for the Contract Performance Status Report (CPSR) and the CMRP portion of the Leidos Biomedical Research Annual Report remain under review, as updates have been requested per process changes. Currently, the document specialist is drafting the CMRP Report of Activities process.

New duties assigned over the past year have included: (1) development of new progress report templates; and (2) creation of a document repository containing sample research subcontract and agreement documents for Technical Project Mangers (TPMs), which will become available through CAMS.

Project Management Office staff maintains the DCCPS progress reports, which were created to enable the tracking of subcontractors' work activities. The reports provide detailed information regarding patient accrual numbers, Institutional Review Board (IRB) approvals, data gathering, work performed, challenges and solutions, invoice due dates, and deliverable tracking. During FY2015, a new version of the final progress report template was created to provide a more detailed summary of the work completed by the subcontractor. The new version contains a cover page, table of contents, and, in addition to the information listed above, contains information pertaining to key personnel, purpose and objectives, experimental design, results, and discussions and conclusions.

Due to the high-profile Ebola work currently conducted within CMRP, a Project Management Office secretary III was assigned to assist with Ebola-related work as needed. The documentation specialist then took on the role of secretary until normal operations resumed. As a result, all administrative duties regarding agendas, meeting schedules, and meeting minutes for the Rakai Project were handled by the documentation specialist.

The documentation specialist has begun providing more support to DCCPS research subcontracts by coordinating and tracking supply orders (e.g., computers) and travel approvals for staff, creating agendas, and taking meetings minutes for two different monthly meetings. The documentation specialist also assisted in the organization (created/prepared documents and binders) and management of a DCCPS Network Meeting held at NCI in May 2015, which consisted of NCI network members, a Leidos Biomedical Research subcontractor, and Leidos Biomedical Research staff members.

CMRP Learning and Professional Development

CMRP training support is provided by the L&PD group, which is composed of a clinical training manager, a training specialist/instructional designer, a training specialist, and a training coordinator. The L&PD group supports CMRP, the NIAID DCR Office of Clinical Research Policy and Regulatory Operations (OCRPRO) and the NIAID Office of Planning and Operations Support (OPOS).

L&PD's CMRP activities fall into four categories, identified below.

Provide Training Sessions to Address Client-Identified Training Needs

The major new L&PD initiative in FY2015 involved development of a job-specific training program for new employees hired for CMRP's special projects. This program, the 2015 NIAID Special Projects Technical Training Initiative, involved identifying job-specific training requirements for a large number of new employees hired to support rapidly expanding projects; identifying topic-specific SMEs; supporting the development, review, and approval of appropriate competency-based training materials; and coordinating the deployment of these materials. This initiative also required that the L&PD staff learn the use of new software, George! for PowerPoint, to produce self-paced learning modules. In addition, this project required extensive rebuilding of the L&PD SharePoint site to allow on-demand access to the new, self-paced training sessions.

The clinical training manager offered training on Influencing without Using Your Authority, Managing Up, Managing Multiple Priorities as part of the Managing Well Program, and the Administrative Professionals Certification Program (APCP).

Provide Training and Professional Development Subject Matter Expertise

Training and professional development are critical activities for numerous clinical research and medical personnel. Continuing education units (CEUs) are a requirement for maintaining licenses and certifications. Fiscal constraints and the United States (U.S.) Department of Health and Human Services (HHS) Efficient Spending Policy have significantly restricted staff's ability to attend relevant conferences and training events. During the reporting period, CMRP continued to offer International Association of Continuing Education and Training (IACET) CEUs for instructor-led training sessions provided by CMRP SMEs and also adapted their processes to provide IACET CEUs for instructor-led training sessions provided by third-party vendors.

L&PD further refined processes to allow granting IACET CEUs for computer-based training. The ability to award IACET CEUs for computer-based training allows CMRP's geographically diverse training audience to participate in high-quality training events asynchronously and collect CEUs.

Provide Administrative Support for Activities with Training Implications

The L&PD group facilitated training sessions on various topics; each session included presentation evaluation and attendance documentation for each participant. Sessions during FY2015 included: (1) Monthly seminar session: Dr. Gause's State of the Union; (2) the Deputy Director of Management webinar series; (3) Clinical Grand Rounds; (4) Ebola: A Ground Level View from a Treatment Center; (5) the NIAID Town Hall Meeting; (6) the NCI Town Hall Meeting; (7) Eight Lessons to Live By; and (8) The Regulatory Intelligence Seminar.

In support of the NEO program, the L&PD group schedules presenters, compiles reference binders for each new employee, and presents the Clinical Training and Training Management Policy sessions to all new CMRP employees. In FY2015, this involved 23 sessions.

The L&PD SharePoint site was updated to make it more user-friendly and valuable to CMRP staff members for their career development planning. This involved redesigning the site to make the location of each type of training resource intuitive and uploading as many electronic training resources as possible. The re-design of the L&PD SharePoint site allows CMRP staff members to utilize training resources for their professional development that had not been available to them previously. It empowers them to pursue supervisor-approved, personal professional development plans, utilizing high-quality training resources, as it fits into their schedule.

Ensure Compliance and Continuous Improvement of Training Processes and Initiatives

The L&PD group conducted a retreat this year to develop a strategic plan to optimize their services to all client groups. This discussion allowed the team to align their services with the mission of the group.

The L&PD group administered the 2015 résumé and curriculum vitae (CV), signature log, and license/certification review for all CMRP staff. This effort includes sending a current résumé and CV, signature log, and license/certification summary to each employee, instructing the employee to update them, if needed, and tracking the return of all documentation to ensure 100 percent compliance. This activity is a requirement for CMRP to operate in a Good Clinical Practices (GCPs) environment.

In addition, all CMRP staff members received a copy of their personal training record twice this year to allow them to review their record and provide the L&PD group with any missing documentation.

CMRP Information Technology

The CMRP Information Technology (IT) group provides software development, computer, network, application, and disaster recovery support to NCI, NIAID, Clinical Center, NHLBI, NIAMS, NCATS, NIMH, and NINDS initiatives. Members of the IT group specialize in evaluating core business processes, utilizing simple and flexible methodologies to transform business needs into suitable, cost-effective technical solutions, while maintaining focus on both satisfying customer requirements and meeting the unique operational requirements for managing clinical trial, regulatory, and clinical safety data. The IT group continually assesses the goals and objectives of CMRP and uses leading-edge technology to provide the best return on investment, while ensuring compliance with all applicable regulatory and security best practices, policies, and standards.

During the past year, the IT group was involved in several key technical initiatives for the program, as described below.

CMRP IT Infrastructure Support

The IT group established, and continues to maintain and operate, a CMRP IT infrastructure within the Building 30 data center to better support CMRP operations and groups located throughout the NIH community. The project required modifications and routing for approval of a Service Level Agreement (SLA) between the Internet service provider (ISP) and CMRP, in which specific information systems and system services were defined, as well as the levels of response, availability, maintenance associated with the services, and the responsibilities of each group in providing assurance that all would function as expected. Maintaining the technical framework required the collaborative effort of staff from the ISP and the CMRP IT group to identify the appropriate rack space, power supply, cooling, and cabling requirements to support the equipment currently placed in the space. The SLA is fully authorized, and the operational environment is in effect, providing program and technical staff members with the capability to utilize multiple platforms, whether production or development, for testing and developing new software or system functionality enhancements; to store program materials, financial reports, and similar content; and to electronically manage business processes. Disaster recovery services and capabilities were integrated and are supported within the technical framework, with the release of a fully redundant, automated tape backup library system that utilizes fiber optic channel cards to collect data from the servers.

During FY2015, the IT staff member appointed as the HIPAA/HITECH compliance officer reviewed all incident reports submitted by program staff, ensured appropriate safeguards were in place and necessary actions were taken, and provided follow-up when indicated.

The CMRP IT group provided continued support of the smart card authentication requirements and standards set forth by Homeland Security Presidential Directive 12 (HSPD-12), enacted in 2004, and associated Federal Information Security Management Act regulations, Office of Management and Budget memoranda, and NIH policy. Per applicable guidance, the ability to use smart cards as a form of dual-factor authentication when utilizing remote-access technologies, such as virtual private networks, was deployed, as was the enforcement of dual-factor authentication for access to laptop and desktop computer systems. Monitoring of any additional requirements or mandates is ongoing.

The IT group participated in the annual Frederick National Laboratory for Cancer Research (FNLCR) intrusion detection tests for the assessment of network host vulnerabilities and in post-remediation efforts to mitigate findings. This exercise was essential in providing a comprehensive review of potential threats to the program's IT assets based at the FNLCR campus and in identifying changes that need to be made to existing business processes to prevent future threats.

CMRP IT staff continues to support the digital signature initiative introduced in FY2012, in which U.S. Department of Health and Human Services (HHS)-verified Public Key Infrastructure software certificates embedded on individual Personal Identity Verification (PIV) cards were utilized to digitally sign Adobe Acrobat program documents in lieu of paper-based, wet signatures for approvals. This effort has been very beneficial to the program, as it has reduced the time it takes to obtain approvals. This initiative continues to have a cost benefit and a positive environmental impact, as less paper is being used.

CMRP SharePoint Sites

The IT group manages and supports three Microsoft SharePoint sites: one for managing the many documents related to supporting the submission of the annual budget, a second for collecting and managing the multiple sections that comprise the CMRP section of the Annual Report, and a third site for tracking, reporting, and managing research subcontracts/agreements and other associated documentation. Each of these site releases were custom implementations, with unique requirements and functionalities. A workflow engine was constructed to provide the sites with the ability to not only manage documents in the system, but to also facilitate the entire review process, from collection to approval. E-mail notifications were included for ease of navigation by the end user. The CMRP IT group continues to serve a critical role by participating in a working group for this application: to support the change request process developed by the group to manage system changes, ensure proper communication channels are open, and ensure changes are made in a consistent and uniform manner. Maintenance and technical support of the centralized CMRP Financial Management and Project Management Office SharePoint platforms has continued, with cumulative Microsoft updates and service packs being applied to both environments, and verification of proper system function conducted post-application. A technical review of the required changes to the sites was completed to support the 2014–2015 budget and Annual Report deliverable cycles, and the sites were updated with the addition of several new program areas, custom reports, and improvements to the visual presentation. An extensive review of the underlying architecture, source code, and platform design was undertaken in order to develop a comprehensive portfolio of systems documentation. Technical changes to one of the sites included: removing unused data columns, developing a custom report to provide a drag-and-drop functionality for sorting and filtering columns, creating dynamic Microsoft Excel biweekly reports containing color-coded statuses and one-click exports, updating embedded InfoPath forms to support change in functionality, creating a new Vaccine Research Center site, creating and integrating organization-specific favicons to sites for branding, transferring 862 documents from sites to an external document library, and refreshing the development environment with source code and structure from the production platform.

CMRP Websites

The IT group maintains a CMRP intranet platform to provide a central location for program-related resources, tools, shared documents, and common links. The custom-developed platform features an online phonebook, public and private team pages, and a repository for previous issues of the program's newsletter, *The CMRP Insider*, and other program materials. As a tool to improve employee productivity, the platform promotes internal collaboration among members of the various areas within the program, as team pages describing the roles and purposes of each group foster an environment in which staff can learn about others and reach out to them for assistance or to share information.

As with the Microsoft SharePoint platform, the site required rebranding to accommodate the company name change from SAIC-Frederick, Inc., to Leidos Biomedical Research. Code and configuration changes were also necessary to provide functionality for hosting internal standard procedure (SP) documents, as well as content and guidance related to the company name change.

The CMRP IT group also provides maintenance and technical support for a public-facing website, which highlights the diverse clinical research support services provided by CMRP. The site provides information about the many high-profile NCI, NIAID, Clinical Center, NHLBI, NIAMS, NCATS, NIMH, and NINDS initiatives to investigators, clinicians, prospective job seekers, and the general public. Content management support, bug fixes, and similar activities continue to be provided for this site.

Support of the sites and underlying platforms continued, with changes being made to reflect our customers' organizational name changes, as well as to resolve minor system issues identified by end users. Additionally, a move of the Internet hosting platform occurred to the FNLCR Demilitarized Zone (DMZ), requiring updates and configuration changes to the platform to fully support the new environment. Both the intranet and Internet sites are in the process of being refreshed during FY2015 to update both content and appearance. CMRP IT staff, in collaboration with CMRP project management staff, developed and issued a survey to program staff, which will assist the team in establishing a product roadmap for additions of functionality and revisions to the layouts of the sites. An iterative approach is being taken to develop and vet models of the sites through small stakeholder subgroups in order to determine the best product for final rollout.

Telecommunications Voice over IP Initiative

To align with telecommunication upgrade efforts underway within the FNLCR and in place at the Advanced Technology Research Facility (ATRF) and to ensure a reliable and supported phone system is available for the Industry Lane location, multiple assessments were conducted by ISP networking and telecommunications staff to determine the impact of and the components needed to deploy a unified communications (UC)/voice over Internet protocol (VoIP) solution. The current Avaya G3R phone system in place at Industry Lane is out of date and has been superseded by new technologies. A meeting took place with the NCI Office of Scientific Operations (OSO) to determine the funding needed and best path forward. A technical cost-benefit assessment was conducted, and, as a result, the NCI OSO agreed to fund the costs associated with deploying the solution at the location. CMRP IT staff, in conjunction with ISP and internal program staff developed a project timeline with a hard cutover occurring in January 2016.

Attending Scheduler Application

CMRP IT staff released a custom clinician attending scheduler application to replace a manual process for the collection, distribution, and management of staffing assignments over a 13-week cycle. To facilitate its deployment, a user guide was developed and a review of the system was conducted with primary stakeholder, the Chief Medical Officer for Leidos Biomedical Research. Additional preparation and support activities included revising the current date range for the application, monitoring activities completed for issues, and ensuring the availability of the system operation throughout the period of use.

Mobile Device Refresh Program

To best serve the growing mobility needs of our internal program clients, a mobile device refresh program was initiated by the IT group to evaluate the equipment being used within the program, establish a prioritized replacement schedule, acquire and configure the new equipment, complete applicable property accountability and loan documents, and facilitate the return and final disposition of existing devices. New equipment, including iPhone 4S, 5C, and Blackberry Z10 models, were procured via a contract with AT&T at no cost, resulting in the offering of a more robust and technologically advanced mobile platform for program users to better serve the needs of our federal clients.

Replacement of Center Numbers with Project IDs

With the release of an organizational Enterprise Resource Planning (ERP) system and the subsequent replacement of center numbers with project identification (ID) codes, functionality changes in the CMRP SharePoint platforms were required. In conjunction with the stakeholder team, requirements were developed that outlined the process by which new fields would be added to each site within the platform and which modifications to current processes and lists/libraries would be needed. The CMRP IT group was able to quickly turn this significant change around by developing new fields for project IDs and sub-project IDs using one-to-many relationships, then using source materials to input new values and link them to reference materials in the sites' document libraries. Additional modifications to support this initiative included changes to all input forms to provide read-only representations of project titles upon selection of project ID values and recoding custom ASP.NET reports to support selection of project ID and sub-project ID values.

Program Close-Outs

The first quarter of FY2015 presented a challenging operational environment as the scope of work for several program areas came to a close, resulting in the reduction in support of two CMRP IT staff members. Focus in this time period was directed on the completion of close-out activities and transition of final deliverables to the customer, as described below:

United States-Latin American Cancer Research Network Close-Out. Due to a change in NCI Center for Global Health (CGH) work scope and direction, the US–LA CRN study was closed to accrual of new participants, and guidance was provided to program staff to direct all current and future efforts towards transitioning activities and functions performed by program staff over to a new external entity. The bioinformatics infrastructure and service model that had been established presented a challenge in transitioning this function without disrupting service as a suitable hosting environment had not yet been identified, and the relatively short period of time in which these activities were to occur further complicated the efforts. IT staff worked closely with the NCI Center for Biomedical Informatics and Information Technology (CBIIT) in attempting to mitigate risks and in facilitating the development of a transition plan that was ultimately

accepted by the NCI Center for Global Health (CGH). Close-out activities included the transfer of final clones to NCI-CBIIT by utilizing an encrypted transfer protocol with verification of materials post-transit using commercial cryptographic hash functions, review of final subcontract invoicing, evaluation and disposition of computer equipment, composition of document and messaging catalogues as reference materials, and reduction in support of one FTE IT staff member who had been appropriated for this project.

NCI Community Cancer Centers Program Close-Out. Due to the formal completion of support to the NCI Community Cancer Centers Program (NCCCP), current and future efforts in providing technical support to the group were refocused on end-of-project activities including inventory management, facilitation of hardware returns and final dispositioning, deactivation of accounts, establishment of electronic and messaging archives, and sanitization of equipment, with all being successfully completed in the first quarter of FY2015.

Information Technology Meeting and Conference Support

To enhance current service offerings and better meet the needs of the federal client, CMRP IT staff has provided on-site technical support, facilitation of web-based videoconferencing, and coordination of audio-visual and IT services for various scientific, working group, and similar high-level meetings, including the National Clinical Trials Network Working Group, the Accelerate Brain Cancer Cure scientific meeting, Clinical Trials and Translational Research Advisory Committee meetings, and Specialized Programs of Research Excellence (SPORE) meetings conducted in coordination with the NCI Coordinating Center for Clinical Trials (CCCT). These services require an extensive amount of pre-planning to carefully assess the technical needs of the project, identify resources required, and respond to IT-related inquiries or issues. The CMRP IT group's ability to provide excellent customer service has been noted by both internal and external customers. On several occasions, thanks and appreciation was provided to the team by the federal customer. Unfortunately, due to NCI budget constraints, a full-time position for IT support was not authorized and formal service was ended on December 31, 2014, with a reduction in support notification issued to the IT staff member that had been supporting this project on an ad hoc basis.

CMRP Financial Management

The CMRP Financial Management Group (FMG) continues to expand its capabilities and take on new challenges in support of NCI, NIAID, NHLBI, NIAMS, NIMH, NINDS, NCATS, and the Clinical Center.

The FMG collaborates with other Leidos Biomed directorates, programs, and departments, as well as with government officials, and manages the following cost centers:

- Office of the Directorate – 4
- NCI Office of the Director (OD), Center for Strategic Scientific Initiatives (CSSI) – 6
- NCI OD-Immediate Office of the Director – 30
- NCI Division of Cancer Epidemiology and Genetics (DCEG) – 3
- NCI Center for Clinical Research (CCR) – 35
- NCI Division of Cancer Treatment and Diagnosis (DCTD) – 13
- NCI Division of Cancer Control and Population Sciences (DCCPS) – 1
- Clinical Center – 4
- NIAID Division of Intramural Research (DIR) – 14
- NIAID Division of Clinical Research (DCR) – 24
- NIAID Division of Acquired Immunodeficiency Syndrome (DAIDS) – 2
- Other Institutes – 5

In addition, the CMRP FMG provided oversight of three CSSI/CPTAC cost centers, which translated to the CRD.

During FY2015, the FMG completed the FY2016 annual budgets by utilizing the FMG SharePoint site, which streamlines the process for the preparation, documentation, review, and internal approval of all FY2016 annual budgets for submission-based contract deadlines.

This site provided quick access from one location to all source documents and financial information, increasing efficiency in preparing the annual budgets. The site also provided quick access to electronic files from various locations to prepare assumptions, include budgeted costs based on existing and new requirements, and submit to appropriate functional managers, financial analysts, and the director of the program for electronic approval. In addition, the inclusion of timelines in the system resulted in all CMRP budgets being submitted to the Financial Planning and Analysis Office by the established deadline. In addition, the information from this SharePoint site was used to more easily and efficiently input 95 staffing and 134 budget files into the new ERP module.

Within the past fiscal year, the FMG expanded the capabilities of its SharePoint site in support of NIAID DCR to include real-time tracking of actual expenses against planned assumptions for FY2015. The inclusion of real-time information enabled the FMG to maintain estimates at completion (EAC), track detailed information related to the efficient spending policy, and share information with management and NIAID DCR government counterparts in an expeditious manner. This improved the program's operational efficiency.

During the reporting period, the FMG continued to manage and develop cost estimates for new and revised work scopes, provide monthly static financial report information, and track project expenses for all budgets to ensure the accuracy and accountability of all costs. In addition, as a result of excellent planning and documenting

of static financial worksheets, the FMG responded to multi-year spending predictions that were used to generate the information required for the submission of the FY2016 budgets to meet contractual deadlines.

In collaboration with other CMRP groups, the CMRP FMG developed self-paced technical training modules on Property Accountability, Budget and Funding, and the ERP system. These training modules were developed for newly hired staff based on the training requirements for each position. These self-paced modules eliminate the need for instructor-led classes, therefore optimizing resources. In addition, these modules ensure consistency in the communication of information and efficiency in the operations of the program.

Within this reporting period, the CMRP American Recovery and Reinvestment Act of 2009 (ARRA) FMG worked closely with CMRP technical project managers to monitor balances of funding to ensure the total expenses, commitments, and encumbrances to close out these ARRA projects, in addition to all nonseverable activities, were processed and closed out correctly. FMG met the reporting deadlines for funding that expired in FY2015, which required working closely with senior management, technical project managers, Leidos Biomedical Research auditors, the Financial Planning and Analysis Office, and Research Contracts to track, analyze, and provide reports on a monthly basis to attempt to utilize all funding. As a result of the expiration of funding for several non-severable efforts within CMRP, it was very challenging to report available funding. This was especially challenging for NCCCP activities because three sets of research subcontracts were funded by one cost center. Two sets of subcontracts were completed and undergoing internal auditing, during which time available balances could not officially be released. With the assistance of the Leidos Biomedical Research auditing team and Research Contracts, this challenge was resolved by reducing existing balances to $1,000 on all completed research subcontracts being audited. A similar situation existed for The Cancer Genome Atlas (TCGA) and CPTAC activities, whereby research subcontracts were continually monitored and the values for many were increased and decreased, depending on performance. With the assistance of the technical project managers, the available funds within multiple cost centers were continually assessed for alignment with the operating budgets.

As part of the reorganization of the CPTAC activities, the CMRP FMG continued assuming the responsibility of overseeing additional cost centers in support of the newly created CPTAC efforts. The CMRP FMG worked closely with the Director of Clinical Program and CSSI technical project managers to gather information relating to the operating budgets and prepare monthly EACs that were shared with the CSSI government counterparts to ensure accuracy and accountability for all active projects.

As a result of an approved YT in support of NIAID-DCR for Ebola, the CMRP FMG increased its staff to include a full-time financial analyst II to support this effort.

With the implementation of the ERP system and its reporting capabilities, the CMRP FMG re-evaluated their current process for the preparation of EACs and made significant changes that reduced resource time for the preparation of all source documents. This also eliminated the chance of error in the data entry, since all information could be directly migrated into a formal financial report summary.

The CMRP FMG expanded on the development of project tracking in support of NCI Office of the Director (OD) CCCT, OD CGH, NIAMS, NCATS, CMRP, DCCPS, and NIAID DCR project cost management requirements. Using project codes, the CMRP FMG can track and generate project reports identified for approximately 5,000 projects based on each proposed operating budget submitted for FY2015. The CMRP FMG, in collaboration with the Leidos Biomedical Research Financial Planning and Analysis Office and project managers, reconciled monthly expenses for accuracy prior to reporting to DCTD. This effort resulted in management of projects based on the projected costs against actuals, in an effort to utilize staffing and operating funds more efficiently and effectively to support the ongoing efforts within DCTD.

The CMRP ARRA FMG worked very diligently by participating in monthly, and for some efforts weekly, meetings between CMRP technical project managers (TPMs), the Leidos Biomedical Research auditing team, and Research Contracts staff to reduce purchase orders that were being audited to free up funds, which were used to support additional subcontracting efforts. This allowed efficient spending of the available resources to support NCCCP and TCGA programs. In addition, the CMRP FMG met on a monthly basis with various CMRP TPMs and managers to review expenses and balances involving all non-severable efforts for which funding was expiring in FY2015 to ensure the complete close-out of expenses and the project accounts.

In addition, the CMRP FMG prepared EACs for quarter one, quarter two, and quarter three for all project IDs within CMRP to ensure adequate funding to support ongoing efforts and communicate any savings to the various divisions that were used to support other (unplanned) initiatives. In addition, special EACs were completed monthly on the NIH Clinical Center D.C. Partnership for HIV/AIDS Progress (DC-PFAP) non-severable activities as part of the descoping of these efforts. This was essential to ensure adequate funds were available to close out all outstanding efforts in support of this project.

As part of the requirements to transition existing project codes to new project accounts by utilizing the new ERP System, the CMRP FMG continued to work closely with CMRP senior managers and TPMs to identify and implement new project accounts in support of NCI DCTD, NCI DCCPS, NCI IOD CCCT, NCI IOD CGH, NIAMS, the Clinical Center, and NCATS. The work was based on knowledge and experience gained in support of NIAID DCR that allowed them to efficiently and

effectively carry out the mission of tracking projects in support of these new divisions. In addition, the CMRP FMG, in collaboration with various senior managers within CMRP, continued the ERP Task Force made up of working groups based on each module utilized in the new ERP to facilitate the communication of issues. The work groups continued to gather information from managers regarding issues or impacts through meetings and discussions, organized information in a database, prioritized them based on impact, and communicated information to the various Leidos Biomedical Research ERP points of contact (POCs). Also, these groups continued preparing the CMRP ERP News e-mails, which communicate updates made to the system. This was a team-building approach between the program and various other departments within Leidos Biomedical Research. This initiative resulted in increased communications, quick resolution of issues, and increased the efficiency of operations.

The CMRP FMG was instrumental in the coordination of training for all ERP Cognos Management Reports for financial, program area, reference, and specialized reports for all managers, and administrative and technical staff. These reports provided information for tracking and monitoring of budgets and costs related to high-level projects and efforts. This training provided necessary information and tools for all CMRP users, which resulted in the ability to track project costs closely and respond to customer inquiries in an efficient manner.

Technical Project Management Support Provided by the Applied and Developmental Research Directorate

Biorepository Subcontract, Fisher BioServices, Inc.

The mission of the National Cancer Institute (NCI) at Frederick Central Repository is to support the research programs of the National Cancer Institute (NCI), the National Institute of Allergy and Infectious Diseases (NIAID), and the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), and other groups. The primary core functions of the Central Repository are the receipt and distribution of biomaterials for research and clinical testing and temperature appropriate storage of over 15.5 million biological specimens. The Central Repository has the capability and capacity to store biological materials at ambient, 4°C, -20°C, -40°C, -80°C, -150°C, and -196°C temperatures.

The Central Repository stores these biological materials in strict accordance with the International Society for Biological and Environmental Repository Best Practices and the NCI Best Practices for Biospecimen Resources. The Central Repository dedicated staff is experienced in the domestic and international shipments of biospecimens in compliance with current International Air Transport Association and Department of Transportation standards.

Infrastructure: The robust design of all three repository locations allows for the capability to accommodate all types of commercially available biospecimen storage mechanical freezers and cryogenic units. NCI at Frederick Central Repository facilities consist of standard administrative offices, and secure biospecimen storage facilities. All repository facilities have dedicated (liquid nitrogen) LN_2, electrical, and HVAC systems with redundant backup multi-fuel electric generators, and multiple building security features/ systems, including an integrated fire alarm system with multiple methods of fire suppression and oxygen level monitoring. In addition, there is complete alarm monitoring of all critical building support systems, facility spaces, and sample storage units 24 hours a day, 7 days a week, 365 days a year. All repositories are controlled-entry facilities that can only be accessed by authorized personnel having an issued key card.

Weather Closings: The Frederick National Laboratory for Cancer Research (FNLCR) experienced numerous base closings this winter (2014–2015) due to inclement weather. Fisher Bioservices, Inc., staff continuously monitored repository sample storage equipment and facilities in the event of an emergency or equipment failure for the duration of these weather-related events.

Initiatives: Leidos Biomedical Research approached an industry leader in commercial cryogenic storage equipment, Chart Industries/MVE Biomedical Division, with a proposal to conduct a pilot study to determine the environmental and economic impacts when comparing the electrically efficient MVE Vario 1800 Series freezer systems using a non-mechanical LN_2-based method of refrigeration to that of the conventional -80°C single- or multi-compressor freezer storage units that rely solely on electricity to operate the compressors and condensers. The scope of the project involved replacing 28 existing conventional -80°C multi-compressor freezer storage units with 18 MVE Vario LN_2-cooled freezers, and performing a side-by-side comparison of electrical use, and building cooling and associated energy use, through the tracking and data capture and analyses of multiple metrics for the quantitative performance assessment during day-to-day normal operations. In 2014, Leidos Biomedical Research conducted the six-month-long study. The data revealed that the Vario freezer system provided a considerable cost savings in operating costs as compared to traditional -80°C mechanical units. A manuscript is currently in preparation to be submitted for publication in the fall of 2015.

Technical Project Management Support Provided by the Management Support Directorate

Scientific Library Subcontract, Wilson Information Services Corporation

Through a subcontract with Wilson Information Services Corporation (WISCO), the Quality Management Office (QMO) provided technical oversight of operations at the NCI at Frederick Scientific Library. As part of this effort, the QMO worked with WISCO staff to develop a plan for the disposal of hard copy journal articles that can be accessed through online subscriptions. A large number of the journal articles were claimed by other institutions and these have been physically removed from the Scientific Library. The remaining unclaimed volumes will be removed by early next year. This move to a more virtual model for library operations maintained service levels while reducing the physical footprint of the Scientific Library.

Immediate Office of the Director

Support Provided by the Cancer Research Technology Program

RAS – Electron Microscopy Laboratory

The Electron Microscopy Laboratory (EML) provides state-of-the-art electron microscopy techniques. EML has processed and analyzed more than 1,100 samples from over 60 NIH investigators. EML has four transmission electron microscopes (TEMs) and two scanning electron microscopes (SEMs). EML provides services to the RAS mission of CRTP and through Yellow Tasks to NCI CCR, the Vaccine Research Center (VRC)/National Institute of Allergy and Infectious Diseases (NIAID), and other NIH institutes.

Significant Achievements

- Image processing, particle classification, and single-particle reconstruction: In an effort to support the increased need for negative-stain electron microscopy from the VRC (NIAID), an expert in image processing and 3D reconstructions was hired in a scientist position. Since then, work flows for 3D reconstruction of negative-stained particles have been improved and newly developed. As evidenced by the large number of samples (about 450) and the publication list, a large number of projects from VRC have been supported.
- Through a cCRADA mechanism, EML has supported Cureport, Inc., and the group of Katherine Ferrara (University of California, Davis) in characterizing liposome preparations by cryo–electron microscopy. Cureport, Inc., is a startup company using proprietary formulation methods to develop nano-based cancer drugs. We also supported MedImmune with negative staining of virus-like particles and Jason McLellan's group (Dartmouth College) with negative staining of virus spike/Fab complexes.
- The RAS mission in CRTP has been supported in several ways by various methods, including visualization of the ultrastructure of RAS KO cell lines with both TEM and SEM, and negative staining of RAS and RAS in nanodiscs (for constitution of RAS on the membrane).

RAS – Optical Microscopy and Analysis Laboratory

The Optical Microscopy and Analysis Laboratory (OMAL) provides microscopy support to the RAS Initiative and conducts research to understand the mechanisms of RAS activation at the plasma membrane.

The following fluorescence microscopes are available at the ATRF: Nikon NSTORM for super-resolution imaging, combined with a spinning-disk confocal microscope, and a laser-scanning confocal microscope with fluorescence correlation spectroscopy instrumentation. Both instruments are providing fluorescence microscopy support, including the imaging of 96-well plates for identifying compounds that disrupt KRas.

The following research studies on KRas have taken place:

- The laboratory demonstrated that a fluorescence resonance energy transfer (FRET) biosensor for detecting KRas interaction with the RAS-binding domain of Raf could be used when FRET was detected using fluorescence lifetime imaging (FLIM).
- The laboratory established the ability to localize at super-resolution or track single molecules of fluorescence-labeled KRas on the cell surface using TIRF. Step-wise photobleaching and Ripley's K analysis indicated clustering of Ras molecules in the membrane.
- Hidden Markov modeling of single-molecule tracking data suggest three dynamic states of KRas on the cell membrane: a stationary state, a slow-moving state, and a faster-moving state. The effective diffusion coefficients of the mobile states are consistent with previous reported values. Estimates of transition probabilities between the states show that transitions between the stationary and fast-moving states are rare. This result supports the pre-existing conjecture that KRas is mobile when in its inactive form, and its mobility decreases progressively as Ras dimerizes and binds to Raf and other complex-forming molecules.

RAS – Protein Characterization Laboratory

The Protein Characterization Laboratory (PCL) provides mass spectrometry support to the RAS Initiative for proteomics and quantitative analysis. During FY2015, PCL has made significant contributions in support of the RAS Initiative by integrating new technologies for

solving research problems related to RAS signaling pathways. Some examples of these contributions include intact RAS protein analysis, RAS protein structural analysis, and Ras inhibitor quantitative analysis.

PCL has great expertise in the field of proteomics. The laboratory has made significant contributions to the RAS Initiative. We established the intact protein accurate mass measurement protocols to support the RAS Initiative and PEL. These protocols have significantly improved the quality assurance/quality control procedures for RAS protein production work and provided detailed quality information for improvement. In addition, we are developing protocols for the quantitative analysis of RAS inhibitors and their efficiency in the cell culture.

RAS – Genomics Laboratory

The Genomics Laboratory (GL) has provided support for several projects within the RAS Initiative. The effort within the GL includes support for the development of MEF lines carrying specific RAS alleles for use in cell-based high-throughput screens. Following the isolation of 33 clonal cell lines, the GL has been involved in the generation of nucleic acids for the characterization of these cell lines, which includes verifying expression of the transgene, identifying sites of integration, verifying the sequence of the RAS genotype, and identifying and verifying specific mutations within the stable cell lines using whole-exome analysis and Sanger sequencing. The GL has also provided whole-exome sequencing support for the cell surface project, and Sanger sequencing support for the RAS reference reagents project and the membrane localization project.

The GL has completed whole-exome analysis for 63 samples during the reporting period, and provided 940 Sanger sequencing reactions for verification of cell lines and 8,463 Sanger reactions for constructs generated by the RAS Initiative. Integration analysis using Illumina sequencing has been performed for more than 25 cell lines. Support for the characterization of gene expression profiles for stable cell lines is under way and will be completed this year.

The GL has developed new droplet digital PCR assays for KRAS 4A and KRAS 4B isoform detection, worked with the PacBio team to develop novel approaches for identifying transcript isoforms, and is developing a high-sensitivity assay for low-level mutations in TRP53. The GL is participating in a cCRADA with the University of Maryland to establish new techniques for identifying viral infection in clinical specimens. The project involves the design of a hybridization capture panel for sequencing on the Ion Torrent Platform. The GL, in collaboration with Bob Stephens, has established a set of target regions for hybridization and provided the set to Life Technologies, Inc., for design and production of capture reagents. The next phase of the project will involve developing laboratory protocols, demonstrating efficient capture of known virus from test specimens, and training staff at the University of Maryland.

NCI Community Cancer Centers Program

Support Provided by the Clinical Monitoring Research Program

High-level administrative, clinical project, and research subcontract management support has been provided to the NCI Community Cancer Centers Program (NCCCP) since May 2006, beginning with the original NCCCP Request for Proposal (RFP). Launched in June 2007 and continued through September 2014, NCCCP was a public–private partnership between NCI and a network of hospital cancer centers, which served as a community-based platform to support basic, clinical, and population-based research initiatives across the cancer care continuum—from prevention, screening, diagnosis, treatment, and survivorship through end-of-life care.

NCCCP officially ended in September 2014, with the completion of the network activities and the end of the period of performance for the subcontracts with the community hospitals. The comprehensive team of dedicated CMRP staff was also reduced at this time, with a more modest team continuing to support the final program close-out activities through the reporting period.

Research Subcontract Management

During the reporting period, CMRP staff continued to manage and support the close-out and internal audit activities for the 55 NCCCP research subcontracts:

- *Ten Original NCCCP Pilot Research Subcontracts to Community Hospitals (July 2007 to June 2012*

Staff supported the internal audit of the original 10 pilot hospital awards, which required a very intense communications plan with the community hospitals in order to address local challenges with the invoicing process for the time and material subcontracts. A very coordinated and successful team approach to the audit process was implemented, which included recurring meetings between members of the CMRP team and the Internal Auditing and Research Subcontracts departments.

- *Ten ARRA Project Research Subcontracts (July 2010 to June 2013)*

Ten ARRA research subcontracts were awarded to the original pilot organizations to support 18 ARRA projects that ended in June 2013. During the reporting period, staff continued to support the subcontract close-out and internal auditing activities.

- *One ARRA Project 9 Research Subcontract (July 2010 to March 2014)*

The research subcontract with the University of Maryland continued through March 2014, to support the multidisciplinary care coordination research study ARRA Project 9. During the reporting period, the University of Maryland completed fine-tuning of the data analysis system and submission of targeted publications.

- *Fourteen ARRA Awards to Additional Community Hospitals to Address the Comprehensive and Overarching NCCCP Activities (July 2010 to June 2012)*

These research subcontracts ended in June 2013. During the reporting period, staff continued to support the research subcontract close-out and internal auditing activities.

- *Eighteen Research Subcontracts to the Community Hospitals (July 2012 to September 2014)*

Eighteen ARRA awards supporting 21 community hospitals were awarded in July 2012 to address the comprehensive and overarching NCCCP activities. In December 2013, NCI requested that the original two-year awards be extended in order to bridge the gap between the end of NCCCP and the official start of the new NCI Community Oncology Research Program (NCORP). As the ARRA resources were exhausted, the research subcontracts were transitioned to appropriated funding for the remainder of the award period. Given the potential for NCCCP sites to successfully compete for NCORP funding, this extension allowed for no lapse in NCI funding. The internal audit process and the official close-out of these subcontracts were completed during the reporting period.

- *Two Additional Research Subcontracts to Support NCCCP Research*

A research subcontract was awarded to the University of North Carolina in June 2013 to conduct a formative evaluation of the NCCCP Clinical Trials Best Practice Matrix tool, to further develop, refine, and evaluate the tool for broader use in NCI community cancer research programs beyond NCCCP. Another research subcontract was awarded to Research Triangle International in November 2013 to analyze the NCCCP American College of Surgeons Commission on Cancer (CoC) Rapid Quality Reporting System (RQRS) data set. The work was built upon the independent comparative evaluation of the pilot project conducted by this organization. The official close-out of these research subcontracts was completed during the reporting period.

Data Collection, Management, and Analysis

Once NCCCP officially ended in September 2014, CMRP staff prepared all documents and procedures related to the closure of the NCCCP database, the private wiki, and the NCCCP public website. This effort included creating a data dictionary, data blueprint, and audit log; housing all program data on the wiki site; and providing NCI with an archive of the database and the database application. CMRP worked closely with NCI to sunset the public website and archive the wiki, as well as transition any remaining responsibilities for these activities to the appropriate NCI representative.

Presentations and Publications

CMRP staff continued to foster publications through the approval and tracking process through December 2014. Through the reporting period, NCI representatives provided status updates to the pending publications. Of special note, NCCCP resulted in the publication of a book by Oxford University Press in July 2015, *Managing Disruptive Change in Healthcare* by Donna O'Brien and Arnold Kaluzny. A CMRP staff member, Ms. Joy Beveridge, was listed as a contributor and chapter co-author.

American Recovery and Reinvestment Act of 2009

CMRP provided extensive program management and administrative support to the NCCCP network, which was expanded in April 2010 to include 30 community hospitals located in 22 states. In July 2012, following a limited competition to receive continued support for an additional two years, the network was reduced to 21 community hospitals in 16 states. During the reporting period, CMRP staff continued to manage and support the subcontract close-out and internal audit activities for the 52 NCCCP subcontracts. Additional information regarding NCCCP can be found in the more detailed section above describing NCCCP activities.

Coordinating Center for Clinical Trials

Support Provided by the Clinical Monitoring Research Program

The Coordinating Center for Clinical Trials (CCCT) was established in 2006. CCCT's overarching goal is to strengthen NCI's clinical trials and translational research enterprises, as well as cooperative endeavors that draw upon the strongest components of clinical research system and scientific infrastructure, and include constant engagement of critical stakeholders.

CCCT guides the implementation of recommendations made by the National Cancer Advisory Board (NCAB) Clinical Trials Working Group (CTWG) and Translational Research Working Group (TRWG). This is achieved through continuing dialogue with NCI leadership and scientific staff, clinicians, researchers, advocates, policymakers, industry, and foundations, in order to enhance the effectiveness of the nation's cancer clinical research enterprise. CCCT oversees implementation of the 22 initiatives recommended by the CTWG in 2005, as well as 15 initiatives recommended by the TRWG in 2007.

In 2008, CCCT made its first request for CMRP to support the NCI Scientific Steering Committees (SSCs). Since then, three additional YTs have been approved to support CCCT. During the reporting period, staff supported three distinct activities: (1) 17 NCI Steering Committees (SCs); (2) Biomarker, Imaging, and

Quality-of-Life Studies Funding Program (BIQSFP); and (3) CCCT Meeting Planning/Travel (MP/T).

Project management was provided at the NCI Shady Grove office, with at least four CMRP staff members detailed to the CCCT office daily. Otherwise, staff worked from the CMRP office at the FNLCR Fort Detrick campus. The clinical project managers maintained consistent and effective communication between CMRP and CCCT program directors and continued to be an integral part of the CCCT team. Currently, the CMRP CCCT support team comprises 8.33 full-time equivalents (FTEs), with the potential to increase to 10.33 FTEs, should programmatic growth occur and needs increase. This represents one additional approved MP/T FTE during FY2015.

NCI Steering Committees

Between 2008 and 2015, the SCs program increased from six SSCs and 140 consulting agreements to the current 17 SSCs and 515 vendor agreements, respectively. CMRP's vendor agreement process, implemented in 2011, continued to have a turnaround time of less than one week from solicitation of the agreement to final award. The structure/process of the SC vendor agreements continued to serve as a model for other Leidos Biomedical Research initiatives and provided rapid response to a number of clinical research enterprise initiatives. In support of the SCs, CMRP staff provided project management support; program analysis; and management of the large vendor agreement effort, which includes quarterly invoicing and payments to the vendors based on SSC attendance.

CMRP continued to maintain the CTWG/CCCT research database, which contains conflict-of-interest and confidentiality disclosure agreement documents, as well as term dates for the 515 SC and Task Force members. Staff also supported weekly meetings, provided progress reports on assigned projects, and designed slide presentations for CCCT program directors.

During the reporting period, CMRP project management staff supported, coordinated, and hosted webinars within the CCCT for NCI task forces and working groups. The clinical project manager continues to be the go-to person for CCCT-sponsored webinars. In addition, CMRP continued to provide updates and maintain the CCCT websites, while maintaining 99.17 percent website 508 compliance, and supported the Clinical Trials Planning Meeting (CTPM) and SC face-to-face meetings.

During FY2015, CMRP provided support to the 515 vendors that were impacted by the Leidos Biomedical Research ERP implementation in June 2014. This included reaching out to each vendor regarding the change in the invoicing process.

During FY2014, NCI redesigned the NCI Cooperative Group model, implementing the National Clinical Trials Network (NCTN) model. During FY2015, this redesign caused a 20 percent increase in SC membership and vendor agreement activity. CMRP effectively managed this additional support without any issues.

During this reporting period, the CMRP clinical project manager designed an Adobe Acrobat fillable version of the NCI Confidentiality Disclosure Form (CDF) and Conflict of Interest (COI) form. In the past, these forms would be sent to NCI SC members and NCI protocol and study reviewers. Respondents would sign them and scan or fax them back to CCCT for verification and paper filling. The fillable forms will allow for both member/reviewer e-signatures, along with CCCT verification e-signatures and e-filling. CCCT began using these forms in July 2015. This procedural modification has resulted in cost savings and has streamlined CDF/COI acquisition and processing, while allowing for e-archiving of the signed forms.

Biomarker, Imaging, and Quality-of-Life Studies Funding Program

CMRP continued to support NCI's Biomarker, Imaging, and Quality-of-Life Studies Funding Program (BIQSFP), facilitating the robust NCI SC evaluations of more than 12 BIQSFP applications. CMRP staff also continued to support 22 active research subcontracts with NCI's National Clinical Trials Network (NCTN) groups and laboratories.

CMRP staff facilitated and supported the March 2015 revision of the BIQSFP announcement, including updating and clarifying the announcement and the requisite revisions on the official BIQSFP website. The main CCCT website, developed by CMRP several years ago, has consistently received over 1,000 page views per month from U.S. and international visitors to the site, with the majority of page views being BIQSFP pages.

The BIQSFP Huddle Log, developed by CMRP and instituted in FY2014, continued with weekly meetings to ensure the monitoring and progress of BIQSFP studies under evaluation.

Meeting Planning/Travel

The Meeting Planning/Travel (MP/T) team began its support to CCCT in April 2013. During FY 2015, the team continued to support CCCT-sponsored meetings, Federal Advisory Committee Act (FACA) meetings, DCTD SPORE meetings, and a Division of Cancer Prevention (DCP)/DCCPS NCORP meeting. CMRP staff successfully planned and facilitated 26 meetings and two webinars; two meetings and one webinar were FACA events. MP/T planning activities are under way for 12 additional meetings through the end of FY2015, with additional meetings anticipated.

The major strength of the MP/T support continued to be that it is based in the CCCT office at the NCI Shady Grove facility, which allows a seamless and robust interface with the CCCT director, team leads, program directors, program analysts, and administrative staff.

The MP/T team's role in the CCCT Integrated Meeting Planning team has grown since the NCI CCCT administrative staff changes in March 2015. This multidisciplinary team, comprising CCCT and CMRP MP/T staff, collaborates on all non-FACA and FACA meetings, holding weekly status updates. The goal of this collaboration between these staffs is to create a seamless process for all non-FACA and FACA meetings. CCCT now relies on the MP/T team to take control of the meeting planning process, starting at the meeting approval stage rather than after.

Notably, during FY2015, the CCCT MP/T team received a 2014 Leidos Biomed Customer Service Achievement Award for their outstanding support to CCCT. In addition, the clinical project manager who represented Leidos Biomedical Research in the Future Link Conference held on May 27, 2015, received an e-mail of appreciation (along with other presenters) from the Science, Technology, Engineering, and Mathematics Coordinator PreK–12, Frederick County Public Schools.

CMRP provided on-site meeting support in Chicago for 50 NCI CCCT/ Cancer Therapy Evaluation Program (CTEP)/DCTD meetings during the 2015 American Society of Clinical Oncology (ASCO) Annual Meeting. These meetings took place over a four-day period and included meetings in four separate rooms from 6:00 a.m. to 9:00 p.m.; more than 18 meetings were held each day.

Center for Global Health

Support Provided by the Clinical Monitoring Research Program

United States–Latin America Cancer Research Network

The United States–Latin America Cancer Research Network (US–LA CRN; the Network) is a partnership between NCI's Center for Global Health (CGH) and participating Latin American countries that was established to develop and implement mutually beneficial cancer research programs in Latin America. The goal of this program has been to increase the capability of these countries to participate and partner in cancer research, including the critical development of clinical trials networks, advanced technology centers, and personnel to deliver state-of-the-art cancer care to patients.

The first project of the US–LA CRN, the *Molecular Profiling of Stage II and III Breast Cancer in Latin American Women Receiving Standard of Care Treatment* (MPBC Study), was designed as an observational pilot study with the main goal of providing information about the distribution of breast cancer subtypes in Latin America while building cancer research capacity at the participating institutions that would enable the conduct of future clinical studies. During the timeframe that CMRP supported the Network, US–LA CRN included eight countries: (1) Mexico, (2) Argentina, (3) Brazil, (4) Chile, (5) Uruguay, (6) Colombia, (7) Peru, and (8) Puerto Rico. Five of these countries were participating in the MPBC Study at sites in Argentina, Brazil, Chile, Mexico (Guadalajara and Sonora), and Uruguay.

Since its inception, the Network has demonstrated applications of capacity and infrastructure building across four core competencies: (1) Biobanking; (2) Bioinformatics, Data Management, and Monitoring; (3) Molecular Biology; and (4) Pathology. CMRP began actively supporting these core competency areas in FY2009, and, as the Network's activities steadily increased, CMRP support expanded to include Epidemiology and Regulatory support, which was pertinent to the scientific and clinical research goal of US–LA CRN. CMRP provided administrative, scientific, technical, operational, and programmatic support to US–LA CRN until December 2014 when support to US–LA CRN was transitioned by NCI to a new entity. This was a result of a change in leadership at CGH and a new direction for the Network and its focus on future high-priority cancer research efforts.

From FY2009 to FY2015, CMRP provided guidance to US–LA CRN partners in meeting the project's scientific objectives through the technical oversight of Network Steering Committees (SCs), including the Basic Research and Advanced Technology Committee, Pathology Committee, Clinical Oncology and Breast Cancer Surgeons Committee, virtual Data Coordinating and Analysis Teams (vDCAT) Committee, Data Monitoring Committee, and Data Sharing and Publications Committee.

CMRP staff also supported the day-to-day functions of the study, collaborating with NCI, Leidos Biomed staff from relevant scientific disciplines, research subcontractors, on-site research staff, and scientific advisers, in order to address queries from the sites and to develop additional guidance documents.

CMRP staff supporting US–LA CRN regularly engaged in capacity-building efforts for sites and investigators by providing training to the Network's personnel on scientific, clinical, regulatory, and administrative research areas through the implementation of the MPBC Study. Specifically, expert regulatory and project management support for the refinement of the study protocol and other clinically relevant documents, and GCP guidance on processes to improve site preparedness was provided.

Additionally, CMRP staff provided direct support for translations into English, Spanish, and Portuguese at meetings and in the production of study documentation; monitored program tasks for progress and submitted reports to Leidos Biomed and CGH management; assisted with planning for new initiatives; interfaced with scientific and technical teams for program development; and prepared technical reports and presentations. CMRP support to the Network ended on March 31, 2015.

During FY2015, the focus of CMRP support to US-LA CRN was dedicated to the implementation and successful finalization of the US–LA CRN Transition

Plan approved by the NCI CGH. This transition plan provided background and status information, next steps, time frames, risks, and mitigation across all relevant MPBC Study subject matter areas, including: biobanking, bioinformatics and data management, epidemiology, molecular biology, pathology, regulatory, business operations/transactions, logistics, committee and communications, and business operations.

The transition plan consisted of three phases. Phase 1 entailed the creation of the US–LA CRN Document Catalogue, which was provided to the NCI CGH. Parts I and II of the catalogue comprised a complete list of documents, including general study documents, biobanking, bioinformatics, data management, study monitoring, epidemiology molecular biology, pathology, regulatory, logistics, business operations, and meeting minutes from annual meetings and various committee meeting. Once assembled, Parts I and II were both placed on an encrypted flash drive and delivered to the NCI CGH by a CMRP courier; part I of the catalogue arrived on October 1, 2014 and part II arrived on December 31, 2014.

Phase 2 of the plan, which ended on December 31, 2014, featured transition planning meetings with NCI CGH and the new entity; completion of Dako orders to all sites (with the exception of Guadalajara, Mexico); continued query support to the US–LA CRN; delivery of part II of the catalogue (mentioned above); dissemination of the latest protocol amendment (v3.4.2) to the Network in English, Spanish, and Portuguese; maintenance and support of databases; and the transfer of all OpenClinica and Biological Specimen Inventory (BSI) databases to the NCI Center for Biomedical Informatics and Information Technology (CBIIT). Notably, Phase 2 included the successful completion of transitioning the bioinformatics infrastructure and service model without disruption of service, because a suitable hosting environment had not been identified, and the relatively short period of time in which these activities were to occur further complicated the efforts. CMRP IT staff worked closely with the NCI CBIIT in attempting to mitigate risks and in facilitating the development of a bioinformatics infrastructure transition plan that was ultimately accepted by the NCI CGH. Close-out activities included the transfer of final clones to NCI CBIIT by utilizing an encrypted transfer protocol with verification of materials post-transit, using commercial cryptographic hash functions; review of final research subcontract invoicing; evaluation and disposition of computer equipment; and composition of document and messaging catalogues as reference materials.

Phase 3, which ended on March 31, 2015, consisted of research subcontract progress and final report reviews, invoice processing, return of equipment, and close-out of research subcontracts and consulting agreements. During this time frame, CMRP held numerous transition meetings, submitted all deliverables on time, and submitted a summary of NCI CGH-directed changes to the transition plan via the YT system.

Center for Global Health Meeting and Conference Support

Scientific and clinical research programs, training programs, and technology and capacity-building programs are among the integrative initiatives and programs that are helping the CGH to achieve its goals. The Scientific and Clinical Research Program is designed to allow investigators to conduct high-quality clinical cancer research that provides important information on treatment response and related pharmacogenomic pathways. The Training Program ensures that the cancer research networks are sustainable by developing specific training opportunities to cultivate a robust pipeline of basic and clinical investigators. The Technology and Capacity-Building Program provides an overarching framework for conducting high-quality cancer research and for adapting advanced technologies and methodologies and managing biospecimens, informatics, and data, with the intention of advancing research capacity, and for developing sustainable research infrastructures.

The role of CMRP within this project is to help the CGH realize its goals through the planning and coordination of meeting and travel activities related to domestic and international meetings, conferences, and training for both government and non-government attendees collaborating on many initiatives and programs. Services include: (1) comprehensive logistics support (e.g., vendor negotiations, lodging, hotel, and/or meeting center coordination, managing reimbursements, arranging transportation, coordinating attendee travel); (2) meeting and travel budget preparation and monitoring; and (3) establishing formal processes and procedures to streamline planning while ensuring all meeting and travel policies and directives are followed.

During the reporting period, CMRP staff was instrumental in the planning and coordination of 16 major meetings in support of NCI and the CGH directors. Domestic meetings included: (1) a CGH Retreat in Gaithersburg, MD; (2) the Symposium on Global Cancer Research (CGH/CUGH) in Boston, MA; and (3) the workshop titled India Visit to NCI's Division of Cancer Epidemiology and Genetics, in Rockville, MD. International meetings included: (1) the Program Planning and Implementation Research Meeting in Buenos Aires, Argentina; (2) the US–LA CRN Annual Meeting in Santiago, Chile; (3) the UICC – World Cancer Congress – Tobacco Control Workshop in Melbourne, Australia; (4) the Pacific Leadership Forum in Melbourne, Australia; (5) the Capacity Building on Oncology Workshop held in Muscat, Oman; (6) the Women's Cancer Program Summit in Lima, Peru; (7) the International Cancer Control Research Workshop in Ankara, Turkey; (8) the Indonesia Tobacco Control Research Workshop in Yogyakarta, Indonesia; (9) the Caribbean Leadership Forum in Bridgetown, Barbados; (10) HPV-related disease in HIV-infected Individuals: Committee for Scientific Research Priorities in Sao Paulo, Brazil; (11) Improving Chronic

Disease in the Caribbean through Evidence-based Behavioral and Social Interventions in Bridgetown, Barbados; (12) the APEC/APCC Cervical Cancer II meeting in Manila, Philippines; (13) the Latin America Leadership Forum in Cancun, Mexico; and (14) the NCI/CGH – USAID Joint Master Course on Implementation Science – Principles and Practices in Bangkok, Thailand.

The Leadership Forums (Pacific, Caribbean, and Latin America) required significant logistical oversight to ensure their success. These forums are very structured and require months of planning individual meetings, and large-volume, in-house printing to be included in large meeting packets for participants and faculty. In addition to hotel sourcing and subcontracting for the forums, logistical support was provided, including website construction and liaison activities between the hotel and CGH travel contractors to ensure proper room block management. Off-site logistical support had to be provided from Frederick, MD, by liaising with the hotel in Barbados since approval for on-site logistical support was not received. This allowed the client to focus completely on the content of the meeting without any interruptions regarding conference space logistics.

CGH has also engaged CMRP Meeting and Conference staff to assist with non-employee travels associated with site visits and non-HHS–sponsored meetings and events. In FY2015, CMRP provided travel coordination for over 35 meetings, resulting in over 78, mostly international, travel packages. Travel support was often full support, including coordination of flights, hotels, ground transportation, visa fees, and/or meal and incidental expenses. At other times, support was limited to one or more of these components.

Given the level of support required to support the increasing portfolio of meetings and travelers, staff increased in July from two (a senior program coordinator and a conference event planner) to three full-time employees (an additional conference event planner). Staff continues to further educate CGH key personnel and travelers to provide very clear guidance, via standard policies, on the required domestic and foreign travel policies and guidelines. This ongoing initiative seeks to manage expectations of all stakeholders for the comprehensive CGH-sponsored meeting and travel portfolio.

Contracting officer approval (COA) requests and HHS approvals are oftentimes received within 48–72 hours of when travel is to commence, presenting a challenge for CMRP staff to meet client requests on short timelines, and also causing stress to the supported travelers. CMRP staff has been successful in liaising with travelers to help them understand the policies and reduce confusion.

Given that our team provides travel support to individuals of low- to-middle-income countries (LMICs), on behalf of NCI CGH, CMRP continues to explore options that minimize the financial burden on the travelers. During FY2015, CMRP staff worked with the accounting, auditing, and travel department to provide an advance for non-employee travelers from a LMIC who were visiting NCI for 12 days, as those travel expenses would pose a significant financial burden on the travelers.

Lessons learned by this team are consistently shared with the CCCT support team and the Leidos Biomedical Research Travel Office. In FY2015, Leidos Biomedical Research presented an operational goal to address the ongoing challenges related to meeting and travel planning/coordination, given cumbersome domestic and foreign meeting and travel guidelines. The successes demonstrated by this team are surely translated across the Leidos Biomedical Research teams and are also shared with NIAID staff members who perform similar tasks for their customers.

Center for Global Health Research Subcontract Support

Pilot Collaborations with LMICs in Global Cancer Research or Global Health Research at NCI-Designated Cancer Centers:

Cancer is a leading cause of death worldwide, with a disproportionate burden occurring in LMICs. It is estimated that by 2020, new cancer cases will reach more than 16 million globally, and the majority of this burden will be borne by residents of LMICs. There is a clear need for research that draws from diverse regions of the world to better address the global cancer burden. Evidence from this research will help populations not only in LMICs, but also in the U.S.

NCI allocated $2.94 million for this initiative for a performance period of one year. The funds were awarded to NCI-designated cancer centers to support work performed by the centers and their collaborating foreign partners, and managed by Leidos Biomedical Research as research subcontract awards. The purpose of this effort is to stimulate cancer research pilot programs in order to expand the reach of cancer centers in international settings. This initiative presents a unique opportunity to strategically develop partnerships between regional institutions and U.S. cancer centers. These partnerships can leverage the scientific expertise and leadership in cancer control, prevention, or treatment to address new research directions as opportunities.

The scope of these projects is to support the pilot collaborations with LMICs in global cancer research or global health research at NCI-designated cancer center initiatives, and includes a range of clinical research projects, training opportunities, advanced technologies, the development of clinical research networks, and other focus areas that support the development of cancer research capacity in selected countries in Africa (Ghana, Nigeria, Tanzania, Malawi, Zambia, Uganda, and Kenya), Central America (El Salvador and Honduras), South America (Chile and Brazil) and Asia (two projects in India). These projects are helping CGH to achieve its goals of fostering scientific and clinical research collaborations, expanding opportunities for training to cultivate a robust pipeline of basic and clinical investigators, and expanding technology and capacity-

building programs. These initiatives will help investigators conduct high-quality research by adapting advanced technologies and methodologies for informatics, data management, and biospecimen management; developing sustainable research infrastructures; providing important information on treatment response; and ensuring that developing cancer research networks are sustainable. It is anticipated that the new findings or discoveries from this collaboration could improve cancer control, prevention, and treatment strategies both in the U.S. and abroad.

During FY2015, CMRP provided programmatic and research subcontracting support to the NCI CGH to provide continuity of support to the fifteen research subcontracts in LMICs between the NCI-designated cancer centers and foreign institutions to implement these mutually beneficial global cancer research programs:

1. A Low-Cost Optical Imaging Tool for Cervical Cancer Prevention: The University of Texas MD Anderson Cancer Center; Barretos Cancer Hospital (Brazil)
2. Cloud-Based Collaboration for Radiotherapy Clinical Trials, Research, and Training: Virginia Commonwealth University Massey Cancer Center; Tata Memorial Center (India)
3. Tobacco-Free Teachers: Pilot Study to Assess Program Adoption in Schools in India: Dana-Farber Cancer Institute; Healis Sekhseria School of Public Health (India)
4. Vincristine Optimization in Kenyan Children with Cancer: Melvin and Bren Simon Cancer Center, Indiana University; Moi Teaching Hospital (Kenya)
5. Cancer Bioinformatics Network in the Central America LMICs: Gastric Cancer Focus: Vanderbilt-Ingram Cancer Center; Ministry of Health, El Salvador; Ministry of Health, Honduras
6. HIV Infection, Viral Hepatitis, and Hepatocellular Carcinoma in Uganda: Johns Hopkins Sidney Kimmel Comprehensive Cancer Center; Makerere University (Uganda)
7. Expanding a Team of Clinical Investigators in Nigeria with a Prospective Colorectal Cancer Biobank and Database: Memorial Sloan-Kettering Cancer Center; Obafemi University (Nigeria)
8. A Study of Etiology of Esophageal Cancer in Tanzania (SEEC-Tanzania): UCSF Helen Diller Family Comprehensive Cancer Center; Muhimbili University (Tanzania)
9. Tanzanian Research Training Program in HIV-Related Malignancies: Dartmouth- Hitchcock Norris Cotton Cancer Center; Ocean Road Cancer Institute and Muhimbili University
10. African Pain Policy Fellowship; a Pilot Regional Collaboration to Improve Opioid Availability for the Treatment of Cancer Pain: Carbone Cancer Center, University of Wisconsin; African Palliative Care Association (Uganda)
11. St. Jude Comprehensive Cancer Center–Pequeno Principe Research Institute Twinning Program: St. Jude Children's Research Hospital Comprehensive Cancer Center; Pele Pequeno Principe Research Institute (Brazil)
12. Building Cooperation and Capacity for Cervical Cancer Research between LCCC, Zambia, and Malawi: University of North Carolina Lineberger Comprehensive Cancer Center (LCCC); Center for Infectious Disease Research (CIDRZ-Zambia); Kamuzu Central Hospital (Malawi)
13. Expanding Capacity for Infection-Related Cancer Research by Examining the Contribution of Viral Genomic Diversity to the Clinical Manifestations of Cancer in Uganda: Fred Hutchinson University of Washington Cancer Consortium; Uganda Cancer Institute
14. Initiative to Improve Cancer Care in Ghana and Nigeria: Roswell Park Cancer Institute; Noguchi Memorial Institute (Ghana); Lagos State University (Nigeria)
15. Training Chilean Bioinformatics Researchers in the Cancer Genomics Field: University of California, San Diego Moores Cancer Center; Centro de Investigacion y Tratamiento del Cancer, Universidad de Chile

CMRP's clinical project managers and administrative assistants provide expert support to CGH staff in all matters related to the administration, execution, and implementation of research subcontract agreements and modifications with the NCI-designated cancer centers and their affiliation with the foreign institutions.

An important role of CMRP in the LMIC project is to assist CGH with financial oversight of the new projects and in obtaining the necessary approvals for the new projects' international workshops, conferences, and training sessions. The services include: (1) assisting sites with compiling the required information to complete the Request for Conference, and with obtaining other approvals in order to ensure compliance with the HHS Efficient Spending Policy and federal travel regulations; (2) preparing and monitoring operating budgets; and (3) establishing formal processes and procedures to streamline the planning process while ensuring all policies and directives are followed. Through the biannual calls with the LMIC subcontractors, the clinical project managers, administrative assistant, and Research Contracts staff and secretaries worked closely with CGH project leaders to maintain communication channels with and provide guidance to the subcontractors' key project personnel. The clinical project managers assisted CGH with developing criteria for the end-of-project scientific and technical evaluation. CMRP ensures regulatory compliance in the area of human subjects protection by documenting current IRB approvals and active Federalwide Assurances.

Prior to the end of FY2015, all work was completed, and final reports and invoices were reviewed and approved for payment.

Global Cancer Resource Project

The CMRP clinical project manager provides ongoing project management support through technical review of deliverables and budget monitoring, as well as support to biweekly meetings with Leidos Biomedical Research, CGH, and the Global Oncology (GO!) initiative teams. The CMRP clinical project manager provided technical expertise to manage the initial research subcontract (May 2014 through May 2015) and the follow-on agreement for additional deliverables and milestones for a one-year continuation through May 2016. Starting in May 2015, data management and curation was the major priority at this phase of the project. During this reporting period, CMRP hired a data analyst to support data management and quality, and to provide data coordination services between the CGH and the GO! project team.

GO! was successful in supporting the official launch of the Global Cancer Project Map (GCPM) on March 25, 2015 at the 3rd Annual Symposium on Global Cancer Research in Boston, MA. The launch of the GCPM provided equal access to cancer research and support projects worldwide. The GCPM is a first-of-its-kind online resource and provides a searchable, interactive database of information about, and access to experts conducting, public health oncology programs. At the time of the launch, the GCPM included information on more than 700 projects that span six continents. The tool will be further developed to enable the ability to visualize portfolios of most NCI-designated cancer centers' self-reported information and the portfolios of international partners, including the American Society of Clinical Oncology and the Union for International Cancer Control. Projects range from cancer prevention and screening to capacity building, training, clinical care, and palliative care. Examples include a project developing methods to improve diagnostic accuracy of mammograms for breast cancer in Turkey, a study evaluating the effects of vitamin E and selenium supplementation on prevention of arsenic-induced skin cancer in Bangladesh, and a search for biomarkers that would create an early screening test for gastric cancer in Mexico.

Global Cancer Project Map

New Initiative

As CGH continues to develop partnerships and programs across the world, there is a need to enhance communication about projects between research programs and organizations. Through the collaboration with the GO! initiative, CGH made significant progress in bringing the global oncology community together by developing a web-based project map for global oncology projects—an innovative tool to align the goals of the government, the nonprofit sector, industry, academia, and the community. The GCPM will enable CGH to better understand the international cancer research and cancer control landscape and will have great potential to lead to synthesis of the geographic and topical information for NCI and its partners' international oncology projects. It will serve as a collaboration tool for all stakeholders, including government, the non-profit sector, industry, academia, and the community. Additional information on the GCPM can be found in the section above.

Center for Biomedical Informatics and Information Technology

Support Provided by the Data Science and Information Technology Program

Strategic Initiatives for High-Performance Computing

In late 2014, efforts commenced to work collaboratively across the NCI Center for Bioinformatics and Information Technology (CBIIT) and Frederick National Laboratory for Cancer Research (FNLCR) to develop a strategy for expanded use of high-performance computing (HPC) to support cancer research. Future directions for high-performance computing became evident in response to the February 2015 NIH request for applications requiring exascale computing (exascale computing systems deliver 10^{18} operations per second, 100 times more powerful than today's largest systems), in which opportunities for high-end computing were identified in several areas, including mapping genetic susceptibility, integrated cancer data analysis, modeling intracellular signaling, characterizing biophysical structures from imaging and instrumental data, and in silico characterization of potential cancer drugs. Efforts of the initiative included exploring opportunities for collaboration with other national laboratories and providing guidance on infrastructure requirements needed to support expanded use of high-performance computing in cancer research. Early efforts were also undertaken to pilot the successful use of HPC resources available at the Advanced Technology Research Facility (ATRF) in Frederick to support instruments located in Bethesda as well as to expand the use of Globus Connect technologies to facilitate the movement of data among sites within and beyond the NIH.

The Clinical Trials Reporting Program

The Clinical Trials Reporting Program (CTRP) was established in response to a recommendation from the NCI Clinical Trials Working Group to the National Cancer Advisory Board and was reiterated by the Institute of Medicine's report titled "A National Cancer Clinical Trials System for the 21st Century: Reinvigorating the NCI Cooperative Group Program." CTRP is a comprehensive database of regularly updated information, including accrual, on all NCI-supported clinical trials. This database of the entire NCI portfolio helps identify gaps in clinical

research and duplicative studies to facilitate effective clinical trial prioritization and enhances patient accrual to trials by making physicians aware of relevant opportunities for participation in clinical trials (CTRP, 2011).

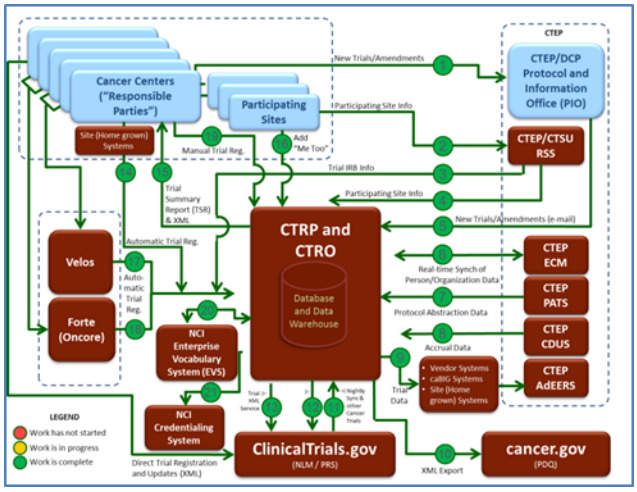
Leidos Biomedical Research has been working on the development of this important system for several years in a phased approach. In the current contract year (CY; 2015), CTRP release 4.2.1 was deployed to production. This version contains a number of enhancements to the suite, including the following:

- New and improved interface to the National Cancer Institute's "Find a Clinical Trial" resource.
  - CTRP is now the source of all NCI-sponsored/-managed trial information and also provides information regarding pharma trials received from Clinicaltrials.gov.
- Improved trial status and participating site status management with the ability to update historical status information, including status dates.
- Made grant field mandatory in the CTRP system.
- Integration Information for Management, Planning, Analysis, and Coordination (IMPAC II) grants management system.
  - Facilitated the inclusion of the correct grant data in order to store the appropriate grant number and title.

During CY2015, Data Table 4 reports were generated for clinical trial accrual reporting for the cancer centers. Generation of the report includes upload of accruals in quarterly batches for all NCI-sponsored/-managed trials.

The security of the application was improved by using the Secure hash algorithm 2 (SHA2) authentication mechanism.

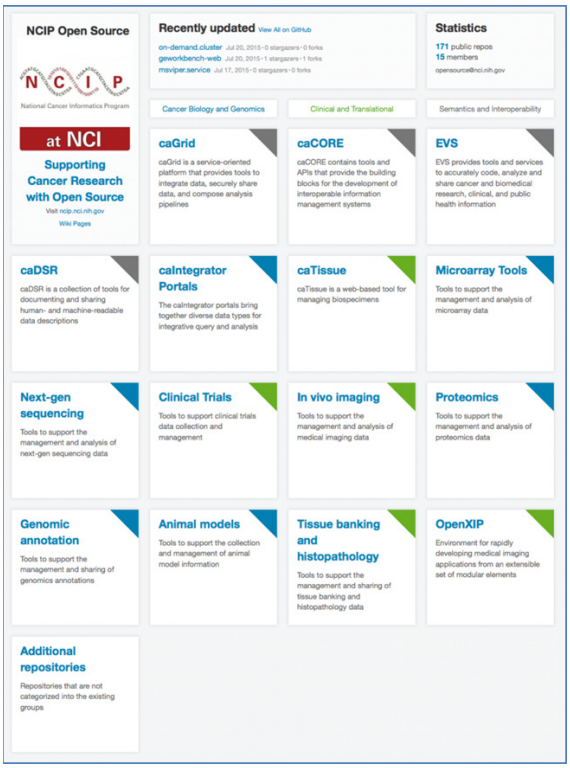
RESTful service interfaces were built into CTRP to facilitate faster development of system interactions with Clinical Trial Management Systems CTMS \s at cancer centers.



Road Map for CTRP 4.2 as of CY2015

Open Source Development Initiative

The Open Source Development project was proposed to the NCI by the Community Code Contribution Working Group as a result of the group's original charter of defining guidelines for integrating community code contribution into the main distribution for the National Cancer Informatics Program (NCIP) software products. Leidos Biomedical Research planned and executed the Open Source Development Initiative, which included the migration of all NCIP software products to GitHub. During CY2015, the Leidos Biomedical Research team completed the migration of over 170 repositories from NCI's Subversion (SVN) system to GitHub. All repositories are now fully available to the open-source community. Additionally, over 60 repositories have been created in the NCI CBIIT channel to support active development at CBIIT.



The National Cancer Investment Program's GitHub Channel

The Clinical Trials Reporting Office

The Clinical Trials Reporting Office (CTRO) is a team of scientific data analysts and curators charged with the arduous task of trials information validation processed by the CTRP system. This team is composed of Leidos Biomedical Research resources and subcontracted resources, and constitutes a critical resource in support of the CTRP operations. The CTRO team accomplished the following critical tasks during CY2015:

- Participated in various CTRP data cleanup activities, including obtaining accurate trial status histories for the Division of Cancer Prevention (DCP), Cancer Therapy Evaluation Program (CTEP), Center for Cancer Research (CCR), and NCI Designated Cancer Centers.
- Completed the Registration and Abstraction of CCR trials from backlog.
- Began to collaborate with the CCR team to obtain participant accruals for their trials in CTRP.
- Completed a thorough review of the NCI Thesaurus (NCIt) for transition from Physicians Data Query (PDQ) to NCIt as the CTRP terminology source for the CTRP 4.1 release.
- Currently collaborating with the Office of Communications and Public Liaison (OCPL) to address Cancer.gov-related user inquiries, as CTRP became the source of Cancer.gov data on June 15, 2015.

The CTRO received over 1,750 NCI-supported clinical trial submissions. With the submission of these trials, validation is performed, which is an in-depth review process to verify that the trial meets all of the CTRP submission requirements. Of these submissions, 1,571 were accepted; 1,506 were abstracted, in a process that requires both protocol and scientific data to be captured accurately for the trial submission; and 1,950 Trial Summary Reports (TSRs) were sent to the NCI-designated cancer centers. In addition, over 3,400 trial amendments were received by the CTRO, with more than 4,300 amendment TSRs sent to the NCI-designated cancer centers. Nearly 19,000 trials with participant accrual information were submitted to CTRP.

National Cancer Informatics Program

The National Cancer Informatics Program (NCIP) leverages the investment made in, and lessons learned from, the retired cancer Biomedical Informatics Grid (caBIG) program. A number of successful caBIG projects have been integrated into the NCIP, and other new initiatives aligned with the NCI mission have been initiated. The section below describes the accomplishments of the main projects under the NCIP for CY2015.

NCI Molecular Analysis for Therapy Choice (NCI-MATCH). The Molecular Analysis for Therapy Choice (MATCH) is a project sponsored by NCI to develop a system for molecularly targeted therapy for patients with defined molecular features with individual tumor types.

The goals of the project include the following:

- Identify mutations/amplifications/translocations in patient tumor samples to use as eligibility determination.
- Assign patients to relevant agents/regimens.
- Perform tumor biopsies and sequencing at progression to illuminate resistance mechanisms.
  - De-identify samples submitted to central labs.
- Provide umbrella protocol for multiple, single-arm Phase II trials.
  - Match each molecular subgroup to a targeted agent.
- Use CTEP-Investigational New Drug for protocol template.
  - Arms could be added or deleted without affecting other arms.
  - Hold device discussion with the Center for Devices and Radiological Health (CDRH).
- Focus on single agents (commercial or experimental) initially.
  - Combination will be considered for targets that have validated combination targeted therapy.
  - Need minimum dose/safety established in Phase I trials.
- Submit study to the NCI Central Institutional Review Board (CIRB) for review.

Eligibility

- Solid tumors and lymphomas that have progressed following at least one line of standard therapy.
- Exclude histologies from a given arm of a clinical trial if they are already approved by the FDA for that indication or if the lack of efficacy has been documented.
- The tumor is accessible for biopsy and the patient is willing to undergo biopsy.
- Patient is at least 18 years of age.
- Eastern Cooperative Oncology Group (ECOG) performance status is 0–2.
- Organ function is adequate.

Study Participation

- ECOG-ACRIN (Eastern Cooperative Oncology Group/American College of Radiology Imaging Network) to lead with full cooperation of the Translational Research Advisory Committee NCI Network (NCTN).
- National access through the Cancer Trials Support Unit (CTSU).

The informatics portion of the NCI MATCH trial is designated as NCI-MATCHBox. NCI-MATCHBox is essentially an integration of several external systems at partner organizations coupled with internal systems to house and process both genomic data and scientific business rules that support the automatic assignment of patients to the different study arms of a clinical trial, based on a strategy that relies on genetic defects.

The NCI-MATCHBox is scheduled to go live on July 24, 2015. A team of software engineers, quality assurance personnel, and a technical manager have worked diligently to ensure the system meets the workflow requirements and properly assigns patients to treatment arms based on their genomic data. System design

documentation has been developed in Visual Paradigm and is updated when changes to the MATCH workflow require revisions. These changes continue to be reviewed with the CBIIT government sponsors.

The system design consists of a centralized system for genomic data analysis and storage coupled with a RESTful messaging framework to allow the relevant clinical and pathology data to remain stored at their external source organizations—ECOG-ACRIN and the University of Texas, MD Anderson Cancer Center, respectively—thereby reducing data redundancy and risk. Because the messaging framework crosses several external networks, initial development and test environments have been established with Amazon Web Services (AWS) because of limitations with the current CBIIT technology catalog and firewall policies. Using an external approach first gives the technical team the flexibility to define the baseline for firewall and server proxy settings in advance before determining whether security waivers will be needed within the NCI firewall. The message framework interacts with an open-source rules engine and repository, which house the business rules to define the criteria for the assignation of patients to treatment arms based on genomic and clinical information. Matchbox further interacts with the Life Technologies Ion Reporter Server system, which processes the genomic data coming in through Ion Torrent suite software at independent sequencing laboratories and creates an annotated list of genetic variants found in each tumor sample. MATCHbox will also provide a series of reports to be defined that will provide stakeholders with the appropriate information based on their system-defined roles.

As of July 20, 2015, NCI-MATCHbox is being used for fit-for-purpose testing, internal training, and testing of trial assignment. All indications are that the system is performing as desired. However, because of the adaptive nature of the trial, testing will continue throughout the life cycle of the trial to ensure continued successful operation.

Clinical and Translational Imaging Informatics Program. The goal of the Clinical and Translational Imaging Informatics Program (CTIIP) is to establish an informatics infrastructure that demonstrates the benefit and feasibility of data interoperability across the three domains: genomics, diagnostic imaging, and digital pathology. This project is divided into several initiatives, which are described below.

- ***Digital Pathology and Integrated Query System:*** This subproject aims to leverage several open-source and previously NCI-funded activities to provide an open-source, digital pathology image server that can host and serve digital pathology images for any of the major vendors without recoding, which often introduces additional compression artifacts. This has been accomplished by incorporating the OpenSlide library to directly read most of the current whole-slide image formats.

  Image annotation is an important aspect of image interpretation and analysis, providing additional metadata and information for use in querying and downstream analysis. The development of a proposal to standardize annotations and markups for pathology images and to harmonize them with the existing standard for annotation of radiology images (annotation and image markup [AIM] language) is part of this subproject. Furthermore, caMicroscope is being expanded to support markup and annotation tools for whole-slide images and to include basic image analysis algorithms utilizing the proposed standard.

  This subproject will conclude with the development of a system that queries across pathology data, radiology data, markup, and annotation of each of these image types, along with genomic data. The system will then link this data to patient (human or animal) and outcome data.
- ***CTIIP Support for DICOM WG 30:*** One component of CTIIP is the Digital Imaging and Communications in Medicine (DICOM) Working Group 30 (WG 30). This group was created to address the lack of standards in the preclinical small-animal space. DICOM is the de facto standard for imaging markup and sharing, and extending this standard will allow for the sharing and use of small-animal research data between preclinical studies and across clinical and translational domains. WG 30 has drafted DICOM Supplement 187 (Preclinical Small-Animal Imaging Acquisition Context) and several DICOM correction proposals.
- ***Co-clinical and Animal Model Data:*** The co-clinical/animal model data subproject provides animal model and co-clinical trial data to the integrative query system and for use in the pilot challenges.
- ***Pilot Challenges:*** This subproject develops a challenge management system that links to radiology and pathology images viewers. Each of the viewers has markup, annotation, and visualization features. Pilot challenges featuring clinical, preclinical, and digital pathology imaging, which will attempt to establish correlations between genomic features and imaging data, will be executed.

Scientific Business Applications Support

Business applications support includes development and operation of a suite of software applications supporting a range of NCI business processes. Software development this year focused on enhancements to a number of existing applications. The web application used by the Office of Advocacy Relations to recruit and manage advocates from the community received the first phase of a major update driven by the evolution of the office's business processes. Other application updates included the information collection request application for the Office of Management Policy and Compliance, annual updates to the Health Communications Internship Program application website, and updates to NCI's Emergency Tier Designation and Telework applications for the Office of Workforce Planning and Development.

These business applications include the government-furnished equipment (GFE) tracking system and NCI central receiving waiver application. In addition, the team staffed and managed a help desk and provided general application support.

The Scientific Management Support Team

Scientific Management includes development and operation of the suite of software applications supporting NCI's extramural grants community. These applications, known as IMPACT II Extensions (I2E), provide process automation and workflow management for selecting and approving grant applications for funding, as well as for managing processes related to processing grant awards for these applications. All $3 billion of NCI annual grants are managed through the I2E Suite of tools.

There were several major development accomplishments during CY2015. All of the grants management system and older technology were migrated from the old data center to the new data center at NCI headquarters, Shady Grove. Additionally, significant upgrades were made to the Grant Portfolio Management and Tracking System (GPMATS) and the Program Funding Request (PFR) applications to handle funding plans. One specific major accomplishment was the development of a form-building application that will allow dynamic content creation for advanced grant application forms.

Medidata Rave/Cancer Adverse Events Reporting System

The Cancer Adverse Events Reporting System (caAERS) is used to manage the collection and reporting of adverse event data obtained during clinical trials. It evaluates adverse event data input according to a set of CTEP-generated business rules and provides a recommendation for expedited reporting based on those rules. It manages the workflow for reporting by producing e-mail notifications until the indicated report is successfully submitted.

caAERS has been adapted to integrate through the CTEP OPEN system for patient registration to Medidata's Rave Electronic Data Capture System (EDC) used for data entry, and passed on to the Adverse Event Expedited Reporting System (AdEERS) back-end system (ABS), a legacy system that manages reporting to the FDA to create a seamless environment for serious adverse event reporting. In December 2014, a production release candidate was created and hosted in an AWS FedRamp-compliant cloud environment for the initial phase of a pilot study conducted by The Alliance for Clinical Trials in Oncology. The system and the subsequently produced data have been released to CTSU, which will host the system during the next phase of the pilot.

Center for Strategic Scientific Initiatives

The mission of the Center for Strategic Scientific Initiatives (CSSI) is to create and uniquely implement exploratory programs focused on developing and integrating advanced technologies, transdisciplinary approaches, infrastructures, and standards to accelerate the creation of publicly available, broadly accessible multidimensional data, knowledge, and tools to empower the entire cancer research community for patient benefits.

Office of the Director

Support Provided by the Data Science and Information Technology Program

The major project completed this year for the CSSI was a joint effort between the CSSI, the Division of Cancer Biology Office of Physical Sciences–Oncology, and the Division of Cancer Treatment and Diagnosis Biorepository and Biospecimen Research Branch to evaluate the use of a high-content screening system to provide a rich data set for evaluating the effect of pre-analytical variables on the detection, enumeration, and characterization of circulating tumors cells (CTCs) in blood collected from breast cancer patients. The project investigated four blood collection tube types and used the best performing tube to analyze the effect of time to assay on CTC identification. The high-content assay was compared to an FDA-cleared commercial assay, Cell Search™, used for the detection of CTCs in blood. These data were made available to the Physical Sciences Oncology Network Data Coordinating Center and will be made publically available to the cancer research community at the end of an embargo period.

Support Provided by the Clinical Research Directorate

Thrombosis in Cancer Patients

The Thrombosis in Cancer Research Project (YT 14-107NS) is a collaborative effort between the National Cancer Institute (NCI), the Center for Strategic Scientific Initiatives (CSSI), and the National Heart, Lung, and Blood Institute (NHLBI) Division of Blood Disorders and Resources (DBDR) to assess issues relating to thrombosis in cancer patients. Since the project kickoff in FY2015, BRG has provided scientific, technical, operational, and project management support to the project.

As is well known, expression and detection of markers in biospecimens are known to be significantly affected by pre-analytical factors introduced during the process of biospecimen procurement, handling, and storage. To solicit input from the research community and identify the unmet needs in the field of understanding the impact of pre-analytical variables on biomarkers of thrombosis in cancer patients, a request for information (RFI) was

issued in December 2015. RFI responses highlighted the most important cancer types, relevant patient populations, lists of markers and types of assays, important patient-associated data elements, and pre-analytical factors to be studied.

Having completed all stakeholders' reviews of RFI responses, BRG is now leading the efforts to work with CSSI, NHLBI, and the Biorepositories and Biospecimen Research Branch to develop a detailed research plan focusing on systematically investigating the impact of specific pre-analytical variables on the measurement of specific markers of thrombosis in defined cancer patient populations.

Office of Cancer Nanotechnology Research

Support Provided by the Data Science and Information Technology Program

YT 14-115–Nanoinformatics. The Advanced Biomedical Computing Center (ABCC) supports the NCI Office of Cancer Nanotechnology Research by developing and deploying software to support and enhance the Nanomaterial Registry. The work includes: (1) facilitating data entry to the Nanomaterial Registry by the generation of a simple, template-based, customizable interface; (2) improving data acquisition and curation by implementing a data-gathering module; (3) implementing a client-based display module for multiparametric analysis (2D); (4) implementing a similarity analysis tool based on data correlation analysis; (5) implementing a 3D modeling tool for the generation of 3D (molecular) scaffolds; (6) exploring new approaches for the visualization of complex data sets.

Initial work has focused mainly on two areas:

- Data mining: This includes data requirements (i.e., selection of data sources and definition of the target information); state-of-the-art analysis; scenario description (i.e., how a hypothetical user will interact with the system and which kind of data could be relevant to different types of user); design of the tools (using model subsets and descriptors), and definition and implementation of a stepwise, multilayered, flexible, and adapted technical architecture in response to the information challenges in the nanomedical domain.
- Enhanced analysis and visualization: Prototype software and workflows have been explored to enhance current data query tools for nanoparticle properties and data analysis. New visualization tools utilize open-source solutions, such as Upset, for interacting with the data. Visualizations (2D and eventually 3D) are being developed and deployed that can be used to convey information as an immersive data set and/or an annotated movie. This prototype will aid in the understanding of how the structure and properties of nanoparticles determine their biological activity and will help identify gaps in structural data as well as potential areas of future development.

Support Provided by the Cancer Research Technology Program

Nanotechnology Characterization Laboratory

The Nanotechnology Characterization Laboratory (NCL) continues to advance the field of nanomedicine by providing its preclinical testing and evaluation program, developing novel methods to better understand the growing complexity of nanomedicine formulations, and offering nanotech-based formulation services for promising drugs that have faltered using traditional formulation strategies.

NCL's Assay Cascade testing program continues to remain in high demand. This fiscal year, the NCL received 30 applications for consideration into the unique, comprehensive nanomedicine evaluation program. Twenty different collaborations were undertaken this year, and a total of 33 formulations were characterized.

The NCL has recently launched a new initiative aimed at increasing the use of nanomedicine delivery systems in drug development. As part of this initiative, the NCL now has two nascent cCRADA collaborations with major pharmaceutical companies to develop improved cancer therapies using nanotechnology-based strategies. In December, NCL's first cCRADA was finalized with Astra Zeneca, and in July, a second cCRADA was executed with Onxy Pharmaceuticals, Inc., a subsidiary of Amgen, Inc. Both companies reached out to leverage NCL's expertise in nanoformulation strategies and characterization. NCL is working to develop nanotechnology-based delivery approaches for anticancer drugs for each company. This work builds on NCL's previous work for USAMRIID creating nanomedicines from several botulinum toxin inhibitors.

Another part of NCL's charter is to continually improve methods for evaluating nanoparticle characteristics, and in vitro and in vivo behaviors. Numerous studies have shown that surface properties of a nanoformulation directly influence and dictate its biological performance. However, quantitative techniques to characterize surface properties have been slow to evolve. This year, the NCL published a manuscript that describes two techniques for quantitation of poly(ethylene glycol) (PEG), the most common surface modifier in nanomedicines, using reversed-phase high-performance liquid chromatography (RP-HPLC) coupled to a charge aerosol detector. Furthermore, the protocol allows for the differentiation of total vs. nanoparticle-bound vs. free, unbound PEG.

NCL scientists also developed a unique method to evaluate drug release, and to differentiate and quantitate the various drug fractions in plasma samples (nanoparticle encapsulated, free, protein associated, and free, unbound drug). The distinction between these drug fractions is critical because the free, unbound fraction is responsible

for biological efficacy. However, most techniques only provide a measure of the total drug fraction. This method has generated interest from industry and regulators, and is currently being written up for publication. The NCL is in talks with the FDA, which has expressed interest in funding further testing and development of the method as a tool for evaluating bioequivalence of complex drug products.

As nanomedicine is maturing, demands for NCL-like services are growing at a rapid pace. The European Union has recognized the importance and value of such a facility, and has engaged the NCL to assist with the planning of a European Union (EU)–NCL. The European Commission announced the funding approval for this venture in January 2015. This new EU-NCL will mirror current NCL testing protocols and standards of operation. The NCL has signed on to the grant agreement as a formal partner of the EU-NCL to assist with the program's initiation and validation of operational and testing procedures. This trans-Atlantic collaboration will be an important contribution to the international harmonization of nanomedicine regulatory science.

Office of Cancer Clinical Proteomics Research

Clinical Proteomic Tumor Analysis Consortium Laboratory

Support Provided by the Data Science and Information Technology Program

Clinical Proteomic Technologies for Cancer Antibody Portal: The Reagents Data Portal (http://antibodies.cancer.gov/) continues to serve as a central source of reagents and resources made available by the Clinical Proteomic Technologies for Cancer (CPTC) initiative for the scientific community to support protein/peptide measurement and analysis efforts. This invaluable resource has been developed and maintained to advance proteomics research platforms for the prevention, early detection, and treatment of cancer. The Advanced Biomedical Computing Center (ABCC) Scientific Web Programming Group (SWPG) continues efforts focusing on data management and interface improvements to better capture user data and to support future scalability. Recent improvements include user interface (UI) updates to the administrative access area to better manage characterization images associated with antigen and antibody records as well as SOP documentation.

The Protein Capture Reagents Program: The Protein Capture Reagents Program (http://proteincapture.org/) continues its collaboration between CPTC and the NIH Common Fund to provide low-cost, high-quality renewable affinity reagents for human proteins as a resource for the scientific community. The overall purpose of the program is to create a library of these reagents for public distribution while simultaneously improving upon technologies for generating protein-affinity reagents in an applicable, high-throughput manner. Reagents are produced through a collaborative effort from UniProt, Rutgers, Johns Hopkins University (JHU), the Recombinant Antibody Network (RAN), and the most recent addition, NCI's Antibody Characterization Program.

The ABCC SWPG continues to maintain and develop the site build. As currently in production, this site imports, sanitizes, and manages data from the JHU/CDI laboratory, RAN, Rutgers, UniProt, and NCI's Antibody Characterization Program, bringing all the data together into a single scientific resource. The site features a robust data filter and easy navigation to assist users in quickly drilling into the data, and it builds on the Bootstrap framework, making it mobile-device compatible. While public users have access (http://proteincapture.org/download) to the database Entity-Relationship Diagram (ERD), full database dumps, table definitions, and the latest JSON data import, authenticated user access provides in-depth reporting on the data histories, including targets and shipments by sources. Supporting the "Cloud First" initiative, migration to Amazon Web Services (AWS) is being implemented and is expected to be complete by September 2015.

Clinical Proteomic Tumor Analysis Consortium Assay Portal: The Clinical Proteomic Tumor Analysis Consortium (CPTAC) Assay Portal (https://assays.cancer.gov/) serves as a public resource of well-characterized quantitative mass spectrometry–based proteomic assays. The goal of the portal is to widely disseminate highly characterized multiple-reaction monitoring (MRM) assays to the community via access to standard operating procedures, reagents, and assay validation data. The portal is designed to bring biologists seeking to ask hypothesis-driven questions of the proteome together with analytical chemists equipped to perform MRM assays.

The ABCC SWPG continues to build out features and maintain current code-base. Currently in production since January 2014, the site features a robust data filter and easy navigation to assist users in quickly drilling into the data. The assay detail pages are highly interactive, providing specific data and parameters, sources, protein maps, chromatograms, and more, all with the ability to drill down further into the data.

Recent add-ons increased the scalability to further support open-ended peptide data management counts, cataloging, and reporting. Also added as a new data source was the Biological DataBase Network (bioDBnet) (http://biodbnet.abcc.ncifcrf.gov), created and maintained by the Core Infrastructure and Systems Biology Group (CISB) of ABCC.

The assay portal currently supports peptide data from Fred Hutchinson Cancer Research Center, Broad Institute, Seoul National University/Korea Institute of Science and Technology, JHU, and Washington University in St. Louis.

Support Provided by the Cancer Research Technology Program

Antibody Characterization Laboratory

The Antibody Characterization Laboratory (ACL) continues to produce antibodies and data as requested by the Clinical Proteomic Tumor Analysis Consortium (CPTAC). The current emphasis is on antibodies for use in advanced techniques such as immunoprecipitation mass spectrometry. Because of this application, rabbit monoclonals are often preferred because of their high specificity for post-translational modifications. Traditional rabbit hybridomas are being generated, and we are evaluating recombinant rabbit antibodies that are now available. The ambitious program for antibodies for immuno-multiple reaction monitoring assays has been initiated, with antibodies now selected for 14 targets from more than 250 candidates.

Support Provided by Clinical Monitoring Research Program

The Clinical Proteomic Tumor Analysis Consortium (CPTAC) is a comprehensive and coordinated effort to accelerate the understanding of the molecular basis of cancer through the application of robust, quantitative proteomic technologies and workflows. The overarching goal of CPTAC is to improve NCI's ability to diagnose, treat, and prevent cancer.

The purpose of the CPTAC program is to investigate applying proteomic technologies and analysis to tissue samples collected under conditions similar to those in TCGA, which is delivering genomic and clinical information relating to 32 cancer types.

To achieve this goal in a scientifically rigorous manner, NCI launched CPTAC to systematically identify proteins that derive from alterations in cancer genomes and related biological processes, and provide these data, with accompanying assays and protocols, to the public. This goal will be met through four overarching objectives: (1) identify and characterize the protein inventory from prospectively collected tumor and normal tissue biospecimens (breast, colon, and ovarian cancer); (2) integrate genomic and proteomic data from analysis of common cancer biospecimens; (3) develop assays against proteins prioritized in the discovery stage as potential biomarker candidates; and (4) perform testing of verification assays in relevant cohorts of biospecimens.

In order to address the program's goal to collect 250 molecularly qualified cases (100 each of breast and colon, and 50 ovarian), the team actively engaged the Tissue Source Sites (TSSs) and worked closely with the Biospecimen Core Resource (BCR) staff to ensure the success of the project.

The CMRP tissue acquisition team, consisting of two clinical technical project managers (TPMs) and one program manager supported the ongoing outreach/recruitment activities to identify 29 TSSs with the required cases through September 2014. Outreach/recruitment was completed at that time since the initial collection period was to end December 31, 2014.

A total of 29 TSS subcontracts were awarded by September 2014. Of this total, 27 sites actively collected and shipped breast, colon, and ovarian tissue cases. Throughout the shipment phase, the subcontracts were monitored for performance and the funds were actively adjusted as appropriate to maximize the ability of high performers to contribute cases towards the qualification goals. Specifically, funds were added for high performers when their earned reimbursement neared the subcontracted value, and funds were deobligated from low performers to match their estimated earned value. Two TSS subcontracts were canceled in February 2015 due to inactivity.

As actual prospectively collected specimen accruals were reviewed and analyzed, the submission end dates for specimens were extended into 2015, based upon the total number of qualified cases, the cases pending histology and molecular qualification, and qualification rates. The goal of 100 qualified colon cases was met in May and 100 qualified breast cases in June 2015; ovarian cases were collected through July 2015 in order to meet the goal of 50 qualified cases. Given the greater difficulty of collecting 50 qualified ovarian cases obtained prospectively, two TSSs provided ovarian biospecimens that were obtained retrospectively, which were then processed via the qualification pipeline. To accommodate the final due date of April 30, 2016, for the submission of all one-year follow-up clinical data, the 27 open TSS subcontracts were modified in June 2015 to extend the period of performance through May 2016.

During the reporting period, the tissue acquisition team (reduced to 0.5 FTE as of April 2015) continued to support the day-to-day CPTAC activities, including TSS activity monitoring, regulatory surveillance, site communications, database maintenance, and invoice review and approval. The TPM also provides weekly status, forecast, and ad hoc reports in order to support the CPTAC tissue acquisition activities. The TPM collaborates closely with the Biospecimen Core Resource (BCR) staff to ensure the timely submission of initial baseline clinical data, formalin-fixed, paraffin-embedded (FFPE) slide submission, and one-year follow-up clinical data. The TPM collaborates with Research Contracts to provide guidance regarding TSS subcontract modifications for extending the period of performance, reducing award ceiling values, and other TSS-related actions. This collaboration is essential for the continued success of the project.

The success in meeting the CPTAC goals led to the new YT for support to CPTAC Phase 3. This third phase follows the pilot and second-phase activities that collected, qualified, and characterized (genomically and proteomically) the 100 breast and colon and 50 ovarian tumor specimens.

Phase 3 was initiated in July 2015 and will investigate 10 additional cancer types with the goal of collecting 200 qualified cases of each. Leidos Biomed will develop a pipeline and manage data and specimen flow through the pipeline to collect, process, qualify, genomically characterize, and distribute biospecimens for further proteomic analysis, as well as collect, analyze, review, store, and distribute the data associated with this research.

Support Provided by the Clinical Research Directorate

Clinical Proteomic Tumor Analysis Consortium Phase II

The Clinical Proteomic Tumor Analysis Consortium (CPTAC) Phase II program achieved its tissue collection and qualification goals in 2015. Over 500 cases were collected, of which more than 300 were qualified. Leidos Biomedical Research's technical and operational management resulted in drastically improved tissue processing rates at the Biospecimen Core Resource (BCR). Ovarian collections were lower than colon and breast collections due to the lower incidence in the population. Therefore, ovarian collections were extended, and retrospective ovarian cases were accepted. Leidos Biomedical Research is ensuring that case report forms (CRFs) submitted by the TSS are complete, as proteomics centers need the CRF data to process cases. Genomic sequencing, including exome, transcriptome, microRNA-seq, and microarray genotyping, is continuing on pace. Publications are now in preparation.

Center for Cancer Genomics

Support Provided by the Data Science and Information Technology Program

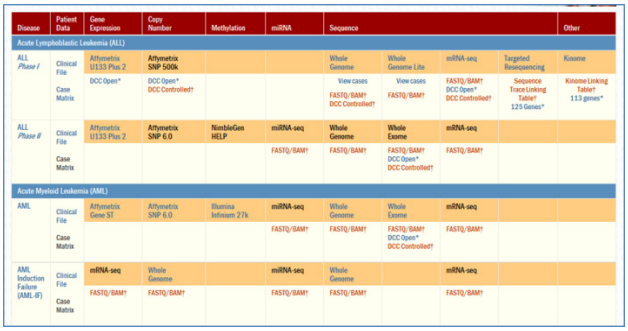
Data Coordinating Center

The Office of Cancer Genomics (OCG) runs several cancer genomics and translation projects, such as:

- TARGET. The Therapeutically Applicable Research to Generate Effective Treatments (TARGET) project is focused on identifying therapeutic targets as well as prognostic and diagnostic markers in multiple childhood cancers. The initiative includes the study of high-risk acute lymphoblastic leukemia, neuroblastoma (NBL), high-risk and treatment refractory acute myeloid leukemia, osteosarcoma, and kidney tumors (including the high-risk Wilms tumor).
- CGCI. The Cancer Genome Characterization Initiative (CGCI) supports cutting-edge genomics research on rare cancers. Researchers develop and apply advanced sequencing and other genome-based methods to identify novel genetic abnormalities in tumors. The extensive genetic profiles generated by CGCI may inform better cancer diagnosis and treatment. Focused cancers are Burkitt lymphoma and HIV+ tumor molecular characterization.
- CTD^2. The Cancer Target Discovery and Development (CTD^2) program works to functionally validate discoveries from large-scale genomic initiatives and advance them toward precision medicine through the efforts of the 13 OCD-supported research teams, called Centers, and open-access data sharing. Through cross-network collaborations, CTD^2 uses innovative bioinformatics and functional biology to: (1) mine data to find alterations that potentially influence tumor biology; (2) characterize the functional roles of candidate alterations in cancers; and (3) identify novel approaches that target causative alterations either directly or indirectly.

These programs all contribute to OCG's mission to help identify genomic alterations that offer pathways to novel therapeutic interventions that may lead to more effective cancer treatments.

A Data Coordinating Center (DCC), managed by Leidos Biomed, was established to accept all the data generated by these programs. The DCC has been in place for several years and has updated its functionalities to meet OCG's evolving needs. At a high level of task description, the DCC accepts, quality controls, inventories, processes, stores, and manages data availability. The figures below show some of the data handled by the DCC.



TARGET Data Matrix

CTD² Dashboard

As seen in The TARGET Data Matrix (a data availability matrix for one subset of the programs the DCC manages; top figure), the data range that the DCC handles is extensive, ranging from metadata to exome sequencing to DNA methylation to RNA sequencing and clinical data. The CTD2 Dashboard (bottom figure) shows a screen shot of the data available for the CTD2 program's output.

Unlike many such programs, the submission groups did not have to adhere to any submission standards for data format. Therefore, the DCC team has been very flexible. For example, the team handles the same data type generated on different platforms. The team also manages those instances when groups present the same data types but in different formats. The DCC has built a range of experience, capabilities, processes, and tools to help process the data. A lot of work has also been devoted to managing the logistical elements of the project: tracking the status of sample submission across many different groups, handling sample updates; updating processes/formats to handle new types of information/assays, and communicating with the submission groups regarding schedule and data definitions. Data are also processed to ensure consistency, quality, and adherence to privacy protection regulations (for example, correct handling of germline variations). Once the data have been thoroughly processed, they are made available using NCI-hosted systems that enable access control; some data are available only to the program's members, whereas data that meet OCG's data release parameters are publically available. Data prepared by the DCC have already been accepted into the Genomic Data Commons, and the DCC has also successfully prepared and submitted data to the International Cancer Genome Consortium (ICGC).

Future activities of the DCC are to maintain current operations supporting the ongoing data activities of the OCG's genomic data generation programs. In addition to maintaining these ongoing operations, the DCC will maintain its flexibility in adapting to new data and data types needed by the community.

The Cancer Genome Atlas Project

Support Provided by the Clinical Monitoring Research Program

In 2005, NCI and the National Human Genome Research Institute (NHGRI) established The Cancer Genome Atlas (TCGA) as a comprehensive and coordinated effort to accelerate an understanding of the molecular basis of cancer through the application of genome analysis technologies, including large-scale genome sequencing. By 2006, a collaborative three-year TCGA pilot project was launched to assess the feasibility of a full-scale effort to systematically explore the entire spectrum of genomic changes involved in select human cancers. Support to TCGA currently continues beyond the original pilot phase of the project.

During the three-year pilot phase, CMRP staff assisted with the oversight and management of tissue source site (TSS) research subcontracts for the three pilot-phase tumors: brain, lung, and ovarian. Together, these tumor types account for more than 250,000 cancer cases in the U.S. each year. Along with NCI's and NHGRI's existing infrastructures, knowledge, and resources, the data from TCGA's pilot project continue to be used to determine whether it is possible to cost-effectively characterize the genomes of a few cancer types and to determine the feasibility of establishing and maintaining an atlas of all major cancer types. The project also supports the development of new technologies.

In September 2011, NCI requested additional acquisition and research subcontract support for TCGA by establishing additional subcontracts to collect retrospective and prospective tumor specimens and clinical data for the expanded TCGA program. This support for the additional 118 subcontracts continued through March 2015.

Critical to the success of TCGA are the clinical data associated with adequately annotated biospecimens. Since its inception, TCGA has established research subcontracts with academic medical institutions to obtain actively and retrospectively collected biospecimens through the Leidos Biomedical Research prime contract.

The CMRP tissue acquisition support team initially consisted of clinical technical project managers (TPMs) and one senior program coordinator, but was reduced to one clinical project manager and one senior program coordinator during the reporting period. Together, the CMRP tissue acquisition support team continued to provide high-level project management and subcontract management to complete the receipt of deliverables, vendor reimbursement, and subcontract close-out activities. In order to accommodate the program, and to ensure the completion of all TSS work before the March 2015 deadline, major efforts during the reporting period were dedicated to: (1) managing awards to ensure that subcontractors submitted all outstanding clinical data; (2) reviewing/approving the multi-tiered invoices for work completed; (3) identifying subcontracts for closure

after invoicing completion; and (4) developing/managing the comprehensive database to track/report all significant TSS activity, invoicing, and research subcontract activities.

In order to facilitate the efficient and comprehensive data management required of TCGA tissue acquisition activities, a TCGA TSS Access database was continually enhanced in order to accommodate discrete tracking of and reporting on technical proposals, evaluation decisions, subcontract agreements, specimen types, invoices, and monthly reports. This dynamic database has been instrumental in managing the voluminous TCGA data and remains an invaluable tool for providing real-time data forecasting and reporting TSS activities to all TCGA stakeholders.

An initial final report was provided to NCI in early April, with the final due end-July. The final report captures the details of all Leidos Biomed subcontract activity, deliverables provided, and TSS funds expensed in support of tissue acquisition.

Research Subcontracting Activities

During the reporting period, staff focused on enhanced collaboration with the Biospecimen Core Resource (BCR) to assess/request submission of follow-on clinical data. Because the one-year follow-up data for some collections would be due after the period of performance ended, subcontractors could submit and be reimbursed for data with at least a six-month interval. In addition, CMRP staff encouraged/facilitated the submission of invoices in order to reimburse as quickly as possible, and to ensure all eligible payments were made as a precursor to officially closing each subcontract.

All TSSs were contacted to alert them to the timelines and stress the urgency of submitting final data and final invoices. The response to the final push for the remaining deliverables was very positive, with subcontractors prioritizing clinical data entry and working with TPMs to generate final invoices.

TPMs communicated with sites, identifying the outstanding clinical data and what actions needed to be taken to fulfill the clinical data obligations. Due to the high volume of cases received at the end of FY2014 and the intensive qualification process at the BCR, qualification notifications to TSSs were backlogged by approximately five months, delaying the entry of the initial clinical data. To accommodate this delay and maximize the clinical data received for TCGA research, vendors were granted three additional months to provide the necessary clinical data and final invoices to Leidos Biomed.

Through March 2015, when support to TCGA tissue acquisition was completed, TPMs assisted subcontractors with identifying remaining payments for reimbursement, and offered guidance on invoice preparation to ensure quick and accurate payment. With the close attention paid by the TPMs, all final deliverables and invoices were received on time. The final TCGA report was provided by August 2015 and captured comprehensive subcontract and financial data for all Leidos Biomed TCGA agreements.

NCI Invoicing Support Activities

The team's success with TCGA tissue acquisition invoicing led to a new Yellow Task (YT) request to provide similar support to TCGA contracts awarded directly by NCI. Concurrently with the Leidos Biomed tissue acquisition activities, NCI managed separate contracts for tissue acquisition. As the end of the period of performance (POP) for these NCI agreements neared, NCI adopted Leidos Biomed's proactive approach in order to obtain final invoices for 57 NCI purchase orders (POs) by end-June 2015. The POs were categorized into two groups: POP end date of September 30, 2014 and POP end date of March 31, 2015. For the POs ending 9/30/2014, one final invoice was prepared and paid. For the POs ending 3/31/2015, two rounds of invoices were prepared, an interim and a final, to pay the outstanding work as quickly as possible.

Over nine months, one clinical project manager comprehensively supported the final invoicing on all POs by: (1) evaluating the invoicing status of the 57 POs at the beginning of the reporting period; (2) identifying vendors that had completed invoicing and notifying TCGA's Program Office that the PO could be closed; (3) identifying uninvoiced, completed work and drafting a site-specific invoice using templates developed from standard NIH documents; (4) collaborating with vendors through the draft invoice review, finalization, and invoice submission processes; (5) coordinating the Program Office approval of the vendor's completed invoice; (6) monitoring the submitted invoices through the NIH financial system to identify and resolve any issues related to invoice receipt, processing, or payment delays; (7) developing templates and reports to track and communicate status and necessary actions with vendors, TCGA's Program Office, and the NIH Office of Acquisitions; (8) and enhancing collaboration with the BCR to facilitate each vendor's submission of clinical data deliverables.

The scope of the 57 POs included 6,725 submitted cases, of which 4,512 qualified for submission of the two follow-on clinical data points (total of 9,024 forms to evaluate for payment eligibility). All final invoices for the 27 POs ending September 30, 2014, were paid by May 13, 2015. As of May 18, 2015, 24 of the POs ending March 31, 2015, had all interim and final invoices paid. The remaining four POs were delayed to accommodate NIH financial system upgrades, and are anticipated to be paid by September 20, 2015. Leidos Biomed support for this activity ended on June 30, 2015.

The team's success with TCGA tissue acquisition led to their providing support for CPTAC tissue acquisition, including: outreach to current TCGA and Biospecimen Pre-Analytic Variables (BPV) Program TSSs and the use of the survey based on the PPD Development, LLC (PPD), survey; revisions to RFP documents/website; facilitation of technical/cost proposals, templates, and examples; and consideration of streamlined awards on a per-case basis. All of the lessons learned from TCGA tissue acquisition activities were applied to CPTAC

activities. Additional information on these activities is described in the CPTAC section of this report.

Notably, the clinical project manager assigned to support the NCI tissue acquisition awards for final invoicing and payment was nominated as part of TCGA's team for the NCI Director's Award. Awardees were announced late June 2015 and awarded in November 2015.

American Recovery and Reinvestment Act of 2009

Beginning in November 2012, CMRP staff provided support to TCGA. Initially, staff supported the competitive SOW that was incorporated into TCGA's RFP, which was solicited to vendors to collect up to 35 different tissue types. During the reporting period, staff continued to provide comprehensive project and fiscal management for the network of TSSs to provide tumor specimens that were collected retrospectively, or prospectively to fill TCGA's pipeline. Staff monitored research subcontract performance, including provision of the specimens and submission of the enrollment and follow-on clinical data; support to the program ended in June 2015. Additional information regarding TCGA can be found in the more detailed section describing TCGA support activities above.

NCI INTRAMURAL

Center for Cancer Research

Support Provided by the Basic Science Program

Human Leukocyte Antigens Immunogenetics Section

Extensive genetic polymorphism is a primary characteristic of the human major histocompatibility complex (MHC) human leukocyte antigen (HLA) class I and class II loci, which encode products that present antigenic peptides to T cells, initiating an adaptive immune response and clearance of foreign material. Variation within these loci is concentrated primarily at positions that alter amino acid sequences and determine specificity for foreign peptides. In addition to their role in antigen presentation to T cells, other characteristics of the *HLA* genes and the molecules they encode have begun to be elucidated. Notably, HLA class I molecules serve as ligands for innate immune receptors, including the killer immunoglobulin-like receptors (KIRs) and the leukocyte immunoglobulin-like receptors (LILRs) encoded by genes in the leukocyte receptor complex (LRC). Another, more newly defined, characteristic of the *HLA* loci is their variable level of mRNA and cell surface expression, which correlates with specific allelic types for some of the loci. This is an important modifier of the strength of the HLA-mediated immune response to cancer and infections, and diversity in expression levels appears to have been selected over time, similar to the variation in the peptide-binding groove. A greater understanding of the evolutionary and molecular genetic characteristics of immune response genes is also a key objective of our group. This is an especially important consideration when studying genetic loci composed of multiple homologues that share functional activity, which both the *MHC* and *LRC* exemplify, because it is a significant aid in identifying the actual disease locus among multiple logical candidates.

The main goal of the HLA Immunogenetics Section is to understand the genetic basis for resistance or susceptibility to disease conferred by polymorphic immune response loci. The group's approach involves direct testing for genetic effects of polymorphic genes within immune response genes on specific disease outcomes, followed by molecular or cellular biological approaches to deciphering the basis for the genetic association. These studies have been very beneficial in that they explain and confirm the genetic data, and thereby provide solid information for potential use in therapeutic development.

Significant Achievements

Life-threatening graft-versus-host disease (GVHD) limits the use of HLA-C-mismatched unrelated donors in transplantation. Clinicians lack criteria for donor selection when HLA-C-mismatched donors are a patient's only option for cure.

The group previously elucidated the range of expression across HLA-C allotypes. Each serologically defined HLA-C allotype has characteristic median fluorescence intensity (MFI) of cell surface expression that is reproducible in both healthy and HIV-infected cells in vitro. Expected levels of HLA-C cell surface expression based on the sum of the two allelic MFI coefficients were shown to predict observed HLA-C expression levels among individuals in two cohorts, indicating that MFI coefficients can be assigned to each HLA-C allotype in lieu of direct ascertainment of expression. Thus, the clinical importance of HLA-C expression can be determined in large-scale retrospective outcome studies in which appropriate materials for measuring HLA-C expression directly are not available. Using this approach, the group previously demonstrated that higher MFI levels correlated with better control of HIV viral load and slower progression to HIV-AIDS across ethnic groups, but with increased susceptibility to Crohn's disease, solidifying the role for HLA-C expression levels in modulating the strength of immune responses. In collaboration with Dr. Effie Petersdorf at the Fred Hutchinson Cancer Research Center, University of Washington, the group applied the MFI as a quantitative proxy of HLA-C expression level to assess the clinical significance of the level of HLA-C expression in an exceptionally large international population of patients and unrelated transplant donors whose only HLA mismatch was a single HLA-C allotype. The association of outcome with the level of expression of patients' and donors' HLA-C allotypes was evaluated in multivariable

models. Increasing expression level of the patient's mismatched HLA-C allotype was associated with increased risks of grades III to IV acute GVHD, nonrelapse mortality, and mortality. This study provides new insight into the strength of the immune response of HLA-C in transplantation. Application of the findings can be envisioned for future patients who do not have HLA-matched donors as an option. The effects of differential allotype expression levels at other HLA loci may further delineate and broaden the pool of acceptable donors for patients, and given the above results, characterizing such effects is warranted.

The expression level of HLA class-I proteins is known to influence pathological outcomes: pathogens downregulate HLA to evade host immune responses, host inflammatory reactions upregulate HLA, and differences among people with regard to the steady-state expression levels of HLA are associated with disease susceptibility. Yet precise quantification of relative expression levels of the various HLA loci is difficult because of the tremendous polymorphism of HLA. Most individuals express six classical HLA alleles, so detecting a particular locus with specificity is challenging. Even if antibodies specific to molecules from each locus can be identified, their binding cannot simply be compared because of differences in affinity for their respective antigens. Relative expression levels of the classical HLA class-I loci are of particular interest on HIV-infected cells, because HIV encodes the Nef protein, which downregulates HLA-A and HLA-B. Nef has multiple functions, but downregulation of HLA was shown to be significant in vivo. Because HLA-A and HLA-B are not reduced with equal efficiency by HIV, and Nef does not modulate HLA-C, it is not clear which HLA locus dominates on HIV-infected cells. The group used two independent approaches, flow cytometry and mass spectrometry (MS), to determine the relative expression levels of HLA class-I proteins on normal and HIV-infected primary cells. Peripheral blood lymphocytes (PBLs)from normal donors showed that HLA-A and HLA-B proteins are expressed at similar levels, which are 13–18 times higher than HLA-C, as measured by flow cytometry, and 4–5 times higher than HLA-C, as measured by mass spectrometry; these differences may reflect variation in the conformation or location of proteins detected. Primary CD4+ T cells infected with HIV in vitro were also studied because HIV downregulates selective HLA types. HLA-A and HLA-B were reduced on HIV-infected cells by a magnitude that varied between cells in an infected culture. Averaging all infected cells from an individual showed HLA-A to be 1–3 times higher and HLA-B to be 2–5 times higher than HLA-C, as measured by flow cytometry. These results quantify substantial differences in expression levels of the proteins from different HLA loci, which are very likely physiologically significant on both uninfected and HIV-infected cells. The large differences in expression levels observed between HLA class-I loci are likely to be functionally significant. Higher HLA expression levels are known to more efficiently initiate cytotoxic T lymphocyte (CTL) responses and modulate the cytokines that CTLs secrete. Further, some inhibitory receptors (such as LILRB1/2 and KIR3DL1) recognize antigens from multiple HLA loci, so allotype-specific expression levels may affect the innate immune response, as well as the acquired immune response. Given the accumulating data pointing to a significant impact of differential allotype-specific and locus-specific expression levels on the immune response, it is important to define this property for each HLA locus to determine its potential effect across human diseases.

The highly polymorphic HLA class I and class II genes map to the human MHC and encode molecules that contribute to both the adaptive and innate immune responses. Genome-wide association studies (GWAS) have identified the MHC as the richest 4 Mb region of the genome in terms of association with virtually all types of complex human disease, and for many of these diseases, GWAS highlight this region as the most important in determining disease risk genome-wide. As noted above, higher HLA-C expression levels have been associated with enhanced HIV control, greater odds of generating HLA-C restricted CTL responses to the virus, and stronger immune pressure on HIV as measured by viral escape mutations. HLA-C expression levels are also associated with risk of Crohn's disease, but in this case, low expression appears to confer protection. Opposing effects of expression levels on various diseases may indicate selection pressure to maintain differential expression across HLA allelic lineages, a model supported by genetic evolution analyses of the HLA-C locus. With this in mind, the group recently examined the expression levels of allelic lineages at the HLA-A locus in a sample of 216 European Americans (EAs) using a real-time polymerase chain reaction assay, and observed a gradient of expression that associates with HLA-A allelic lineage. DNA methylation of the HLA-A gene appears to contribute to the variation in HLA-A mRNA expression levels, as a significant inverse correlation was observed between HLA-A mRNA expression levels in untreated cells and the degree to which expression is increased after treatment of the cells with a DNA methyltransferase inhibitor. Further, deep-sequencing and immunoprecipitation assays revealed allelic lineage-specific methylation patterns within the HLA-A promoter region, where increased DNA methylation levels correlated significantly with reduced HLA-A expression levels. These data demonstrate HLA-A allelic lineage-specific variation in expression levels, which is due at least in part to differential DNA methylation patterns, in which low HLA-A-expressing lineages have higher DNA methylation levels, and vice versa, in healthy EA donors. This mode of transcriptional regulation is distinct from HLA-B and HLA-C, as all HLA-B and -C lineages are completely unmethylated in spite of having CpG target sites for methylation that are similar to those of HLA-A, further distinguishing the evolutionary history of the classical HLA class I loci. Several factors are likely to

contribute to the variation in expression levels of HLA-A lineages, and characterizing these factors may present the potential for the development of drugs that specifically target these factors.

Molecular Immunology Section

Cytotoxic Cell Studies Group

The Cytotoxic Cell Studies group provides support to the Cancer and Inflammation Program (CIP) in expanding knowledge of the function of the innate immune response and its potential application to the treatment of cancer. The characterization of receptors that regulate the activation of natural killer (NK) cells is a major focus of the group. The Cytotoxic Cell Studies group provides expertise in molecular biology in support of the laboratory and program goals. This group has cloned and characterized a large number of murine receptors (Ly49 gene family) that recognize major histocompatibility antigens and control the activation of NK cells. The study of the Ly49 gene family has also led the group to a major discovery in the field of gene regulation: they have found a probabilistic transcriptional switch that controls Ly49 gene activation. This discovery has important implications for controlling stem cell differentiation and may one day lead to techniques for modulating cell fate in differentiating systems such as bone marrow cultures.

Current research is focused on the KIR family of human class I *MHC* receptors. Probabilistic switches have been identified in the KIR genes, even though this gene family is not related to the murine Ly49 genes. In addition, each KIR gene has been found to contain multiple promoters that are active at different stages of NK development. In collaboration with a program project grant headed by Dr. Jeffrey Miller (University of Minnesota), a classical genetics approach is being used to gain a better understanding of KIR regulation. Bone marrow donors have been screened for KIR gene content and expression patterns. Individuals with atypical KIR expression are selected for complete sequencing, and sequence variation predicted to influence expression is then studied in detail. This approach has already revealed a previously unknown upstream promoter element that is required for KIR expression, and this discovery was featured in the October 2014 issue of *Genes & Immunity*. Collaborative projects currently under way include: analysis of Ly49 Pro1 function in SLP76-knockout mice, in collaboration with Dr. Taku Kambayashi (University of Pennsylvania); functional studies of single-nucleotide polymorphisms (SNPs) implicated in cancer susceptibility, in collaboration with Dr. Michael Dean (CIP); analysis of RNA seq data to reveal differences in gene expression in resting vs. activated monocytes, in collaboration with Dr. Dan McVicar (CIP); role of miRNA in the regulation of gene expression, in collaboration with Dr. Ram Savan (University of Washington); investigations of the role of KIR expression in bone marrow transplantation, in collaboration with Dr. Miller.

Significant Achievements

In the past year, the Cytotoxic Cell Studies group has focused efforts on the characterization of novel promoters in the KIR genes, together with a complete characterization of polymorphisms in the human HLA-C promoters. The study of a novel upstream KIR promoter has revealed an important role in controlling the tissue specificity and level of expression of different subclasses of KIR genes. The HLA-C genes are key ligands of KIR, and analysis of allelic variation in HLA-C promoters has demonstrated a role for SNPs in key transcription factor binding sites in tuning the level of HLA-C expression. Both of these studies are near completion, and a manuscript is in preparation. In addition, several collaborative studies have been completed, and a manuscript is in preparation.

Other achievements include: a change in the properties of the Ly49 probabilistic switch in SLP76-knockout mice that leads to decreased Ly49 expression has been discovered in collaboration with Dr. Taku Kambayashi at the University of Pennsylvania; a gene array characterization of licensed versus unlicensed mouse NK cells has been completed, in collaboration with Dr. Bill Murphy, University of California, Davis; and a manuscript on the regulation of interferon gamma with Dr. Ram Savan is being revised for *PLOS Biology*. Results of the characterization of Pro-I in all of the known KIR genes indicate that the new KIR promoter region will provide important insights into the expression patterns of KIR, including the observation that the KIR2DL2, KIR2DS2, and KIR2DL3 proteins are the first to appear in reconstituting NK cells after bone marrow transplantation. This work is being conducted in collaboration with the laboratory of Dr. Miller at the University of Minnesota Cancer Center. The Miller laboratory is leading the field in the use of adoptive NK transfer for improving the outcome of bone marrow transplantation. The ability to control the frequency of KIR expression in developing NK cells may improve clinical outcomes.

Molecular Immunotherapy Section

One of the two major goals of the Molecular Immunotherapy Section (MITS) is to specifically enhance tumor cell death using chemical, biological, or pharmaceutical agents that sensitize cancer cells to the cytotoxic effects of immunotherapy. Most studies have focused on identifying compounds that sensitize cancer cells to the apoptotic effects of tumor necrosis factor–related apoptosis-inducing ligand (TRAIL), a pro-apoptotic member of the tumor necrosis factor family of proteins that is produced by various immune cells. MITS has continued its work on identifying novel compounds that sensitize tumor cells to TRAIL apoptosis and determining their molecular mechanisms of action. The second major goal is to isolate populations of cancer stem cells (CSCs) and study their interactions with other cells in the tumor microenvironment (particularly immune cells). It has

recently become apparent that many solid tumors contain cancer cells in different states of differentiation. Importantly, some of these cells may be CSCs, a subpopulation of cancer cells that are resistant to standard anticancer therapies, have an increased ability to metastasize to other organs, and may be responsible for cancer relapse. Therefore, there is much interest in targeting this minor subpopulation of cancer cells to help improve cancer therapies. One major practical problem confronting investigators is the isolation of populations of CSCs, since they usually are present in tumors or cancer cell lines in very low numbers. Also, using phenotypic cell surface markers is not always a reliable method for identifying CSCs. Therefore, we have utilized a method to incorporate various reporter constructs (such as green fluorescent protein [GFP]) into CSCs, where marker expression is based on a CSC function rather than a phenotype. If such populations can be isolated, they should be useful for future studies of many aspects of CSC biology.

Significant Achievements

Analysis of combinations of pharmaceutical agents with death ligands. MITS published the first in vivo evidence that a combination of the proteasome inhibitor bortezomib (Velcade) and an agonist antibody to the TRAIL receptor could provide a more significant therapeutic benefit than either agent alone. Human Genome Sciences carried out a clinical trial of the Velcade/agonist TRAIL receptor antibody combination in patients with advanced multiple myeloma at multiple clinical centers worldwide.

In a collaboration between NCI colleagues and Basic Sciences Program (BSP) scientists in the Molecular Targets Laboratory (MTL), a high-throughput cellular screening (HTS) assay using the human renal carcinoma cell line ACHN was developed to look for novel compounds that could sensitize tumor cells to TRAIL. More than 50,000 pure compounds or natural products were screened using this assay. The researchers identified a number of natural products, purified from extracts by MTL, with the ability to sensitize cancer cells to apoptosis in the presence of TRAIL (Henrich et al., *Apoptosis*, 2012, 17:79). More recent studies suggest that certain withanolides (derived from medicinal plants) significantly sensitize tumor cells to TRAIL apoptosis both in vitro and in vivo. Interestingly, the most active withanolide for sensitizing renal cancer cells to TRAIL apoptosis was withanolide E, whereas other withanolides that are closely related structurally (such as withanone) lacked any activity. Withanolide E could sensitize a wide variety of human cancer cell lines to TRAIL-mediated apoptosis. However, for unknown reasons, not all human cancer cells are sensitized, and this is under further investigation. An extensive analysis of the molecular signaling pathways involved in TRAIL-mediated apoptosis suggested that the main molecular mechanism of action of withanolide E involved a rapid reduction in the protein levels of the anti-apoptotic protein cFLIP. Interestingly, this reduction of cFLIP involved an increased degradation of the protein rather than any major effects on cFLIP transcription. A patent application was filed covering these findings, and these data were published earlier this year (Henrich el al., *Cell Death and Disease*, 2015, 6:e1666). In contrast to Velcade, withanolide E does not cause cell shape and adherence changes, does not provoke a cell stress response, and exhibits very low levels of toxicity as a single agent.

In current studies, MITS is attempting to determine in more detail the molecular mechanism of action of withanolide E that results in a sensitization of cancer cells to TRAIL. In August 2014, we invited Dr. Leslie Gunatilaka, director, University of Arizona Natural Products Center and an expert on withanolides, to give a talk at NCI at Frederick, and then established a collaborative research project with his group. Since then, they have supplied us with about 45 chemical derivatives based on the withanolide E structure. We have identified derivatives that are 4- to 8-fold more potent than withanolide E in sensitizing cancer cells to TRAIL. These findings will help in structure–activity relationship (SAR) studies on withanolides. MITS is further testing the anticancer activity of these derivatives in vitro and in vivo. The active derivatives are more potent in reducing cFLIP levels in sensitized cancer cells and seem to enhance the assembly of the death-inducing signaling complex (DISC) of proteins critical for the initiation of TRAIL apoptosis.

Isolation and characterization of CSCs. Using DNA reporter constructs that contained GFP under the control of the embryonic transcription factor Nanog, MITS researchers were able to isolate a small subpopulation of GFP+ cells from both the human (SUM159) and mouse (4T1.2) breast cancer cell lines. These cell lines are derived from the triple-negative subgroup of breast cancer, which is highly aggressive, more prevalent in women of African origin (for unknown reasons), and has few treatment options. Further, studies on the characterization of these small subpopulations of GFP+ cells suggest that they have many in vitro and in vivo characteristics of CSCs.

These populations are currently being studied in more detail by MITS, and, based on this procedure for CSC isolation, a number of scientific collaborations have been set up with small biotech companies and a number of other academic institutions. A three-way collaborative agreement has been signed between Leidos Biomed/ Frederick National Laboratory for Cancer Research (FNLCR), Sheffield Hallam University (SHU), and Nottingham Trent University (NTU), both in the United Kingdom, to outline future planned collaborative studies.

In addition, the MITS has an active Material Cooperative Research and Development Agreement (MCRADA) with a small biotech company Verastem (Cambridge, MA), which was founded on the premise of targeting CSCs. These collaborations are also ongoing, and Verastem has provided $30,000 to assist in the financing of the MITS research. Some collaborative

studies on the effect of NK cells on CSCs are also in progress with the laboratory of Dr. Murphy at the University of California, Davis, and a collaborative study with Dr. Murphy's lab was published in 2015 (Canter et al., *BMC Cancer*, 2015, 14:756). In some of these studies, the effects of withanolide E on the response of minor CSC populations to TRAIL apoptosis are being compared to the response of the bulk cancer cell population.

We also instigated a study on differences in secreted proteins between mouse breast cancer cell lines that were moderately (4T1) or highly (4T1.2) metastatic. The 4T1.2 cells seem to more closely resemble CSCs. A thorough analytical biochemical analysis identified secreted leukocyte protease inhibitor (SLPI) as a protein secreted at much higher levels by the more metastatic 4T1.2 cells. This study was performed in collaboration with Dr. Oleg Chertov of the RAS Program at the Advanced Technology Research Facility (ATRF) and was published recently (Sayers, K. et al., *PLoS One*, 2014, 9:e104223) Future studies will assess whether SLPI can act as a biomarker for aggressive triple-negative breast cancers, whether increased secretion of SLPI has any functional role in promoting breast cancer metastases, and how SLPI secretion might affect immune responses to cancer cells.

Hematopoiesis and Stem Cell Biology Section

The major task of the Hematopoiesis and Stem Cell Biology Section (HSCBS) is to define the molecular events that regulate hematopoietic stem cell (HSC) quiescence, survival, self- renewal, and cell fate decisions. The HSCBS efforts continue to focus on defining the physiological function of transcription factors, which are the downstream mediators of signal transduction pathways activated by nonautonomous mechanisms from cells in the microenvironment, and on cell-intrinsic programs in HSCs and their progeny. In addition, the group is focused on how individual transcription factors are integrated into wider transcriptional regulatory networks and how combinatorial transcription factor interactions within these networks drive lineage-specific gene expression programs. The HSCBS is pursuing these studies to identify novel gene targets and pathways to treat hematopoietic malignancies, myeloproliferative disorders, and/or anemia.

Significant Achievements

The HSCBS has continued its efforts to identify novel transcriptional regulators of HSC proliferation, self-renewal, and differentiation. The HSCBS previously discovered a novel zinc finger transcription factor, pogo transposable element with zinc finger domain (Pogz), in a screen to identify transcriptional regulators of HSC growth and differentiation. They found that Pogz is an essential gene for embryonic development, since mice that lack Pogz did not survive beyond embryonic day 16. In addition, the researchers observed a block in erythroid differentiation and discovered that the expression of transcription factors that regulate erythroid development were greatly reduced in Pogz-/- FL, including Bcl11a, which is required to repress fetal globin gene expression. The HSCBS researchers examined globin gene expression and found that fetal globin gene expression was upregulated in Pogz-/- FL. The researchers also discovered that Pogz directly regulates Bcl11a expression by binding to three DNA hypertensive sites in an enhancer region shown to be specifically required for Bcl11a expression in erythroid lineage cells. In addition, the HSCBS found that Pogz enhances the expression of luciferase in a reporter that contains the Bcl11a enhancer region. Finally, the HSCBS has demonstrated that fetal globin is expressed in peripheral blood cells (PBCs) of mice transplanted with FL HSC from Pogz-/- and mice with conditional loss of Pogz in erythroid cells (*EpoR-cre;FlcnF/F* mice). Thus, HSCBS studies provide evidence that regulating Pogz expression might be a novel therapeutic opportunity to treat patients with sickle cell anemia and other hemoglobinopathies, by upregulating fetal globin expression in these patients.

In other studies to identify the function of novel molecular regulators of hematopoietic development, the HSCBS examined the role of *Folliculin (Flcn)* in hematopoiesis, in collaboration with Drs. Laura Schmidt, Masaya Baba, and W. Marston Linehan, NCI Center for Cancer Research (CCR), and Dr. T. Suda (Keio University, Tokyo, Japan). *Folliculin (Flcn)* is an autosomal dominant tumor suppressor gene that modulates diverse signaling pathways required for growth, proliferation, metabolism, survival, motility, and adhesion. Flcn is an essential protein required for murine embryonic development, embryonic stem cell (ESC) commitment, and *Drosophila* germline stem cell maintenance, which suggests that Flcn may be required for adult stem cell homeostasis. The HSCBS conditionally inactivated *Flcn* in adult hematopoietic stem/progenitor cells (HSPCs) and discovered that loss of this gene drives HSCs into proliferative exhaustion, resulting in the rapid depletion of HSPCs, loss of all hematopoietic cell lineages, acute bone marrow failure, and, after 40 days, mortality. The HSCBS determined that HSCs that lack *Flcn* fail to reconstitute the hematopoietic compartment in bone marrow transplantation assays, which demonstrated a cell-autonomous requirement for *Flcn* in HSC maintenance. The HSCBS showed that the phosphorylation of Akt and mTorc1 was greatly increased in bone marrow cells (BMCs), and that treatment of mice with rapamycin, an inhibitor of mTorc1, significantly inhibited extramedullary hematopoiesis, which suggested that the mTorc1 pathway was activated by the loss of *Flcn* expression in hematopoietic cells in vivo. The HSCBS also discovered that the transcriptional regulator Tfe3 was activated in BMCs that had lost *Flcn* gene expression and preferentially localized to the nucleus of *Flcn*-/- HSPCs. The HSCBS confirmed that overexpression of Tfe3 in HSPC impairs long-term hematopoietic reconstitution in vivo, which recapitulates the *Flcn*-/- phenotype, supporting the notion that abnormal activation of Tfe3 contributes to the *Flcn*-/- phenotype. Finally, the HSCBS

found that *Flcn-/-* mice develop an acute histiocytic hyperplasia in multiple organs, representing a novel phenotype and suggesting a novel function for *Flcn* in macrophage development. Collectively, the HSCBS found that Flcn is intrinsically required to maintain adult HSC quiescence and homeostasis, and that *Flcn* loss leads to bone marrow failure and mortality in mice.

Molecular Genetic Epidemiology Section

The objective of the Molecular Genetic Epidemiology Section (MGES) is to identify causal genetic factors that modify risk for complex and infectious diseases, with the goal of informing clinical decisions and providing new targets for intervention. The focus in recent years has been on chronic kidney disease associated with chromosome 22 (C22) variants and HIV-1. In an effort to understand HIV- associated kidney disease, the group identified C22 comprising *MYH9* and *APOL1* as a locus for renal susceptibility, and has since extended this finding to a spectrum of kidney glomerular disease independent of HIV infection. African Americans with chronic kidney disease (CKD) have more severe disease, tend to progress more rapidly, and are four times more likely to develop end-stage renal disease (ESRD). In a series of collaborative studies, MGES has shown that this propensity is due largely to variant alleles in *APOL1* that are restricted to people of African ancestry and are rare to absent in other world populations. The causal variants are *APOL1,* encoding apolipoprotein L1, a protein that confers resistance to trypanosomes and is a component of high-density lipid (HDL) particles. In a series of collaborative studies, the group has shown extremely strong associations for two common codon-altering *APOL1* variants (termed G1 and G2) for HIV-associated nephropathy (OR 29), focal segmental glomerusclerosis (OR 19), and ESRD due to hypertension (OR 7). The group is now extending these associations to other phenotypes, including HIV- associated renal insufficiency, left ventricular hypertrophy, and stroke—all of which are more prevalent in people of African ancestry.

A series of studies is ongoing to determine the effects of APOL1 variants on the 14 percent of African Americans carrying two renal risk variants. MGES researchers are investigating the effects of *APOL1* renal risk variants on living kidney donors and recipients of kidneys carrying two risk alleles. Recent epidemiological studies indicate that African American kidney donors are fourfold more likely to develop kidney failure than their European counterparts. The MGES is now testing, in two multicenter studies, the hypothesis that living kidney donors are at a greater risk of developing future kidney failure if they carry two APOL1 risk variants. The MGES is also interested in the worldwide distribution of *APOL1* variants since ApoL1 protein is an innate restriction against *Trypanosoma brucei brucei*, the cause of trypanosomiasis in a wide range of mammals, but not in humans and certain primates who have acquired and retained the *APOL1*gene. APOL1 is also thought to confer innate immunity against other extra- and intracellular pathogens. The researchers embarked on a large sequencing project to determine the extent and character of variation in more than 2,000 individuals representing 53 global populations. In addition, the MGES has contributed to several notable studies published over the past year on the extent of genetic variation among human populations, the evolutionary history and migration of world populations, the identification of genetic factors associated with asthma in the Hispanic population, and the selection of pathogen- driven genes.

Significant Achievements

Sequencing rare and common APOL1 coding variants to determine kidney disease risk. One-third of African Americans with sporadic focal segmental glomerulosclerosis (FSGS) or HIV-associated nephropathy (HIVAN) do not carry APOL1 renal risk genotypes, suggesting that other APOL1 variants may contribute to kidney disease. To address this question, the MGES sequenced all APOL1 exons in 1,437 Americans of African and European descent, including 464 patients with biopsy-proven FSGS/HIVAN. Testing for association with 33 common and rare variants with FSGS/HIVAN revealed no association independent of strong recessive G1 and G2 effects. Seeking additional variants that might have been under selection by pathogens and could represent candidates for kidney disease risk, we also sequenced an additional 1,112 individuals representing 53 global populations. Except for G1 and G2, none of the seven common codon-altering variants showed evidence of selection or could restore lysis against trypanosomes causing human African trypanosomiasis. Thus, only APOL1 G1 and G2 confer renal risk, and other common and rare APOL1 missense variants, including the archaic G3 haplotype, do not contribute to sporadic FSGS and HIVAN in the U.S. population. Hence, our study suggests that, in most potential clinical or screening applications, sequencing APOL1 exons is unlikely to provide any more information than genotyping only APOL1 G1 and G2 risk alleles. This study was recently published in *Kidney International*.

***APOL1* genotype of kidney donors and recipients.** The group, in collaboration with Dr. Jeffrey Kopp, National Institute of Diabetes and Digestive and Kidney Diseases, Walter Reed, the University of Maryland transplant centers, and the University of Chicago, is testing the hypothesis that allograft kidneys with the two *APOL1* risk alleles will have a shorter survival time than kidneys carrying no or one risk allele post-transplantation. The group is also investigating the genetic correlates of kidney failure in former donors who are now in need of a kidney transplant due to ESRD. These studies will settle the debate about the benefits of genetic screening for *APOL1* renal risk alleles in potential donors and in cadaveric kidneys. Restricting living kidney donations and cadaveric kidneys due to unfavorable *APOL1* genotype will have a significant impact on kidney availability, as 13 percent of potential African American donors will carry two *APOL1* risk alleles. Subject

enrollment is under way for both studies, and recruitment goals are ahead of target: 200 subjects are enrolled; 150 are living donors with kidney failure.

***APOL1* alleles are associated with HIVAN in South African adults but not children.** *APOL1* variants are strongly associated with HIVAN (OR 29) and FSGS (OR 17) in African Americans. The prevalence of these variants in southern African populations and their impact on CKD in a setting of high HIV-1 subtype C prevalence has not yet been investigated. The MGES, in an international collaboration, determined the role of *APOL1* variants on 124 HIVAN and CKD cases, and 108 controls drawn from a South African black population. Genotypes were determined for *APOL1* G1 and G2 variant sites and 42 SNPs, including 18 ancestry-informative markers; 38 HIVAN cases; 41 HIV-positive and 41 HIV-negative CKD cases; 54 HIV-positive controls; and 54 population controls. Two risk alleles were carried in 79 percent of the HIVAN cases but only in 2 percent of the population controls. Individuals carrying any combination of two APOL1 risk alleles had 89-fold higher odds (95% CI 17.7–911.7; $P = 1.2x10^{-14}$) of developing HIVAN than those with low-risk APOL1 genotypes. Population allele frequencies were 7.3 percent for G1 and 11.1 percent for G2. *APOL1* risk alleles were not significantly associated with other forms of CKD, including FSGS. This is the only study to report the impact of *APOL1* risk variants on HIVAN in patients infected with HIV-1 subtype C. HIV-positive, antiretroviral therapy–naïve South African blacks with two APOL1 risk alleles are at very high risk for developing HIVAN. This study was recently reported in the *Journal of the American Society of Nephrology*. Although APOL1 renal risk variants greatly increase the risk of HIVAN in adults with HIV infection, the role of APOL1 risk alleles in children has not been established. We investigated the role of APOL1 in children with HIVAN and found no association, suggesting that South African children with perinatal acquisition of HIV infection may develop renal disease through different pathways, as compared with adults.

Developing tools for mapping by admixture linkage disequilibrium. Mapping by admixture linkage disequilibrium (MALD) is a whole-genome gene mapping method that uses linkage disequilibrium (LD) from extended blocks of ancestry inherited from parental populations among admixed individuals to map associations for diseases that vary in prevalence among human populations. The extended LD queried for marker association with ancestry results in a greatly reduced number of comparisons, as compared with standard genome-wide association studies (GWAS). As ancestral population LD tends to confound the analysis of admixture LD, the earliest algorithms for MALD required marker sets sufficiently sparse to lack significant ancestral LD between markers. However, current genotyping technologies routinely provide dense SNP data, which convey more information than sparse sets; however, there were no software solutions that offer both local ancestry inference using dense marker data and disease association statistics. The MGES, in collaboration with Leidos Biomed statisticians, developed an R package, ALDsuite, which accounts for local LD using principal components of haplotypes from surrogate ancestral population data, and includes tools for quality control of data, MALD, downstream analysis of results, and visualization graphics. ALDsuite provides a fast, accurate estimation of global and local ancestry and comes bundled with the tools needed for MALD, from data quality control through mapping and visualization of disease genes. This software is now being used in several large consortium studies, including the Women's Health Initiative, to identify loci associated with renal disease in African Americans and to identify genes that interact with APOL1 to modify penetrance of APOL1 genes.

Clinical features and histology of apolipoprotein L1-associated nephropathy in the FSGS clinical trial. To determine whether children with focal segmental glomerulosclerosis (FSGS) who carry APOL1 high-risk genotypes differ in treatment response or progression of kidney disease compared to children with low-risk genotypes, the MGES investigated participants enrolled in the FSGS Clinical Trial. The trial involved 138 children and young adults who were randomized to cyclosporin or mycophenolate mofetil plus pulse oral dexamethasone with a primary outcome of proteinuria remission. DNA was available from 94 subjects who were genotyped for *APOL1* renal risk variants, with two risk alleles comprising the risk genotype. Individuals with the *APOL1* high-risk genotype tended to present at an older age and had significantly lower baseline epidermal growth factor receptor (eGFR), more segmental glomerulosclerosis and total glomerulosclerosis, and more tubular atrophy/interstitial fibrosis. There were differences in renal histology, and in particular, more collapsing variants in those with the high-risk genotypes ($P = 0.02$). The *APOL1* risk genotype did not affect response to either treatment regimen. Individuals with the risk genotype were more likely to experience kidney failure ($P < 0.01$). This study was the first to show that *APOL1* high-risk genotypes are common in African American subjects with primary FSGS and may also be present in individuals who do not self-identify as African American, indicating that all patients presenting with focal segmental glomerulosclerosis should be screened for APOL1 high-risk genotypes regardless of self-reported ancestry. APOL1 high-risk genotypes, carried by 13 percent of the African American population, are associated with decreased kidney function, more glomerulosclerosis and interstitial fibrosis, and greater propensity to progress to ESRD. Unfortunately, knowledge of *APOL1* risk genotype did not influence proteinuria responses to cyclosporin or mycophenolate mofetil/dexamethasone, and cannot be used to predict treatment response. This study was recently published in the *Journal of the American Society of Nephrology*.

Computational Structural Biology Section

Recent advances in experimental techniques and the accumulation of unprecedented genome-scale experimental data enable the Computational Structural Biology Section (CSBS) to address fundamental questions on a large scale. These questions relate to molecular interactions, principles of biomolecular recognition, and mechanisms of signal propagation. Biomolecules work together to provide specific functions, so perturbations in intermolecular communication channels often lead to cellular malfunction and disease. Research at CSBS seeks to obtain an in-depth grasp of the biophysical principles underlying the individual interactions of biomolecules, as well as their organization in cellular networks, processes, and mechanisms. It targets protein function and misfunction in disease, and attempts to unravel key factors that could aid drug discovery. CSBS has been continuing its research in the framework of these fundamental principles in normal physiological functions and dysfunction in disease, particularly focusing on cancer and inflammation.

Significant Achievements

Some examples of the significant achievements of the group are presented below:

- K-Ras4B is a highly oncogenic Ras isoform and is the only isoform associated with initiation of adeno-carcinomas. Mechanistic insight into why and how K-Ras4B mediates ductal adenocarcinomas, particularly of the pancreas, is vastly important for developing its therapeutics. The current review points out the overlooked but critical role of calmodulin (CaM), which selectively binds to GTP-bound K-Ras4B, but not to its isoforms. Cell proliferation and growth require the MAPK (Ras/Raf/MEK/ERK) and PI3K/Akt signaling pathways. We proposed how Ca2+/CaM promotes PI3K/Akt signaling and how Ca2+/CaM involvement explains enigmatic observations like the elevated calcium levels in adenocarcinomas. We hypothesized that CaM recruits and activates PI3K at the membrane, and that this is the likely reason for Ca2+/CaM-dependence in adenocarcinomas. CaM contributes to initiation and progression of many ductal cancers (e.g., pancreatic, colorectal, lung) via both PI3Kalpha/Akt and Raf/MEK/ERK pathways. Therefore, blocking the K-Ras/MAPK pathway and CaM/PI3Kalpha binding in a K-Ras4B/CaM/PI3Kalpha heterotrimeric complex has promising clinical potential as an adenocarcinoma-specific therapeutic strategy.
- Ras proteins recruit and activate effectors, including Raf, that transmit receptor-initiated signals. Monomeric Ras can bind Raf; however, activation of Raf requires its dimerization. It has been suspected that dimeric Ras may promote dimerization and activation of Raf. We showed that the GTP-bound catalytic domain of K-Ras4B, a highly oncogenic splice variant of the K-Ras isoform, forms stable homodimers. We observed two major dimer interfaces. The first, a highly populated β-sheet dimer interface, is at the switch I and effector-binding regions, overlapping the binding surfaces of Raf, PI3K, RalGDS, and additional effectors. This interface has to be inhibitory to such effectors. The second, a helical interface, also overlaps the binding sites of some effectors. This interface may promote activation of Raf. Our data reveal how Ras self-association can regulate effector binding and activity, and suggest that disruption of the helical dimer interface by drugs may abate Raf signaling in cancer.
- K-Ras4B belongs to a family of small GTPases that regulates cell growth, differentiation, and survival. K-ras is frequently mutated in cancer. K-Ras4B association with the plasma membrane through its farnesylated and positively charged C-terminal hypervariable region (HVR) is critical to its oncogenic function. However, the structural mechanisms of membrane association are not fully understood. Using confocal microscopy, surface plasmon resonance, and molecular dynamics simulations, we observed that K-Ras4B can be distributed in rigid and loosely packed membrane domains. Its membrane-binding domain interaction with phospholipids is driven by membrane fluidity. The farnesyl group spontaneously inserts into the disordered lipid microdomains, whereas the rigid microdomains restrict the farnesyl group penetration. We speculated that the resulting farnesyl protrusion toward the cell interior enables oligomerization of the K-Ras4B membrane–binding domain in rigid microdomains. Unlike other Ras isoforms, K-Ras4B HVR contains a single farnesyl modification and positively charged polylysine sequence. The high positive charge modulates not only specific HVR binding to anionic phospholipids, but also farnesyl membrane orientation. Phosphorylation of Ser-181 prohibits spontaneous farnesyl membrane insertion. The mechanism illuminates the roles of HVR modifications in deciding which membrane microdomain K-Ras4B anchors into and suggests an additional function for HVR in the regulation of Ras signaling.
- The Ras/Raf/MEK/ERK signal transduction pathway is a major regulator of cell proliferation activated by Ras-guanosine triphosphate (GTP). The oncogenic mutant RasQ61L is not able to hydrolyze GTP in the presence of Raf and thus is a constitutive activator of this mitogenic pathway. The Ras/Raf interaction is essential for the activation of the Raf kinase domain through a currently unknown mechanism. We presented the crystal structures of the Ras-GppNHp/Raf-RBD and RasQ61L-GppNHp/Raf-RBD complexes, which, in combination with molecular dynamics simulations, reveal differences in allosteric interactions leading from the Ras/Raf interface to the Ras calcium-binding site and to the

remote Raf-RBD loop L4. In the presence of Raf, the RasQ61L mutant has a rigid switch II relative to the wild-type and increased flexibility at the interface with switch I, which propagates across Raf-RBD. We showed that, in addition to local perturbations on Ras, RasQ61L has substantial long-range effects on the Ras allosteric lobe and on Raf-RBD.

- A major challenge facing the community involves identifying mutations that drive cancer. Performing analyses of cancer genomes to detect and distinguish "driver" from "passenger" mutations is a daunting task. We suggested that there is a third, "latent driver," category. Latent driver mutations behave as passengers and do not confer a cancer hallmark. However, coupled with other emerging mutations, they drive cancer development and drug resistance. Latent drivers emerge prior to and during cancer evolution. These allosteric mutations can work through "AND," "all-or-none," or "Graded" logic gate mechanisms. Current diagnostic platforms generally assume that actionable driver mutations are those appearing most frequently in cancer. We proposed that detection of a latent driver may help forecast cancer progression and modify personalized drug regimes.
- Linking cell-signaling events to the fundamental physicochemical basis of the conformational behavior of single molecules and ultimately to cellular function is a key challenge facing researchers in the life sciences. We outlined the emerging principles of allosteric interactions in cell signaling, with emphasis on the following points: (1) Allosteric efficacy is not a function of the chemical composition of the allosteric pocket but reflects the extent of the population shift between the inactive and active states. That is, the allosteric effect is determined by the extent of preferred binding, not by the overall binding affinity. (2) Coupling between the allosteric and active sites does not decide the allosteric effect; however, it does define the propagation pathways, the allosteric binding sites, and key on-path residues. (3) Atoms of allosteric effectors can act as "driver" or "anchor" and create attractive, "pulling," or repulsive, "pushing," interactions. Deciphering, quantifying, and integrating the multiple co-occurring events present daunting challenges to our scientific community.
- EphB2 interacts with cell surface–bound ephrin ligands to relay bidirectional signals. Overexpression of the EphB2 receptor protein has been linked to different types of cancer. The SNEW (SNEWIQPRLPQH) peptide binds with high selectivity and moderate affinity to EphB2, inhibiting Eph-ephrin interactions by competing with ephrin ligands for the EphB2 high-affinity pocket. We used rigorous free-energy perturbation (FEP) calculations to re-evaluate the binding interactions of SNEW peptide with the EphB2 receptor, followed by experimental testing of the computational results. Our results provide insight into the dynamic interactions of EphB2 with SNEW peptide. While the first four residues of the SNEW peptide are already highly optimized, change of the C-terminal end of the peptide has the potential to improve SNEW-binding affinity. We identified a PXSPY motif that can be similarly aligned with several other EphB2-binding peptides.
- Cancer treatment decisions rely on genetics, large data screens, and clinical pharmacology. We pointed out that genetic analysis and treatment decisions may overlook critical elements in cancer development, progression, and drug resistance. Two critical structural elements are missing in genetics-based decision making: the mechanisms of oncogenic mutations and the cellular network, which is rewired in cancer. These elements lay the foundation for the structural basis for cancer treatment decisions, which is rooted in the physical principles of the molecular conformational behavior of single molecules and their interactions. Improved tumor mutational analysis platforms and knowledge of the redundant pathways that can take over in cancer may not only supplement known actionable findings, but also forecast possible cancer progression and resistance. Such forward-looking analyses can be powerful, endowing the oncologist with mechanistic insight and cancer prognosis, and, consequently, more informed treatment options. Examples of forward-looking analyses include redundant pathways taking over after inhibition of EGFR constitutive activation, mutations in PIK3CA p110α and p85, and the non-hotspot AKT1 mutants conferring constitutive membrane localization.
- A key issue in drug discovery is how to reduce drug dosage and increase specificity while retaining or increasing efficacy, as high dosage is often linked to toxicity. There are two types of drugs on the market: orthosteric and allosteric. Orthosteric drugs can be noncovalent or covalent. The latter are advantageous because they may be prescribed in lower doses, but their potential off-target toxicity is a primary concern. The chief advantages of allosteric drugs are their higher specificity and their consequently lower chance of toxic side effects. Covalent allosteric drugs combine the pharmacological merits of covalent drugs with the additional benefit of the higher specificity of allosteric drugs. In a recent promising step in therapeutic drug development, allosteric disulfide-tethered fragments successfully modulated the activity of a protein kinase and K-Ras. We provided an outline for the design of covalent allosteric drugs.
- Inflammation plays significant roles in all phases of tumor development, including initiation, progression, and metastasis. Interleukin-10 (IL-10) is a well-known immunomodulatory cytokine with an anti-inflammatory activity. Lack of IL-10 allows the induction of pro-inflammatory cytokines and hinders

antitumoractivity, thereby favoring tumor growth. The IL-10 network is among the most important paths linking cancer and inflammation. The simple node-and-edge network representation is useful, but limited, hampering the understanding of the mechanistic details of signaling pathways. Structural networks complete the missing parts, and provide details. The IL-10 structural network may shed light on the mechanisms through which disease-related mutations work and on the pathogenesis of malignancies. Using a tool known as PRISM (PRotein Interactions by Structural Matching), we constructed the structural network of IL-10, which includes its first- and second-degree protein neighbor interactions. We predicted the structures of complexes involved in these interactions, thereby enriching the available structural data. In order to reveal the significance of the interactions, we exploited mutations identified in cancer patients, mapping them onto key proteins of this network. We analyzed the effect of these mutations on the interactions, and demonstrated a relation between these interactions and inflammation and cancer. Our results suggest that mutations that disrupt the interactions of IL-10 with its receptors (IL-10RA and IL-10RB) and α2-macroglobulin (A2M) may enhance inflammation and modulate antitumor immunity. Likewise, mutations that weaken the A2M–amyloid precursor protein (APP) association may increase the proliferative effect of APP through preventing β-amyloid degradation by the A2M receptor, and mutations that abolish the A2M–Kallikrein-13 (KLK13) interaction may lead to cell proliferation and metastasis through the destructive effect of KLK13 on the extracellular matrix. Prediction of protein–protein interactions through structural matching can enrich the available cellular pathways. In addition, the structural data of protein complexes suggest how oncogenic mutations influence the interactions and explain their potential impact on IL-10 signaling in cancer and inflammation.

- Cytokines are messengers between tissues and the immune system that play essential roles in cancer initiation, promotion, metastasis, and immunotherapy. Understanding the structural pathways of cytokine signaling and signaling interactions can help in understanding the cytokines' action in the tumor microenvironment. Our aim is to provide an overview of the role of cytokines, from a structural perspective, in tumor development. Atomic details of protein–protein interactions can help in understanding how an upstream signal is transduced; how higher-order oligomerization modes of proteins can influence the function of cytokines; how mutations, inhibitors, or antagonists can change cellular consequences; why the same protein can lead to distinct outcomes; and which alternative parallel pathways can take over when needed. Such details also help in the design of drugs/inhibitors against proteins de novo or by mimicking natural antagonists, as in the case of interferon-γ. Since the structural database is limited, structural pathways are largely built from a series of predicted binary protein–protein interactions. To illustrate how protein–protein interactions can help illuminate roles played by cytokines, we modeled some cytokine interaction complexes using PRISM.

Epigenetics Section

The epigenome regulates gene expression and thus controls the phenotype of a cell. DNA methylation is one of the major epigentic modifications that is established early in development and is maintained through replication. Our group has previously identified lymphoid-specific helicase (Lsh) as a regulator of DNA methylation in mammalian cells. Mice with a deletion of Lsh die at birth, and every tissue has compromised DNA methylation pattern. As a consequence, Lsh-/- mice have several stem cell defects, including impaired hematopoiesis, reduced overall growth, and defective germ cell development. One goal of our group is to define the molecular mechanisms by which Lsh modulates cytosine methylation patterns during development and to understand how these epigenetic changes relate to chromatin structure.

Significant Achievements

We have previously shown that Lsh can influence the methylation pattern at retroviral sequences and endogenous genes, but the precise role of Lsh in the establishment of DNA methylation at a given site remained unclear. In particular, it is not known whether Lsh, a member of the SNF2 family of chromatin-remodeling proteins, can alter chromatin structure or how this can modulate DNA methylation.

In order to study the molecular function of Lsh on chromatin, we established an in vitro embryonic stem cell (ESC)–based system. DNA methylation levels vary during development and are lowest in the inner cell mass of blastocysts before implantation. After implantation, a wave of de novo DNA methylation occurs and is associated with tissue differentiation. ESCs that differentiate in vitro show a similar wave of de novo methylation and can serve as a suitable model to study the molecular function of Lsh in this process.

We generated Lsh-/- ESCs and found that de novo methylation at several repeat sequences was incomplete in the absence of Lsh and fully restored when Lsh was re-introduced into Lsh-/- ESCs. This indicated that Lsh plays a critical role in the establishment of DNA methylation during cellular differentiation. Furthermore, we found that Lsh is directly associated with those repeat sequences that are undergoing de novo methylation and that the presence of Lsh is required for association of the major DNA methyltransferase 3b with these loci.

When we tested functional domains of Lsh, we discovered that the ATP-binding site of Lsh is required for complete methylation and Dnmt3b association with these repeat target sequences. The ATP binding site is essential for ATP hydrolysis and the chromatin remodeling function of SNF2 factors. Thus, our results indicate that the chromatin remodeling function of Lsh is required for effective DNA methylation. To assess chromatin structure, we applied the nucleosomal occupancy assay, in which we detected lower nucleosomal density in Lsh-/- cells at repeat sequences, as compared with wild-type controls. Nucleosomal density was restored to wild-type levels upon re-introduction of Lsh into Lsh-/- cells, indicating that nucleosomal occupancy at repeat sequences depends on the presence of Lsh. Finally, we could demonstrate that nucleosomal density depends on the ATP function of Lsh, indicating that Lsh performs chromatin remodeling at those repeat loci.

Our results suggest that the primary molecular function of Lsh is chromatin remodeling via altering nucleosomal density at loci that are undergoing de novo methylation. Altered nucleosomal occupancy in turn modulates the association of Dnmt3b with target sequences and hence supports de novo methylation. Our results connect two major epigenetic features, chromatin remodeling and DNA methylation, and provide mechanistic insights into the interplay of epigenetic pathways.

Chemistry and Nanotechnology Section

Biophysics Resource Group

The Biophysics Resource Group (BRG) provides operational support to scientific instrumentation and computing resources for several laboratories in the NCI Center for Cancer Research (CCR). This support includes: (1) operation, maintenance, and technical support for all nuclear magnetic resonance (NMR) spectrometers located in the Structural Biophysics Laboratory (SBL), Chemical Biology Laboratory (CBL), and Molecular Targets Laboratory (MTL); (2) operational support (through the BRG in the SBL) of a shared-use facility that provides all CCR researchers access to biophysical instrumentation and technologies; (3) laboratory management and operational support for the Protein–Nucleic Acid Interactions laboratory; and (4) management and support of the high-power, dedicated computing facility in SBL, which includes a network of multiprocessor cluster computers, file servers, a backup server, personal workstations, and instrument-connected computers supporting data acquisition, molecular modeling, and structure calculations.

Molecular Targets Group

The Molecular Targets Group is organized into three subgroups: (1) assay development and screening; (2) natural products chemistry; and (3) protein chemistry and molecular biology. All three groups collaborate extensively with CCR investigators to develop and apply assays focused on specific cancer-related targets and/or pathways. The goals of these assays are the identification of bioactive molecules through high-throughput screening (HTS) and the subsequent characterization of the activities of active compounds. Of particular interest to the group is the identification of novel compounds (and novel activities of known compounds) from natural product extracts obtained from the NCI Natural Products Repository and academic collaborators. A typical work flow starts with the development of a highly reproducible assay compatible with HTS and use with natural product extracts. This is followed by a screen of pure compound libraries (currently up to approximately 70,000 compounds) and of natural product extracts (more than 180,000 partially purified samples and approximately 40,000 crude extracts from various sources) for samples able to affect the molecular target or pathway of interest. Natural products chemistry focuses on purification and characterization of active compounds from extracts. The group works directly with the MTL and has more than a dozen currently active collaborations with other CCR laboratories (or sections) or clinical branches, as well as non-NCI (including international) collaborating labs.

Significant Achievements

For the purposes of this report and because the work of the three subgroups is closely coordinated and highly interactive, accomplishments are combined. A large number of targets are being investigated in the laboratory at any given time. Currently, more than a dozen projects are active in the group. Each subgroup contributed to work focused on the following targets:

Antiviral proteins. Evaluation of biochemical, biophysical, and cellular effects of griffithsin and its tandemers has been completed, using calorimetry, differential scanning fluorimetry, and electron microscopy (*Retrovirology* 2015, 12:6). Additional antiviral proteins isolated from natural product extracts are undergoing physical, biochemical, and functional characterization. New publications describe the use of scytovirin on Ebola virus (*Antiviral Res*. 2014, 112:1-7) and the production of cyanovirin in plants (*Plant Biotechnol J.* 2015, in press).

Cancer-associated fibroblasts. Purified natural products from a number of active extracts are being characterized by their ability to differentially affect cancer-associated fibroblasts (CAFs) by comparison to bone marrow mesenchymal stem cells, from which they are derived. Several of these have been shown to induce apoptotic cell death in CAFs.

Colon cancer cell line growth inhibition. Data mining of NCI-60 cell line data identified a series of colon-specific growth inhibitory extracts from which a number of new natural products are being isolated and characterized (*J. Nat. Prod*. 2014, 77:2475-80).

DENV RNA (RNA thermal stability). A differential scanning fluorimetry (DSF) assay to screen for natural product extracts that will target the Dengue virus (DENV) minigenomic RNA is being developed. Three structural motifs of the DENV RNA will be screened individually to

identify substances that stabilize/destabilize the RNA structures. Further assessment will include DSF and RNA structure analysis.

Epithelial cell adhesion molecule (EpCAM) assay for liver cancer stem cells. EpCAM is a cancer stem cell marker in hepatocellular carcinoma (HCC) and several other cancers. Three purified active natural products are being pursued to establish differential activity (EpCAM+ versus EpCAM- HCC cells) and their mechanisms of action. One of these products appears to be growth inhibitory, while the others induce apoptosis.

Ewing sarcoma-related transcription factor. Work has been completed on the study of the increase in cytosolic calcium levels as a mechanism for inhibition of Ewing sarcoma–related transcription factor (EWS-FLI1) activity by Englerin A, and a manuscript has been submitted for publication. Animal studies with mithramycin combinatorial biosynthesis analogs have also been completed.

HIV integrase. An assay for inhibition of HIV integrase activity has been developed and reagents obtained from an academic collaborator. The initial screening of pure compound libraries has been initiated, and adaptation of the assay for natural product extracts is under way.

MALT1 (inhibition of a protease implicated in B-cell lymphoma). Purification of active compounds from natural product extracts continues, along with biochemical characterization of active compounds.

NF1 (neurofibromatosis type 1 involved in astrocytoma). A pair of compounds (deguelin and dehydrodegeulin) have been purified from extracts and found to have differential effects on a variety of NF1null astrocytoma cell lines. The identification and purification of these compounds demonstrates the power and utility of the prefractionation approach taken by the natural products group (i.e., partial purification of crude extracts to eliminate or sequester interfering compounds). A manuscript is in preparation.

PAX3/FOXO1 (fusion transcription factor involved in rhabdomyosarcoma). A cell-based HTS assay was developed and validated for the discovery of inhibitors of the aberrant fusion transcription factor PAX3-FOXO1. HTS has begun.

p38 (non-canonical activation pathway for p38 in T cells). A manuscript describing novel synthetic p38 inhibitors has been submitted. Bioassay guided fractionation for natural products discovery is ongoing and progressing towards isolation and characterization of active pure natural products.

P300-Hif1 (protein–protein interaction required for hypoxic response). Natural product inhibitors of this interaction continue to be purified and characterized (*J. Am. Chem. Soc.* 2015, 137:5569-75).

Pdcd4 (tumor-suppressor protein). In what has become an international collaboration, more novel stabilizers of Pdcd4 have been identified and published (*Marine Drugs* 2014, 12:4593-601).

Tyrosyl-DNA phosphodiesterase 1 (TDP1). A novel TDP1-inhibitory cyclic peptide has been isolated from a marine organism and is undergoing structural and biochemical evaluation.

TDP2 assay (inhibition of kinase activity). Development and validation of a chromogenic assay for the discovery of natural product inhibitors of TDP2 has been completed. Assay reagents (enzyme and substrate) and plates have all been purchased. Assay formats for pure compound and pre-fractionated natural product extract libraries have been finalized. Screening of the pure compound libraries will begin soon.

Small ubiquitin-like modifier(SUMO) proteins. Purification of active compounds from natural product extracts continues, along with biochemical characterization of active compounds.

TNF-related apoptosis-inducing ligand. Characterization of the natural product withanolide E and a series of analogs with variable activity in sensitizing TNF-related apoptosis-inducing ligand (TRAIL)–resistant renal carcinoma cells to TRAIL-induced apoptosis was completed and published (*Cell Death Dis.* 2015, 6:e1666). A new series of natural product inhibitors of protein synthesis initiation is being characterized.

Yeast chemical genomics. Using MTL's collection of heterozygous and homozygous deletion mutants of the yeast *Saccharomyces cerevisiae* (*S. cerevisiae*), a novel insight was gained into cycloheximide's mechanism of action as an inhibitor of actin cytoskeleton dynamics via the inhibition of the RhoA GTPase. A manuscript describing the findings has been submitted for publication.

Other support activities. The group has been very active in supporting continued expansion of the MTL screening libraries. In particular, a number of extracts from culturable fungi have been obtained, plated for screening, and added to HTS resources. The group also continues to participate in the evaluation of potential new MTL projects (four formal project proposals and multiple informal discussions in the last year).

Biomolecular Informatics Group

Scientists of the Biomolecular Informatics Group (BMIG) are involved in computationally characterizing RNAs, DNAs, proteins, and small molecules, and their interactions. Areas of expertise include the computational design of novel RNA nanoscale structures, RNA secondary structure prediction, characterization of protein–ligand interactions, virtual ligand screening, and computational analysis of antibody sequences and structures, as well as techniques related to the design and characterization of RNA and DNA nanoparticles. One BMIG scientist is involved in the experimental testing of de novo–designed RNAs and their delivery formulations. This research supports the groups of Drs. Bruce A. Shapiro and Marc Nicklaus (CCR).

Significant Achievements

Computational Modeling of Ribosomal Frameshifting in the CCR5 mRNA. Using computational three-dimensional modeling and simulations, a novel mechanism for microRNA-mediated gene downregulation has been elucidated. In this mechanism, a microRNA stabilizes an mRNA-pseudoknot by forming a triple-helix structure with it that then leads to a ribosomal frameshift, subsequent activation of the nonsense-mediated decay pathway, and destabilization of the messenger RNA. Evidence for the proposed mechanism has been provided for the case of the CCR5 mRNA in the form of a large variety of experiments (performed by a collaborating group from the University of Maryland). This work has led to a publication in *Nature*.

Computational and experimental characterization of RNA/DNA hybrids. Recently, RNA/DNA hybrid structures where developed in the laboratory of Dr. Bruce Shapiro. Such designed RNA/DNA complexes have many potential uses: they can, for example, be used for the controlled re-association into RNA/RNA and DNA/DNA complexes; the RNA/RNA complexes correspond to active small interfering RNA (siRNA), which then can lead to controlled silencing of programmed target genes. Using the hybrid approach, RNA-based functionalities are intentionally disrupted through the hybridization of the two RNA counterparts with DNAs. The functionality is only restored if the two RNA/DNA hybrids are co-delivered in a cell providing control on their activation as well as better in vivo lifetimes, as hybrids are less susceptible to degradation. This hybrid approach can be applied at the level of RNA nanoparticle scaffolds, such as a nanocube scaffold. The proportion of DNA and RNA within those constructs has implications on their immunogenicity as evidenced recently. Leidos Biomedical researchers also contributed to a novel computational approach that allows multistrand secondary structure prediction involving RNA/DNA hybrid interactions.

Development of drug delivery formulations. The therapeutic potential of nucleic acids–based nanoparticles can be unlocked only with the help of agents that facilitate the delivery of the designed molecules into the target cells. For this reason, ongoing research focuses on the development of molecular drug delivery vehicles amenable to RNA and DNA nanoparticles. The goal of the delivery vehicles is twofold: to facilitate cellular entry and to allow delivery specifically to the targeted cells (thus minimizing side effects).

We are working on liposome formulations that encapsulate the drugs, are enriched in the cancer sites through an enhanced permeation and retention (EPR) effect, and can be disrupted at the target site. We described the potential of bola amphiphiles and oxime ether lipids as delivery agents in two recent publications. The characterization of bola amphiphiles as drug delivery vehicles involved not only a variety of transfection experiments, but also computational molecular dynamics simulations. The computational analysis helped to understand how the molecular properties of the delivery agents contribute to in vivo delivery properties.

Computational characterization of protein SUMOylation. The conjugation of small ubiquitin-like modifier (SUMO) proteins can lead to modified functions of substrate proteins. Protein SUMOylation plays a role in the localization and stabilization of proteins with a possible role in chromatin remodeling as well as cancer progression. Previously, two synthetic peptide sequences were identified to have a SUMOylation reactivity higher than that of a native peptide sequence.

In order to elucidate the mechanism of protein SUMOylation, these two highly reactive peptides were characterized using in silico docking studies with respect to the SUMOylation enzyme SUMO E2 (Ubc9). The computational studies identified a substrate-binding site on the Ubc9 surface adjacent to the active site. It was found that the reactive peptides bind to the Ubc9 enzyme in extended conformations. These results suggest that the synthetic peptides mimic the native protein–ligand interactions of the endogenous SUMOylation substrates. This computational study has shed new light on the mechanistic aspects of SUMO biology.

Basic Research Section

Retroviral-Biochemistry Group

The Retroviral Biochemistry Group (RBG) supports research of the Reverse Transcriptase (RT) Biochemistry Section at the Basic Research Laboratory (BRL) and the HIV Dynamics and Replication Program (HIV DRP).

RBG explores nucleic acid–based strategies to investigate conserved structures in the retroviral genome, mutations, and host-virus interactions as possible targets for new antiretroviral drugs. This work is complemented by chemical biology approaches to identify small molecules that interact with, and antagonize, cellular and viral regulatory RNAs.

The group also supports efforts to mutagenize, purify, and analyze key retroviral proteins to aid in drug development. The RBG Model Development Section (MDS) seeks to translate basic research findings into model systems that more faithfully mimic HIV infection in vivo in order to address questions on viral transmission, viral pathogenesis, and the contributions of the host immune system in these processes.

Significant Achievements

RBG improved methods to generate large amounts of highly purified fluorescently labeled RNAs for screening small molecule microarrays (SMMs) to identify novel therapeutic RNA-binding small molecules.

Macromolecular Crystallography Group

Noninvasive fluorescent protein biomarkers: research and development. Fluorescent protein (FP)–based biomarkers are considered to be emerging and

valuable tools in molecular biology, medicine, and cancer research. They are widely used in the studies of dynamics processes in living cells, tissue visualization, whole-body imaging, and drug efficiency testing.

This year the Macromolecular Crystallography Group focused on improving the photostability of the recently developed green-emitting fluorescent biomarker NowGFP and on studying the photo-induced dynamics of a blue FP, mKalama1.

A green-emitting fluorescent variant, NowGFP, with a tryptophan-based chromophore (Thr65-Trp66-Gly67) was recently developed from the cyan mCerulean by introducing 18 point mutations. NowGFP is 30 percent brighter than EGFP and exhibits the longest fluorescent lifetime of 5.1 ns, compared with 2–3 ns for other green FPs, making it suitable for simultaneous high-contrast fluorescence lifetime imaging (FLIM) imaging with regular green FP. NowGFP is characterized by bright green fluorescence at physiological and higher pH and by weak cyan fluorescence at low pH. Illumination with blue light induces irreversible photoconversion of NowGFP from a green-emitting to a cyan-emitting form. We have determined the X-ray structures of intact NowGFP at pH 9.0 and pH 4.8 and of its photoconverted variant, NowGFP_conv, at 1.35, 1.18, and 2.5 Å resolution, respectively. The structure of NowGFP at pH 9.0 suggests the anionic state of Trp66 of the chromophore to be the primary cause of its green fluorescence. Our analysis shows that Lys61, adopting two distinct pH-dependent conformations, plays a central role in the chromophore ionization. The structure of NowGFP_conv revealed that photoconversion of NowGFP is accompanied by decomposition of Lys61 with a predominant cleavage of its side chain at the C^{γ}—C^{δ} bond. Lys61, Glu222, Thr203, and Ser205 form a local hydrogen-bond network connected to the indole ring of the chromophore Trp66; mutation of any of these residues dramatically affects the spectral properties of NowGFP. Ala150Val replacement in the vicinity of the chromophore indole ring aimed at restricting its conformational mobility resulted in a new advanced biomarker with a 2.5-fold improved photostability.

Understanding the photoinduced dynamics of FPs is essential for their application to bioimaging. Despite numerous studies on the ultrafast dynamics, the delayed response of these proteins, which often results in the population of kinetically trapped dark states of various origins, is largely unexplored. By using transient absorption spectroscopy with a time scale ranging from picoseconds to seconds, we revealed a hidden reactivity of the bright blue–emitting protein mKalama1, previously thought to be inert. This protein shows no excited-state proton transfer during its nanosecond excited-state lifetime; however, its tyrosine-based chromophore undergoes deprotonation coupled to non-radiative electronic relaxation. Such deprotonation causes distinct changes in the optical absorption in the broad UV-to-NIR spectral range (ca. 300–800 nm); the disappearance of the transient absorption signal has a complex nature and spans the whole microsecond-to-second time scale. We proposed the mechanisms of the relaxation kinetics based on the X-ray structural analysis of mKalama1 and on high-level electronic structure calculations of the proposed photocycle intermediates. It was concluded that the non-radiative excited-state decay follows two major paths: (1) internal conversion coupled to intraprotein proton transfer, where a conserved residue E222 serves as the proton acceptor; and (2) ionization induced by two consecutive resonant absorption events, followed by deprotonation of the chromophore radical cation to bulk solvent through a novel water-mediated proton-wire pathway. Our findings open up new perspectives on the dynamics of fluorescent proteins as tracked by their optical transient absorption in the time domain extending up to seconds.

Radiation damage studies. Radiation damage is an unavoidable phenomenon during X-ray data collection from macromolecular crystals, and it impacts structure determination. Therefore, it is important to know how much radiation the sample can withstand before being degraded below an acceptable limit. In the literature, the threshold at which the average intensity of the recorded reflections decreases to a certain fraction of their initial value is called the "dose limit." The first values for the dose limit D_{50}, corresponding to a 50 percent decrease of the average intensity, were derived from electron diffraction experiments and were estimated to be 20 MGy. Later, an X-ray study carried out at 100 K on ferritin protein crystals resulted in a D_{50} value of 43 MGy, and it was suggested that a more appropriate limit for macromolecular crystallography is D_{70} (a 30 percent intensity reduction from the initial level), which corresponds to the absorbed dose of 30 MGy. This value was then assumed to be similar in all protein crystals, despite the fact that the rate of radiation damage depends on numerous factors, including X-ray energy, the temperature at which the data are collected, and the composition of the crystal. While investigating the relationship between diffraction data quality and photon energy, we noticed that the reflection intensities measured from the crystals of thaumatin decayed with dose significantly faster than expected. Thus, we decided to study these observations in more detail, since they suggested that there may be no generally applicable radiation dose limit and that different crystals may have different susceptibility to radiation damage. We recorded a series of diffraction images at identical, 2-degree rotation intervals at three different energies (6.33, 12.66 and 19.00 keV) and analyzed the data in terms of radiation damage. The decay in the average diffraction intensity of 70 percent of the initial value, for data extending to 2.45 Å resolution, was determined to be about 7.5 MGy at 6.33 keV, and about 11 MGy at the two higher energies.

Proteasome inhibitor study. Proteasomes are high-molecular-mass multicatalytic enzyme complexes localized in the nucleus and cytosol of all eukaryotic cells. They are involved in the wide set of activities, ranging from the destruction of abnormal and misfolded proteins

to the specific proteolytic activation of signaling molecules. The ubiquitin–proteasome pathway has been implicated in several forms of malignancy, as well as in the pathogenesis of some autoimmune disorders, age-related cardiac dysfunction, diabetic complications, and neurodegenerative diseases. Therefore, the study of proteasome functions, along with the design and development of proteasome inhibitors, is being pursued in many laboratories. A great amount of effort has been made to explore proteasome inhibition as a novel targeted approach in cancer therapy. The first success came with the approval from the U.S. Food and Drug Administration of Bortezomid for treatment of multiple myeloma. Since then, numerous compounds have been reported to inhibit the components of the ubiquitin–proteasome system, and several new drug candidates undergoing clinical trials have emerged. Peptide aldehydes were the first inhibitors designed to target the proteasome, and are still the most commonly used and best-characterized group of such inhibitors. A notable one among them, Ac-Leu-Leu-Nle-H (ALLN, MG101), is also a potent inhibitor of nonproteasomal cysteine protease calpain I. ALLN was the first inhibitor crystallized in a complex with a eukaryotic proteasome. Crystallographic analysis of the complex at 2.4 Å resolution revealed a structural organization of the proteasome and the way the inhibitor binds to its active site. We have determined the structure of the ALLN inhibitor at 0.65 Å resolution. High-resolution structural data from this study provide better accuracy for future modeling of the inhibitor interactions with proteasome and potential intracellular targets.

Interleukin-36 study. Interleukin-36 (IL-36) belongs to the IL-1 family of cytokines, which play a critical role in the function of the innate and adaptive immune systems. The IL-36 subfamily consists of three cytokines: IL-36α, IL-36β, and IL-36γ. Binding to their primary receptors (IL-36R) allows for recruitment of a second receptor subunit, the IL-36R accessory protein. The formation of the receptor heterodimer induces signaling, which typically involves the activation of NF-kB or MARK pathways. To understand the underlying molecular basis for IL-36 cytokine signaling through IL-36R, we initiated the structural study of 36α, IL-36β, and IL-36γ. The study began with the expression and purification of 36α, IL-36β, and IL-36γ with N-terminal His tag. Crystallization screening on those samples did not yield any hits. At present, we are working on the expression of the N-terminal truncated version of IL-36 based on reports that truncated IL-36 enhances the binding activity of IL-36R.

Crystallographic studies of 3CL protease from Middle East respiratory syndrome coronavirus (MERS-CoV). MERS-CoV is a highly pathogenic virus that was first identified in September 2012. The virus causes severe respiratory illness that is accompanied by multi-organ failure, resulting in a mortality rate of approximately 40 percent. Although the number of worldwide infections seemed to decrease towards the end of 2014, new outbreaks of MERS-CoV infections in South Korea and China have once again raised concerns about the potential for rapid spread of the disease. Currently, there are no approved vaccines or drugs available for the prevention or treatment of MERS-CoV infection. The MERS-CoV 3C-like protease (3CLpro) is an essential enzyme for viral replication due to its role in the proteolytic processing of replicase polyproteins. Accordingly, it is a promising drug target for the discovery of novel therapeutic agents. Within the past year, the combined efforts of the Protein Engineering Section (Molecular Crystallography Laboratory [MCL], NCI) and the MTS Laboratory (U.S. Army Medical Research Institute of Infectious Diseases [USAMRIID]) have resulted in the determination of three crystal structures of the catalytically inactive (C148A) MERS-CoV 3CLpro up to 1.55 Å resolution. One aim was to co-crystallize the enzyme with a peptide substrate representing a recognition cleavage site. To that end, the structure of the free-enzyme was solved at 2.56 Å resolution. Co-crystallization and peptide-soaking experiments failed to yield a structure with peptide bound in the active site. Fortuitously, however, another crystal form of the 3CLpro enzyme in space group C2 was obtained, in which the C-terminus of a neighboring protomer in the asymmetric unit was bound to the active site of the homodimer, enabling us to capture the enzyme-product state of the enzyme. The enzyme-product complex structure not only provides structural insights into substrate recognition, but also sets the stage for a structure-based drug design platform for developing new inhibitors. A third crystal form, obtained in space group $P2_12_12_1$, diffracted X-rays to 1.96 Å resolution. In this crystal form, a canonical 3CLpro homodimer was observed with the C-terminal tail of a third molecule in the asymmetric unit bound to the active site. Surprisingly, the third molecule was observed to have a significant rigid-body rotation of its C-terminal domain. This form likely represents a crystallographically trapped monomeric form of the enzyme. This work was published in *Needle, D., *Lountos, G.T., and Waugh, D.S. (2015) Structures of the Middle East Respiratory Syndrome coronavirus 3C-like protease reveal insights into substrate specificity. *Acta Cryst. D* 71:1102-1111 (2015) (*authors contributed equally).

Our current work is focused on screening libraries of previously identified cysteine protease inhibitors to identify those with activity against the MERS-CoV 3CLpro enzyme, but we are applying fragment-based screening methods as well.

Dual-Specificity Phosphatases. Human dual-specificity phosphatases (DUSPs) are a specialized subset of protein tyrosine phosphatases (PTPs) that hydrolyze phosphates of tyrosine and serine or threonine residues of proteins involved in the regulation of cell growth, proliferation, apoptosis, migration, and innate immunity. The human genome encodes 61 DUSPS that cluster into seven homology groups, while variations in regulatory domains and binding partners guide the functional diversity of each enzyme. Catalytic domains are

conserved in all DUSPS and harbor the recognition sequence motif (H/V)CX_5R(S/T), where X denotes a varied amino acid residue. Because of their pivotal role in phosphorylation-dependent cellular pathways, modulating DUSP activities may have therapeutic advantages in many chronic or infectious human diseases. Considering the potential medical benefits of selectively targeting DUSPs, progress in developing therapeutic drugs has been very slow. To aid in the search for inhibitors of specific DUSPS, we have carried out crystallographic studies of human DUSP7 and DUSP22. DUSP7 has been shown to be overexpressed in peripheral blood mononuclear cells and bone marrow from patients diagnosed with acute leukemia, and has been identified as a potential cancer drug target. DUSP22 has been associated with various forms of cancer, including breast cancer and lymphoma, and in Alzheimer's disease, but its role in these diseases is not understood. The crystal structure of DUSP7 was solved at 1.67 Å resolution bound to a phosphate ion, which represents an enzyme–product complex. This structure adds to the growing structural knowledge base of the DUSP family members and also provides insight into the active site architecture, which will aide in the design of small-molecule inhibitors. A high-resolution structure of DUSP22 in complex with the phosphotyrosine mimetic p-nitrophenyl phosphate was obtained at 1.34 Å resolution. This structure represents the first crystal structure of a human DUSP bound to a small-molecule substrate analog. This finding will provide the structural information needed to guide the development of this small-molecule substrate into a potential DUSP22 inhibitor. Publications related to this work include:

Lountos, G.T., Cherry, S., Tropea, J.E., and Waugh, D.S. Structural analysis of human dual-specificity phosphatase 22 complexed with a phosphotyrosine-like substrate. *Acta Crystallographica F Structural Biology Communications*, 71:199-205 (2015).

Lountos, G.T., Austin, B.P., Tropea, J.E., and Waugh, D.S. Structure of human dual-specificity phosphatase 7, a potential cancer drug target. *Acta Crystallographica F Structural Biology Communications*, 71:650-656 (2015).

Structural Studies of Protein Tyrosine Phosphatase Epsilon. The protein tyrosine phosphatase epsilon (PTPepsilon) has been shown to be overexpressed in breast cancer and is a potential cancer drug target. PTPepsilon contains two cytoplasmic PTP domains, a membrane proximal D1 domain and a membrane distal D2 domain, in addition to a single transmembrane segment and an extracellular domain. While both the D1 and D2 domains are PTP domains, catalytic activity is observed only in the D1 domain. Previously we solved the structure of the D1 domain to 1.7 Å resolution. We are currently in collaboration with the NCI Chemical Biology Laboratory to develop multi-dentate inhibitor scaffolds for drug design. Additionally, we have solved the structure of the D2 domain at 2.27 Å resolution. We are analyzing the crystal structure of the D2 domain to understand why it lacks catalytic activity. Mutagenesis is being applied to develop a catalytic-rescue mutant of the D2 domain to identify structural features that are responsible for the lack of catalytic activity.

Structure-based drug design targeting TDP1. Topoisomerase 1 (Top1)-mediated cleavage complexes resulting from trapping Top1 by DNA lesions, including abasic sites, oxidized bases, carcinogenic adducts, and anticancer Top1 inhibitors, are removed by tyrosyl-DNA phosphodiesterase I (TDP1). TDP1 acts by cleaving the covalent bond between a 3′-DNA phosphate group and the catalytic tyrosine residue of the trapped Top1. TDP1 is currently being evaluated as a drug target for cancer therapy; however, to date no inhibitors exhibiting synergistic activity with Top1 have been identified. We are currently collaborating with the Molecular Pharmacology Laboratory at NCI to develop TDP1 inhibitors. We are currently aiming to obtain co-crystal structures with preliminary hits identified from inhibitor screens. We have recently obtained a 1.5 Å resolution data set from TDP1 crystals soaked with the compound SV-295. However, the electron density in the active site reveals that the compound has undergone a dimerization reaction, resulting in a new chemical scaffold. We are currently working on developing a synthetic route towards this new compound, to characterize its activity against TDP1. Current efforts being applied towards inhibitor development include crystallographic fragment screening.

Bacterial Genetics Group

The Bacterial Genetics Group (BGG) uses the bacterial virus λ and its host, *Escherichia coli* (*E. coli*), as paradigms for ongoing developmental and gene regulation studies. Coevolution of λ with *E. coli* has produced genetic systems that are exquisitely connected to the most basic functions of the bacterial host. By examining the interface between λ and host systems, BGG follows the trail of the phage to understand what is most important and vital to both cellular life and viral exploitation of cellular systems. The virus provides clues as to how those cellular functions work and how to study them. Recent characterizations of the λ genetic network have provided a framework for systems biology approaches using λ as a prototype for theoretical modeling methodologies, which have become important for addressing signal transduction, cancer development, and other complex genetic networks of eukaryotes.

BGG continues to develop recombineering, a highly efficient technology for precise in vivo manipulation of DNA in *E. coli* and other bacteria, using genetic recombination. Recombineering at short (50 base pairs) homologies mediated by bacteriophage functions (collectively known as "Red") is used to modify mammalian genes resident on bacterial artificial chromosomes (BACs); these altered sequences can then be introduced back into the organism of interest. Recombineering with double-strand polymerase chain reaction (PCR) products is used to precisely replace a defined region with a drug marker, enabling the creation

of a null mutation in a gene. Recombineering with single-strand oligonucleotides (oligos) 70 nucleotides in length is extremely efficient in the absence of methyl-directed mismatch repair, and 50–75 percent of the viable cells can become recombinant. Single-strand recombination enables point mutations to be created on large molecules, such as BACS, and these recombinants can be identified with a PCR screen. In bacterial genomes, this technology enables targeted mutagenesis and can be used to make specific mutations in even essential genes, the most interesting, yet often the most difficult to manipulate, class of genes. BGG also studies a second recombineering system from a defective bacterial virus, the RecET system. Like the Red system, RecET consists of a single-strand annealing protein and a 5′ –> 3′ dsDNA exonuclease. RecET is better than Red for fragment joining, which is an in vivo cloning method of assembling nonreplicating linear DNA fragments using short homologies. The Red system is superior for all other recombineering reactions.

To further probe the molecular mechanism of recombineering, BGG continues to explore the dependency of recombinant formation on active DNA replication of the target. For λ Red, BGG has demonstrated that DNA replication strongly stimulates plasmid by single-stranded oligo recombination mediated by the single-strand annealing protein Beta, providing strong evidence that Beta recombination is mechanistically coupled to DNA replication of the DNA molecule targeted for recombination. Both Red and RecET can recombine a nonreplicating linear dimer plasmid substrate with high efficiency. The BGG replication studies are consistent with both Red and RecET recombination proceeding primarily by a single-strand annealing mechanism rather than by strand invasion.

The bacterial virus λ has two developmental life styles: active viral reproduction and lysogeny, or viral latency, where the virus exists as a prophage. It is of interest to understand how a quiescent virus is reactivated, since viruses are responsible for a number of human diseases, including cancer. For the λ prophage, the CI repressor protein prevents expression of most viral genes. BGG has devised a reporter system to monitor viral induction from the prophage state and has identified two viral genes that are expressed in the prophage along with CI, and that modulate viral induction, *rexA* and *rexB*. Genetic analysis shows that the RexA protein promotes induction of the virus and the RexB protein controls this activity of RexA. In order to understand the molecular mechanism of these effects, BGG is working to identify host factors impacted by the Rex system and has engaged in a collaboration with a biochemist in the Department of Molecular Medicine at Cornell University, Dr. Josh Chappie, who has crystallized the RexA protein and is examining in vitro interactions of RexA, CI repressor, and the DNA operator sites to which CI binds.

In its long-standing effort to study transcription fidelity as part of a collaboration with members of the NCI at Frederick Gene Regulation and Chromosome Biology Laboratory, BGG has developed a highly sensitive gene reporter assay to analyze transcription misincorporation errors in *E. coli* cells. The assay design was based on a *cre/lox* assay first developed in Dr. Jeff Strathern's laboratory for *S. cerevisiae*. The novel assay allows BGG to specifically monitor transient transcription errors by preserving them as stable genetic changes, and substantially minimizes the impact from translation errors by using a mutant Cre protein, the activity of which can be restored only at the level of transcription. The assay was optimized using G –> A misincorporation as a model. Utilizing recombineering technology and sampling various cellular growth conditions and assay media, BGG has developed robust and highly reproducible protocols for quantitative and qualitative analyses of transcription misincorporation errors in *E. coli*.

BGG has used the assay to study the role of transcription elongation factors GreA and GreB in transcription fidelity. Both GreA and GreB have been considered to be transcription fidelity factors because they have a similar activity of binding to RNA polymerase and inducing its intrinsic RNA cleavage activity. This cleavage eliminates misincorporated nucleotides in mRNAs. Single *greA*, *greB*, and the double *greAB* gene knockouts were made and tested in the newly developed assay. BGG found that the absence of GreA caused a thousand-fold increase in G –> A errors. The absence of GreB had no effect, either alone or in combination with GreA. These data indicate that GreA, but not GreB, is a transcription fidelity factor. The differential effect of the GreA and GreB factors on transcription fidelity is intriguing and warrants further investigation.

Urologic Oncology Group

The focus of the BSP Urologic Oncology Group (UOG) within the Urologic Oncology Branch of CCR is the discovery and characterization of kidney cancer susceptibility genes through studies of families with rare inherited renal cancer syndromes, and deep sequencing of sporadic histologically defined renal tumors. The goal of UOG is to provide insight into the molecular mechanisms that lead to the development of kidney cancer through functional studies of the proteins encoded by these kidney cancer susceptibility genes, and to apply this knowledge to the development of effective molecular targeted therapies. UOG has developed genetically engineered mouse models for in vivo studies of protein function and for testing novel therapeutic agents to treat kidney cancer patients.

Significant Achievements

Discovery that mtDNA mutations can differentiate BHD-associated renal oncocytomas from their sporadic counterparts. Oncocytomas are benign tumors characterized by the accumulation of defective mitochondria, and in sporadic cases, are associated with disruptive mitochondrial DNA (mtDNA) mutations. Renal oncocytomas develop in patients with Birt-Hogg-

Dubé syndrome (BHD), an inherited renal cancer susceptibility syndrome caused by germline mutations in the tumor suppressor gene *FLCN*, but the role mtDNA mutations play in these and other renal oncocytomas with an apparent genetic component is unknown. To address this question, UOG sequenced the mitochondrial genome in BHD-associated renal oncocytomas, in sporadic renal oncocytomas from patients with bilateral, multifocal (BMF) tumor presentation but no family history of renal oncocytoma, and in non-oncocytic renal tumors with a variety of histologies. mtDNA sequencing revealed that all BMF oncocytomas carried disruptive mutations, which impair the assembly of the NADH-ubiquinone oxidoreductase. Multiple tumors from a given BMF oncocytoma patient had the same somatic mutation, whereas renal oncocytomas from patients with BHD syndrome and renal tumors with different histologies displayed no disruptive mtDNA mutations. These results show that pathogenic mtDNA mutations affecting complex I of the respiratory chain are strongly correlated with the oncocytoma phenotype in non-BHD-related renal tumors and support a role for mtDNA mutations in respiratory chain complexes as diagnostic markers to distinguish BMF renal oncocytomas from renal oncocytomas associated with BHD.

Development of a TFE3 translocation renal tumor preclinical model. The structurally related microphthalmia transcription (MiT) family members *TFE3*, *TFEB*, *TFEC*, and *MiTF* transcriptionally regulate a variety of tissue-specific functions that contribute to cell differentiation, and their deregulation may drive tumorigenesis. Gene fusions involving members of the MiT family genetically define a group of sporadic renal tumors comprising about 5 percent of all reported cases. *TFE3* and, less frequently, *TFEB* form fusions with other genes in sporadic renal tumors, designated translocation renal cell carcinoma (RCC), which develop in children and young adults, and are very aggressive. Effective targeted therapies are lacking; therefore, UOG has developed mouse models in which two of the known fusion genes, *PRCC-TFE3* and *PSF-TFE3*, preceded by a loxP-flanked termination codon, are knocked into the ROSA 26 locus. Targeting *TFE3* fusion gene activation with a kidney-specific *CDH16 Cre* transgenic mouse cross resulted in the development of multiple renal cysts and tumors by 6 months of age. These preclinical models of translocation RCC will be useful for testing potential therapeutic agents to treat TFE3 translocation RCC, and these drug studies are now in progress.

Development of FLCN missense mutation preclinical models. The pathogenicity of *FLCN* missense mutations is not confirmed without clear evidence that they cause disease. Two patients were seen at the NIH Clinical Center who carry a germline *FLCN K508R* missense mutation. One developed renal oncocytomas, and the other presented with bilateral multifocal papillary type 1 renal tumors, neither of which is a typical BHD renal manifestation. Furthermore, neither of the patients nor their family members had developed other typical BHD manifestations, raising the question of whether the *FLCN K508R* mutation was the disease-causing variant in these patients. A third patient was seen who had inherited a germline *FLCN H255Y* missense mutation. This patient presented with a chromophobe renal tumor (frequently seen in BHD), BHD cutaneous and lung manifestations, and a family history of BHD. To determine whether these missense mutations were pathogenic, UOG generated BAC transgenic mice carrying the *FLCN K508R* or *FLCN H255Y* missense mutation and genetically introduced these mutant transgenes into kidney-targeted *Flcn* knockout mice that develop a cystic kidney phenotype, resulting in renal failure by 3 weeks of age. The *H255Y* mutation did not rescue the *Flcn*-deficient kidney phenotype, proving that this mutation was pathogenic and the likely cause of renal cancer in the *FLCN H255Y* patient. Interestingly, although the *K508R* mutation reduced the cystic phenotype and extended the lifespan of the kidney-targeted *Flcn* knockout mice, the mice eventually developed a detrimental kidney phenotype and died. These results suggest that the *FLCN K508R* variant is a weak pathogenic mutation that can cause a more indolent renal cancer in patients who inherit this *FLCN* mutation in their germline, which is consistent with the histologic subtypes that developed in the two *FLCN K508R* patients. These preclinical models will be important for studying the mechanism by which these amino acid substitutions alter FLCN function and for testing therapeutic agents to treat BHD-associated kidney cancer.

Development of a genomic sequencing pipeline to search for *FLCN* intronic variants that affect gene regulation. *FLCN* sequence variants or intragenic deletions have been identified in more than 90 percent of BHD families managed by the Urologic Oncology Branch. However, there still remain a small number of families who present with the classic clinical features of BHD syndrome and for whom no sequence variant or intragenic deletion in *FLCN* has been identified. This small group includes the original family described by Birt, Hogg, and Dubé in their seminal paper, and used by UOG to genetically link the BHD disease locus to chromosome 17p11.2. This and other BHD families without *FLCN* coding sequence variants may harbor a germline sequence variant in a regulatory site (miRNA or transcription factor–binding site, or cryptic splice site) located in the untranslated or intronic regions surrounding the *FLCN* locus, or they may have inherited a large structural rearrangement that could negatively affect FLCN expression. To investigate these possibilities, UOG researchers have developed a long-range PCR method to amplify large, overlapping amplicons that cover 40 kb of genomic sequence surrounding and encompassing *FLCN,* and they have generated continuous long-sequence reads using large-insert whole-genome sequencing technologies developed by Pacific Biosciences. Sequence data for one affected and one unaffected BHD family member are being analyzed to identify novel disease-associated sequence or structural variants. Candidate sequence

variants will be evaluated in other affected family members for co-segregation with the BHD phenotype, and will be subjected to bioinformatic analysis. This pipeline will be used to investigate the *FLCN* mutational status of other BHD-affected patients without a *FLCN* coding sequence variant, and the findings may reveal additional mechanisms of *FLCN* inactivation that lead to BHD-associated kidney cancer.

Flow Cytometry Group

The CCR-Frederick Flow Cytometry Core (the Core) is a dedicated resource embedded in the Cancer and Inflammation Program for CCR investigators at NCI at Frederick. Its services include analyzing and/or sorting stained or transfected samples, and training individuals to understand the principles of flow cytometry, so they may ultimately operate the analyzer instruments that the Core makes available to them. These services enable investigators to use flow cytometry to design experiments that will yield reliable data. The staff also consults with investigators to develop and refine new flow cytometry techniques. To serve the needs of CCR investigators at NCI at Frederick, the Core houses five analyzers and three cell sorters. The instruments vary in capability, ranging from having two lasers with the ability to detect four fluorochromes to having three to five lasers capable of detecting up to 18 fluorochromes or antibodies.

Significant Achievements

The CCR-Frederick Flow Cytometry Core is an indispensable resource for NCI at Frederick investigators. In FY2015, 97 investigators from 30 laboratories have used the expertise of the Core staff and the instrumentation maintained by the staff. During the past year, the Core has upgraded all but its oldest instrument, to increase the capabilities of all the instruments and enable seamless moves from instrument to instrument and from analyzer to sorter. These improvements prevent the loss of data due to instrument down time or unavailability, and decrease the wait time for sorting appointments.

The Core staff and instrumentation have provided sorting support for limb bud differentiation of transgenic mice expressing a tdTomato fluorescent protein, as well as support for the following studies: the role of myeoloid-derived suppressor cells; the regulation of suppression of T-regulatory cells by TNFalpha and the homoeostatic activity IKKalpha; the regulation of erythropoietic stem cells by Id2 and the gfl-1 protein; the role of microbiota in autoimmune disease; the role of gamma interferon in hematopoietic stem cell differentiation in aplastic anemia; and the role macrophages in Lewis lung carcinoma.

During the first three quarters of the year, the Flow Cytometry Core staff has trained 15 investigators, including 6 from CCR labs outside of the Cancer and Inflammation Program, to run their own samples, thus greatly increasing the output of the flow instruments. Without individual investigators acquiring and analyzing their own data, the government would need to hire two or more full-time, experienced individuals to perform the same volume of work. Between October 2014 and July 2015, the staff of the Flow Cytometry Core sorted 424 samples and ran 8,474 samples for various investigators. During the same period, at least 13 papers have been published by investigators using data generated using the Flow Cytometry Core instruments.

Media Laboratory

The Media Laboratory has been in operation since 1984, and its employees are skilled at making microbiological media for both bacteria and yeast work. They also routinely make buffers and other reagents for biochemistry, molecular biology, and genetics research. All media are custom made (liquid and plates); thus, additives such as antibiotics, isopropyl β-D-1-thiogalactopyranoside (IPTG), counter-selective agents, anticancer drugs, and reverse transcriptase inhibitors, can be added at the request of the researcher. (Ingredients not commonly used by most labs need to be provided by the ordering lab.) The Media Laboratory is usually able to accommodate requests for new reagents when provided with a recipe. Because it is located on the NCI at Frederick campus, the laboratory's staff members are available to answer any questions. They can also accommodate requests for dispensing products in a variety of sizes (e.g., 10 bottles of LB at 100 ml/bottle). All products use the highest-quality reagents: only Difco agar, Tryptone, and yeast extract are used. Most products are delivered within three days of the order. At present, the laboratory provides services to about 50 laboratories. On-site media and reagent preparation is a highly cost-effective and valuable resource for many scientific laboratories that require microbiological media or other molecular biology reagents.

A more reasonable cost-sharing pricing system was implemented to replace the flat-rate system. Under the cost-sharing system, buffers, plates, and reagents fall into different pricing tiers, depending on the cost of reagents and labor.

Media Laboratory Products

- **Bacterial growth media:** LB, TB, and minimal broth and plates using Difco products, with or without antibiotics or other additives
- **Diagnostic growth media:** MacConkey with sugar of choice, EMB
- **Yeast growth media:** YEPD, YEA, drop-out plates
- **Buffer and solutions:** Tris buffers, Q-buffers
- **Gel electrophoresis and transfer buffers:** Tris-glycine buffer, SDS-PAGE, TAE
- **Bacteriophage growth media for phage lambda and M13:** NZY, YT.

The Media Laboratory provides services to NCI CCR laboratories at two Frederick locations, the NCI Campus at Frederick and the Advanced Technology Research Facility, as well as to the laboratories at NIH Bethesda.

Basic Science Program CCR Genetics Core

The Basic Science Program CCR Genetics Core (BCGC) is involved in the genetics research of CCR investigators. The BCGC provides support to CCR investigators in three main areas: bioresources, genotyping, and bioinformatics. The BCGC works closely with investigators in the initial stages of cohort development, sample processing, storage, support, and maintenance of patient samples and data associated with each patient. BCGC has been tasked with continued support to a core group of principal investigators (PIs; Drs. Carrington, Dean, and Winkler). In total, BCGC has supported many researchers in CCR and its programs, including the CCR Office of the Director and BSP administration.

In FY2015, BCGC services supported scientific studies that resulted in 9 articles published and 21 submitted. BCGC researchers remain an integral part of the core PIs' research. The BCGC consisted of seven personnel at the beginning of FY2015, but with the departure one researcher, the BCGC will comprise six personnel, who will continue to support and aid researchers with their research projects and sample support.

Cohorts

This section involves no personnel; the monies are provided to develop new cohorts of patients for study by CCR investigators. Internal grants, approved by Dr. Strathern, are provided to investigators and are used to collect new clinical data, process tissues for research, and archive new samples for future studies. During FY2015, the lab saw the addition of 10 new cohorts and expansion within 10 existing cohorts.

Bioresources and Genotyping Sections

The Bioresource and Genotyping sections process samples received by CCR investigators (e.g., issuing permits, culturing cells, performing tissue extraction, providing data entry, and genotyping). Shipping permits, IRB approval, and Material Transfer Agreements (MTAs) are managed by BCGC staff and tracked in the BCGC database. To ensure that all patient data and samples collected are in accordance with NIH policies, all entries in our database system are able to be cross-referenced with their pertinent paperwork. During FY2015, BCGC processed the following: 7 Institutional Review Board (IRB) reviews; 26 Office of Human Subjects Research Protection (OHSRP) approvals; 54 Research Donor Program (RDP) requests; 4 Multicenter AIDS Cohort Study (MACS) Concept Sheets; and 17 NIH Quarantine Permits. The staff also obtained numerous export and import permits, MTAs, Simple Letter Agreements (SLAs), and data agreements for CCR investigators. All clinical data and samples received by the BCGC are barcoded and entered into the database system, which allows all study-pertinent information to be available to CCR researchers and their collaborators (with proper security credentials) at any time during processing, data collection, and analysis of these samples.

A major success of the BCGC in its sample management and handling is the reliance on bar coding, robotics, and database integration. Samples are received, bar-coded, and scanned into our database system during each phase of processing. Each sample is associated with all relevant information collected on that specimen. All core PIs use the BCGC's processing system in all samples that are handled by BCGC and in their own labs. This has greatly facilitated research in the CCR labs that utilize our system because it reduces errors and increases efficiency. This type of tracking has made the clean sweep required by NIH a much easier task. Our system tracks over 9 million DNAs on plates and tubes and nearly 1 million tissue samples. In all, more than 10 million samples from over 189 cohorts are archived in our database system. During FY2015, the BCGC handled over 20,048,120 ngs of DNA and 426,816 samples.

Samples from investigators or BCGC samples are fed into the BCGC genotyping section, where state-of-the-art genotyping and sequencing are used to provide genetic data to investigators. The genotyping staff is trained on a number of low- and high-throughput systems. During FY2015, the staff generated hundreds of millions of genotypes on various high-throughput genotyping platforms, in response to requests from PIs. The BCGC sequenced 71,904 samples on its ABI3730 and handled over 163,968 samples on its robotics, all targeted at sequencing. FY2015 has also seen the addition of the iSCAN system from Illumina to the BCGC Core. We have the capability of running the Infinium and Methylation systems by Illumina, and in FY2015, we produced over 300 million genotypes for 1,340 patients using Infinium EXOME chips. The BCGC has also completed the necessary training to work on the MiSeq Platform and the staff is ready to run this platform.

In addition to sample handling and genotyping, BCGC personnel provide constant assistance to CCR investigators. Core staff facilitates research in CCR investigators' labs by refining and improving protocols, training other lab personnel (especially students and visiting scientific staff) on techniques, providing space and equipment that other investigators do not have in their own labs for projects and studies, and extra hands on studies when needed. All this is accomplished by the BCGC staff members because they are available locally, highly skilled, cross-trained, and familiar with the science that is being conducted at the CCR.

Traditional, New, and Emerging Technologies Supported

High-throughput genotyping. We have continued our extensive involvement in array-based genotyping, refining the SNP calls for GWAS as well as studies related to AIDS, hepatitis B virus, and kidney disease. We

have acquired the iSCAN Illumina system in FY2015, and we are constantly exploring new high-throughput technology to enhance data collection on our samples.

Mi-seq Illumina system. The BCGC has received training in this new platform so that we may provide CCR investigators with targeted gene sequencing, metagenomics, small-genome sequencing, targeted gene expression, amplicon sequencing, and HLA typing.

Cell culture. In addition to normal immortalization of cells for current and future experiments, our cell culture group has also been maintaining HEK293 cells for weekly and biweekly experiments in which the cells are transfected with proper gene and control constructs. These cells have been used for FRET/FLIM exploration by one of our collaborators. The cell culture group has also expanded cell lines in order to provide needed quantities for RNA expression assays.

Cancer and Inflammation Program Genetic and Microbiome Core

The Genetic and Microbiome Core (GMC; the Core) has played a prominent role in the statistical analyses of case-control studies investigating associations of common genetic variants associated with HIV-1 risk. The GMC expertise has been utilized to determine that much of both protective and risk associations between human leukocyte antigens (HLA) and HIV progression can be explained by the binding specificity conferred by polymorphisms at specific sites of HLA.

The GMC has also investigated the role that HLA expression plays in disease. Much of the association between HLA-C variants and HIV viral load could be shown to be attributable to differences in expression governed by miR148A binding to certain HLA-C alleles. The GMC supported both the experimental and epidemiological work that underlies this finding. Additional uncharacterized differences give rise to a continuum of allelic lineage–specific HLA-C expression levels. The work of the Core was used to demonstrate that both infectious disease (HIV viral load) and autoimmunity (risk of Crohn's disease) can be associated with this continuum, treating HLA-C allelic effects as a continuous rather than a categorical variable.

The GMC is quite active in the area of regulation of HLA expression. The HLA is central to immune responses and provides epidemiological association signals that are among the strongest in studies of both infectious and autoimmune diseases as well as of some cancers. The Core participated in bioinformatic analyses of HLA-C sequences in Chinese populations, characterizing two new variants and showing that gene conversion is a rare event in the evolution of HLA-C, with different regions of the gene showing congruent phylogenies.

The core has also been prominent in showing that HLA-C expression (rather than binding repertoire) is an important determinant of HIV viral load and that a polymorphism of a miR148A binding site can control such expression. GMC was able to show that the miR binding site was originally present on all HLA-C alleles, but that a rare gene conversion from HLA-B some 4 million years ago generated an HLA-C allele without the binding site. The allele gave rise to half the lineages and 33 percent of extant HLA-C alleles in a manner that independently recapitulated known functional HLA-C polymorphisms on a high-expression background.

Mir148A maps to chromosome 7 and is itself polymorphic, having high- and low-expression variants. It was possible to show that the miR148A genotype influenced both autoimmune status (Crohn's disease) and infectious disease (HIV) severity in a manner indicative of action through HLA-C expression control. Since tight linkage to HLA-B generally confounds the determination of HLA-C-specific effects but HLA-B has no miR148A binding site, the miR148A influence is attributable to HLA-C-specific disease effects. More recently, the GMC participated in the study of HLA-A expression. Our statistical expertise was used to determine the contribution of individual allelic lineages of HLA-A to expression in individuals, using linear regression analysis. The role of HLA-A methylation and the effects of HLA-A expression on HIV disease risk and progression are also being investigated.

HLA expression has also been implicated in transplantation outcomes, and the GMC has worked with collaborators to show that expression of both HLA-C and HLA-DP can play a role in determining allograft outcomes and can be novel indicators of donor suitability. The GMC participated in the analysis of the role of specific variants of the ApoL1 gene implicated in kidney disease and in trypanolysis.

The GMC also participated in the study of HPV and cervical cancer in Latin American populations. Somatically mutated genes were identified using exome sequencing and the activation of the PIK3CA gene implicated in the etiology of HPV-associated tumors. As part of the widening role of the GMC, facilities and personnel for microbiome preparation, sequencing, and analysis have been established at the Bethesda campus. Pipelines for microbiome sequencing and downstream sequence analysis are in development, and collaborations are being established. It is expected that the role of the microbiome in health will be explored and will become a larger focus of GMC's work in the coming year.

Support Provided by the Cancer Research Technology Program

Sequencing Facility

The primary mission of the Sequencing Facility (SF) is to utilize high-throughput sequencing technologies to enrich cancer research and ensure that the NCI community can remain at the leading edge of next-generation sequencing technology. The CCR-funded SF provides CCR and NCI investigators with access to one MiSeq sequencer, three NextSeq 500 sequencers,

and two state-of-the-art Illumina HiSeq 2500 sequencers. In addition, a third-generation sequencing technology, a Pacific Biosciences RS sequencer, was brought into limited production at the SF, in conjunction with the CCR-Genomics Laboratory and CRTP technology development project management. The PacBio sequencer is funded through a combined effort between CCR, the Office of Scientific Operations, NCI at Frederick, and the CRTP, FNLCR.

Significant Achievements

- The SF operated as a fully functional core facility in support of 68 investigators largely from CCR, but also from the Division of Cancer Epidemiology and Genetics (DCEG) and the Division of Cancer Treatment and Diagnosis (DCTD), along with the National Human Genome Research Institute, NIAID, and FNLCR.
- As of July 2014, the Illumina Sequencing Laboratory had processed and sequenced more than 3,512 samples for 68 NCI principal investigators, and delivered more than 35 trillion bases. The SF Illumina Sequencing Laboratory also generated more than $950,000 through Core Services Accession System (CSAS) chargeback. Sequencing services have been expanded to include the RNA-Seq for FFPE samples and ultra-low input for mRNA-Seq protocol at as low as 100 pg. We have implemented new Clarity Genologics LIMS into production, which will allow us to track all processes and reagents in our lab. The team worked collaboratively with Dr. George Miles (Laboratory of Pathology, CCR, NCI) on project design, sequencing, data analysis, and manuscript preparation for the Multiplex Proteomic Analysis by DNA Sequencing Project. This manuscript has been accepted by *Nature*.
- For FY2015, the Illumina informatics team has expanded informatics work flow and data analysis pipelines to support new lab protocols. A new set of software tools and in-house scripts has been developed to support the new analysis work flows, and to compare data analysis for RNA-Seq and Exome-Seq of degraded or low-input FFPE samples. The team has customized the Clarity LIMS to fit SF's work flows, projects, and samples tracking needs. The team also integrated all Illumina sequencers and lab QC instruments into LIMS for instrument run and QC result tracking automation. The team also collaborates with the High Performance Computing group at the Center for Biomedical Informatics and Information Technology (CBIIT), and with CCR bioinformatics groups to define and implement a centralized genomics repository for data storage and distribution.
- The PacBio team has successfully prepared 77 sequencing libraries for 16 principal investigators. With the release of new sequencing chemistry and polymerase, the average PacBio read-length has nearly doubled in the last year to over 15,000 base pairs. This has resulted in a nearly doubling of the sequencing yield, with an average of approximately 850 mega–base pairs per SMRT Cell. The PacBio team has implemented several new applications for production in the past year, which required installation of new instrumentation protocols, kit validation testing, and procedural optimization in the laboratory, as well as installation and validation of new bioinformatics tools. The PacBio informatics team has designed primers and performed targeted sequencing of five RAS-related genes, and deployed several versions of the IsoSeq pipeline to process the IsoSeq data, working closely with its developer at PacBio. The team has also developed software to correlate IsoSeq output with genome annotation data to find novel transcripts (an Employee Invention Report has been filed and approved), and developed a protocol for normalizing IsoSeq read-lengths to enhance transcriptome coverage.

CCR-Dedicated Core Service Programs

Protein Expression Laboratory

The 4.25 FTEs in the CCR-dedicated Protein Expression Laboratory (PEL) carry out cloning, virus production, protein expression, and protein purification in support of CCR activities. In order to better serve CCR, PEL was transitioned in FY2015 into a new structure with two groups.

The Cloning and Nucleic Acids Group (CNG), led by Carissa Grose, constructed 344 entry and expression clones for 44 investigators (70 CSAS requests by the end of July 2015) in FY2015. About half of these clones were sent back to investigators for in vivo work in model organisms and cell lines. A quarter of the constructs were used for lentivirus production, and the remainder was used for protein expression work in PEL. Almost all of the cloning and subcloning was done using Gateway recombinational cloning on our in-house-developed combinatorial cloning platform (CCP). The Virus Production section of CNG worked on 32 CSAS projects in FY2015 for 21 investigators, and produced 114 lentiviral supernatants, most of which were titered by CNG prior to delivery.

The Protein Production Group (PPG) provides protein purification and production of cells and cell-derived products via expression in bacterial, insect, and mammalian systems. Primary expression activities include production of cytoplasmic and secreted recombinant proteins from *E. coli*, baculovirus-infected insect cells, and transfected mammalian cells. Following expression, PPG carries out high-throughput, micro-scale purification methodologies to screen samples for positive lead constructs and/or expression conditions, and then proceeds to scale-up purification using affinity, ion exchange, and size-exclusion chromatography to purify native and recombinant proteins. A new group

leader, Jane Jones, took over as head of the PPG during FY2015 and helped to transition the group to their new CCR-dedicated role. During the time period covered, PPG worked on 54 projects for 27 investigators. Approximately 65 percent of this work focused on insect expression work in support of investigators in the CCR Laboratory of Cell Biology. This group had unexpectedly high demands for expression work in support of structural biology studies, and, as a result of this higher demand, capacity for eukaryotic expression in PEL was reduced. PEL requested additional FTE support from CCR for FY2016 to support the higher workload anticipated in the future. PPG carried out over a dozen protein purification scouting projects for seven investigators, and performed scale-up purification for another eight projects. PPG anticipates additional workload in future years as CCR investigators who were previously forced to go to outside companies due to the loss of PEL resources are beginning to return to PEL. PPG generated over 100 baculoviruses in FY2014 and produced over 250 liters of insect and mammalian expression materials.

Protein Characterization Laboratory

Protein Characterization Laboratory (PCL) provides state-of-art mass spectrometry support to CCR for proteomics and metabolomics analysis, as well as to the Division of Cancer Epidemiology and Genetics (DCEG) for estrogen and androgen quantitative analysis. This year, PCL has established two supporting units (the Protein Mass Spectrometry Support Unit funded by CCR and the Hormone Analysis Unit funded by DCEG) through a Yellow Task mechanism. PCL has successfully integrated three new mass spectrometers (a Fusion tribrid orbitrap mass spectrometer and two Quantiva triple-quadruple mass spectrometers) for servicing CCR and DCEG. PCL has also successfully developed an androgen assay. The Hormone Analysis Unit is working on the androgen production assay in FY2015.

During FY2015, the laboratory continues its efforts to integrate new instrumentation and technologies in order to solve research problems related to protein signaling complexes. PCL established metabolomics support for CCR. Our staff has shown excellent professionalism and overcome many difficulties in order to support NCI intramural research community with a limited number of staff members.

Significant Achievements

PCL provides crucial proteomics and mass spectrometry services for the NCI/NIH research community through its efforts to identify protein complexes and post-translationally modified proteins, as well as to offer targeted and global protein quantitation. For example: (1) we identified several phosphorylation sites on CENP-Q, a kinetochore component associated with the kinetochore scaffold protein. Polo-like kinase 1 regulates a kinetochore-associated complex through the phosphorylations (with Dr. Kyung Lee); (2) we identified that disks large homolog-1 is associated with G protein–coupled receptor 124 (GPR124) and revealed how GPR124 is involved in WNT7-induced canonical beta-catenin signaling (with Dr. Brad St. Croix); and (3) we identified how Apela interacts with hetero-geneous nuclear ribonucleoprotein L (hnRNPL) and modulates p53 activity (with Dr. Jing Huang). These efforts have been published in a number of high-impact journals, such as *Cell Reports*, *Journal of Immunology*, *Journal of Biological Chemistry*, and *Stem Cell*. PCL has also worked with several research groups to identify protein post-translational modifications (with Drs. Kylie Walters, Ying Zhang, Kyung Lee, and Christopher Westlake). Our results indicated the specific ubiquitination or phosphorylation sites as the "molecular switches" during the cellular process. We are finishing two large global phospho-proteomics projects for Drs. Nicholas Restifo and Peter Blumberg. In addition, we have worked on several large protein complex identification projects (with Drs. Ira Daar, Ronald Gress, Mirit Aladjem, Brian Lewis, and Philipp Oberdoerffer). Furthermore, PCL has been establishing and developing ChIP-mass spectrometry methods to study chromatin protein complexes. We are now using these methods to study the H3.3 and Pax3-Foxo1 chromatin protein complexes with Drs. Paul Meltzer and Javed Khan. Several additional researchers both within CCR and DCEG have shown an interest in using this method to study chromatin-binding protein complexes. PCL continues to provide SPR support to CCR, and we have worked on several projects for Drs. John Schneekloth and Udo Rudloff. PCL has continued to work with DCEG investigators (Drs. Kevin Brown and Laufey Amundadottir) on identifying single-nucleotide polymorphism allele-specific binding proteins, and these results have now been submitted for publication. PCL has taken on a highly challenging project for Dr. Udo Rudloff, supporting the clinical development of a therapeutic peptide by developing methods and carrying out several different experiments involving biophysical measurements, identification of a potential receptor for the peptide, and PK measurements.

On the metabolomics side, with increasing demands, we have successfully established small-molecule support for CCR and developed several protocols for lipid and drug metabolite quantitative analysis (with Drs. Acharya Jairaj, Stefan Ambs, and Stuart Yuspa).

PCL continues to provide mass spectrometry support to DCEG for estrogen metabolite quantitative analysis. In FY2015, we successfully integrated two new ThermoFisher Quantiva triple-quadruple mass spectrometers into service. We also established the Hormone Analysis Unit that is dedicated solely to DCEG through a Yellow Task fund. We have worked on several estrogen and androgen projects in FY2015 (with Drs. Charles Matthew, Rebecca Troisi, and Britton Trabert). Meanwhile, we are finalizing a new hormone

analysis protocol: progesterone assay development (with Dr. Katherine McGlynn). We have also done comparison analysis with estrogen reference samples from the Centers for Disease Control and Prevention (CDC). Our results showed very high correlations with CDC references in terms of accuracy and reproducibility. We also have several manuscripts submitted to publications focused on the subject of hormone analysis (with Dr. Louise Brinton).

Optical Microscopy and Analysis Laboratory

The Optical Microscopy and Analysis Laboratory (OMAL) focuses its research on quantitative microscopy for understanding carcinogenesis by analyzing signaling pathway kinetics and molecular spatial organization in individual cells. Research is in collaboration with multiple NCI principal investigators. Technical developments aim at providing an integrated resource for analyzing biological samples across multiple scales, from the molecular to the animal level, thus providing a seamless, bi-directional transition between basic and translational research.

OMAL continues to provide substantial microscopy and image analysis support to NCI, with the number of users and level of usage of the microscopes remaining approximately the same as last year. OMAL trains microscope users to be independent in order to maximize productivity. OMAL recognized that its aging equipment was no longer cutting edge, which is a significant drawback to NCI research. Therefore, significant effort was undertaken to procure new fluorescence microscopy instrumentation. Three cutting-edge fluorescence microscopes were acquired: a multi-focus microscope for rapid, single-molecule 3D imaging, a laser-scanning confocal microscope, and a bench-top, long-term, live-cell microscope. The structured illumination microscope was enhanced with additional instruments, and light-sheet microscopy was thoroughly investigated for imaging mouse embryos. Instrumentation at the ATRF is available for CCR use when not needed by RAS Initiative researchers.

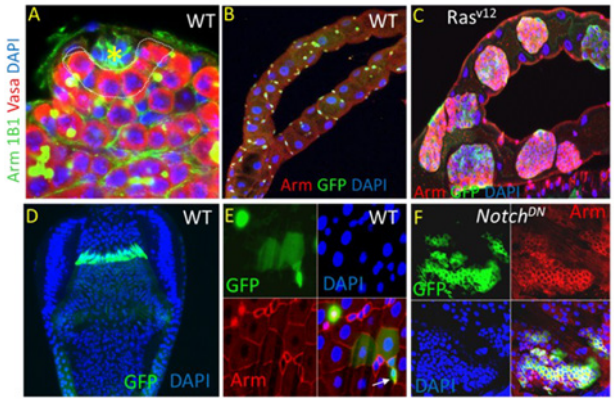
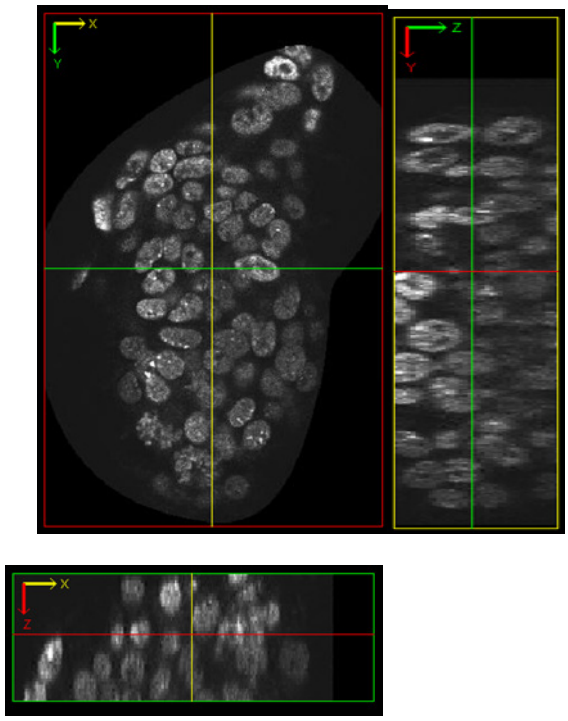


Figure 1. *In vivo labeling of germline and gastrointestinal stem cells in Drosophila. (A) Drosophila male germline stem cells in adult testis. Vasa (red) marks germ cells including germline stem cells (GSCs-dotted line), Arm (β-catenin-green-membrane) marks the hub cells (niche, asterisk), 1B1 (adducin-related protein), in green dots and branched, marks the spectrosomes and fusomes. (B) Drosophila adult renal and nephric stem cells (RNSCs) marked by STAT-GFP. (C) Expression of a constitutively activated form of RAS transforms RNSCs into stem cell tumors. (D) Gastric stem cells in Drosophila are marked by Stat-GFP. (E) Midgut (small intestine) stem cells (ISCs-arrow) in adult Drosophila. (F) Knockdown of Notch transforms ISCs into stem cell tumors. In collaboration with Drs. Shree Ram Singh and Steven Hou, CCR, NCI at Frederick.*

Major OMAL research in the past year has continued on improving methods to segment (delineate) individual cells and cell nuclei from tissue images. Dr. Kaustav Nandy has developed segmentation methods based on graph theory to automatically delineate nuclei in a variety of 3D tissue images (Figure 2). The accomplishments in this area have led to two accepted papers and one submitted paper, the filing of two employee invention reports, and Dr. Nandy earning his Ph.D. from the University of Maryland.

A



B

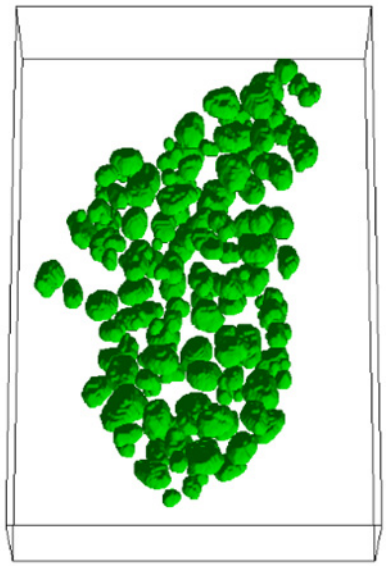


Figure 2. *Automatic, graph theory–based segmentation of cell nuclei in a mouse embryo. (A) Slice views through a mouse embryo image with fluorescence-labeled nuclei. (B) Surface-rendered visualization of the segmented nuclei (in green). In collaboration with Dr. A. Kumar, CCR, NCI at Frederick.*

Significant Achievements

- Evaluated a ratiometric two-color method for dSTORM.
- Built software to evaluate the proximity of gene loci to each other and to the nuclear envelope in support of research by Dr. Petr Kalab (CCR – Bethesda).
- Developed a new and significantly enhanced website, including microscope training material.
- Demonstrated the ability to perform single-molecule FRET when molecules are attached to the substrate, in support of Dr. Yun-Xing Wang (CCR – Frederick).

OMAL conducted the following collaborations with CCR labs:

- 3D live cell imaging showed that IFN-gamma limited the directed movement of metastatic melanoma cells. Abstract submitted. With Drs. Julio Valencia and Howard Young, CCR – Frederick
- Studied the dimerization of the APO-L1 protein and mutations of the protein in acidic compartments of cells using FLIM–FRET. With Dr. Cheryl Winkler, CCR – Frederick.
- 3D super-resolution imaging of the distal appendage protein cep164 surrounding the centriole imaged with STORM and compared to SIM imaging. With Dr. Jadranka Loncarek, CCR – Frederick.
- Quantified the increase in stress fibers in cEBPD KO cells cultured on glass and on micropatterns. With Dr. Esta Sterneck, CCR – Frederick.
- Non-invasive fluorescence imaging using two-photon illumination of photo-inducible metabolic reporter for the fumarate hydratase mutation. With Dr Jordan Meier, CCR – Frederick.
- Utilized second harmonic generation imaging for imaging urea crystals. With Dr. Yun-Xing Wang, CCR – Frederick.
- Studied the mobility of the HIV matrix domain in supported lipid bilayers. The study utilized TIRF microscopy and a unique reaction vessel, and stringent cleaning protocols for coverslips were developed. With Dr Alan Rein, CCR – Frederick.
- Investigated the interaction of the Mad2 protein in live cells by single-molecule imaging. With Dr. Steven Hou, CCR – Frederick.
- Performed fluorescence correlation spectroscopy (FCS) measurements to monitor MAX1 peptide size, and dynamic changes in different buffer conditions and as a function of time. With Dr. Joel Schneider, CCR – Frederick.
- Created the smoothened-SNAP construct and confirmed it with SNAP-JF549 dye. Performed live cell imaging with SMO-SNAP with organic dye and quantum dots. With Dr. Chris Westlake, CCR - Frederick.
- Verified CNK2 staining and performed live cell imaging of GFP-CNK2A. With Dr. Deborah Morrison, CCR – Frederick.

- Quantified polymerase ligation assay signals in cells to determine RAS protein dimerization. With Dr. Nadya Tarasova, CCR – Frederick.
- Determined the leucine-zipper transcription factor-like 1 dynamic interaction at the immunological synapse and then its movement to the distal pole. With Dr. Ven Natarajan, NIAID, and Dr. Howard Young CCR – Frederick.
- Dynamics of HIV-1 RNA near the plasma membrane during virus assembly. With Dr. Wei-Shau Hu, CCR – Frederick.
- Super-resolution imaging of multi-vesicular bodies with stimulated emission depletion microscopy. With Dr. Charles Lin, CCR – Frederick.
- Fluorescence fluctuation techniques to investigate HIV particle assembly in single live cells. With Dr. Wei-Shau Hu, CCR – Frederick.
- Quantitative evaluation of FCS and FRET to support biophysical studies, including fluorescence correlation spectroscopy analysis of HIV Gag and RNA interactions. With Dr. Alan Rein, CCR – Frederick, and Dr. Rajat Varma, NIAID.

Electron Microscopy Laboratory

CCR has been supported with at least two FTEs during FY2015, but most of the time the support went far beyond that. EML has supported several challenging projects from NCI CCR (e.g., cryo–electron microscopy of mutant MLV for Dr. Alan Rein's group, immune-labeling of exosomes for Dr. Stuart Yuspa's group, imaging of fly brain and testis for Dr. Jairaj Acharya's group, and serial sectioning and tomography for the groups of Drs. Chris Westlake and Jadranka Loncarek). The EML has also continued to support the HIV Drug Resistance Program (CCR), with about 200 samples processed during FY2015.

Genomics Laboratory

The CCR-dedicated Genomics Laboratory (GL) is funded by a new Yellow Task through CCR. The primary mission is to provide dedicated genomics services to CCR laboratories. The GL provides a broad range of genomics services, including gene expression analysis such as microarray, qPCR, droplet digital PCR, NanoString, and Fluidigm services; mutation analysis; single-nucleotide polymorphism and copy number analysis; DMET array; and next-generation sequencing services, including 16s microbiome analysis, integration site analysis, and exome sequencing in conjunction with the CCR Sequencing Facility.

Significant Achievements

- During last year, the GL finished transitioning from an open genomics core serving the RAS Initiative, NCI, and other NIH intramural agencies to a dedicated unit. The CCR-dedicated GL was established in January 2015 and managed to retain all currently available services requested by CCR with only half of the GL staff (five dedicated FTEs), which involves significant cross-training and re-assignment of duties.
- From February 2015 to July 2015, the GL had worked with 62 CCR investigators and fulfilled 82 CSAS requests, with $581,172 cost recovery. The GL continued to see strong demand for the microarray service, with 44 CSAS requests worth more than $230,000.
- The GL saw increasing demand for exome-sequencing projects (13 CSAS requests worth more than $230,000). Users include Drs. Nicholas Restifo, Glenn Merlino, Guha Udayan, Li Yang, and Electron Kebebew. Working with the SF, the GL has expanded the capability with low-input and ultra-low-input DNA and FFPE samples, enabling many studies with limited clinical samples that were not possible previously, such as Dr. Raffit Hassan's mesothelioma project.
- The GL continued to provide 16-s metagenomics analysis for Drs. Giorgio Trinchieri, Dennis Klinman, and Scott Durum. In addition to standard core service projects, the GL continued to provide custom assay support for many CCR laboratories. These include integration site analysis and droplet digital PCR assay. Among the new technologies that the GL is working on is the Oxford Nanopore sequencing platform. The GL is in the process of testing and setting up new experiment. The GL also acquired HTG Edgeseq for miRNA and mRNA quantification.

Support Provided by the Laboratory Animal Sciences Program

Molecular Imaging Laboratory

The Molecular Imaging Laboratory (MIL) develops new methods for preclinical and clinical in vivo imaging in support of the NCI Molecular Imaging Program (MIP) in Bethesda. MIL supports a collaborative effort between MIP, the Urology Oncology Branch (UOB), and the NIH Center for Interventional Oncology on focal therapy of prostate cancer by developing diagnostic magnetic resonance (MR) imaging and analysis methods to localize and monitor the lesions, and to guide interventional devices for targeted diagnosis and therapy. MIL is directly involved in a new NCI director initiative in collaboration between MIP, the Radiation Biology Branch, and UOB to study cancer metabolism by mapping injected metabolites and their conversion to other metabolites in patients, using hyperpolarized C-13 MRI.

The preclinical component continues to focus on the development and application of novel methods and instrumentation for small-animal optical, MR, and radionuclide imaging to complement MIP's effort in developing new diagnostic and therapeutic agents. In

addition, the group provides imaging expertise to the SAIP at the FNLCR and the NCL at the Advanced Technology Research Facility (ATRF).

Significant Achievements

Work on the NCI major opportunity project to study cancer metabolism using hyperpolarized C-13 MRI continued. The quality control (QC) unit for the hyperpolarizer (GE SpinLab) used to ensure that the polarized agent is effective and safe for injection to the patient was installed and tested. The number of multinuclear channels on the MRI (Philips Achieva 3.0 T) was increased from 2 to 6. Coils for clinical and preclinical studies ($^{13}C/^{1}H$ endorectal prostate coil and a ^{13}C six-channel array coil for kidney and other organs, $^{13}C/^{1}H$ rat body coil and $^{13}C/^{1}H$ mouse body coil) have been interfaced to the scanner. MIL also designed and built specialized $^{13}C/^{1}H$ coils (leg, head, whole body, and short abdomen) with associated animal support systems for mice studies on the cryogen-free 3.0 T small animal MRI (MR Solutions) that operates with the preclinical hyperpolarizer (Oxford Instruments HyperSense) in the Radiation Biology Branch (RBB).

A prototype scanner capable of simultaneous imaging of positron and single photon emitting compounds in a small animal has been built and demonstrated in mice. A description of the system was presented at the IEEE Medical Imaging Conference in 2014 and the results of simultaneous imaging of a PET tracer, F18-albumin, a SPECT tracer, and a Tc-99m-labeled RBC, to map hematocrit in live mice are being presented at the World Molecular Imaging Congress in 2015. Dual mouse PET and SPECT flat beds, and animal support systems have also been developed to allow for more consistent positioning of mice for imaging studies.

MIL personnel, along with their collaborators, published 10 journal articles, conducted at least three presentations, and developed several posters for international scientific meetings during the past year.

Center for Advanced Preclinical Research

The mission of CAPR is to develop strategies for predictive preclinical research using genetically and biologically engineered murine cancer models, and to facilitate their routine application in clinical research to achieve optimal outcomes in the management of cancer diseases. Early genomic, biomarker, and preclinical drug assessment studies of recent years have illustrated both the value of using well designed GEM models to accelerate biomarker/molecular signature discovery, and the potential for significantly increased accuracy in efficacy determination. CAPR is dedicated to developing preclinical approaches that can be integrated into the routine practice of human research to improve overall clinical care, including the process of selecting novel treatment strategies for clinical trials.

Significant Achievements

In February 2015, in response to a request by NCI CCR leadership, CAPR was evaluated for its scientific achievements and contribution to intramural and outside collaborative activities in a site visit format by a panel of external expert reviewers. CAPR senior staff members were each tasked with preparing a 25-page research summary, and a 20-minute oral scientific overview. The site visit panel also assessed CAPR's financial performance over the six-year operational history and was apprised of the funded outreach activities identified and initiated by CAPR. CAPR staff also participated in a poster session designed to provide the highlights of the program's research, technology, and operational achievements since its inception. The site visit committee expressed overall enthusiasm and positive scores for CAPR's accomplishments and recommended support for the program's proposed research and collaborations. At the same time, the review panel suggested several additional activities to be pursued by CAPR to further enhance its visibility and deliver on the mission of facilitating clinical translation efforts. The reviewers strongly felt that refocusing CAPR objectives towards clinical collaborations will emphasize the program's value and expertise in early stage drug development, and validate the underlying concept of exploring next-generation cancer models as promising experimental platforms for translational discovery and cancer drug development.

In addition, this year CAPR successfully made advancements in several disease modeling programs. An orthotopic mouse model for glioblastoma multiforme (GBM) was successfully developed by adapting a genetically engineered model carrying activating mutations in the RB, RTK/RAS, and PTEN network nodes, representing the major signaling pathways altered in human GBM. This tractable, reliable, syngeneic, and orthotopic model retains key characteristics of the human disease, including vascularity and aggressive invasion into surrounding tissue, and an intact immune system. The relative importance of inhibiting the PI3K and MAPK pathways was examined both in vitro in primary cultures and in vivo in the orthotopic model, employing drugs currently in clinical trials for GBM. The results were published as "A preclinical orthotopic model for glioblastoma recapitulates key features of human tumors and demonstrates sensitivity to a combination of MEK and PI3K pathway inhibitors" in *Disease Models and Mechanisms*. The aggressive nature of GBM in the model, as well as its molecular and histopathological features, warrant continued use for improving upon existing therapeutic strategies as well as for testing novel targeted drug treatments or immunotherapy approaches. CAPR's collaboration with Laboratory of Cancer Biology & Genetics (LCBG) (Dr. Glenn Merlino) on modeling and treatment of metastatic melanoma resulted in an Employee Discovery and Invention Report (EIR) for a new allograft mouse model of hepatocyte growth factor (HGF) driven melanoma as well as studies in which

melanoma tumors labeled with imageable reporters to track preclinical assessment of cancer therapeutics. The findings were published as "'Glowing head' mice: a genetic tool enabling reliable preclinical image-based evaluation of cancers in immunocompetent allografts," in *PLoS One*. The collaboration has now been expanded to include a partnership with MedImmune to evaluate immune checkpoint inhibitors in the metastatic model, under NCI's umbrella Cooperative Research and Development Agreement (CRADA). These studies are now under way.

In the spring of 2015, CAPR completed, or advanced close to completion, several experimental projects in collaboration with a large pharma (AbbVie, Inc.) designed to evaluate a set of proprietary therapeutics in murine models for Kras-driven lung adenocarcinoma and pancreatic ductal adenocarcinoma. Completion of the projects represented a significant milestone in the large-scale funded partnership supported by the Leidos Contractor Technical Service Agreement (TSA) mechanism. These studies address investigation in two preclinically validated GEM models of pharmacokinetic properties, toxicity and anti-cancer efficacy of candidate therapeutics that are in development by AbbVie, Inc. Assisted by the Leidos offices of Partnership Development and Technology Transfer, CAPR not only successfully advanced the initial list of experimental modules, but also was able to sustain continuous interest from the company by extending the collaboration to test additional compounds. Negotiations are currently in progress to prepare corresponding documentation to enable further partnership activities with AbbVie.

CAPR scientists continued to refine and optimize operational workflows aimed at the production of experimental cohorts of animals engineered to develop pancreatic ductal adenocarcinomas (PDAC), an oncologic malady still largely remaining the most challenging gastrointestinal tract malignancy with rapid disease progression and poor survival of clinical patients suffering from PDAC. To emulate one of the most frequent aggravations of PDAC course-secondary disease spread and formation of metastatic lesions-CAPR scientists devised a modified model that combined the biological precision of spontaneous carcinogenesis induced in pancreatic tissue by a clinically relevant assortment of genetic aberrations with the affordability and scalability of grafting methodology. This GEM-derived allograft (GDA) model features a high-rate of metastatic dissemination and is ready to be applied in a multitude of preclinical paradigms interrogating the biological aspects of metastatic disease, or testing experimental compounds targeting the metastasis.

Finally, in regards to CAPR's scientific and collaborative activities, the program actively sought adoption and application of cutting-edge technologies capable of either increasing the bandwidth and breadth of the program's partnering endeavors, optimizing the existing models, or offering more robust avenues for production of novel engineered mouse strains to support better modeling efforts. On this path, CAPR embarked on a project aimed at embracing a technology of targeted mutagenesis using recently announced CRISPR/Cas9 technology, practiced either in somatic format to prepare tumor-bearing animals via targeted mutagenesis in adult tissues, or via genome editing alterations introduced into murine ovocytes to develop new germline mutant alleles instrumental in subsequent cancer modeling projects. The latter strategy has been explored in a collaborative study with DCTD to establish a conditional mutant allele in a gene responsible for synthesis of an enzyme with critical importance in metabolic pathways leading to the production of a reactive oxygen species. The resulting mutant strain has been molecularly validated and currently awaits assessment in the context of the aforementioned KPC model of pancreatic cancer as potentially modifying the carcinogenesis outcomes.

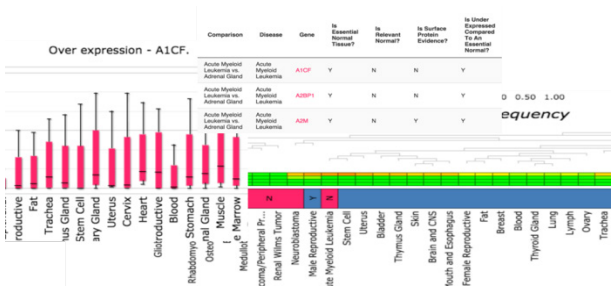
Support Provided by the Data Science and Information Technology Program

Pediatric Oncology Branch

The mission of the Pediatric Oncology Branch (POB) of the NCI Center for Cancer Research (CCR) is to leverage high-throughput biomedical technologies to improve outcomes in children with high-risk metastatic, refractory, and recurrent cancers. The Advanced Biomedical Computing Center (ABCC) supports the mission of the POB by providing dedicated expertise in large-scale data processing and analysis and in software development. The efforts of the ABCC analysts embedded with POB included the implementation of next-generation sequencing (NGS), and clinomics data processing and analysis pipelines and web-based visualization tools for research data and scientific images. These tools aid investigators and clinicians in addressing several topics in cancer research: deciphering the role of alterations in *NRAS*, *KRAS*, *HRAS*, *FGFR4*, *PIK3CA*, *CTNNB1*, *FBXW7,* and *BCOR* in rhabdomyosarcoma tumors; detection of variants with low mutational burden; detection of high-frequency deletions in the cohesion complex subunit *STAG2*, and mutations of TP53 of the Ewing sarcoma family of tumors. The group has also created a ChIP-seq pipeline to identify the linkage between the super-enhancers and their regulated genes. The results provide the underlying epigenetic mechanisms of *MYC*/*MYCN*-driven transcriptional programs with *PAX3* fusions in rhabdomyosarcoma. In the last year, along with software development, the group has supported the processing, analysis, and integration of approximately 900 samples sequenced using Illumina's MiSeq™ platform.

In addition to data processing/analysis pipelines, with guidance from the NCI Office of Scientific Operations (OSO)–funded part of ABCC, the group has enhanced the functionality of the widely used oncogenomics application. Oncogenomics provides the cancer research community with web-based access to gene expression data sets from in-house and publicly available microarray and RNA-Seq studies on

normal and cancerous tissues across several organs and tissue types. The interface allows custom integration and normalization of data sets across studies and provides visualization features, such as heat maps and box plots; allows interactive exploration of studies, analysis, and gene level annotations; and has options to run algorithms, such as gene set enrichment analysis (GSEA). Oncogenomics has over 2,000 active registered users worldwide.



Screen shots from the development version of the new oncogenomics interface.

Radiation Oncology Branch

The mission of the Radiation Oncology Branch (ROB) is to conduct preclinical and clinical research on the biological and therapeutic effects of radiation on cancerous tissue and to develop biomarkers to guide the choice of tailored therapies. The ABCC provides dedicated bioinformatics and wet-lab support to the ROB in fulfilling its mission. In the last year, ROB-embedded analysts have taken part in three major projects: (1) identifying radiosensitizing agents in the treatment of glioblastoma multiforme (GBM); (2) adding enhancements to the Stress Response Array Profiler (StRAP) web application; and (3) designing and implementing a new web resource that centers on a novel anticancer strategy termed "synthetic lethality."

As part of the GBM project, analysts processed and analyzed over 150 normal and cancerous samples using microarrays to collaboratively identify MPS1 as a radiosensitizing target for GBM (Maachani, U.B., et al., *Targeting MPS1 Enhances Radiosensitization of Human Glioblastoma by Modulating DNA Repair Proteins.* Mol Cancer Res, 2015. **13**(5): p. 852-62).

The StRAP database (http://strap.nci.nih.gov/main.php) is a web-based, open-source application that enables the storage, visualization and sharing of cancer genomic data, with an emphasis on radiotherapy studies. StRAP has undergone major advances in the last year with the inclusion of additional biological data sets, enhanced features, and improved usability.

Finally, ABCC analysts are designing and implementing a web application centered around synthetic lethality. The application is being built as a data repository for a wide range of data types, including gene–gene/protein–protein interactions, gene expression, drug activity, and mutation and clinical data collated from multiple major public data sources. A systems-level approach will be used to integrate and analyze these big data sets, to predict/identify effective drug combinations, and to construct tissue-specific networks. The application is being designed to provide scientists and clinicians, who have no expertise in bioinformatics, access to diverse, multidimensional clinical/biological data sets through an integrated and easily navigable interface.

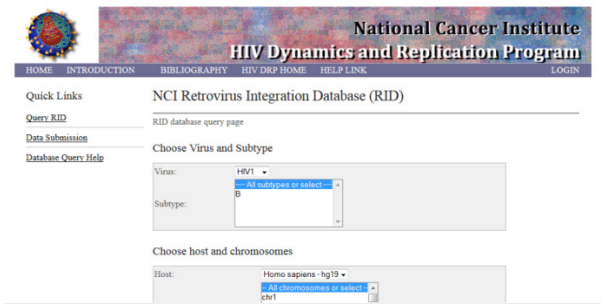
HIV Drug Resistance Program

The last survey by the World Health Organization in 2013 shows that there were 35 million people living with HIV, and 2.1 million people were newly infected with HIV in 2013. The Simulation, Analysis, and Mathematical Modeling (SAMM) group provides bioinformatics support for the NCI HIV Dynamics and Replication Program (DRP), particularly the Translational Research Unit (TRU) and Clinical Retrovirology Section (CRS), in its mission to study HIV persistence, drug resistance, and evolution. A key aspect of this work involves HIV single-genome sequencing (SGS) assembly and comparison. SGS assembly and analysis of HIV samples allow researchers to identify the development of drug resistance mutations and clonal expansion of HIV-infected cells in patients.

A second area of collaboration and support for the HIV-DRP is HIV transmission network analysis, which is useful in discovering the transmission risk factors and endemic in a particular region. Briefly, Bayesian Markov chain Monte Carlo (MCMC) analysis of the sequences was performed for transmission network detection.

Finally, it is known that the HIV genome inserts into the host genome after infection; a recent TRU and CRS study indicates that some HIV proviruses integrated in expansion cell clones are infectious. The SAMM group is performing additional analysis to support this research.

Numerous studies on retrovirus integration into host genome have been published. Because of the increasing application of NGS technology to integration studies, millions of integration data will be available. However, no public database exists to store the published data. The ABCC has been working with colleagues at NCI HIV DRP to construct the NCI Retrovirus Integration Database (https://rid.ncifcrf.gov) for public use.



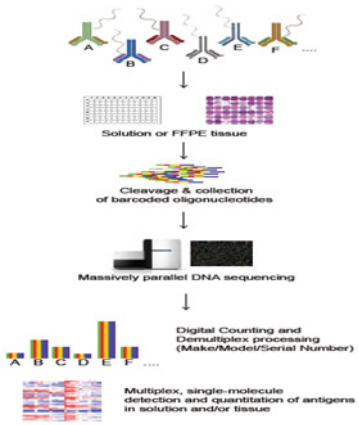
CCR Sequencing Facility

The Center for Cancer Research Sequencing Facility (CCR-SF) Bioinformatics Group provides NGS and bioinformatics analysis support to CCR investigators across NCI. Specialized in NGS data analysis and quality control, the group provides services ranging from sequencing technology consultation, experiment design, data analysis and management to result interpretation. The group has established standard workflows and pipelines to process the rapidly growing volume of sequencing data, and has worked closely with investigators alongside their projects to deliver high-quality data and reproducible analysis results in a timely manner.

During CY2015, the CCR-SF Bioinformatics Group has received more than 240 sequencing and data analysis requests from over 70 laboratories and branches within CCR, and a number of requests from other institutes within NIH. The group processed over 3,500 samples in diverse sequencing applications, delivered more than 35 trillion base pairs of pass quality control data to CCR investigators. The group has successfully completed all project requests with fast turnaround time. The throughput has increased over 30 percent compared with the previous year.

To further facilitate cancer research and provide investigators easy access to latest sequencing technologies, the CCR-SF Bioinformatics Group has been actively working with researchers and lab technicians from CCR labs, CCR Sequencing Facility and Genomic Laboratory at FNLCR for new protocol development and validation. There is new range of sequencing protocols and applications developed or tested in 2015. The following are the highlights some of the key accomplishments:

Multiplex Proteomic Analysis by DNA Sequencing. High-throughput proteomic analyses remain a challenge to precision medicine. There is a growing need for the development of a more direct, quantitative approach to multiplex analysis of proteins in tissues and clinical assays. Dr. George Miles, of the Laboratory of Pathology, NCI, worked collaboratively with us, designed the antibody conjugate signature oligonucleotides that carry an expanded barcode set and are compatible with the NGS platform (Illumina) for digitizing antibodies for single-molecule detection. We helped design and execute a series of experiments, analyzed data, and successfully profiled the abundance of selected targets in breast carcinoma samples. The sequencing counts correlated with the visual intensity of staining by immuno-histochemistry (IHC). In addition, the technology could detect and measure the amount of single or multiple pooled antigens in solution using an ELISA-like assay. This technology may serve as means for quantitative investigation of functional genomics, and for diagnostic applications. Currently, we are in the process of preparing a manuscript to publish this result.



Chromatin Profiling Using NGS Technologies. NGS technologies have been used in investigating various aspects of chromatin biology by identifying genomic loci that are bounded by transcription factors, occupied by nucleosomes, or accessible to nuclease cleavage, or loci that physically interact with remote genomic loci. Many protocols have been developed, such as Chip-seq, MNase-seq, FAIRE-seq, ChiA-PET, Hic-Seq, and each reveals different aspects of the chromatin structure. In 2015, the Laboratory of Receptor Biology and Gene Expression utilized new protocols such as DNase-seq and ATAC-seq for studying patient samples from clinical trials. ATAC-seq is an alternative method to DNase-seq that uses an engineered Tn5 transposase to cleave DNA and to integrate primer DNA sequences into the cleaved genomic DNA. It requires much less input DNA and significantly reduces library preparation time. However, there are various sources of bias, including enzymatic chromatin cleavage, size selection, nucleic acid isolation, PCR bias and duplication, as well as read-mapping effect. During the protocol validation process, we worked closely with the investigator's lab to identify the source of bias via comparison analysis of different sample sets. We helped to refine the protocol and analytical techniques in data analysis to mitigate bias effect. This new protocol helped with the clinical study.

"Our group in the Laboratory of Receptor Biology and Gene Expression (Chief: Gordon Hager, Ph.D.) studies the mechanisms of transcription and regulatory factor interactions with chromatin in vivo. Since the CCR sequencing facility commenced about six years ago, we have frequently been utilizing their Illumina (previously Solexa)-based sequencing services. Through the years, we have generated a remarkable amount of high-quality data sets and numerous publications based on the information gleaned from these data. The sequencing facility ensured quality processing and sequencing of our samples and delivered us data that are reproducible and reliable." – Dr. Myong-Hee Sung, Laboratory of Receptor Biology and Gene Expression

RNA and Target Capture Sequencing Analysis of Degraded or Low-input FFPE Samples. Formalin-fixed, paraffin-embedded (FFPE) tissues are an invaluable resource for clinical research. However, nucleic acids extracted from FFPE tissues are fragmented and chemically modified, making them difficult to use in molecular studies. In the

CCR-SF and the Genomic Laboratory at FNLCR, there is an active effort to standardize protocols to optimize the retrieval of information from FFPE samples. In collaboration with several NCI laboratories from the Lymphoid Malignancies Branch, Laboratory of Pathology, and Thoracic and Gastrointestinal Oncology Branch, we tested three sets of protocols for selected FFPE samples and paired fresh frozen (FF) specimens for transcriptome and exome sequencing. Our group performed data analysis. The samples include 38 pairs FF/FFPE samples representing different age points (1–5 years) and two different human tissue types and a human cell line (RH16 p6). We observed a high correlation between differentially expressed genes in FF/FFPE pairs (Pearson correlations of 0.90 +/- 0.07). For the exome-seq FF/FFPE pairs, good-quality genomic DNA extracted from FFPE samples (260/280 ratios within a range of 1.7 to 2.0) can produce the same high-quality target capture enrichment as the FF samples. There is high concordance for the high-confidence variants called from the FF/FFPE pairs and a similar mutation rate and variant categories were observed. Our pilot study results are promising and suggest that NGS can be used to study FFPE specimens to retrieve useful information for clinical studies.

Iso-Seq Full-Length Transcript Sequencing Protocol and Software Development. In human, plant and other higher eukaryotic organisms, the majority of genes are alternatively spliced to produce multiple transcript isoforms. Using microarray or short-read NGS technologies to build complete transcripts to study gene isoforms has been challenging. PacBio has introduced the Iso-Seq method for full-length transcript sequencing and isoform detection without assembly. Our staff has worked collaboratively with CCR-SF lab scientists to develop and test protocols for both targeted capture and whole-transcriptome sequencing, including a normalized protocol to reduce the prevalence of highly expressed transcripts, to obtain better resolution on rare transcripts. A set of software tools has been developed by the CCR-SF Bioinformatics Group: MatchAnnot python package for Iso-Seq sequencing cluster reads annotation and ClusterView software to display transcript reads in a compact view. Both software tools are now on GitHub and are fully available to open source community. The MatchAnnot software is widely used by the PacBio user community.

Other Accomplishments and Ongoing Efforts:

- Expanded informatics workflow and data analysis pipelines to support new lab protocols
- Fully customized Clarity LIMS to fit CCR-SF workflows, project and sample tracking needs. The LIMS has been in production mode since beginning of 2015.
- Participated in a collaborative effort with CCR Collaborative Bioinformatics Resource CCBR bioinformatics groups to develop standard pipelines for exome-seq and RNA-seq data analysis, and share the software tools with the open source community.
- Participated in a collaborative effort with CBIIT and the CCR bioinformatics groups to design and implement a centralized genomics repository for data storage and distribution.

Selected Publication: Histone H3 lysine 27 demethylases Jmjd3 and Utx are required for T cell differentiation, Sugata Manna, Jong Kyong Kim, Catherine BAUGE, Margaret Cam, Yongmei Zhao, Jyoti Shetty, Melane Vacchio, Ehydel Castro, Bao Tran, Lino Tessarollo, and Remy Bosselut. 2015, July; accepted by Nature Communication.

CCR Collaborative Bioinformatics Resource (formerly CCRIFX Bioinformatics Core)

The CCR Collaborative Bioinformatics Resource (CCBR https://bioinformatics.cancer.gov/) was established in 2014 as an umbrella organization to provide collaborative bioinformatics support to investigators across the CCR, NCI. The CCBR provides a single-point access to a broad range of bioinformatics expertise that exists across several bioinformatics groups within NCI. Two key ABCC groups have been subsumed within the CCBR: the CCR Informatics Core (CCRIFX) and the Basic Science Program (BSP)-CCR Genetics Core (BCGC). The CCRIFX was set up in 2011 as a shared bioinformatics support group for the CCR investigators. The BCGC originated as an embedded core of the Laboratory of Genomic Diversity, a leading laboratory in research on population genetics and evolution.

In the last year, the CCBR team has worked on approximately 120 analysis requests (complete and ongoing) that were submitted from across the 49 programs, branches, and labs. The analysis requests addressed a wide spectrum of questions in cancer research, ranging from basic biology to clinical applications. The requests typically involved the processing, analysis, and interpretation of high-dimensional data sets generated by microarray, Exome-seq, RNA-Seq, ChIP-seq, metagenomics, and mass spectrometry platforms, and of publicly available data.

In addition to providing bioinformatics support, the CCBR has actively engaged in technical development (Tech-Dev) projects to keep abreast in the evolving field of biological data analysis. The Tech-Dev projects have been of two types: (1) development of best practices in data analysis and (2) implementation of robust, scalable, and flexible scientific workflows. Best practices and software pipelines have been developed for the processing and analysis of Exome-seq and RNA-seq data. The software pipelines have been designed to semiautomatically process large data sets. They reduce total data processing time; ensure uniform data processing standards across the team; reduce manual hands-on time; and reduce the probability of manual errors.

The CCBR holds an annual workshop series, the Bioinformatics Training and Education Program (BTEP), which is designed to educate and empower researchers who lack the necessary computational skills in processing, analyzing, and interpreting their data according to state-of-the-art analysis protocols. In the past year, CCIRFX/BCGC members participated in five workshops to educate the CCR research community on topics ranging from programing in R to data integration and microarray data analysis.

The CCBR's activities impact both the CCR research community and the state of science. At the community level, the CCBR has been instrumental, through its Tech-Dev and BTEP sessions, in developing and transmitting to the CCR researchers sound and rational data-analysis practices that represent the latest advances in bioinformatics and are accepted by the wider research community. The CCBR's impact on the state of science is best illustrated by the following selected accomplishments by the CCRIFX and BCGC analysts in the past year:

- Anaplastic astrocytoma (AA) and glioblastoma multiforme (GBM) are fatal forms of cancer, with no effective treatment. Research on these cancers in humans is limited, as samples are accessible only at advanced stages; profiling genomic changes during the progression of the disease is not feasible. CCBR is working with the Center for Preclinical Research (CAPR) to develop a mouse model for AA and GBM. CAPR has developed genetically engineered mouse lines to study the initiation and progression of GBM. CCBR analysts are analyzing diverse high-dimensional data sets generated from these mouse models to perform a comprehensive and integrated analysis of somatic copy number alterations, somatic mutations, gene expression changes, and miRNA expression changes. Preliminary analyses have confirmed several perturbations in key GBM genes and have revealed putative pathways involved in the initiation and progression of disease from grade II to grade III/IV stages.
- Triple negative breast cancer (TNBC) accounts for 15–25 percent of all breast cancer cases and remains difficult to treat using standard chemotherapies. CCBR analysts collaborated with the Mouse Genetics Program (MGP) to identify *Cripto-1* as a novel therapeutic target for TNBC. The MGP developed a mouse model that establishes spontaneous lung metastasis from JygMC(A) cells; the resulting primary tumors resembled TNBC both phenotypically and molecularly. CCBR assisted in the analysis of microarray and nanostring data generated from this novel mouse model, along with the data mining of publicly available human breast cancer data, to establish the gene-expression similarities between the metastatic model and the TNBC subtype and, most importantly, to identify of Cripto-1, a member of the TGF-β family and a player in early embryogenesis, as a potential therapeutic target for TNBC (Castro, N.P., et al., Cripto-1 as a novel therapeutic target for triple negative breast cancer. *Oncotarget*, 2015. **6**(14): p. 11910-29).
- Familial non-medullary thyroid cancer (FNMTC) accounts for 3–9 percent of all thyroid cancer cases and exhibits an autosomal dominant pattern of inheritance; however, no susceptibility gene(s) have been identified. CCBR, in collaboration with the Endocrine Oncology Branch, has analyzed exome-sequencing data from 132 individuals from 22 families. A family-wise search for germline variants has identified, for the first time, mutations in the *HABP2* gene as a possible correlate of FNMTC. Functional studies are being conducted to evaluate these findings.
- HIV-associated nephropathy (HIVAN) is common among African Americans in the absence of effective therapy, but rarely, if ever, seen in European Americans, pointing to an African inheritance. A mapping by admixture linkage disequilibrium (MALD) analysis by BCGC analysts identified an extremely strong association with a region of chromosome 22. Further research focused this association on two protein-altering variants in the *APOL1* gene. This is the most significant genetic association with kidney disease, applying to many conditions beyond HIVAN, and one of the strongest genetic associations with any common disease (Limou, S., Kopp, J., Johnson, R.C., Neaton, J., Ross, M., Neuhaus, J., Dolan, M., Hodder, S., Ganesan, A., Bergmann, F., Lundgren, J.D., Lane, C., Lempicki, R., Winkler, C.A., APOL1 renal risk alleles are associated with decreased kidney function in HIV-treated subjects with African descent. *J Am Soc Nephrol*, in preparation).
- The Noble rat is a model for several important human cancers and, in particular, is subject to a nephro-blastoma analogous to Wilms tumor; the standard lab Fischer rat is not susceptible. The Cancer and Developmental Biology Laboratory has an ongoing effort to map susceptibility loci for this tumor using backcrosses between Noble and Fischer. BCGC analysts provided the experimental design for the current mapping effort, in particular, specifying a

backcross of hybrid rats to Fischer. (The alternative backcross provides three times as many tumor-bearing rats, but each provides less than one-third the information.) For this project, they devised and are testing a novel method of mapping by very-low-coverage sequencing. Previous experiments used an Affymetrix rat genotyping chip, which is no longer manufactured. The analysts considered that, starting from high-coverage sequencing of the parental inbred Noble and Fischer strains, very-low-coverage sequencing of the backcross rats would identify enough variant SNPs distinguishing the strain to provide a high-coverage map; the standard approach of a custom genotyping chip would be more expensive and provide a less dense map.

With a responsive and effective team that maintains expertise in the diverse domains of bioinformatics, the CCBR has evolved into an integral part of the CCR research community.

Office of Science and Technology Resources

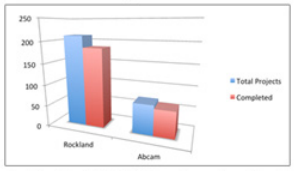
The ABCC Scientific Web Programming Group (SWPG) maintains the build of the Office of Science and Technology Resources (OSTR) website (https://ostr.cancer.gov/) to support CCR and the OSTR. The project goal was to create a single location to consolidate all of the OSTR resources that are offered to NCI and customers of OSTR. The ABCC also continued the management of the open-source Drupal CMS system and modules, including the custom Subsidy Request and Assay Depot Management modules. Integrated application resources such as the CCBR (https://bioinformatics.cancer.gov/) and BTEP (https://bioinformatics.cancer.gov/btep) have been updated to support the migration from the CCRIFX Bioinformatics Core to support new initiatives.

Continued oversight for other OSTR-supported laboratories include: NCI Optical Microscopy Laboratories (https://confocal.cancer.gov), comprising the Laboratory of Cancer Biology and Genetics; Laboratory of Receptor Biology and Gene Expression; Cell and Cancer Biology Branch; Laboratory of Cellular and Molecular Biology; Experimental Immunology Branch; and Optical Microscopy and Analysis Laboratory. Support includes required Drupal management and updates as well as support of customer needs and requests.

Rockland and Abcam Antibody Request Portals

The ABCC SWPG has continued to support CCR antibody request portals for both Rockland Immunochemicals, Inc., (https://ccrrockland.cancer.gov) and Abcam (https://ccr-abcam.cancer.gov). The project was created to assist CCR in managing and reporting on custom requests for rabbit polyclonal and mouse monoclonal antibodies as well as to meet NIH standards and compliance requirements. These portals share a common code base and utilize the latest technology models. A single code base enables both sites to be easily managed while maintaining data integrity and privacy. Continued account support is offered as both portals continue to grow their user base and project lists.

Custom Rabbit Polyclonal and Mouse Monoclonal Antibodies Production



Rockland: *In 2005, CCR formed a partnership with Rockland Immunochemicals for the development of rabbit polyclonal antibodies against key phospho- and non-phosphoproteins implicated in cancer.*
Abcam (formerly Epitomics, Inc.): *In December 2008, the OSTR established a unique partnership with Epitomics Inc. for the development of rabbit monoclonal antibodies.*

Support Provided by the Clinical Monitoring Research Program

Leidos Biomedical Research provides medical, data management, and administrative support to the NCI Center for Cancer Research (CCR) and its clinical programs. CMRP provides comprehensive, dedicated clinical support to the CCR, serving as an important resource for the development of new technologies and the translation of basic science discoveries into novel agents for the prevention, diagnosis, and treatment of cancer and AIDS. CMRP continues to propose new ideas to meet our customers' needs, as well as modify existing positions, when possible, to aid the continuing developments within each program. In addition, CMRP also provides excellent programmatic and research subcontract support services to the various branches and sections within CCR. With the support provided by Leidos Biomedical Research and CMRP, the CCR is able to streamline operations, increase patient accrual, evaluate and treat patients more efficiently, and gather complete and accurate clinical data for advancements in science and health.

In support of CCR's protocol and laboratory re-engineering, a clinical project manager continued to manage a Basic Ordering Agreement (BOA) and two Task Orders (TOs) that were awarded to Dilts + Partners, LLC. The first TO supports CCR's effort to re-engineer its protocol development processes related to the development and opening of clinical trials, and to the effective management of its clinical trials portfolio. The goals of the project are to: (1) decrease the time from scientific review to opening for patient accrual for a clinical trial at CCR from 208 median calendar days to 60 days, while maintaining or increasing quality and safety; and (2) strategically manage the clinical trials portfolio such that it reflects CCR scientific priorities, takes advantage of CCR strengths, and is cost effective.

To date, Dilts + Partners has successfully completed four of five efforts that are outlined within its scope of work for TO 1. The four completed efforts include: (1) translation of strategic plan (vision, mission) into scientific priorities; (2) modification of strategic alignment and resource planning form and associated processes to prospectively collect clinical trial input and

feedback; (3) assistance in the development and implementation of thematic areas and major opportunities; and (4) development of leadership-level dashboards for portfolio management capabilities. Effort five (5), evaluation of portfolio of current and incoming clinical trials, is anticipated to be completed by the end of FY2015. Ongoing work to enhance and support the implementation of the strategic plans is expected to continue in FY2016.

Specifically, the work accomplished for the Dilts + Partners research subcontract under TO 1 included: facilitation of nine on-site leadership meetings, four ancillary on-site meetings, analysis of FY2014 Strategic Alignment and Resource Planning studies, support for the CCR all-hands meeting, roll-out of the refined concept review, finalization and roll-out of Strategic Alignment and Resource Planning (SARP) 3.0, a revision of the SARP form, initial development of the clinical Compensation Tool, development and pilot initiation of the 5 + vision Branch Interview Guide, development of analytics and dashboards to support 5 + vision interviews, and compilation of 19 CCR Chair concept reviews for five Scientific Concept Review Meetings.

The second TO awarded to Dilts + Partners supports the Laboratory of Pathology (LP) in the development and implementation of a strategic plan that allows the laboratory to carry out its tripartite mission in the most effective and efficient manner, in the unique setting of the CCR and NIH. The goals of the project are to: (1) create, implement, and evaluate the LP's strategic vision and plan; (2) facilitate the data-driven identification of necessary organizational changes to successfully implement the strategic plan; and (3) analyze and recommend changes to processes used to evaluate and estimate resource usage and to prioritize requests by clients who use LP service cores. This work is of critical importance in the effective management of the clinical trial portfolio. To date, Dilts + Partners has successfully completed three of five TO efforts, including: (1) creation and facilitation of working groups to initiate the strategic plan; (2) development and implementation of a communication plan to disseminate the new strategic plan; and (3) investigation of various organizational models and approaches that best fit LP's strategic plan. Effort four (4), translation of the strategic plan into key metrics and data that will determine baseline performance and resource utilization, and effort five (5), creation of a capacity management system that supports a fair, equitable, and priority-driven process of utilizing scarce LP resources, were slightly revised and included in a modification (Modification #6) to the TO 2 agreement. Modification 6 replaces the original efforts 4 and 5 with three new efforts: (1) development, implementation, and evaluation of metrics; (2) assistance with implementation, evaluation, and course corrections for the Clinical Operations Advisory Committee (COAC); and (3) exploration of various organization models and approaches that best fit the LP's strategic plan. These efforts are expected to be completed before the end of FY2015.

The work accomplished for TO 2 included 14 on-site meetings to assist in the development of the: LP strategic planning process; LP all-hands meeting; orientation meeting with the Clinical Protocol Administrator; COAC initiation meeting and subsequent meetings; development of the COAC internal worksheet, COAC response forms, COAC tracking forms, and draft interview guide for use by Clinical Protocol Administrator; and finalization of the LP strategic plan.

Office of the Clinical Director

The NCI Office of the Clinical Director (OCD) serves as the interface between the CCR and the NIH Clinical Center, the nation's largest hospital devoted entirely to clinical research. The NIH Clinical Center includes 242 inpatient beds and 90 day-hospital stations, which house units and clinics where cancer and HIV patients are treated during CCR clinical trials. The OCD oversees and assures the quality of medical care delivered to patients participating in CCR clinical trials. The OCD also supports CCR's clinical research program by providing biostatistical expertise for trial design and analysis, administrative support for the protocol review and monitoring process, training of clinical research personnel, an outreach program to promote patient accrual, data management, auditing and monitoring of in-house and multi-institutional trials, and informatics for data collection and storage.

CMRP provides full-time shuttle and courier support services to and from the NIH campus and the OCD. The shuttle bus driver is responsible for transporting various staff members and time-sensitive documentation (e.g., medical records) to various locations within the NIH campus.

During this reporting period, the clinical program administrator's position was expanded to a full-time appointment based at NIH, Building 10, in Bethesda, MD and at the Industry Lane building in Frederick, MD. The clinical program administrator provides direct supervision of the patient care coordinators located at NIH, Building 10. The clinical program administrator oversees the scheduling and coordination of the outpatient hematology and oncology clinics on Floors 12 and 13 of Building 10, acts as a liaison between Leidos Biomedical Research staff at NIH and CMRP, and works closely with the customer to provide administrative support as needed.

NCI Protocol Review Office

The Protocol Review Office (PRO) is under the direction of the CCR Office of the Clinical Director's Office and provides administrative support for the NCI Intramural Institutional Review Board (IRB). Currently, the IRB has approximately 400 protocols under its review. PRO staff reviews protocol actions (e.g., expedited, full board) for completeness before submission for review and approval by the IRB chair, clinical director, and/or deputy clinical director.

The protocol coordinator assists IRB staff with the review of documents submitted for IRB review by the PIs and/or study coordinators and extracts relevant technical information to include in the IRB packets and database. The protocol coordinator is responsible for distributing correspondence and approved documents by the IRB chair and clinical director to the PIs and study contacts. Additional duties include: processing and distributing other protocol actions (e.g., Problem Forms, emergency-use Investigational New Drug [IND] forms, protocol status updates, short consent forms, and miscellaneous documents) to the NCI IRB chair, NCI clinical director, and/or deputy clinical director using the iRIS database; assisting in preparing IRB meeting packets in a timely manner; receiving internal calls regarding protocol submissions using iRIS; monitoring the task box in iRIS; and routing issues to the appropriate analyst. The protocol coordinator updates/maintains the CCR wiki for the IRB Administrative Office; prepares documents to renew IRB members before their terms expire; prepares the IRB meeting agendas for 23 IRB meetings each year; and attends biweekly IRB meetings. The protocol coordinator also updates the SOPs for PRO processes.

CMRP manages a research subcontract providing the chair for the NCI IRB. The IRB chair position is of utmost importance, ensuring the safety of clinical trial participants as well as the scientific validity of study findings. Support provided by the IRB chair includes: leading IRB meetings twice a month; playing an active role in establishing and reviewing IRB policies and procedures; identifying issues within research proposals; and conducting expedited reviews of recruitment materials, informed consents, and special exemptions. Due to new study application, PRO staff assisted CCR employees with a step-by-step process on how to complete the application.

Protocol Support Office

CCR re-engineered its processes related to the development, review, and initiation of clinical trials in order to decrease the time from scientific review to opening clinical trials for patient accrual, while maintaining or increasing quality and safety. As a result, CCR established a Protocol Support Office (PSO) in addition to the PRO, described above. The PSO oversees services in three major areas: (1) writing and editing, (2) regulatory and compliance, and (3) protocol navigation and administration.

CMRP is responsible for assisting with the preparation of new proposals/protocols and progress reports for IRB meetings. CMRP assists PSO staff in reviewing and making recommendations and/or changes to protocol amendments and other documents related to research studies. The team also assists with training new staff. Members of the PSO are required to attend IRB, SMC, and Scientific Review Committee (SRC) meetings. In addition, staff members are in charge of contacting PIs for the review board, as needed.

In support of the PSO, CMRP employs three protocol coordinators to serve as liaisons between CMRP and CCR/NCI staff for the initiation and completion of tasks related to protocol support. Two medical writers attend IRB, SMC, and SRC meetings; take minutes; create and edit SOPs and templates; maintain the PSO wiki pages; and review and edit protocol amendments and continuing reviews. These staff members also edit and/or create associated documents, such as informed consents. The PSO has helped in increasing the development, review, and opening of clinical trials by decreasing the time required from scientific review to opening for patient accrual.

Staff members have played key roles in processing clinical protocols for submission to various regulatory agencies, such as the IRB, the U.S. Food and Drug Administration (FDA), the Office of Biotechnology Activities (OBA), and the Institutional Biosafety Committee (IBC). The team assisted clinical investigators with the review of 51 new protocols and informed consent documents, 176 protocol amendments, and 21 OBA/IBC submissions. Staff was involved in 35 protocol navigation projects and three Office of Human Subject Recruitment and Protection (OHSRP) applications, as well as in the maintenance of 25 regulatory binders. Currently, the team provides support to 14 different branches within CCR for approximately 28 active Investigational New Drugs (INDs)/Investigational Device Exemptions (IDEs)/Drug Master Files (DMFs).

During FY2015, staff assisted in preparing for the NIH Association for the Accreditation of Human Research Protection Programs (AAHRP) accreditation, including organizing files and interviewing with AAHRP staff. Staff also administers, organizes, and coordinates the CCR Scientific Review meetings, and supports investigators with preparing submissions under the new process. Many new processes were introduced following the NIH AAHRPP accreditation; staff learned and executed the new processes for all active protocols including: updating all study applications, obtaining conflict of interest certificates, ensuring training certificates have been obtained by all investigators, and submitting protocols via the new CCR scientific review process.

Endocrine Oncology Branch

The Endocrine Oncology Branch (EOB) focuses on treating patients with endocrine malignancies. The ultimate goal of the EOB is to establish an integrated basic, translational, and clinical research program with the goal of developing innovative diagnostic and prognostic approaches, and treatments for endocrine cancers. This goal is consistent with the mission of the Center for Cancer Research to: understand the causes and mechanisms of cancer, improve early detection and diagnosis of cancer, understand the factors that influence cancer outcomes, and develop effective and efficient treatments for patients with cancer.

The EOB is made up of researchers who have specialized training and an interest in endocrine malignancies. The Branch incorporates the major functions of clinical research, clinical care, and clinical training in pursuit of treating patients with endocrine cancers. The EOB routinely handles referrals from medical centers across the United States and overseas, the National Institute of Digestive, Diabetes and Kidney Disease (NIDDK), the National Institute of Child Health and Development (NICHD), and NCI.

During this reporting period, a patient care coordinator was hired to support the EOB. The patient care coordinator assists with all administrative functions for the branch. The patient care coordinator triages incoming calls, and acts as a liaison between physicians, research nurses and other departments within and outside of NIH, Specifically, the patient care coordinator collects outside medical records, to include medical imaging scans and pathology reports and delivers them to various departments within NIH. The patient care coordinator also coordinates the biweekly clinic schedule, arranges patient schedules, and communicates with various clinical support offices, clinics, and diagnostic centers concerning the scheduling of new and returning patient appointments. The patient care coordinator completes the weekly clinic schedule for EOB and prepares for clinics by: confirming appointments; preparing necessary consent forms for signatures; coordinating a weekly clinic meeting; preparing pathology reports for post-op patients; and scheduling procedures, including all surgeries, through an electronic scheduling database.

The EOB currently has 11 active protocols and evaluates patients with an array of rare endocrine diseases and disorders which may include: multiple endocrine neoplasia type 1 (MEN1); multiple endocrine neoplasia type 2A (MEN2A); Von-Hippel Lindau (VHL) syndrome; Cushing's syndrome; papillary, medullary, and anaplastic thyroid cancers; parathyroid disorders; adrenocortical carcinoma; pheochromocytomas; and adrenal and neuroendocrine tumors. The protocols include tissue analysis, genetic analysis, and interventional treatments (i.e., surgery, systemic treatment, and imaging). Additionally, studies with significant interest include one titled Evaluation of ^{68}Gallium-DOTATATE PET/CT for Detecting Primary and Metastatic Neuroendocrine Tumors; and a Phase I ATR-101 multi-institutional trial treating patients with metastatic adrenocortical carcinoma. The Phase I ATR-101 multi-institutional trial opened in August 2014 and is one of the few studies in the world focusing on adrenocortical cancer. Finally, the EOB's newest study involves targeted therapy in advanced neuroendocrine tumors. Patients being treated on this protocol receive treatment with either sunitinib or everolimus, based on the germline or somatic mutations identified by the tumor genotyping performed by a collaborating laboratory.

Experimental Transplantation and Immunology Branch

The Experimental Transplant and Immunology Branch (ETIB) is dedicated to coordinating efforts for basic, preclinical, and clinical investigations related to transplantation science. The goal of this program is to generate information from basic and preclinical investigations leading to the development of novel, curative therapies for cancer. Information from new treatment protocols, including novel endpoints generated in the course of basic and preclinical research, is used to generate new questions and studies in basic and preclinical research efforts.

CMRP staff members serve as associate investigators on 15 protocols, two of which are with NIAID, three with NHLBI, and 10 with NCI. Twelve of these protocols are active transplant protocols that involve the CMRP staff searching for donors. Nine of these protocols are cord blood access protocols, two are data collection protocols, and two are post-transplant follow-up or donor apheresis protocols. The clinical research nurse has been actively involved in approximately 140–150 preliminary searches for transplant candidates during this reporting period. Twenty-four patients have been formalized for transplants since September 2014. That number is expected to rise because the team is opening a new protocol, so an estimate of 45–50 formal searches will be done during this reporting period. The clinical nurse administrator facilitated the opening of one new protocol in FY2015 (protocol 15-C-0067) and has successful collaborations with multiple investigators within three institutes and four branches of NIH.

The clinical research nurse is responsible for coordinating all clinic-related functions and administrative support for ETIB. The Clinical Core group coordinates graft-versus-host disease patient recruitment; processes patient intakes; facilitates patient accrual into clinical trials; works closely with patients, donors, and families throughout the protocol screening process; and maintains communication with patients and referring physicians' offices. CMRP staff members serve on the work group for Thaw and Infusion of Cord Blood Units, under the HHS Advisory Council on Blood Stem Cell Transplantation and, when requested, provide programmatic updates to the Health Resources and Services Administration, which is the primary federal agency for improving access to health care services for people who are uninsured, isolated, or medically vulnerable.

CMRP staff maintains records and tracks program-wide expenditures, while focusing on ways to reduce search costs. Staff members have requested and received assistance from the ETIB Administrative Office with this aspect of program management.

CMRP staff participates in weekly team meetings for human leukocyte antigen (HLA)/donor selection. The CMRP administrator participated in discussions between NIH and the National Marrow Donor Program (NMDP) that resulted in a memorandum of understanding (MOU)

between the NIH Office of Human Subjects Research Protections (OHSRP) and NMDP. The MOU clarifies the role of the NMDP and NIH IRBs in the approval of NIH protocols that involve the unrelated donor as a research subject. Additionally, the CMRP administrator was involved in the creation of a new Clinical Research Information System (CRIS) note, titled HSCT Donor Selection Note, that documents key donor information in the recipient's medical record. The CMRP administrator participated in discussions with medical records, legal department, and the Department of Clinical Research Informatics (DCRI). The note generated from those discussions was approved by a consortium, and will be live in June 2015. The related donor section of the note is an innovative use of technology; DCRI was able to create a link between the donor and recipient medical record, thus pulling in the donor's medical records while maintaining donor privacy. The CMRP nurse administrator is the point of contact for the NMDP IRB, and ensures that protocols that use unrelated donors as research subjects are up-to-date with the NMDP IRB. Five protocols have NMDP IRB approval.

Three CMRP physician extenders supporting ETIB perform assessments by obtaining comprehensive medical histories and by performing physical examinations. In addition, these individuals manage patients with complex and difficult multisystem aspects; provide continuity-of-care; and support and educate patients, family members, and staff on matters relating to health and research studies, and protocols. The physician extenders/physician's assistants also participate in clinical rounds and meetings/ conferences related to study protocols and research.

CMRP staff expertly managed the conflicting needs and priorities of multiple NIH intramural institute programs and developed trust by conducting a fair and equitable distribution of available grafts, while maintaining excellent regulatory and administrative compliance with federal regulations; developed a high degree of collaboration with supporting personnel at the NMDP; and directly reduced costs accrued to the NIH by their expert management of stem cell donor searches and by obtaining local stem cell products to obviate the fees for couriers.

The CMRP nurse administrator also participated in activities for a new protocol in FY2015, protocol 15-C-0067 A Phase I/II Open Label, Dose Escalation Study of Palifermin (Kepivance) in Persons Undergoing Unrelated Donor Allogeneic Hematopoietic Cell Transplantation.

The complex coordination among groups requires superior skills in communication. The CMRP nurse administrator has demonstrated mastery in customer service skills by building effective working relationships with outside stakeholders, coordinating program activities and protocol developments, and collaborating with multiple institutes/section within and outside of NIH. For example, she continues to participate in weekly team meetings for HLA/donor selection, and participates in many work groups, seminars, and donor drives to provide information on how patients can communicate and/or exchange information with their unrelated volunteer donors.

The CMRP administrator regularly provides education to the incoming NCI and fellows by conducting lectures on donor/cord blood search and selection strategies. In FY2015, this staff member participated in and facilitated discussions between NMDP and NIH OHSRP, which resulted in an MOU that clarified the research oversight of unrelated donor participation in NIH protocols between the two programs.

HIV and AIDS Malignancy Branch

The HIV and AIDS Malignancy Branch (HAMB) is instrumental in focusing on AIDS-related malignancies that are positive for Kaposi's sarcoma–associated herpesvirus (KSHV). Research efforts related to the pathogenesis of KSHV, a causal agent of Kaposi's sarcoma, primary effusion lymphoma, and Castleman's disease, are ongoing.

The patient care coordinator is responsible for providing administrative support to HAMB. This staff member assists three investigators and two research nurses with approximately 200 patients who are enrolled in seven active protocols. In addition, the patient care coordinator works with the team on the recruitment process to increase patient referrals and accrual.

The patient care coordinator continues to monitor a new coding system for storing research specimens and cataloging old protocols (dating from 1984 to the present). This system is used to gather clinical information from research specimens that describe previously unknown syndromes.

Additionally, the patient care coordinator works with patients and staff from physicians' offices to obtain medical records and other pertinent documents prior to a patient's appointment or admission. This effort includes coordinating appointments, making travel and lodging arrangements, and providing patients with information about their appointments (e.g., dates, times, and hospital maps). The patient care coordinator routinely orients and guides new patients as they begin their enrollment process, and is instrumental in directing new patients through the administrative process that allows them to be evaluated in clinic.

The patient care coordinator prepares scientific research samples for transport to the repository, collects and disseminates medical resource documents on new patients for fellows' review prior to initial assessment of the patient, and obtains saliva specimens from protocol recipients for scientific testing.

Currently, the HAMB team is experiencing the transition of several key staff members. The branch is in the process of regrouping and hiring new staff to replace those that transitioned to other positions within and outside of NIH. The patient care coordinator has become an even greater asset to the team administratively by assisting them through this process.

Lymphoid Malignancies Branch

The Lymphoid Malignancies Branch (LYMB) focuses on the identification of abnormalities in the regulation of the immune response and the definition of molecular disorders that underlie lymphoid malignancies. A mainstay of LYMB is gene-expression profiling, which provides a foundation for understanding the molecular pathogenesis of these cancers and their response to therapies. A research goal is to define the pivotal roles played by IL-2 and IL-15 in the life and death of normal and neoplastic lymphocytes. The branch also focuses on T-cell malignancies, with emphasis on human T-cell lymphotropic virus 1 associated with adult T-cell leukemia. The major clinical research emphasis is the development of the most effective treatment in molecular subtypes of aggressive B-cell lymphomas. Also, protocol 14-C-0157, Phase I Study of Ibrutinib and Immuno-Chemotherapy Using Dose-Adjusted-Temozolomide, Etoposide, Doxil, Dexamethasone, Ibrutinib, Rituximab (DA-TEDDI-R) in Primary CNS Lymphoma, was launched to focus on primary central nervous system (CNS) lymphoma (a rare form of diffuse large B-cell lymphoma), which is difficult to treat around the blood–brain barrier.

During this reporting period, the patient care coordinator resigned and a replacement was hired. The patient care coordinator provides administrative support to the LYMB and their clinical research efforts. The patient care coordinator facilitates all administrative activities and coordinates schedules for new and currently enrolled LYMB patients. Currently, the team has 15 active protocols. During this reporting period, the LYMB has evaluated 65 new participants and enrolled 37 for active treatment.

In addition, LYMB personnel, including physicians and research nurse staff members, have published several articles identifying various types of malignancies involving lymphoma and its possible relationship(s) with other malignancies.

Pediatric Oncology Branch

CCR's Pediatric Oncology Branch (POB) includes a Behavioral Sciences Core that consists of two separate, but interrelated, components: the neurobehavioral program and the psychosocial program. The Behavioral Sciences Core was created to facilitate the development of studies investigating the neuropsychological and psychosocial effects of chronic illness; provide specialized research support to clinical trials using neuropsychological and quality-of-life outcome measurements; and offer clinical services to the patients and families enrolled in studies throughout NCI.

The main objectives of the neurobehavioral program are to: study the effects of disease and treatment on the neurobehavioral functioning of children and adults with chronic illness through comprehensive, state-of-the-art longitudinal assessments; examine the pathogenesis of central nervous system dysfunction by exploring the relationships of neuropsychological measurements to disease parameters, neurological abnormalities, biomedical and genetic variables, and environmental and psychological factors; and investigate potential cognitive interventions that could help ameliorate some of the cognitive deficits and declines as a result of the disease and treatment.

In addition, the neurobehavioral group offers clinical services to patients, including: providing assessment results to families, making recommendations and coordinating at-home psychoeducational services, and implementing clinical interventions based on patient needs. The neurobehavioral group also conducts a training program that provides psychology students with valuable clinical and research experience in a medical setting.

The CMRP psychometrician works primarily with the neurobehavioral program to conduct longitudinal neurobehavioral assessments of children, adolescents, and adults on collaborative research protocols or in response to clinical referrals.

The psychometrician conducts comprehensive neuropsychological research evaluations of patients and prepares clinical reports to help families, schools, and/or mental health agencies locally manage the child's educational services and psychological care. The psychometrician also provides clinical interventions to children who are enrolled in protocols and have developmental delays, problems with medication adherence, severe emotional disturbances, or other behavioral issues, in an effort to improve the child's well-being and help the child remain in the study and comply with treatments.

The psychometrician is integrally involved in training incoming employees and students, where appropriate, and in completing data entry, administrative, and other research-related tasks.

During FY2015, the psychometrician was part of the team that supported 13 IRB-approved protocols. In addition, the psychometrician provided support for patient recruitment and assessments to two newly-opened Neurobehavioral Group-initiated protocols. The psychometrician conducted 38 comprehensive protocol-related assessments during this period; in addition, 34 hours of clinical intervention (therapy) were provided as a service to patients referred due to social–emotional issues. The psychometrician also completed two clinical reports as requested by the families. These reports summarized the results from the psychological testing and contained recommendations for use in an educational setting.

In June, the psychometrician presented a poster at the 2015 Annual Children's Tumor Foundation Conference in Monterey, CA, and participated in the collaborative development of other research posters presented at the conference. The psychometrician also participated in the Cognitive Committee of the Response Evaluation in Neurofibromatosis and Schwannomatosis International Collaboration as one of the test reviewers and contributed to the development of a manuscript

highlighting the committee's recommendations regarding measures to use in clinical trials in neurofibromatosis type 1.

Radiation Oncology Branch

The Radiation Oncology Branch (ROB) designs and conducts preclinical and clinical research on the biologic and therapeutic effects of radiation therapy. The research clinical trials that ROB develops and conducts involve novel technology- and/or imaging-based approaches to radiation therapy treatment.

During FY2015, the nurse case specialist transferred to a government position within the branch and the position through Leidos Biomedical Research/CMRP was closed. CMRP currently has two patient care coordinators and one clinical program administrator supporting ROB. These individuals provide administrative support to the branch by scheduling patient appointments, creating clinic schedules, and referring phone calls. The clinical program administrator maintains office supplies and manages the daily operations within ROB.

CMRP clinical support staff provides critical protocol support to the Neuro-Oncology Branch (NOB). During the time when NOB was without a chief, NOB and ROB collaborated to provide special accommodations, which consisted of ROB following NOB's patients (approximately 100). The CMRP patient care coordinators facilitated planning meetings between NOB and ROB nurse practitioners, patient care coordinators, clinical fellows, and ROB's chief to ensure a smooth transition of activities from NOB to ROB. In addition to following up with NOB patients, the CMRP patient care coordinators were responsible for distributing correspondence regarding the temporary changes to NOB patients. CMRP patient care coordinators also scheduled follow-up visits, including MRI scans, necessary diagnostic tests/labs, port access, VAD appointments, consult visits, and nurse visits, and coordinated travel authorizations.

Additionally, CMRP patient care coordinators staff took a more active role in providing multidisciplinary coverage, which included disseminating patient welcome packages, sending out scheduling notices to patients, requesting outside records, obtaining screening consent, and scheduling patient follow-up visits.

Thoracic and Gastrointestinal Oncology Branch

The main objective of the Thoracic and Gastrointestinal Oncology Branch (TGIB) is to conduct laboratory and clinical research focused on improving the care, management, and outcomes of patients by developing innovative surgical and adjunctive approaches.

The TGIB support team consists of two clinical research associates and one clinical coordinator. These staff members support six clinical investigators (three within the Thoracic team and three within the GI team), who conduct approximately 14 active clinical studies and have been instrumental in maintaining the work for the TGIB. Data support is provided by the two clinical research associates, and patient care coordination is provided by the clinical coordinator. The staff works closely with the PIs and research nurses to ensure all support activities are handled in a timely and efficient manner.

Combined, both clinical research associates support eight protocols that have accrued approximately 567 patients. The clinical research associates also assist with data and statistical analyses, and Spanish translations for patients, as needed.

During this period, both clinical research associates trained surgical fellows on a variety of surgical oncology projects that included toxicity assessments, review of data, and patient records.

The clinical research associates assist the CCR PSO with reports for NCI IRB continuing reviews, assist the surgical fellows and PIs in creating and completing database forms for use in the clinic, and assist in evaluating and following research-related adverse events (AEs) and toxicity assessments for patients participating in the active clinical trials.

The clinical coordinator provided patient care coordination support to five investigators for 14 protocols for both the Thoracic and GI teams. The clinical coordinator supporting both the Thoracic and GI teams transitioned to supporting only the Thoracic team and was tasked to train a new full-time clinical coordinator for the GI team, which was accomplished in May 2015.With this change in May 2015, the clinical coordinator now supports three Thoracic team investigators for eight protocols. The clinical coordinator also interacts with many different departments, both within and outside NCI, and schedules patient appointments, testing, screenings, consults, itineraries, and lodging. The clinical coordinator also assists in Spanish translation for patients, as needed.

At the urgent request of a GI PI, the clinical research associates created a surgical caseload spreadsheet for surgeries done by the PI from FY2012 through FY2014. This was required to assist this PI, who is on tenure track for a site visit, to evaluate progress. The clinical research associates also reviewed all of the PI's protocols' study progress reports, results and outcomes, IRB continuing reviews, and summaries of publications in preparation for the site visit. As a result of this request, the clinical research associates compiled a surgical caseload list for both PIs in the GI team for this time period to enable them to evaluate their surgical case workload over time. This spreadsheet has been updated over time to include more fields to capture the surgery type, investigator or surgeon name, requesting branch for consults, and patient information. Also, as the surgical workload has increased for the surgeons, the caseload spreadsheet created by the CMRP support team has been critical in mitigating scheduling conflicts and ensuring smooth workflow of the surgical cases.

The clinical research associates initiated the re-activation of inactive study protocol 09-C-0079, The Natural History of Solid Organ Cancer Stem Cells, to amend it to allow for the enrollment of patients with

familial GI malignancies for genetic analysis, life-saving preventive surgeries and procedures, and longitudinal follow-up. After much deliberation, the PI is planning to write protocols to study such patients with familial gastrointestinal malignancies for genetic analysis, life-saving preventive surgeries and procedures, and longitudinal follow-up. The clinical research associates will provide support for the new protocols once they are written and implemented.

At the request of one of the GI investigators, the clinical research associates recently began work on a project to create a pancreatic cancer master spreadsheet, which will include all patients with pancreatic cancer who have been enrolled in any of the surgical oncology protocols. This spreadsheet will serve as a registry for pancreatic cancer cases seen by the team.

The clinical coordinator maintains the Outlook calendar for the Thoracic team. This task includes adding patient schedules, surgery dates, admissions, and pre-operative schedules to the common Outlook calendar for the Thoracic team to ensure everyone has current and up-to-date information.

In this reporting period, the clinical coordinator also started assisting the Thoracic team research nurse with delivery of the vaccine product for study 14-C-0053, Adjuvant Tumor Lysate Vaccine and Iscomatrix With or Without Metronomic Oral Cyclophosphamide and Celecoxib in Patients with Malignancies Involving Lungs, Esophagus, Pleura, or Mediastinum, from the laboratory to the patient clinic.

In May 2015, the clinical coordinator transitioned from supporting both the Thoracic and GI teams to providing support only to the Thoracic team. This was because the GI team required a full-time clinical coordinator and it was decided to transfer a full-time employee from another department to assist the GI team for their clinical coordination activities. The CMRP clinical coordinator played an instrumental role in training him on all the required tasks.

Surgery Branch (Immunotherapy)

The main objective of the Surgery Branch (SB) (Immunotherapy) is to conduct laboratory and clinical research focused on improving the care, management, and outcomes of patients by developing innovative, autologous T-cell/gene therapy, and surgical and adjunctive approaches.

CMRP staff supporting SB Immunotherapy consists of a senior IND manager and a protocol development coordinator. These staff members provide administrative, scientific, and regulatory support for the SB Protocol Support Office (PSO).

CMRP staff supports five clinical investigators, who conduct approximately 30 active clinical studies and have been instrumental in maintaining and improving the SB's reputation for high-quality work. Of these 30 active protocols, 25 were amended to include new clinical fellows in July 2015.

The protocol development coordinator continues to play a key role and provide an organizational framework for tracking due dates to ensure processing and timely submissions of 30 protocols, and maintains databases to track all submissions to various regulatory agencies, such as the IRB, the FDA, the Institutional Biosafety Committee (IBC), and Office of Biotechnology Activities (OBA). In addition, this staff member spearheaded the development and design of a new Access database for patient screening and referrals for the SB. The database is currently being used to generate queries and reports for meetings. The protocol development coordinator continues to develop the database to generate different types of reports for regulatory submissions.

The senior IND manager assists other SB PSO staff, as needed, with submission and maintenance of protocols, and reviews and assists in the updates of up to 31 standard operating procedures (SOPs) for the SB PSO, including writing new SOPs and setting up template documents for routine submissions and maintenance of 30 protocols. The senior IND manager also assists the Cell Production laboratory in reviewing and organizing their SOPs for submission to the Surgery Branch master file submission to the FDA. In addition, the senior IND manager has prepared and submitted more than eight annual reports and two initial IND applications to the FDA during this reporting period. Of these two initial IND applications, one was a gene therapy protocol IND and required an initial IBC and OBA application submission.

In April and May 2015, PBS ran a three-part documentary titled, Cancer: The Emperor of All Maladies, based on the Pulitzer Prize winning book *The Emperor of All Maladies: A Biography of Cancer* by Siddhartha Mukherjee. This documentary included a 15-minute segment on the immunotherapy research being conducted within the SB and included commentary by the branch chief.

During this reporting period, one new protocol was submitted to the NCI IRB, IBC, OBA, and FDA as a new IND: 15-C-0090, Phase I/II Study Administering Peripheral Blood Lymphocytes Transduced with a Murine T-Cell Receptor Recognizing Human Thyroglobulin to Patients with Thyroglobulin Expressing Thyroid Cancer. Another new protocol was submitted and reviewed by the IRB: 15-C-0153, A Phase I Trial for the Evaluation of the In Vivo Persistence of Adoptively-transferred Tumor-Infiltrating Lymphocytes Cultured with a Pharmacologic Inhibitor of AKT in Patients with Metastatic Melanoma. This protocol was submitted to the FDA as a new IND in May 2015 and approved in August 2015.

Due to the publicity received for some of the SB protocols, the number of patient referrals has increased. To assist the SB referral nurses in handling an increasing volume of patient calls, the SB PSO created a call-log spreadsheet which was eventually put into the ACCESS database to set up a central system for all the nurses to use when calls are answered and to document relevant patient information, including cancer type, major histo-compatibility complex (MHC) haplotype, antigen marker

expression type, etc. This database is currently being used by the referral and research nurses in the SB and continues to be enhanced with new features by the SB PSO as needed. The protocol development coordinator created work instructions and provided training to the referral and research nurses prior to its implementation. The protocol development coordinator continues to enhance the ACCESS database for patient referral information entries. This database has significantly improved the workflow processes and has enabled the clinical staff to review and get updates on potential patient referral statuses in an efficient manner. The referral nurses also rely on this database to address weekly queries from the branch chief during the immunotherapy patient meetings.

Conflict of Interest (COI) policy changes were implemented by the CCR in this reporting period. As a result, all protocols had to be reviewed to determine which category the PI and associate investigators (AIs) fell under with the new changes prior to submitting paperwork to the Deputy Ethics Counsel (DEC) for clearance. The SB PSO proactively reviewed, created a spreadsheet, and figured out the different forms required by our investigators and worked with the DEC staff to confirm that the SB was following the updated procedures correctly. The SB PSO will continue to maintain this as new investigators are added.

The NCI PSO supervisor requested the senior IND manager to review their new IND section for their gene therapy protocol as a subject matter expert. Since the senior IND manager has experience in preparing and filing IND submissions for gene therapy protocols for the SB protocols, feedback was provided based on this experience. The protocol development coordinator, who is an expert on the use of Reference Manager software, was requested by the SB administrative staff to train a newly hired secretary on this program.

Urologic Oncology Branch

The Urologic Oncology Branch (UOB) conducts clinical and basic research designed to develop better methods for detection and prevention of genitourinary malignancies, and therapy for patients who have them. The primary focus of the UOB is the study of the genes associated with initiation and progression of kidney and prostate cancers.

Staff supporting UOB have collaborative relationships with many investigative sites and client personnel, and are responsible for coordinating and collaborating with multi-clinical teams, including internal medicine, pre-anesthesia, and outside primary care providers, to successfully recruit new patients for the expansion of their prostate program. Staff members actively participate in all aspects of the UOB's research efforts at NIH, which include the recruitment of new patients, management of patients with low-volume and low-risk prostate cancer who are interested in active surveillance, and management of patients' clinic follow-up visits. The management of these patients entail monitoring patients' outside prostate-specific antigen (PSA) level, scheduling all re-staging visits, coordinating and arranging MRI-guided biopsies, providing patient education to prepare patients for MRI-guided biopsies, and entering orders for diagnostic labs and tests. Management of the clinic follow-up patients requires ongoing communication with UOB fellows regarding patient needs, scheduling diagnostic tests/labs and consultations, entering studies/labs orders, assisting in generating follow-up test schedules and travel authorization, and calling patients to discuss their biopsy results.

Laboratory of Molecular Biology

The Laboratory of Molecular Biology (LMB) pursues three major areas of research to understand and treat cancer. One area comprises the study of antibody-based cancer treatments for hematologic, liver, and mesothelin-based cancers. Another area is modeling of thyroid hormone-based cancers. The third area focuses on basic biochemical processes of gene transcription, post-translational regulation, molecular chaperone systems that manage protein damage, and the localization and assembly of large protein structures.

The senior nurse practitioner serves as associate investigator for all treatment-related protocols and supports the PI and a team of three research nurses by reviewing all new patient records and writing a concise history of present illness, including a medication list and co-morbidities. The senior nurse practitioner, in conjunction with the PI, is responsible for managing patients who are in active treatment, including performing routine physical exams, evaluating lab and imaging results, and determining if patients can safely proceed with treatment at specified time-points. The nurse practitioner also evaluates and manages co-morbid conditions, treatments, and disease-related symptoms/ toxicities such as nausea, rash, fatigue, etc., throughout the active treatment cycle. The nurse practitioner sees patients in the Outpatient Clinic, in collaboration with the PI, who are scheduled for routine, annual, and semi-annual protocol-driven follow-up evaluations.

During this reporting period, the LMB went through a protocol evaluation audit. Subsequently, all protocols were placed on hold during this time. The senior nurse practitioner was instrumental in navigating the PI through the audit processes, answering questions regarding audit findings and providing solutions. The senor nurse practitioner also served as a primary contact for all patients actively enrolled, in follow-up status, or being evaluated for eligibility. Following the audit, all treatment protocols resumed (seven are actively recruiting, and one is open for follow-up only).

Host Virus Interaction Branch, HIV Drug Resistance Program

As the clinical arm of the HIV Drug Resistance Program, the Host-Virus Interaction Branch (HVIB) conducts fundamental studies on the nature of HIV drug

resistance in vivo. Ongoing studies are focused on: characterizing the replicating population size and genetics of HIV in infected individuals before, during, and after antiretroviral therapy (ART); defining the genetic mechanisms, kinetics of emergence and decay, and clinical consequences of HIV drug resistance; identifying the tissue and cellular sources of persistent viremia despite suppressive ART; and testing novel therapeutics to reduce persistent viremia and deplete HIV reservoirs.

The Clinical Retrovirology Section of the HVIB directs protocol development, regulatory affairs, patient recruitment, and sample collection efforts for the HVIB at the NIH Clinical Center, in collaboration with: the AIDS clinical research programs of the NCI HAMB, NIAID, and the Critical Care Medicine Department. The Clinical Retrovirology Section also conducts fundamental studies of HIV pathogenesis in vivo, including studies of HIV genetic variation and the emergence of antiretroviral drug resistance. CMRP provides a protocol nurse coordinator to support these efforts.

The primary responsibility of CMRP support to HVIB is to coordinate clinical studies under the Clinical Retrovirology investigator. Studies include: clinical research to test novel therapeutics to reduce persistent viremia and deplete HIV reservoirs, and observational research to gather understanding from enrolled participants with suppressive HIV who are using ART over a period of time. Team responsibilities include: screening, enrollment, and coverage of colleague studies, including IND research specifically studying curative therapy for hepatitis C.

The protocol nurse coordinator participates in all aspects of the Clinical Retrovirology Section of the HIV Drug Resistance Program efforts at NIH. Among the contributions is the independent management and coordination of every aspect of three active protocols, which includes coordinating patient visits to NIH, directing the patients to admissions, consenting the patients for screening, preparing monthly patient calendars, and acting as a liaison between the patients and the health care providers.

During FY2015, the protocol nurse coordinator maintained regulatory binders, reviewed clinical trial data, and completed numerous AE reports. The protocol nurse coordinator was also responsible for ensuring liver biopsy procedures were scheduled by the hepatitis C team after a study coordinator on the team transferred to another department. The protocol nurse coordinator also cross-covers coordination for five other protocols within the HVIB, one of which involves setting up and coordinating a new multicenter drug study with co-enrollment to a procedure study. Additionally, on a daily basis, the protocol nurse coordinator reviews notes with the PI and prepares presentations for continuing reviews, Data Safety Monitoring Board (DSMB) meetings, and weekly multicenter conference calls. This staff member coordinates a weekly multi-site conference call and ensures all attendees are made aware of active issues for three protocol sites.

During FY2015, the protocol nurse coordinator successfully completed a continuing review and DSMB report for protocol 13-I-0062, A Double Blind Randomized Placebo Controlled Study Examining the Effects of a Non-Absorbable (Rifaximin) Antibiotic on the Chronic Immune Activation Observed In HIV-Infected Subjects; completed one amendment, one continuing review, and two DSMB reports for protocol 11-I-0057, Effect of Interferon Alpha 2b Intensification on HIV-1 Residual Viremia in Individuals Suppressed on Antiretroviral Therapy; and one continuing review for protocol 08-I-0221, Analysis of HIV-1 Replication during Antiretroviral Therapy.

Additionally, the protocol nurse coordinator worked on a new protocol, a lymphoid biopsy study in HIV patients using CT/PET and interventional radiology for the biopsy, titled Localizing Cellular Sources of HIV Infected Cells Persisting in Lymphoid Tissue during Combination Antiretroviral Therapy.

Molecular Imaging Program

The goal of the Molecular Imaging Program (MIP) is to develop targeted imaging methods that accelerate the development of cancer therapies. This program performs translational research in targeted cancer imaging for purposes of early tumor detection and characterization, treatment monitoring, and drug development. CMRP provides a dedicated team of individuals to support the operations of the NCI Research Imaging Clinic in the most efficient, effective, and compassionate way.

CMRP staffs a positron emission tomography (PET) physicist to work with the National Institute of Standards and Technology (NIST). This support has been instrumental in determining the accuracy of the program's PET/computed tomography (CT) scanner, performing radiation dosimetry for clinical trials, credentialing the PET/CT scanner for clinical trials experiments, performing quantitative analysis, and solving technical image-quality problems. In the absence of the nuclear medicine dosimetry calculations physician, the PET physicist is responsible for solving technical problems with imaging and quantitative analysis.

The senior chemist provides extensive practical and technical knowledge regarding the clinical development of a broad array of potential imaging agents, including new chemical entities, and nano and biotechnologies. The senior chemist investigates the feasibility of labeling new imaging agents based on their chemical properties and determines translational feasibilities, including viability of commercial production from a chemistry development viewpoint. The senior chemist defines required experiments for preclinical testing, and provides process development and analysis of the data, to include in presentations and publications.

MIP PET/CT technologists perform highly-skilled PET/CT scans on patients involved in clinical trials. The technologists are instrumental in writing policy relevant to PET/CT and maintaining quality assurance (QA) for

radiation safety. CMRP staff has met the rigorous credentialing requirements necessary to function as authorized users of radiopharmaceuticals. This accomplishment provides support directly to the PI, as well as to the entire department. The PET/CT technologists scan an average of 30–40 patients a week. During FY2015, MIP staff worked on technical evaluations of the PET/CT clinical scanners sold by Siemens, Philips, and GE as possible replacements for the current Philips Gemini TF. This is a multi-million dollar purchase, and extensive evaluation work was done by performing phantom tests on all three potential replacement scanners. Evaluation metrics were developed by MIP staff to help decide how to proceed with the PET/CT scanner replacement options.

The MRI/CT/radiology technologist is credentialed in three modalities and is a candidate for PET certification training. This technologist is responsible for developing and implementing SOPs related to MRI contrast and delivery.

The patient care coordinator is responsible for scheduling patients who visit the Molecular Imaging Clinic to participate in clinical trials and consistently schedules an average of 30–40 patients per week. Other responsibilities include serving as an interpreter for Spanish-speaking patients and interfacing with other branches, such as urology, to coordinate referrals to the department. In addition, the patient care coordinator provides administrative support to the PI, as well as to the clinical trials clinic.

During the last reporting period, a new protocol was opened to evaluate the use of ferumoxytol-enhanced MRI for the detection of lymph node metastases in genitourinary cancers. Thus far, 25 patients are enrolled. Notably, the usage of the same agent in preclinical work in non-human primates has shown its utility for sentinel node imaging in prostate cancer and led to peer-reviewed publication of findings.

The MIP team had previously succeeded in demonstrating Ablavar MR prostatic imaging and lymphatic tracking in size-relevant dogs. The agent is intended for initial clinical trials for prostate cancer sentinel node imaging, and the approvals for this indication are currently being sought.

The MIP has investigated a gadolinium dendrimer composition in non-human primates to track the progress of SIV infection as a model for the spread of HIV infection in humans, and data resulting from these studies has been published.

The MIP developed the preparation of precursors and intermediates for the study of ^{18}F-glutamine PET imaging for a range of cancers. During FY2015, the agent was successfully prepared and tested in initial in vitro studies. Initial in vivo studies in preclinical animal models are planned.

A new project proposal, titled A New, Highly Sensitive β-Galactosidase Probe for Visualizing Peritoneal Cancer Metastases, was prepared in February 2015 for collaborators within MIP, which will benefit the broader extramural scientific community upon its successful completion.

Previously, the MIP successfully submitted a new NCI Experimental Therapeutics (NExT) proposal on IR700-monoclonal antibodies (MAbs) for immunotherapy, which received positive reviews. Due to a strategic change, the agent is being developed by a commercial MIP collaborator rather than within NCI and has undergone successful toxicology studies and FDA approval for a Phase I clinical trial.

Notably, in FY2014, the MIP team developed a novel method for tracking cells, including stem cells, which may be used with novel in vivo cell therapies and basic research studies, and a related patent application (Sato N, Griffiths GL, Wu H, Choyke PL: Zirconium-89 oxine complex as a cell labeling agent for positron emission tomography. U.S. Patent Application No. 61/973/706) was filed in April 2014. Most recently, publications on the agents have been authored and investigational development continues.

In late 2014 a comprehensive Cooperative Research and Development Agreement (CRADA) was reached between NCI and Medimmune, Inc., to investigate multiple research avenues of common interest to the two institutions. As part of this CRADA, the MIP has committed to preclinical imaging investigations related to Medimmune antibodies that are being developed for two distinct therapeutic targets. This collaboration will continue for the next three years. During this reporting period, the first six-month progress report was prepared and submitted to senior NCI and Medimmune management teams.

A collaborative effort has begun within the intramural program, between MIP and the team led by Dr. Jeffrey Schlom and their commercial pharmaceutical partner. Under this agreement, MIP is in the process of pre-clinically testing radiolabeled anti-checkpoint antibodies being developed for clinical therapy. Once results are obtained, MIP is likely to commit to translation of the agent into clinical development within NIH.

CMRP staff members supporting MIP were also involved in collaborations with NCI and The University of Texas MD Anderson Cancer Center in the study and development of a new imaging agent, tumor necrosis factor weak inducer of apoptosis (TWEAK), which is of potential importance in detecting androgen-resistant prostate cancer. However, the agent did not prove promising during initial preclinical animal testing and investigations have been suspended.

As part of all these collaborations, MIP has established a collaborative agreement with the Laboratory Animal Sciences Program to evaluate agents in all appropriate preclinical animal models.

MIP staff worked on a software application, which is now registered and licensed by NCI and allows for efficient data management of the preclinical images generated by the MIP Bioscan PET/CT animal scanner. The software allows for editing of key identifier fields and provides a mechanism to properly calibrate the PET data and fix some bugs in the CT image headers. The software also manages the transport of the image data

from the scanner to the MIP image archiving system for permanent storage and retrieval. In developing the software, the PET data calibration method used within the software was tested and validated. This PET calibration method was presented at the 2015 World Molecular Imaging Congress in September 2015.

Final results of ^{89}Zr panitumumab clinical trial 06-C-0164, titled A Phase II Study of BAY 43-9006 (Sorafenib) in Combination with Cetuximab (ErbituxTM) in EGFR Expressing Metastatic Colorectal Cancer (CRC), have been generated and initially published as a poster presentation at the 2015 Society of Nuclear Medicine and Molecular Imaging annual meeting. A full paper is planned for publication in a peer-reviewed journal during the summer of 2015.

Data analysis on study 11-C-0061, Phase I Trial of Z-Endoxifen in Adults with Refractory Hormone Receptor-Positive Breast Cancer, Desmoid Tumors, Gynecologic Tumors, or Other Hormone Receptor-Positive Solid Tumors, is currently underway.

During FY2015, 45 subjects were enrolled in multi-arm study 14-C-0140, A Pilot Study of 18F-DCFBC PET/CT in Prostate Cancer. During the summer of 2015, a concentrated effort went into generating early results for each of the three arms of the trial.

MIP staff began a data management project designed to organize the clinical and imaging data acquired in both the clinical imaging trials and preclinical imaging experiments. The objective is to provide a mechanism to collect and archive all the data in an organized manner to ensure data can be accounted for. This will also speed up the process of generating the final publications, which will document the work done at the MIP. To date, a data server has been purchased, installed, and configured to store the data. Part of the data management project involves documenting the data analysis methods and goals for each clinical trial and preclinical experiment. Data analysis plans have been developed for the current accruing clinical trials and work is ongoing in executing these plans to ensure timely analysis of the data by the scientific staff. Weekly meetings are held and minutes for these meetings are recorded to keep track of the data analysis effort.

Genitourinary Malignancies Branch

The Genitourinary Malignancies Branch (GMB) focuses on investigating the biology of genitourinary cancers, developing new strategies for treating those cancers, and evaluating new therapeutic approaches through science-driven clinical research. These clinical trials investigate novel approaches in immunotherapy, hormonal therapy, chemotherapy combinations, and small-molecule targeted therapy.

During this reporting period, CMRP received a YT request cancelling support for the clinical research nurse due to a change in work scope. CMRP also received a YT request to recruit and hire a physician extender to provide direct patient care support for the GMB. The physician extender was hired in September 2014, and now provides direct patient care support to the inpatient and outpatient clinics for GMB. The physician extender performs routine exams, administers history and physical exams, interprets lab results, and manages treatment plans for patients. In May 2015, the physician extender transferred into another position and CMRP is currently recruiting a replacement for this position.

Laboratory of Tumor Immunology and Biology

The Laboratory of Tumor Immunology and Biology (LTIB) functions as a multidisciplinary and interdisciplinary translational research effort with the goal of developing novel immunotherapies for cancer. The LTIB strategic plan focuses on the development of novel immunotherapeutics for human carcinomas, not only as monotherapies, but in combination with other immune-mediating modalities and conventional or experimental therapies, as part of an immuno-oncology programmatic effort.

Within this effort are several research groups: a clinical trials group, two independent investigators, multiple collaborations with intramural and extramural scientific and clinical investigators, and collaborations with investigators in the private sector. The program takes advantage of the uniqueness of the NCI intramural program in that it spans high-risk basic discovery research in immunology and tumor biology, through preclinical translational research to paradigm-shifting clinical trials. Focus is placed on the design and development of novel recombinant vaccines and immunomodulators that can be used in clinical studies at numerous institutions and do not involve costly and labor-intensive ex vivo manipulations that can be carried out in only one or two centers. This work is accomplished though Cooperative Research and Development Agreements (CRADAs) with private-sector partners who provide agents for preclinical studies in appropriate animal models.

During FY2015, the protocol nurse coordinator maintained collaborative relationships with investigative sites and client personnel; coordinated and collaborated with multi-clinical teams, including internal medicine consultants and outside primary care providers; and successfully recruited and managed patients for the LTIB clinical trials.

The protocol nurse coordinator also managed routine follow-up patients, conducted internal audits to ensure protocol compliance, prepared required study-related documentation, and assisted with close-out visits.

During FY2015, the protocol nurse coordinator actively supported three protocols, and peripherally supported other ongoing protocols within the LTIB, including the newest protocol, titled Humax-IL8: A Dose Escalation, Multiple Dose Trial with HuMax-IL8 in Patients with Metastatic or Unrespectable, Locally Advanced Malignant Solid Tumors. More specifically, the protocol nurse coordinator is responsible for independently coordinating patient visits to NIH,

directing patients to admissions, consenting patients for screening, preparing monthly patient calendars, acting as a liaison between the patient and the providers, coordinating specimen pickups, and recording all unanticipated problems and adverse events (AEs). The protocol nurse coordinator is also instrumental in the timely reporting of all AEs, protocol deviations, and protocol violations, as stipulated in each clinical trial.

CMRP's protocol nurse coordinator supported the accrual of 118 patients to protocol 13-C-0063, A Phase I, Open-Label, Multiple-Ascending Dose Trial to Investigate the Safety, Tolerability, Pharmacokinetics, Biological and Clinical Activity of MSB0010718C, a Monoclonal Anti-PD-L1 Antibody, in Subjects with Metastatic or Locally Advanced Solid Tumor, as well as the closing of protocol 14-C-0142, An Open Label Phase I Study to Evaluate the Safety and Tolerability of a Modified Vaccinia Ankara (MVA) Based Vaccine Modified to Express Brachyury and T-Cell Costimulatory Molecules (MVA Brachyury-TRICOM), to accrual within seven months of opening, after enrolling 38 patients on that trial. Additionally, the protocol nurse coordinator functions as the lead nurse (of 10 nurses) for protocol 13-C-0063 and successfully oversees all of the queries and deviations in the trial. During FY2015, the protocol nurse coordinator successfully oversaw two amendments for protocol 13-C-0063 and two amendments for protocol 14-C-0142.

Medical Oncology Service

New Initiative

The Medical Oncology Service's major functions are to translate laboratory observations to the clinic, and to conduct clinical research and training. Their goals are: to develop novel therapeutic research strategies for the treatment of cancer and to test those strategies by conducting clinical research in medical oncology across a spectrum of diseases and disease mechanisms; to provide clinical care to adult cancer patients enrolled in research protocols, including inpatient and outpatient care services; to support the clinical research effort emanating from principal investigators in laboratories and branches across CCR; and to train physician-scientists in a laboratory-to-clinic translational research setting to promote the development of their expertise in medical oncology research and to support their board certification by the American Board of Internal Medicine.

Currently, CMRP has two nurse practitioners and two physician extenders supporting the Medical Oncology Service. These practitioners provide comprehensive health care to patients in a research environment, for the inpatient service, at the NIH Clinical Center. The practitioners perform routine examinations and procedures, administer history and physical examinations, and manage protocol compliance. These individuals provide an outstanding level of direct patient care support to the service. With their support, the Medical Oncology Service is able to streamline their operations, increase patient accrual, and provide continuity of care to their patients.

Neuro-Oncology Branch

New Initiative

Primary tumors of the central nervous system (CNS) are the second leading cause of cancer mortality in people under the age of 34 and the fourth leading cause of cancer mortality in individuals under the age of 54.

The Neuro-Oncology Branch (NOB) Brain Tumor Clinic comprises a multidisciplinary team of physicians, other healthcare providers, and scientists who are dedicated to developing new therapies and improving outcomes for patients with primary brain and spinal cord tumors. The team provides expert evaluations, examinations, tests, and imaging to patients. The Brain Tumor Clinic provides state-of-the-art neurosurgery and radiation therapy based on genetic characteristics of specific tumors.

During this reporting period, CMRP recruited and hired two nurse practitioners and one patient care coordinator to support the expanding clinic efforts within NOB. The nurse practitioners provide direct patient care support in the outpatient clinic. The patient care coordinator provides administrative support, such as coordinating patient schedules, scheduling various appointments, creating a weekly schedule for clinic, sending new patient information packets, and various other interdepartmental administrative tasks, as needed.

Recently, a YT was submitted and approved for CMRP to provide staffing support for the newly established Brain Tumor Trial Collaborative, Neuro-Oncology Branch (BTTC NOB), NCI, NIH. The BTTC NOB is a network of medical centers with the expertise and desire to participate in state-of-the-art clinical trials investigating new treatments for malignant brain tumors. CMRP is currently recruiting a protocol coordinator and clinical project manager to support BTTC NOB efforts.

Vaccine Branch

New Initiative

Cancer and HIV are both chronic diseases that suppress and evade the immune system. By combining expertise in both cancer and retroviral vaccines, the Vaccine Branch (VB) aims to promote cross-fertilization of ideas and progress in both areas in a unique way that is not duplicated elsewhere. The VB conducts a program of clinical and laboratory research designed to: 1) elucidate basic mechanisms of immune response and molecular virology, and 2) apply these to the design and development of vaccines and immunotherapy for the prevention and treatment of cancer and AIDS, as well as viruses that cause cancer.

Research studies within the VB are focused on: the mechanisms of T-lymphocyte activation and regulation, cancer immunosurveillance, mucosal immunity, retroviral

molecular biology and pathogenesis (including transcriptional and post-transcriptional regulation of retroviruses involved in causing cancer or AIDS), regulation of cellular gene expression, immune responses to retroviruses, and strategies for rational vaccine design. Study results are used to design novel vaccines for cancer, HIV, and cancer- and AIDS-associated viruses. The Branch also carries out clinical trials of vaccines for treatment of patients with some of these diseases.

During this reporting period, CMRP recruited and hired a patient care coordinator to support the VB. The patient care coordinator is responsible for various administrative tasks, including scheduling participants seeking treatment and coordinating their initial visits and follow-up appointments, coordinating team schedules, scheduling diagnostic tests, communicating with outside physicians, and creating databases and reports.

Dermatology Branch

New Initiative

The Dermatology Branch (DB) conducts clinical and basic research to study the etiology, diagnosis, and treatment of inflammatory and malignant diseases involving the skin, and the host's response to these diseases. Research involves biochemical as well as biological studies of skin, and is carried out in laboratories and in the clinic. Research areas of interest include characterizing skin as an immunological organ and defining the role of dendritic cells and molecules expressed by these cells in the generation of skin-centered immune responses. There is significant emphasis on inflammatory skin diseases in mice and humans, on the cutaneous microbiome in normal individuals, and on the cutaneous microbiome in patients with atopic dermatitis and selected primary immunodeficiencies. Other investigations involve long-term clinical and laboratory studies of DNA repair, skin cancer risk, and developmental abnormalities in cohorts of patients with xeroderma pigmentosum or trichothiodystrophy.

DB's laboratory research includes studies of skin stem cells and cutaneous malignancies, including Merkel cell carcinoma. DB's consultation service is one of the busiest clinical services in the CCR and is responsible for all outpatient and inpatient dermatologic patient care delivered at NIH.

During FY2015, CMRP was asked to provide clinical and medical support services to DB. These will include patient recruitment, enrollment, and screening, and various support services to research and regulatory activities for interventional and biospecimen acquisition protocols, such as monitoring and maintaining clinical research protocol compliance, assisting in data collection and analysis, conducting updates on patient care with clinical staff and community physicians, and consulting with other healthcare providers to meet various patient needs. CMRP is actively recruiting a clinical research nurse to fulfill the needs of the DB.

While this is a new activity for CMRP, the DB has a long tradition of being a laboratory and clinical fellowship training center for individuals who have become outstanding physician/scientists and leaders in investigative dermatology in the U.S. and abroad.

Genetics Branch, Clinomics Core

New Initiative

Among the defining concepts of the Genetics Branch (GB) is that cancer is a genetic disease caused by genetic instability. That instability is a function of all the inherited and acquired effects that mediate plasticity and alterability at the level of DNA. The success of molecular genetics over the past two decades has been the identification of genes involved in pathways of growth and development, and the identification of the mechanisms by which the normal regulation and/or products of these genes are altered in cancer.

The GB conducts clinical, genetic, and epidemiologic studies of individuals at high genetic risk of cancer in order to improve the understanding of cancer etiology and to advance clinical care.

At the clinical level, GB research includes patient cancer risk screening, education, counseling, genetic testing (for those who choose to be tested, with testing provided in a setting that is attentive to all the ethical and legal aspects of the testing decision), and the development of appropriate surveillance and prevention options that take into account the category of risk that an individual patient, family, or population represents.

The translational research that supports this clinical enterprise consists of four components: (1) molecular diagnostics, (2) genotype/phenotype correlations, (3) the development of biomarkers that can be used for risk assessment and as intermediate endpoints for chemoprevention trials, and (4) targeted therapy and assays for active agents based on the underlying genetics and mechanism(s) of genetic instability that distinguish a tumor from the normal cells from which it arose. GB is also the site for the intramural NCI initiative to develop a repository and database for high-resolution fluorescence in situ hybridization (FISH)-mapped, STS-tagged bacterial artificial chromosome (BAC) clones spaced at 1–2 Mb intervals across the human and murine genomes.

During FY2015, CMRP was asked to provide nursing support services to GB. These services will include recruiting and enrolling patients on clinical research protocols, monitoring and maintaining clinical research protocol compliance, assisting in data collection and data analysis, conducting updates on patient care with clinical staff and community physicians, and consulting with other healthcare providers to meet various patient needs. To fulfill this request for support, CMRP is actively recruiting a clinical research nurse.

Support Provided by the Applied and Developmental Research Directorate

The Applied and Developmental Research Directorate (ADRD) has dedicated laboratories and support functions funded by the Center for Cancer Research (CCR) to provide clinical trial support, including specimen processing and testing. Multiple laboratories provide testing support that is used in making patient treatment decisions and is regulated under the Clinical Laboratory Improvement Amendments (CLIA). Both the Clinical Support Laboratory and Laboratory of Cell-Mediated Immunity offer testing services through the Shared Services system, and those activities for non-CCR investigators are described in relevant sections of this report.

Clinical Support Laboratory

The Clinical Support Laboratory (CSL) is a CCR-funded core that was established to provide multifaceted clinical trial support to CCR investigators. CSL is organized into three laboratory sections. The Clinical Monitoring section is responsible for receipt, processing, cryopreservation, and database entry of clinical samples. The Lymphokine (Biomarker) Testing section performs enzyme-linked immunosorbent assay (ELISA), electrochemiluminescent multiplex assays, and bioassays for a wide range of biomarkers. The Flow Cytometry section performs immunophenotyping, intracellular staining, tetramer staining, and other flow cytometry–based assessments of cell activity, as requested. While the bulk of CSL's activities are in support of clinical trials, the laboratory also performs research sample testing in support of CCR principal investigators, with support requests submitted primarily through the Core Service Accessioning System (CSAS) request system. The laboratory works with investigators to ensure that critical clinical samples received late on Fridays or on weekends are processed and/or tested in a timely manner. The laboratory is CLIA certified for performing several high-complexity assays.

- **Pediatric Oncology Branch Support**
  - The laboratory received over 2,500 samples of whole blood, serum, plasma, leukapheresis products, elutriation cell fractions, bone marrow, cerebrospinal fluid, and DNA PAXGene from 13 clinical trials, with approximately 9,500 vials stored.
  - On nine occasions, the laboratory was asked to perform immediate cytokine testing in support of a Pediatric Oncology Branch clinical trial. Each sample submitted was tested in a panel of five single-cytokine ELISAs. A total of 12 samples were submitted, and test results were provided to the requester on the same day that the testing was performed.
  - In response to 11 requests for testing, CSL performed multiplex testing of human and mouse serum/plasma or tissue culture samples. A total of 933 samples were submitted for testing, with 9,066 data points evaluated.
  - At the request of Dr. Lee Helman, the laboratory worked with the Biorepository to perform quality control (QC) and discard of the I99 Source Code collection that contained over 140,000 vials.
- **Surgery Branch Support.** The laboratory processed 800 blood samples from branch-sponsored trials received in Cell Preparation Tube™ vacutainer tubes for isolation and cryopreservation of mononuclear cells, with 3,020 vials produced. The laboratory responded to multiple investigator requests to pull samples from the repository for return to the Surgery Branch for testing.
- **Lymphoid Malignancies Branch Support**
  - In support of the Cytokine Immunology and Immunotherapy Section, the laboratory received 273 samples in support of nine clinical trials, including three offsite trials, with 1,074 vials of serum or cells cryopreserved.
  - In support of the Lymphoma Therapeutics Section, the laboratory processed 553 samples in support of 10 clinical trials, with approximately 2,300 vials of serum stored.
  - The laboratory provides testing for anti-daclizumab, anti-human Mikβ1, detection of human Mikβ1, and anti-interleukin (IL)-15 as CLIA-regulated assays to support branch trials. Some testing is also identified as "research only." Each of these assays requires testing each sample at multiple dilutions. Sample testing included the following:

Assay	# Test Requests	Total Samples
Anti-daclizumab	1	1
Anti-huMikβ1	14	15
HuMikβ1	1	2
Anti-IL-15	13	72

  - Additional biomarker support included the following:

Assay	# Test Requests	# Samples	Data Points
IL-15 PK	9	573	1,146
IL-18	5	153	306
IL-6 Receptor	5	153	306
sIL2Ra	6	119	238
Multiplex	12	546	3,276

- **Vaccine Branch Support.** The laboratory received 92 samples from two clinical trials, with 1,193 vials stored.
  - The laboratory worked with Dr. Jay Berzofsky and Fisher BioServices to complete the transfer of over 25,000 vials of clinical material to Dr. Samir Khleif, director, Georgia Reagents University Cancer Center, under a Material Transfer Agreement.
  - In support of Yellow Task (YT) 13-074 and Dr. George Pavlakis, the laboratory performed an IL-15 bioassay to assess the biological activity of an assay standard and a toxicology lot of heterodimer, as well as the cGMP IL-15 heterodimer drug product to be used for clinical trials. Assays were also performed to evaluate product stability and to confirm assay performance. A total of 19 assays were set up, testing 19 samples on 71 test plates. Maintaining this assay required long-term culture of multiple passages of the NK92 cell line.
  - Further testing in support of hetIL-15 product development included 20 test plates to evaluate a neutralization assay for the detection of antibodies that inhibit the bioactivity of hetIL-15, as well as 2 ELISA plates for preliminary screening of patient samples for anti-Het-IL15.
- **Laboratory of Tumor Immunology and Biology Support**
  - The laboratory provided support to 21 branch trials, including several trials conducted at off-site locations, which required additional coordination of couriers and close interaction with clinical staff. One trial required specialized cryopreservation media, while another required segregated sample processing to address Institutional Biosafety Committee (IBC) safety concerns related to the receipt of swabs obtained from vaccinia vaccination sites. A total of 3,350 samples were received or isolated, including peripheral blood mononuclear cells (PBMCs) from blood and leukapheresis products, serum, plasma, urine, and swabs, with over 35,000 vials of clinical materials stored into eight different repository sample collections.
  - In support of CSAS-16483, the laboratory performed multiplex or singleplex electro-chemiluminescence testing on 152 samples, resulting in the evaluation of 2,584 data points.
  - Multiplex testing of 38 mouse samples resulted in the evaluation of 380 data points (CSAS-17453).
- **Molecular Imaging Program Support.** In response to CSAS-16794, the laboratory performed 4 assays to evaluate endotoxin levels in radiolabeled test products, with a total of 11 samples tested.
- **Laboratory of Molecular Immunology Support.** In response to multiple CSAS requests for ELISA and multiplex testing of human and mouse samples, a total of 4 sets of assays were performed on 321 total samples, resulting in the evaluation of 1,405 data points.
- **Urologic Oncology Branch Support.** In response to CSAS-17085, the laboratory expanded six cell lines for cryopreservation in order to distribute to branch collaborators. In response to CSAS-17446, the laboratory established 10 Epstein-Barr virus–transformed cells lines from clinical samples.
- **Thoracic and Gastrointestinal Oncology Branch Support.** In response to CSAS-17299 and -17764, the laboratory performed testing to optimize an assay for the detection of antibodies to mesothelin, and to establish a normal donor range for the assay and use the assay to evaluate patient samples from two studies.
- **Laboratory of Human Carcinogenesis.** In response to CSAS-16116 from Dr. Brid Ryan, the laboratory performed evaluation of a custom 33-plex cytokine panel on 367 samples for 12,111 test results.

Blood Processing Core

Leidos Biomedical Research provides core staffing support to the Blood Processing Core (BPC), with additional staffing provided from the NCI Clinical Pharmacology Program. Core personnel also provided weekend, holiday, and after-hours on-call support for human sample processing.

Laboratory of Cell-Mediated Immunity

The Laboratory of Cell-Mediated Immunity (LCMI) is a CCR-dedicated laboratory that offers testing support to CCR investigators and the research community at large through the Shared Services system. Dr. Anatoli Malyguine, head of LCMI, retired at the end of fiscal year (FY) 2014, and Dr. Ludmila Krymskaya was hired in FY2015. The laboratory relocated from Building 560 to Building 469, allowing for more coordination between LCMI and CSL activities. It is anticipated that the two labs will merge at the beginning of FY2016.

- **Support to the Laboratory of Immunoregulation**. LCMI staff analyzed 18 ELISPOT plates at the request of Dr. Arthur Hurwitz (YT04-154) and Dr. Katie Stagliano (CSAS-17350).
- **Support to the Vaccine Branch**
  - LCMI staff analyzed 10 ELISPOT plates at the request of Dr. George Pavlakis (CSAS-16851, -16928, -17028).
  - LCMI staff performed 600 ELISPOT tests at the request of Dr. Lauren Wood (CSAS-17320 and -17692).

- LCMI staff performed 210 in vitro stimulations at the request of Dr. Masaki Terabe (YT14-130). As part of the same request, CSL evaluated in vitro–stimulated cells and tetramer expression.

Laboratory of Molecular Biology

The Human Cancer Immunotoxin Therapy Assay Support and Development Laboratory provides dedicated laboratory support to Dr. Ira Pastan, co-chief of the Laboratory of Molecular Biology (LMB/NCI), Dr. Robert Kreitman, head of the Clinical Immunotherapy Section (LMB/NCI), and Dr. Raffit Hassan, co-chief of the Thoracic and Gastrointestinal Oncology Branch and head of the Solid Tumors Immunotherapy Section (NCI). This includes both support for investigator-initiated studies (non-CLIA) and NCI-sponsored clinical trials (CLIA). The laboratory is CLIA certified as mandated by the Cancer Therapy Evaluation Program (CTEP) and actively supports CTEP-approved Investigational New Drug (IND) immunotoxin clinical trial protocols. The support provided for LMB investigators includes immunotoxin cell-based neutralization assays, and cell-based assays to measure immunotoxin concentrations present in patient serum and plasma samples drawn during immunotoxin treatment. Patients who have exhausted the benefit derived from all other standard approved cancer therapies are identified by NCI investigators for potential immunotoxin therapy. The laboratory performs immunotoxin-specific, cell-based neutralization assays to screen these patients in order to detect the presence of a preexisting antibody for the particular immunotoxin, which would exclude them from treatment. Once patients have been treated with a particular immunotoxin, they must be reevaluated at defined intervals to determine the degree of their immune response to the immunotoxin, and this testing determines their continued treatment cycle eligibility. The SS1 immunotoxin treatment schedule is time sensitive, and the SS1 neutralization assays must be performed and their results sent for analysis in order to avoid violating the approved protocol treatment schedules. Fewer samples are being run per assay because of the time sensitivity associated with these assays, which prevent sample batching. When a patient is treated with an immunotoxin infusion, during the course of treatment, blood samples are obtained at specified time intervals for later testing in an immunotoxin-specific, cell-based pharmacokinetic (PK) assay, to determine the quantity and half-life of the drug present in the patient's circulation.

Immunotoxins being evaluated clinically include: LMB2 for certain lymphomas; HA22, which is a high-affinity immunotoxin for the treatment of certain lymphomas and hairy cell leukemia in adult and pediatric patients; and SS1 immunotoxin, which is specifically designed for the treatment of mesothelioma, a solid tumor of the lung. This year, the Phase IV clinical trial of the HA22 immunotoxin continued in conjunction with Med-Immune and NCI. Also this year, a new, less immunogenic, experimental SS1 immunotoxin was tested after development of a new in vitro cell assay. This assay is more complex than the one currently in use and uses a different cell line that requires a 42-hour intracellular incubation for the immunotoxin to be processed and for the cell to be killed. Several assays were completed, and the resulting data was evaluated and submitted to NCI investigators.

Significant Achievements

LMB2 assay support. Twenty-six immunotoxin neutralization assays were performed with 86 patient samples, and two PK assays were performed on 120 patient samples. These assays are cell-based, multiple-microplate radiological assays. A total of 376 patient serum and plasma samples were processed and frozen for future study.

HA22 assay support. Thirty-six immunotoxin neutralization assays were performed on 138 patient samples. These assays are cell-based, multiple-microplate radiological assays. A total of 414 patient samples were tested in 10 PK assays, and 420 patient serum samples were processed and frozen for future studies.

SS1 assay support. Forty-six immunotoxin neutralization assays were performed with 68 patient samples, and 20 PK assays were performed on 240 patient samples. These assays are cell-based, multiple-microplate radiological assays. A total of 816 SS1 study serum samples were processed and frozen for future study.

FDA validation of LMB2 immunotoxin (stability and potency). The laboratory continued long-term stability testing of LMB2 immunotoxin lots that are used in patient treatment. LMB2 immunotoxin potency stability assays were performed using a specific cell-based microplate assay format, and the results were submitted to the U.S. Food and Drug Administration (FDA) in support of the LMB2 IND protocols. One LMB2 assay was performed on two samples. These are all cell-based, multiple-plate radiological assays.

FDA validation of SS1 immunotoxin (stability and potency). The laboratory performed long-term stability testing on one SS1 immunotoxin lot that is used in patient treatment. SS1 immunotoxin potency stability assays were performed using a specific cell-based microplate radiological assay format, and the results were submitted to the FDA in support of the SS1 IND protocol.

CLIA recertification. The laboratory was inspected on January 21, 2015, and has received CLIA recertification for two years.

HIV and AIDS Malignancy Branch

The AIDS Monitoring Laboratory (AML) provides dedicated clinical trials support to the HIV and AIDS Malignancy Branch:

- In support of Dr. Robert Yarchoan, AML monitored seven active clinical research protocols for patients with HIV/AIDS, AIDS-related malignancies, and viral-induced tumors. The laboratory is responsible for the receipt, processing, and cryopreservation of

clinical specimens; performing immunophenotypic analysis of whole-blood specimens; and performing ELISA assays for a wide range of serum/plasma biomarkers. This work resulted in the processing of 140 whole-blood specimens, 319 serum specimens, 545 plasma specimens, 12 pleural effusions, and 85 urine specimens. AML performed 72 CLIA-regulated cell immunophenotype determinations by flow cytometry and 840 cytokine measurements. AML cryopreserved 420 vials of patient PBMCs; 3,186 vials of serum; 180 vials of pleural effusion fluid; 853 vials of urine; 8,178 vials of plasma; and 1,486 vials of PBMC cell pellets. AML coordinated 16 shipments of clinical specimens to investigators and institutions located at several domestic and international sites.

- In support of Dr. Hiroaki Mitsuya, AML performed 724 HIV-1 p24 antigen determinations on cell culture supernatants.

Laboratory of Pathology

Leidos Biomedical Research provides limited staffing support to the Flow Cytometry Unit of the Laboratory of Pathology. The staff member is fully integrated into routine laboratory activities. During FY2015, the staff member was commended by CCR laboratory management for the multiple responsibilities he successfully handled during the relocation of the laboratory.

Division of Cancer Epidemiology and Genetics

Support Provided by the Applied and Developmental Research Program

Applied and Developmental Research Directorate (ADRD) support to the Division of Cancer Epidemiology and Genetics (DCEG) includes both program-dedicated support and support through the Shared Services system.

HPV Immunology Laboratory

Infections and Immunoepidemiology Branch – The Human Papilloma Virus (HPV) Immunology Laboratory provides dedicated support to investigators in DCEG, NCI. Research efforts at the laboratory currently focus on two main areas: (1) immunological mechanisms responsible for the efficacy observed in the HPV virus-like particle (VLP) vaccine under evaluation in Costa Rica; and (2) immune/inflammatory markers associated with increased risk of cancer. The laboratory also has a broader interest in elucidating the immunological mechanisms involved in the natural history of cervical cancer, and developing assays and tools for immune-epidemiological research.

The laboratory continued to evaluate antibody responses to the HPV vaccine in the context of immune responses to less than three doses of vaccine. In addition, as part of the DCEG Initiative on Cancer and Inflammation, the laboratory conducted a number of studies to evaluate the associations between circulating inflammation and immunity markers, and the development of various types of cancers using multiplex Luminex-based bead arrays. In addition, the laboratory continued efforts to validate the use of Luminex technology for analyses of a large number of cytokines, chemokines, and growth factors in bile. Specific achievements are listed below:

HPV vaccine immunity studies – It is generally accepted that the efficacy of HPV VLP prophylactic vaccines is mediated in large part by neutralizing antibodies against the L1 protein. Efficacy for less than three doses of vaccine was previously demonstrated within the Costa Rican Vaccine Trial (CVT) of Cervarix in healthy young women. Antibody levels from three, two, or even one dose all exceeded levels of natural immunity, and all remained stable for four years of follow up. During this year, the laboratory examined the levels and durability of HPV-16 and HPV-18 antibody responses generated by different doses of the vaccine, at different follow-up times after vaccination. An initial study, published in November 2013, involved 2,700 samples, while the study conducted this year involved a 884 specimens for antibody titers and 1,364 samples for antibody avidity.

To extend and support recent findings from the NCI-sponsored CVT showing efficacy for less than three vaccine doses, the laboratory has been comparing antibody responses in women who received less than three doses of vaccine to those who received the full course of vaccinations. A total of different follow-up time points after vaccination were evaluated, to determine longevity and stability of the response. This study involved HPV-16/HPV-18 ELISA testing (16,400 wells) as well as avidity assays (21,824 wells). More than 10,000 wells were also tested for routine assay QC and validation.

Associations between immune/inflammatory markers and cancer risk – Chronic inflammation and immune alterations are recognized as important etiologic factors for several cancers, but studies of immunity and cancer in the past have been limited in scope and size. A previous study of samples from the Prostate, Lung, Colon, and Ovarian (PLCO) Cancer Screening Trial cohort evaluated the reproducibility of multiplex panels for the measurement of a large number of immune markers (97 different markers). Based on the results of that study, a Luminex-based multiplex immune panel was designed for use in DCEG studies. Over the past year, the laboratory continued to evaluate patterns of immune/inflammatory markers associated with the development of the following cancers or infections: gallbladder, lung, colon, and endometrial cancers, and HPV persistence at the cervix. In addition, the laboratory conducted methodological studies to evaluate kit stability and the effects of freeze/thaw. A total of about 7,000 specimens were tested for different markers (up to 65 markers) in

different panels, with a total of over 38,000 wells tested for Luminex assays, including QCs and standards.

During FY2015, the results from various studies were published. These studies contributed to the identification and understanding of the association between immunity/inflammation and cancer risk in well-characterized cohorts. The laboratory also published the results of a validation study of a large number of immune markers in bile, using the Luminex technology. Over 28,000 wells were tested in the various immune marker studies conducted during this year.

HPV VLP production – Because of the large demands for HPV VLPs in ongoing projects, the HPV Immunology Laboratory continued production of a large amount of HPV-16 VLPs (10 mg). The laboratory also continued the production and validation of various plasmids necessary for HPV VLP production of new HPV types of interest. More than 10,000 wells were also tested for routine assay QC and validation.

Clinical Support Laboratory

The Clinical Support Laboratory (CSL) provides 0.5 dedicated full-time equivalent staff support to Dr. Margaret Tucker for receipt of blood samples in order to produce and cryopreserve Epstein-Barr virus (EBV)–transformed B cell lines or skin biopsy samples for the generation of primary fibroblast cell lines. A total of 24 blood samples and 21 skin samples were received, with 15 EBV and 11 fibroblast cultures completed. For each sample, the target was to obtain vials from two separate freezes of each sample for long-term storage.

The generation of EBV-transformed B cell lines and primary fibroblasts was also performed through the Shared Services system for other DCEG investigators under YT11-231, as summarized below:

Investigator	EBV (Received/ Completed*)	Primary Fibroblast (Received/ Completed*)
Dr. Sharon Savage	191/83	N/A
Dr. Blanche Alter	37/20	12/9
Dr. Doug Stewart	115/12	8/8

**Includes samples received in FY2014 but finished in FY2015.*

Biomarker testing support:

- The laboratory performed testing in support of CSAS-17248 from Dr. Charles Rabkin, Viral Epidemiology Branch (VEB), to measure erythropoietin and lactoferrin by ELISA in 110 breast milk samples.
- In support of CSAS-17237 from Drs. Alina Brenner and Martha Linet, Radiation Epidemiology Branch, the laboratory tested 1,800 serum samples in a customized panel of multiplex and singleplex electrochemiluminescence assays. A total of 150 test plates were set up, with a total of 25,200 data points collected.
- In response to CSAS-16764 from Dr. Jonathan Hofmann, Occupational and Environmental Epidemiology Branch (OEEB), the lab tested soluble CD27 and soluble CD30 in 137 serum samples from the Agricultural Health Study.
- In response to CSAS-16797 from the Infections and Immunoepidemiology Branch (IIB), the laboratory performed a four-plex vascular injury panel on 147 serum samples from the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study.

Additional support:

- In response to CSAS-16702 from Emily Vogtmann and Dr. Christian Abnet, Nutritional Epidemiology Branch, the laboratory processed approximately 400 saliva samples for repository storage.
- CSL worked with LCMI staff to complete multiple aliquoting projects, which are summarized below:
  - Biostatistics Branch
    - CSAS-15785 = 130 serum aliquots
  - Hormonal and Reproductive Epidemiology Branch
    - CSAS-16954 = 170 serum aliquots
    - CSAS-17245 = 1,086 serum aliquots
    - CSAS-17724 = 330 serum aliquots
  - OEEB
    - CSAS-16313 = 1,269 serum aliquots
    - CSAS-17274 = 654 urine aliquots
  - Nutritional Epidemiology Branch
    - CSAS-16946 = 2,112 serum aliquots
    - CSAS-17201 = 4,572 serum aliquots
    - CSAS-17585 = 124 urine aliquots
  - IIB
    - CSAS-16669 = 100 serum aliquots
    - CSAS-16828 = 28 urine aliquots
    - CSAS-17051 = 18 aliquots from serum and cerebrospinal fluid samples
    - CSAS-17362 = 530 plasma aliquots
  - Clinical Genetics Branch
    - CSAS-17180 = 8,153 cervical sample aliquots
  - VEB
    - CSAS-17292 = 789 serum aliquots
  - Genetic Epidemiology Branch
    - CSAS-17172 = 4,950 sputum aliquots

In multiple instances, these requests included preparing shipments for collaborators, including international shipments.

Bioprocessing Laboratory

The BioProcessing Laboratory coordinated fresh blood collection and fractionation for a DCEG investigator to generate quality assurance/quality control (QA/QC) samples for assay development and hormone receptor testing, resulting in the generation of 8,885 aliquots of serum, plasma, and urine, and in the distribution of 651 plasma specimens for intramural use for the PLCO Cancer Screening Trial.

Human Genetics Program

Support Provided by the Cancer Genomics Research Laboratory

Over the past year, the Cancer Genomics Research (CGR) Laboratory has continued to function as a high-throughput genomics laboratory in service to NCI's Division of Cancer Epidemiology and Genetics (DCEG). In a highly collaborative endeavor, CGR works closely with investigators to design, plan, and execute a variety of scientific projects. With a focus on automation and cutting-edge technology innovation, CGR provides comprehensive genomics laboratory and scientific research support from project inception through specimen preparation, data generation, analysis, and publication of findings.

Significant Achievements

Development of formalin-fixed paraffin-embedded DNA quality control: Formalin-fixed paraffin-embedded (FFPE) tissue is a widely collected specimen type. However, recovery of good quality nucleic acids is challenging, making the use of these specimens difficult. Improvements in technology for various genomic applications have resulted in a reduction of required nucleic acid input. This reduction has opened the door for use of samples with limited DNA or RNA availability, such as those from FFPE sources. Additional challenges exist with respect to nucleic acid quality which becomes cross-linked during the fixation process.

Industry leaders in the genomics analytic space have realized the usefulness of FFPE specimens and have developed specialized protocols for overcoming the particular issues these sample types often present. CGR has been working to evaluate various methods for quality assessment and restoration of FFPE DNA samples for use with arrays for genotyping and methylation as well as sequencing applications. Early data shows different results depending on the length of time since the samples were initially fixed. However, restoration results are promising and quality control kits from various vendors have proven helpful for selection samples that have the best chance of performing well in downstream assays. These upfront procedures help avoid wasting samples, time, and costly reagents for specimens that will likely fail. Research studies utilizing these samples are finally a reality as a result of the validation work.

Oral and fecal microbiome sequencing validation: Microbiome research is the newest application of next-generation sequencing technology. Research is being conducted on various sources of microbial profiles to define possible associations between the subject's microbiome and various disease phenotypes. DCEG has several sources of microbiome specimens, including those from oral and fecal sources. CGR recently participated in the Microbiome Quality Control (MBQC) Project, a collaborative effort with several institutions to evaluate different methodologies for human microbiome analysis. Following the experiences with MBQC, CGR continued with development for microbiome research by designing a series of pilot studies for validation and optimization of extraction methods, methods of quality control (QC), and 16s rRNA sequencing parameters to determine some best practices guidelines.

As this is a very different application when compared to sequencing human genomic DNA, informatics optimization is also required for analysis of this unique data type. Pilot data from the various wet-lab experiments has also been used to begin development of a pipeline for standard microbiome 16s sequence analysis.

Laboratory Information Management System version upgrade and Chrome support: CGR utilizes a highly customized and integrated Laboratory Information Management System (LIMS) for sample and project tracking across the organization. This system is integrated with laboratory automation and drives all processes within the laboratory. The LIMS tracks samples, plates, barcodes, and leads technical staff through procedures required for sample processing and staging, genotyping, and sequencing. Additionally, this system is used to track all inventory, equipment, and standard operating procedures (and associated deviations). It has become a living record of all work the CGR has undertaken in the past 13 years. It is maintained by dedicated staff members who are responsible for fixing any errors, developing new applications and workflows, and maintaining the data integrity. A major version upgrade occurred this year from the vendor of CGR's LIMS platform. These upgrades require extensive developer testing and troubleshooting, as well as end user testing in a development environment prior to application of the upgrade to the production LIMS server. This allows the staff to catch and correct issues that arise as a result of the upgrade.

New this year is support for LIMS via the Google Chrome browser. Functionality for various pages and displays must be tested for compatibility before allowing users to access the LIMS via the new browser. Most of the LIMS has been tested for compatibility and is available for use via Chrome.

Human papillomavirus whole-genome sequencing: The human papillomavirus (HPV) sequencing project is a major focus of the CGR Research Group. This project has been ongoing and significant progress has been made. Recent activities include defining the analysis pipeline to be developed and scaled up for screening projects including tens of thousands of samples. The major areas

of focus have included refining variant calling, phylogenetic tree analyses and assigning lineages to individuals, detecting co-infection, and determining HPV16 integration into the human genome. Over 500 subjects have been sequenced via the whole-genome HPV16 assay this year. Additionally, CGR is working on the development of a low cost HPV typing assay that could potentially revolutionize detection of HPV in developing countries and other under-served areas of the world. This collaboration with DCEG is the largest known study of its kind and is groundbreaking within the HPV research community. Several interesting findings have been made as a result of the data and manuscripts are underway.

Epidemiology and Biostatistics Program

Support Provided by the Clinical Monitoring Research Program

Esophageal Cancer Precursor Lesion Genomic Study – China

Esophageal cancer is the sixth-most-common fatal human cancer in the world, with more than 406,000 deaths annually, and the fourth-most-common new cancer in China. More than half of all esophageal cancer deaths in the world occur in China, due to its large population and high rate of this cancer's occurrence. North central China has esophageal cancer rates that are among the highest in the country; nearly all of these cases are esophageal squamous cell carcinoma (ESCC).

ESCC is an aggressive tumor that is typically diagnosed only after the onset of symptoms, when prognosis is very poor. One promising strategy to reduce ESCC mortality is early detection and a better understanding of molecular mechanisms underlying esophageal carcinogenesis and its molecular pathology, which will facilitate the development of biomarkers for early detection.

CMRP staff is working to support the overall esophageal and gastric cancers initiative of the NCI Division of Cancer Epidemiology and Genetics (DCEG). Specifically, support is focused on a cancer precursor lesion genomic study to be conducted in China. The overall objective of this project is to identify and test strategies to reduce mortality from esophageal and gastric cancer in high-risk populations in China, where rates of these cancers are the highest in the world. Building on collaborative research that has been ongoing between the Cancer Institute & Hospital of the Chinese Academy of Medical Sciences (CICAMS) and NCI since 1982, this new initiative will conduct new studies in this high-risk population to further evaluate etiologic and early-detection hypotheses, and advance disease prevention strategies.

CMRP provides programmatic and project management support for the field study. Research subcontracts are being established to conduct the first study under this program, NCI's Esophageal and Gastric Cancer Field Study initiative. The goal of this study is to understand the molecular underpinnings of premalignant esophageal lesions. The proposed field study has two components: (1) a field study to obtain data and biologic samples, which will be conducted by CICAMS, and (2) a genomic analysis to perform sequencing of the biological samples and bioinformatics analysis of the sequencing data, to be conducted by BGI Americas.

During this reporting period, CMRP and Leidos Biomedical Research Contracts fully executed Task Order #1 (TO#1) in October 2014, under the Basic Ordering Agreement (BOA) with CICAMS. TO#1 pertains to the conduct of the field study, enrolling a minimum of 150 subjects.

Following the execution of the agreement, the Leidos Biomedical technical project manager met with the NCI PI serving as the main contact for this project to discuss timelines, and expectations on deliverables. Per discussions, it became apparent that the first field study would not begin before July/August 2015 due to NCI and China protocol review processes. The second phase of this project pertains to the gene sequencing analysis of biological samples collected during the field study, which began in August 2015. The finalization and full execution of the BOA and TO with BGI Americas was postponed slightly, but ultimately began in September 2015.

Applied Molecular Pathology Laboratory, Tumor Heterogeneity

The Applied Molecular Pathology Laboratory (AMPL) is a collaboration between the CCR and DCEG to facilitate research using novel, high-throughput techniques for studying tissues in large cancer investigations. The work focuses on handling, processing, and evaluating fixed tissues, with a particular emphasis on using tissue microarrays for immunohistochemical analysis, with subsequent digital imaging and manual or automated evaluation of stains. A physician provides ongoing scientific and pathology support with a focus on: (1) identifying occupational, environmental, and other factors affecting cancer risk; (2) characterizing exposure response relationships; (3) identifying biomarkers for disease detection, diagnosis, and prognosis that are associated with certain risk factors; (4) identifying susceptible populations and gene environment interactions; and (5) improving research methods for occupational investigations. Projects involve sophisticated methods and intensive collaboration among epidemiologists, pathologists, industrial hygienists, and molecular biologists.

Specifically, the physician provides: (1) immunohisto-chemical staining of tissue arrays (assay development and review); (2) image, digital image, and stain analysis (developing algorithms for specific staining patterns); (3) pathology slide and report review; (4) annotation of tumor tissue for RNA extraction; and (5) manuscript preparation and review.

The assessment of micro-vessel density in breast tissue, a collaboration with PIs from the Hormonal and Reproductive Epidemiology Branch, evaluates the association of micro-vessel density and mammographic density with breast cancer risk. This study included 465 participants in the Vermont Breast Cancer Surveillance System who underwent an image-guided biopsy to evaluate an abnormality identified on a mammogram. A novel component of this study was the evaluation of global and peri-lesional volumetric breast density. Formalin-fixed, paraffin-embedded (FFPE) tissue was sectioned into whole slides and immunohistochemically stained for CD31, a marker of vessel endothelium. The physician developed detailed scoring criteria that were applied to a portion of the slides for a pilot study that evaluated the vessel density in normal terminal ductal lobular units and surrounding normal breast tissue. Randomly selecting three areas of tissue, the physician panned right to left and counted the number of CD31-positive vessels in 10 microscopic high-power fields, resulting in 30 fields per slide. In a second pilot study, a subset of slides from breast cancer cases was scored using the same scoring criteria. A third pilot study evaluated intra- and inter-observer agreement. After completion of the pilot studies, the remaining 220 study slides were scored by the physician.

The physician also provided pathology expertise to the Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial, a large, population-based randomized trial evaluating screening programs for these cancers.

For the bladder arm of the PLCO trial, FFPE tissue specimens from 600 participants diagnosed with bladder cancer (N~500) or in situ breast cancer (N~100) are included in the study. From each cancer case, up to three tissue blocks were collected, including two blocks of primary tumor and one block of uninvolved tissue, for a total of approximately 1,800 blocks. The physician reviewed all slides from this study and manually annotated regions of interest to select tissue for the tissue microarray (TMA) construction. The physician also designed the array maps for this project, and TMA construction has been completed.

The Polish Gynecology study evaluated the expression of p53 in ovarian cancers using the Polish ovarian and endometrial cancer TMAs. Approximately 1,200 cores were manually evaluated and scored for extent and intensity of staining. Scoring of the tumor tissue has been completed, and the data have been provided to the customer for analysis.

In collaboration with Dr. Wentzensen and Dr. Sherman, cervical cancers from the Study to Understand Cervical Cancer Early Endpoints and Determinants (SUCCEED) are being contributed to TCGA. The physician pre-screened hematoxylin and eosin (H&E)-stained sections of tumor tissue to document several histopathologic measures, including histologic subtype, percent of tumor nuclei, and extent of necrosis, before submitting eligible candidates. In all, 80 cases were evaluated.

In addition, the physician selected and ordered new imaging equipment (NanoZoomer-XR Brightfield Slide scanning system, Hamamatsu). Instrument use and evolving technologies rendered the old equipment insufficient to serve the growing demand for high-throughput, whole-slide imaging.

During FY2015, the following new efforts were initiated:

- **Collaboration with the Hormonal and Reproductive Epidemiology Branch within DCEG and the Pathology and Histotechnology Laboratory of FNLCR:** Cancer tissue, primary and secondary Gleason scores and normal prostate tissue had been previously collected from a total of 76,693 men and assembled into a total of 27 TMAs. In order to investigate correlations between the expression of selected biomarkers and various histologic and epidemiologic factors the prostate TMAs were immunohistochemically stained with antibodies against RAD-9, survivin, Raf-1, and cyclin B1. CMRP staff was actively involved in the validation and optimization of staining protocols for these antibodies and reviewed the digitalized study slides for tissue and staining quality. Slides were then analyzed using Aperio Image Scope software. First, the physician wrote a nuclear algorithm for the automated analysis of RAD-9 protein expression by selecting one core at a time and optimizing a large number of parameters. The optimized algorithm is excellent at eliminating stromal cells and giving a balanced distribution of staining intensities. The final RAD-9 nuclear algorithm was then applied to analyze the study TMA slides. The results of the automated scoring have been reviewed and are currently statistically analyzed. In addition, the physician developed algorithms for survivin and Raf-1, which show a cytoplasmic staining pattern.
- **Collaboration with the Occupational and Environmental Epidemiology Branch within DCEG and the Pathology and Histotechnology Laboratory of FNLCR:** During FY2015, the physician completed six project requests for this arm of the study, analyzing a total of 470 colorectal cancer slides. The physician reviewed the pathology reports as well as H&E-stained tissue sections and identified regions of interest that are selected for TMA construction.

NCI EXTRAMURAL

Division of Cancer Biology

Support Provided by the Data Science and Information Technology Program

This Division of Cancer Biology Office of Physical Sciences–Oncology (OPSO) brings together cancer biologists, oncologists, and scientists from the fields of

physics, mathematics, chemistry, and engineering to address some of the major questions and barriers in cancer research One of the resources available to these centers is a well-characterized set of approximately 40 commonly used cancer cell lines. The Physical Sciences Oncology Centers (PSOC) cell line panel is provided to all of the researchers at the same passage number. All users of the cell lines must follow protocols to ensure that all measurements across all centers are done at the same cell passage number. This design allows a more direct comparison of the results across experiments by carefully controlling that variable.

This year, the Data Science and Information Technology Program (DSITP) supported several projects for the Physical Science Oncology Program: genomic characterization of the PSOC cell line panel; physical characterization of the PSOC cell line panel; proteomic characterization of the PSOC cell line panel; and support for the Physical Sciences Oncology Centers Data Coordinating Center (PSOC DCC). The genomic and physical data are being housed in the PSOC DCC and will be made publicly available to the cancer research community. The proteomic characterization will be completed next year.

Support Provided by the Laboratory Animal Sciences Program

NCI Mouse Repository

Mouse models of human cancer have had a profound impact on our current understanding of the mechanisms of tumorigenesis and the pathways regulated by cancer-related genes. These models hold the promise of serving as critical tools in the discovery and testing of novel therapeutics to be used in the treatment and prevention of cancer.

The NCI Mouse Repository is a resource funded by the NCI Division of Cancer Biology for maintenance and distribution of mouse models and associated strains. The repository, which is managed by LASP, makes strains available to all members of the scientific community (academic, nonprofit, commercial). Depending upon demand, the NCI Mouse Repository strains are maintained as live colonies or as cryoarchived stocks.

Significant Achievements

- The repository currently houses 137 strains, 49 of which are maintained as live colonies under specific pathogen-free conditions. An additional 9 strains accepted during FY2015 are at various stages of importation. 313 orders for live and cryoarchived mice were filled. In total, 1,003 live animals and 9 embryo shipments were distributed worldwide.
- In an effort to address the function that miRNAs play in human cancer, their use as diagnostic tools, and their potential role as new targets for therapeutic intervention in the treatment of cancers, NCI's Division of Cancer Biology is supporting the generation of mouse embryonic stem (mES) cells engineered to express 500 known mouse miRNAs. The NCI Mouse Repository was charged with making this new, important resource available to the cancer research community. The entire collection was made available for distribution to the scientific community in July 2013. Information regarding this resource is available on the NCI Mouse Repository web site (http://mouserepository.cancer.gov). The web site also includes validation documentation of the mES cells generated and sequencing data for each miRNA. A manual including all protocols utilized in the generation, care, manipulation, and use of the available mES clones is also provided.
- 28 orders for mES cell lines were processed.

Support Provided by the Applied and Developmental Research Directorate

The Clinical Support Laboratory (CSL) provided testing in support of the DREAM Validation Project (YT12-101NS). At the request of the Division of Cancer Biology, this project is now being subcontracted to Columbia University.

Support Provided by the Cancer Research Technology Program

The goal of the Antibody Characterization Laboratory (ACL) is to generate and thoroughly characterize a series of monoclonal antibodies to targets known to be important in cancer. The work is being done at the request of the Clinical Proteomic Technologies for Cancer (CPTC) Initiative.

The ACL has successfully completed the generation of more than 350 antibodies, with multiple antibodies in production. The data is all published on our web portal (http://antibodies.cancer.gov). The scope of antibodies has changed, with a heavy emphasis on specialized applications with immuno-multiple reaction monitoring assays being the most frequently requested. Those antibodies are now referenced on the CPTAC assay portal (http://assays.cancer.gov). We have generated a number of mouse antibodies for this application and are evaluating their performance against the much more expensive rabbit antibodies. In addition, we will be evaluating alternative recombinant technologies for generating rabbit antibodies because the hybridomas demonstrate very low production yields and have unproven stability.

We have initiated the immuno-multiple reaction monitoring assays project specifically for the purpose of generating a panel of assays for RAS pathway targets. This effort calls for antibodies to be raised to approximately 100 separate targets and approximately 40 phospho-specific targets. The initial approach is to raise antibodies to all 100 non-modified targets in mice in order to try to save on cost. To date, a total of 15 targets of 20 tested have yielded

successful antibodies in mice. Second fusions are being performed on the five failed targets, and those that fail will be converted to rabbit monoclonal antibodies. The development of rabbit antibodies to the phosphor-specific targets is a longer process because the rabbits are slower to respond. We are beginning to receive the initial materials for evaluation before the spleens are harvested for fusion. This large project is in collaboration with the Fred Hutchinson Cancer Research Center, the Broad Institute, and the Moffitt Cancer Center. Staff at these institutions will assemble the assays with the resulting reagents.

The ACL has completed the evaluation of affinity binders (monoclonal antibodies and recombinant Fabs) produced by CDI, Inc., in partnership with Johns Hopkins University and the Recombinant Antibody Network. This work evaluated a large number of reagents for reactivity in ELISA, Western blot, SPR, immune precipitation mass spectrometry, and immunohistochemistry.

Other Activities

The ACL is administering 24 active contracts through CPTC Yellow Tasks that are associated with antibody production and evaluation, and to the analysis of CPTC-generated data. The ACL also manages the distribution of reagents from previous Division of Cancer Biology (DCB) Yellow Tasks and reagents for evaluation of tumor-associated macrophages through an active DCB Yellow Task.)

Division of Cancer Control and Population Sciences

Behavioral Research Program

Support Provided by the Clinical Monitoring Research Program

The primary goals of the Division of Cancer Control and Population Sciences (DCCPS) are to reduce risk, incidence, and deaths from cancer, and to improve the quality of life for survivors. Over the past 15 years, CMRP has assisted DCCPS in its mission by providing programmatic and scientific support services to all branches within the DCCPS Behavioral Research Program (BRP), including: the Process of Care Research Branch (PCRB); the Science of Research and Technology Branch (SRTB); the Tobacco Control Research Branch; the Basic Biobehavioral and Psychological Sciences Branch (BBPSB); and the Health Behaviors Research Branch (HBRB). Beginning in FY2015, the DCCPS began a major reorganization. This reorganization led to the creation of the Healthcare Delivery Research Program (HDRP), which includes several branches—such as the Health Systems and Interventions Research Branch (HSIRB)—and the dissolution of the BRP's PCRB.

CMRP's senior behavioral scientist and behavioral scientist have been pivotal in researching causes, incidence, prevalence, and prevention of cancers, and have worked closely with BRP and HDRP program staff to generate the research necessary to inform evidence-based practice and policy. In addition, CMRP staff plays a critical role in national surveillance efforts, building the data research infrastructure, developing web-based research tools for the extramural research community, and providing program and scientific support to research networks and collaborations. CMRP staff members have published numerous papers and abstracts in peer-reviewed journals, and presented papers at leading scientific conferences. Given the reorganization of DCCPS, the behavioral scientist provided scientific support to PCRB and then continued support in this same capacity, but for HSIRB. Program activities and work efforts that began while PCRB was operational transferred to HSIRB.

New work efforts included the establishment of research subcontracts, RFPs, conference planning and execution, portfolio reviews, and dissemination of ongoing scientific activities. Specifically, the senior behavioral scientist, in support of HBRB, initiated, facilitated, and managed five subcontracts awarded to extramural institutions across the U.S. related to the Family Life, Activity, Sun Safety, Health and Eating (FLASHE) Study. CMRP staff assisted BBPSB with the development of two RFPs to support pilot studies related to early-stage breast cancer and integration of mHealth technologies for studying cancer and multiple morbidities. The senior behavioral scientist, in support of SRTB, successfully co-led the creation and implementation of the Science of Team Science (SciTS) Conference, which saw its highest attendance rate ever. The behavioral scientist also supported planning for a new colorectal cancer screening conference as well as initiated a new review of Health Information Technology grants.

The senior behavioral scientist initiated a cost-saving measure in support of the FLASHE Study. The senior behavioral scientist quickly realized that the contractor analyzing the FLASHE Motion Study data lacked the skills necessary to perform the complex analytic tasks; as such, work was stopped and transitioned to the subcontractor, who was able to execute the task for no additional cost. In support of SRTB's SciTS 2015 conference, the senior behavioral scientist leveraged no-cost resources at the NCI Office of Communications and Public Liaison and the NIH Office of Behavioral and Social Science Research (OBSSR) to develop and implement a very successful communications campaign. In addition, the senior behavioral scientist continues to leverage interns and volunteers to support SciTS team activities.

During FY2015, the senior behavioral scientist was proactive in the creation of multiple symposium submissions at leading scientific conferences to act as a "soft launch" for the FLASHE Study data release planned for early FY2016. This led to a very visible presence for the FLASHE Study at these meetings and generated significant interest in the forthcoming FLASHE data among the extramural scientific community.

The senior behavioral scientist continues to serve as a member of the Networking and Information Technology Research and Development subcommittee on Team Science, out of the White House Office of Science and Technology Policy. As a core member of this group, she has coauthored a document titled, "How to Write a Collaboration Plan", which provides guidance to investigators around how to plan for collaboration as part of their written grant applications to federal authors, when applying for funds to conduct team-based research.

Basic Biobehavioral and Psychological Sciences Research Branch

The mission of the Basic Biobehavioral and Psychological Sciences Branch (BBPSB) is to advance research in biobehavioral mechanisms and psychological processes to reduce cancer risk and improve outcomes. The BBPSB research agenda includes, but is not limited to: (1) basic mechanisms of cognition, emotion, judgment, and decision making; (2) biological mechanisms of psychosocial influences on cancer biology and outcomes; (3) methodology and measurement of basic psychological, cognitive, and affective processes; (4) biobehavioral mechanisms of co-morbidities associated with cancer and cancer treatment; (5) basic mechanisms of sensation, attention, and perception as related to cancer risk and control; and (6) basic mechanisms of the placebo effect.

CMRP provides scientific, programmatic, and administrative support, and travel coordination, and establishes consulting agreements and research subcontracts for the BBPSB. In particular, CMRP staff is part of the Network on Biobehavioral Pathways in Cancer Scientific Management Committee (SMC) and provide guidance and support to network initiatives and research projects.

A clinical project manager was hired in November 2014 to provide support to BBPSB initiatives, as well as to other DCCPS initiatives as a whole. The clinical project manager, working with the BBPSB chief, assists with developing RFPs for new research initiatives, as well as maintaining and providing oversight for research subcontracts. Two research subcontracts were awarded in FY2014 and continued in FY2015: (1) Case Western Reserve University, which seeks to evaluate the hypothesis that mixed-gender housing is more effective than same-gender housing, and both are more effective than social isolation, for improving survival of tumor-bearing mice; and (2) University of Rochester, which seeks to demonstrate whether a novel psychosocial stress paradigm promotes spontaneous mammary tumor development and metastasis in MMTV-PyMT mice A third project was awarded in FY2015 to the Medical College of Wisconsin to assess whether gene expression of beta-adrenergic signaling pathways can be altered in individuals undergoing autologous hematopoietic stem cell transplantation (HCT) for multiple myeloma (MM) by administering a daily beta-blocker (propranolol).

Support continued in FY2015 for the international research subcontract with Tel Aviv University for a pilot study aiming to reduce long-term breast cancer recurrence and metastasis by targeting excess perioperative catecholamines and prostaglandins. Support also continued for a research subcontract established with the University of California, Los Angeles, to identify and pilot test functional magnetic resonance imaging (fMRI) probe tasks that can be used to capture systematic individual differences in neural activity associated with performance of probe tasks among individuals who differ in relevant measures of experienced social support. A proposal for Phase II of this project is currently under evaluation.

CMRP staff members continued support for a research subcontract with Rutgers Robert Wood Johnson Medical School to investigate the hypothesis that chronic stress promotes DNA damage and enhances mutation frequency and copy number variation in $Apc^{min/+}$ mice in a largely p53-dependent manner.

Two additional RFPs were issued for the Branch in FY2014, resulting in research subcontracts awarded or continuing in FY2015. The first RFP, soliciting small-scale pilot research in affective science and cancer palliative care decisions resulted in awards to Massachusetts General Hospital and Maine Medical Center. The Massachusetts General Hospital project investigates potential support for an association between oncologists' emotional state, including burnout, and their practices for administering chemotherapy to patients with metastatic cancer at the end of life. This project is ongoing and expected to conclude early in FY2016. Results from this project will contribute to the investigator's submission of an NIH U01 grant for the June 2015 deadline. The Maine Medical Center project sought to understand factors that affect the extent to which physicians communicate prognostic information to cancer patients at the end of life, including uncertainty, tolerance of uncertainty, and patient affective state. This project was completed in January 2015.

The second RFP was established to solicit the review, evaluation, and summarization of data regarding the representation of individuals with multiple chronic conditions in randomized, controlled trials of behavioral and psychosocial interventions published in general medical, behavioral medicine, behavioral science, health psychology, social science, and public health journals. An award was made to Washington University of St. Louis in early FY2015. CMRP staff assisted with the development of two new RFPs for BBPSB, including assisting with development of the statement of work and deliverables, creating a proposal cost template, defining proposal requirements and evaluation criteria, and editing the final document. These RFPs were released in May FY2015. The first RFP seeks to fund a pilot study to assess the impact of beta blockade on gene expression in early-stage breast cancer. The second seeks to support a multi-stage planning effort for-N of-1 trial designs that incorporate sensor and mHealth technologies to address the problem

of patient-by-treatment interaction in the context of depression symptom management, cancer survivorship, and multi-morbidity. Proposals are being evaluated with the goal of establishing awards at the beginning of FY2016.

Challenges for these research subcontracts are typically issues which impact the project schedule, such as delays in research subject recruitment or materials backorder. CMRP staff work with the subcontractor, in conjunction with BBPSB, to extend the contract to accommodate the extra time needed. In some cases, this has resulted in projects extending forward into the next fiscal year. For those instances, CMRP staff work with BBPSB to accommodate the needed funds in the budget for that fiscal year. Prospectively, to reduce the risk of schedule delays, staff worked with BBPSB in the development of language in the RFPs issued in May 2015 to ensure that offerors are suited for quick start-up of projects and are likely to meet recruitment goals.

CMRP staff supported and participated in the Network for Biobehavioral Pathways in Cancer Scientific Steering Committee meeting in May 2015. A biannual status report of Network projects was developed for the Network chair, and the first issue of the report was completed for the Steering Committee meeting. CMRP staff also developed and produced binders for the meeting, which included the status report; a table of projects with titles, subcontractors, and timelines; a list of contact information for Network participants; and information regarding current and past RFPs.

Health Behaviors Research Branch

The mission of the Health Behaviors Research Branch (HBRB) is to support research on cancer prevention behaviors and outcomes, which includes diet, physical activity, sedentary behavior, energy balance, obesity, sun safety and indoor tanning, genetic influences on behaviors, and virus exposure. Activities include: providing leadership in developing methodologies for measuring health behaviors and psychosocial correlates of behaviors, focusing research on effective multilevel influences and examining the interaction between the environment and psychosocial factors, evaluating interventions and policies, and promoting training and dissemination of information related to behavioral health research.

Several key program initiatives surrounding energy balance include the FLASHE Study and the Classification of Laws Associated with School Students (C.L.A.S.S.) website. Additionally, the HBRB is embarking on new strategic planning for the development of novel initiatives. A priority area of the HBRB is systems science and its application to behavioral research. CMRP's senior behavioral scientist provides programmatic leadership and management for these initiatives.

During FY2014, the senior behavioral scientist was instrumental in the implementation of the FLASHE Study, which seeks to examine psychosocial, generational, and environmental correlates of cancer-preventive behaviors in a one-time observational survey. The goal of this survey is to advance the understanding of the dynamic relationship between the environment, psychosocial factors, and behavior from an intergenerational perspective (i.e., assessing adolescent–parent dyads). Specifically, the current senior behavioral scientist serves as the FLASHE Study director, overseeing daily management and implementation. The senior behavioral scientist also leverages expertise in physical activity measurement to design, implement, and manage the Motion Study, a sub-study of the larger FLASHE protocol. In this capacity, the senior behavioral scientist helped facilitate a research subcontract between NCI and Iowa State University to conduct further validation study of self-report and observational data collected in FLASHE. Additionally, the senior behavior scientist facilitated the development of two additional research subcontracts. One focused on developing algorithms for estimating dietary intake from the FLASHE dietary screener (awarded to the Gretchen Swanson Center for Nutrition), and a second focused on dyadic analysis and was awarded to scientists at Delaware University and Columbia University. The senior behavioral scientist utilized her multidisciplinary expertise to guide the framing and implementation of these subcontract awards. This included, but was not limited to, the development and implementation of a short course on dyadic analysis, which reached over 25 staff members and fellows across the Division. A webinar that is anticipated to reach about 500 extramural scientists was planned for November 2015.

The senior behavioral scientist has been instrumental in navigating the government customer through the strengths, challenges, and limitations of systems modeling in behavioral research. This is an innovative and novel research area, and the senior behavioral scientist has extensive experience in this arena. As such, the senior behavioral scientist has been instrumental in brokering a second research subcontract with a leading systems scientist to continue to develop intramural and extramural capacity. Key activities include direct consultation, short training courses, an analytic project, and two conceptual projects. The senior behavioral scientist designed and helped implement a short course for NCI/NIH staff on Social Network Analysis. Over 25 staff members and fellows attended these training sessions and indicated their desire for more training in this area. The senior behavioral scientist is actively engaged in the development and writing of two papers focused on the application of dynamic modeling to dietary patterns research and data systems to support energy balance research. She is also leading an analysis using data from an NCI data resource. The senior behavioral scientist also helped secure approximately $20,000 worth of extramural funds from NIH's OBSSR to support the subcontract with the systems scientist.

The senior behavioral scientist supported activities related to HBRB's C.L.A.S.S. website, http://class.cancer.gov, during FY2015. This website includes features developed specifically for researchers, policy makers, practitioners, and the lay audience.

Specific tools managed by the senior behavioral scientist include a policy-mapping tool, state policy profiles, data updates, development of policy briefs, fact sheet updates, and the inclusion of new policy areas on the website and database.

The senior behavioral scientist's main role was to support the ongoing implementation of the FLASHE Study. The FLASHE Study closed its data collection period effective October 6, 2014. Since that time, the senior behavioral scientist has been overseeing all aspects of data management, and preparation of the FLASHE data for public release. This work includes providing guidance and oversight of the Methods report, performing quality control checks on data prepared by the Contractor (Westat), developing the dissemination plan, and preparing documents for public release. Additionally, the senior behavioral scientist oversees the implementation of several subcontracts focused on analyzing the FLASHE Motion Study, FLASHE dietary screener, and FLASHE dyadic data. This work involves engagement and management of diverse research teams spread across four extramural institutions. As such, the senior behavioral scientist is responsible for the main FLASHE Study protocol and three sub-study protocols. In anticipation of the public release of FLASHE data beginning late fall of 2015, the senior behavioral scientist has been instrumental in writing and submitting several abstracts to relevant scientific meetings. The senior behavioral scientist prepared eight abstracts that were accepted for presentation: one panel presentation (Society for Behavioral Medicine), three short oral presentations (International Society for Behavioral Nutrition and Physical Activity), and four poster presentations (ISBNPA and European Congress on Obesity. The senior behavioral scientist participated in five additional abstract submissions and presentations to the above mentioned meetings. She was also senior author on an accepted FLASHE-related manuscript regarding family meal interventions.

Additionally, the senior behavioral scientist provides logistical and scientific support for the systems-modeling contract, including organizing short courses and direct consultation hours, facilitating new project ideas, and overseeing the three modeling projects (one analytic and two conceptual). Lastly, the senior behavioral scientist supports HBRB's C.L.A.S.S. database and provides expert input and review of new coding procedures, analyses, and the translation of scientific findings into research briefs for diverse audiences. This work entails routine engagement with the subcontractor (University of Illinois at Chicago) and contractor for the NCI C.L.A.S.S. website (ICF).

The senior behavioral scientist helped initiate five new research subcontracts. Two involved work with existing subcontracts, but focused on new and novel projects (Brookings Institutions for systems modeling and Iowa State University for advanced data analysis of FLASHE Motion Study data). Another was awarded to the Gretchen Swanson Center for Nutrition, and the senior behavioral scientist utilizes her nutrition expertise to frame and guide the development and implementation of this subcontract focused on developing algorithms for the FLASHE dietary screener. Another two were award to scientists at Columbia University and Delaware University to focus on developing intramural and extramural capacity in dyadic analysis, including short courses and webinars, leading internal analyses of the FLASHE data to evaluate key outcomes, and developing relevant syntax to support FLASHE data users in conducting dyadic analysis. Expertise in dyadic analysis is nonexistent within the HBRB and the senior behavioral scientist has been filling this gap by developing her own skills in this area.

Analyzing the FLASHE motion study data has proven to be more difficult than anticipated as the FLASHE data outpaces the existing methodological base. Because of this, the senior behavioral scientist aligned analytical work being conducted by the FLASHE contractor (Westat) and subcontractor (ISU) so that they would operate in parallel. This provided a means of cross-validation and reliability of work being performed and also allowed for beneficial collaboration. However, it became clear that the subcontractor was much more adept at the data processing than the contractor. The senior behavioral scientist worked with the government contractor to end the analytic activities of the contractor, saving approximately $20,000 in costs. The subcontractor was able to finish the work in the estimated budget that was originally approved.

Process of Care Research Branch

The Process of Care Research Branch (PCRB) supports and encourages behavioral research on how individuals, teams, and health care organizations can act and interact more effectively to improve health through health care delivery. PCRB focuses on behavioral health issues in health care settings across the cancer continuum, from prevention and screening through diagnosis and treatment. PCRB's focus encourages a broad array of studies and methodological approaches that increase understanding and promote behavioral interventions that affect health through health care delivery.

The behavioral scientist provides scientific support to PCRB by performing data and portfolio analyses, preparing manuscripts, and managing other research-related projects. The behavioral scientist also provides leadership and guidance for many projects that span the scope of the PCRB and involve a multidisciplinary group of scientists external to BRP and NIH.

The behavioral scientist acts as PCRB's liaison to BRP's communication team by preparing reports of Branch products for communication planning purposes, monitoring the PCRB portfolio listings on the web page, and proposing changes to PCRB's web pages that reflect the its new mission and scientific priority areas.

PCRB activities during FY2015 reflected key initiatives identified in PCRB's earlier strategic planning process. The behavioral scientist continued to serve as a member of three of the four scientific priority area teams,

attending meetings to discuss priorities, conducting portfolio reviews to define research needs, creating presentations, and providing input into new projects. The behavioral scientist participated in extramural activities developed by the PCRB for receiving input about scientific focus, including quarterly PCRB cyber discussions led by external investigators and a Care Transitions Research meeting that consisted of external researchers who provided feedback about priority needs in the area of cancer care transitions research.

Key activities during FY2015 included continued management of a national survey about cancer awareness and beliefs. The behavioral scientist's management of the population-level survey consists of scientific research and writing, and administrative support required to renew NCI IRB approval.

The behavioral scientist served as a member of the editorial board for a proposed set of manuscripts on health care teams. The behavioral scientist contributed to PCRB's interests in cancer screening and genetic testing by co-authoring a paper on the topic of primary care providers' beliefs and attitudes about genetic testing.

The NCI's Teams in Cancer Care Delivery has been in development for over three years. During FY2015, NCI collaborated with the American Society of Clinical Oncology (ASCO) to plan a research meeting and a 2016 supplement in the *Journal of Oncology Practice*. The behavioral scientist supported the meeting planning through drafting or revising task orders, the meeting justification, the co-sponsorship agreement, an agenda and timeline, promotions, and content for the meeting website. The behavioral scientist also served as a member of the editorial committee for the planned journal supplement, performed a structured review and co-authored one scientific manuscript about teams in cancer care, and edited another manuscript about teams in cancer care.

The Awareness and Beliefs about Cancer survey was completed in the fall of 2014. The behavioral scientist supported the project's next steps, including serving as a liaison to the NCI project team and the subcontractor to resolve technical issues, planning project meetings and agendas, and drafting two background papers describing the methodology employed and the challenges faced during the project. The behavioral scientist also proposed an analysis of the data and created a presentation introducing the survey to the Division.

Two other areas of ongoing work are in genetics and cancer screening. The behavioral scientist supported NCI priorities in genetics by co-authoring a paper about primary care providers' beliefs and attitudes about genetic tests for cancer predisposition. The behavioral scientist contributed to the study design, data collection, analysis, and manuscript drafting. Work supporting the NCI's cancer screening interests included moderating a symposium on cancer screening decisions in older adults at a national conference and revising a scientific paper on that same topic.

A new task involved supporting the planning of a colorectal cancer screening conference. The behavioral scientist drafted or revised meeting justification, co-sponsorship agreement, and budget forms.

Grant portfolio reviews represented both new and ongoing work efforts. The behavioral scientist led updates to previously performed portfolio reviews on health care teams and aging and initiated a new review of Health Information Technology grants.

The PCRB was dissolved on December 31, 2014. The behavioral scientist began supporting projects for the HSIRB within DCCPS beginning January 1, 2015. Additional information pertaining to the support provided by the behavioral scientist is captured in the HSIRB section of this report.

Science of Research and Technology Branch

The Science of Research and Technology Branch (SRTB) supports the development and application of innovative research approaches, theories, methods, measures, analytic tools, and technologies that advance social and behavioral science as they relate to cancer prevention and control.

The senior behavioral scientist is assigned to support key activities of SRTB, particularly the work of the Branch's SciTS team. The SciTS team is charged with developing the knowledge base on effective and efficient team collaboration in science, and facilitating the growth of the SciTS field, a rapidly growing interdisciplinary area of research dedicated to building our collective knowledge for fostering maximal effectiveness in team science. NCI has been a national leader in funding team science, with the aim of accelerating innovation and progress around scientific priority areas.

The senior behavioral scientist also supports broader BRP goals related to developing an understanding of behavioral factors influencing clinical trials accrual and supporting integration of knowledge across behavioral domains.

During FY2015, the senior behavioral scientist coauthored five invited talks, each presented to a different audience with an interest in team science:

1. Hall KL and Vogel AL. Scientific Identity and Leadership in the Era of Collaboration. Society for Industrial and Organizational Psychology 20th Annual Conference. Philadelphia, PA. April 23, 2015.
2. Hall KL, Gehlert S, and Vogel AL. Applying a Conceptual Model of TD Team Science to Guide and Interpret TD Science Initiatives. Transdisciplinary Research in Energetics and Cancer (TREC) 2 Webinar Series. April 14, 2015.
3. Hall KL and Vogel AL. Team-Based Science: Strategies for Success. Howard University. April 14, 2015.
4. Hall KL and Vogel AL. Based Science: Strategies for Success, Practical Tools, and Future Directions. Center for Biomedical Informatics and Information

Technology (CBIIT) Speaker Series, National Cancer Institute. Bethesda, MD. December 10, 2014.

5. Vogel AL and Hall KL. Team-Based Science: Strategies for Success, Practical Tools, and Future Directions. University of Miami Team Science lecture series. Miami, FL. December 9, 2014.

During this fiscal year, the senior behavioral scientist also coauthored three peer-reviewed posters, all presented at the Science of Team Science 2015 Conference held at the NIH main campus in Bethesda, MD on June 3–5, 2015:

1. Huang GC, Dathe MC, Gibbs KD, Stipelman BA, Serrano KJ, Vogel AL, Larsen N, Williams C, Tsakraklides SP & Hall KA. "Developing a systems map of team science: A spotlight on methods and preliminary results."
2. Hall KA, Vogel AL & Crowston K. "Collaboration plans: planning for success in team science."
3. Vogel AL, Hall KL, Stipelman BA, Tsakraklides S, Garner D, Grant E & the Team Science Toolkit Editorial Board. "The Team Science Toolkit: spotlight on new content and functionality."

During this reporting period, as co-editor for the *Handbook of Interdisciplinary Research in Behavioral Science*, along with NCI clients Drs. Kara Hall and Bob Croyle, Director, DCCPS, the senior behavioral scientist completed development of the book's prospectus, and it was approved by Springer, Inc. As of June 1, 2015, the prospectus is under review at the DCCPS level at NCI.

In addition to the scholarly activities described above, during FY2014, the senior behavioral scientist continued to co-lead the enhancement, dissemination, and evaluation of the Team Science Toolkit—www.teamsciencetoolkit.cancer.gov—an online one-stop-shop for resources for using, facilitating, supporting, evaluating, or studying team-based collaboration in science. During this reporting period, the senior behavioral scientist continued to lead a successful communications and dissemination campaign for the Toolkit. In June 2015, the Toolkit was featured on NCI's website homepage. The senior behavioral scientist led a set of successful projects, in fall 2014 and early 2015, to enhance key content in and functionality of the Team Science Toolkit. One of these enhancements was the development and implementation of a rating system called "Editors' Picks". Another enhancement was the development and implementation of an interface system to conduct batch downloads of resources from the Team Science Mendeley group to the Team Science Toolkit. A third project was the continued shepherding of the blog portion of the Toolkit, by cultivating new authors, reviewing their blogs, publishing their blogs on the Toolkit, and promoting the blogs via listservs.

The senior behavioral scientist served as conference program co-chair for the 2015 SciTS Conference, held at the Natcher Conference Center on the NIH Main Campus on June 3–5, 2015. Her activities in this leadership role included: identifying invited speakers; developing the call for abstracts; recruiting abstract reviewers; managing the peer review process; designing and leading the communications campaign; creating the conference schedule, program book, and abstract book; recruiting, training, and managing on-site staff; and co-presenting the welcome session at the conference. This was an extremely successful conference, with approximately 450 persons attending. Featured speakers included a Nobel laureate, a New York Times best-selling author, faculty from top-tier universities, and top leadership of multiple NIH Institutes and Centers. The senior behavioral scientist will be leading development of a scholarly manuscript capturing key themes of the conference and identifying future directions for the SciTS field.

The senior behavioral scientist has been working with the SciTS team and a systems-mapping expert from the Brookings Institution to develop: (a) a systems map of the many complex and interacting factors influencing processes and outcomes of team collaboration in science; and (b) a systems map of key health behaviors, with related constructs, theories, and measures. This ongoing project was highlighted in a poster presented at the 2015 SciTS Conference.

In addition to this work in the SciTS field, the senior behavioral scientist continues to serve as co-lead on an important theory development study to build the evidence base on how oncologists' cognitive, emotional, and motivational traits influence their decisions to refer patients to cancer clinical trials. This is a priority topic for BRP and NCI, as there continue to be severe shortages of patients participating in cancer clinical trials, which delays production of important research findings related to cancer therapeutics. Physicians are a main influence on enrollment of patients into clinical trials. During the reporting period, the senior behavioral scientist led a team of experts from multiple programs and divisions within NCI to develop the final portions of a draft of the survey instrument for this research. It will be piloted in fall 2015.

In addition, the senior behavioral scientist is part of a group of collaborators in BRP who are working on supporting crosstalk among investigators studying an array of health behaviors of interest to the BRP. The senior behavioral scientist was on the planning committee for a "Crosstalk Symposium" hosted at the NCI Shady Grove campus by BRP on October 30–31, 2014. This group has developed a scholarly manuscript to build upon what was discussed at the symposium, and it is projected to be published in late 2015. In addition, the senior behavioral scientist is working with colleagues in BRP to develop ideas for a new funding initiative that will support work in this vein of crosstalk. The senior behavioral scientist is also leading a group of colleagues in SRTB to develop ideas for new funding opportunities in mixed-methods research.

In support of cost savings, the senior behavioral scientist leveraged no-cost resources at the NCI Office of Communications and Public Liaison and the NIH OBSSR to develop and implement a very successful communications campaign for the 2015 SciTS Conference. This included the use of NCI Twitter accounts, the NCI LinkedIn web page, NCI electronic

sign boards, the NCI and NIH homepages, OBSSR's blogs and website, and graphic design assistance. These collaborations contributed to the fact that the conference registration hit its cap before advance registration closed. Likewise, the senior behavioral scientist used preexisting relationships with the NIH website content development staff to feature both the 2015 SciTS conference and Team Science Toolkit on the NIH homepage in May and June 2015, in consort with the SciTS 2015 conference.

In addition, the senior behavioral scientist continues to leverage interns and volunteers to support SciTS team activities and continues to serve as a preceptor for undergraduate and graduate students from the University of Maryland Department of Community and Behavioral Health. The senior behavioral scientist hosted a fulltime intern from that department from January through June 2015, who provided invaluable administrative support related to conference planning and implementation. In addition, the senior behavioral scientist mobilized 10 volunteers, including five NCI staff members and five students from the University of Maryland, to work on-site at the 2015 SciTS Conference. Tasks performed included staffing the registration desk, helping attendees when needed, serving as microphone runners, helping with IT issues, and performing other tasks ordinarily done by paid conference staff.

The senior behavioral scientist continues to serve as a member of a subcommittee on Team Science, out of the White House Office of Science and Technology Policy. As a core member of this group, she has coauthored a document titled, "How to Write a Collaboration Plan," which provides guidance to investigators on how to plan for collaboration as part of their written grant applications to federal authors, when applying for funds to conduct team-based research. This document is available at: https://www.teamsciencetoolkit.cancer.gov/Public/TSResourceBiblio.aspx?tid=3&rid=3119

This work was also presented as a scientific poster at the SciTS 2015 Conference. It is available at: https://www.teamsciencetoolkit.cancer.gov/Public/TSResourceBiblio.aspx?tid=3&rid=3261

Finally, the senior behavioral scientist continues to serve in an expert advisory capacity to support colleagues at NCI and in related groups. The TREC 2 initiative is a major funding initiative of NCI that supports four research centers and a coordination center to conduct team-based transdisciplinary research to examine the relationship between obesity and cancer. As a member of the TREC 2 Collaboration and Outcomes Working Group, the senior behavioral scientist provided expert advising to members of the TREC 2 coordination center to support their work in evaluating processes and outcomes of transdisciplinary team science in TREC 2 research centers. She helped them revise interview guides for qualitative research, and shared with them her coding scheme from research she conducted with prior TREC grantees. She has also provided expert advice and assistance to NCI Cancer Prevention fellows and university faculty colleagues who are entering the SciTS field.

Health Delivery Research Program

Health Systems and Interventions Research Branch

New Initiative

Support Provided by the Clinical Monitoring Research Program

The Health Systems and Interventions Research Branch (HSIRB) was formed within the new Health Delivery Research Program (HDRP) as part of DCCPS's reorganization. The behavioral scientist's support to HSIRB is of the same nature as the support provided to PCRB. Program activities and work efforts that began while PCRB was operational transferred to HSIRB.

HSIRB's mission is to advance observational and intervention research on structural, organizational, social, and behavioral factors that influence the delivery of cancer care—from early detection through end of life.

The behavioral scientist provides scientific support to HSIRB by performing data and portfolio analyses, preparing manuscripts, and managing other research-related projects. The behavioral scientist also provides leadership and guidance for many projects that span the scope of the HSIRB and involve a multidisciplinary group of scientists external to HDRP and NIH.

Epidemiology and Genomics Research Program

Office of the Associate Director

New Initiative

Support Provided by the Clinical Monitoring Research Program

The Epidemiology and Genomics Research Program (EGRP) funds research in human populations to understand determinants of cancer occurrence and outcomes. The Program fosters interdisciplinary collaborations and the development and use of resources and technologies to advance cancer research and its translation to serve as the basis for clinical and public health interventions. EGRP's aim is to reduce the cancer burden in human populations by identifying determinants of cancer risks and improving outcomes.

The National Human Genome Research Institute (NHGRI) has partnered with NCI to fund efforts to gather evidence on clinically relevant genetic variants, identified through whole-genome sequencing (WGS), in order to ease the burden on clinicians and patients. The effort currently referred to as the Clinical Genome Resource (ClinGen), formerly called the Clinically Relevant Variants Resource (CRVR), will demand detailed, systematic evidence about each variant that is being considered for clinical relevance.

CMRP staff awarded a Phase I research subcontract to Kaiser Permanente in March of FY2014 in support of this effort. The objective of Phase I was to develop an evidence synthesis protocol for each proposed gene/phenotype pair; produce evidence-based reports (case studies); and coordinate with the other groups of the CRVR. Phase I work continued into December of FY2015. Phase II of the project was awarded in November of FY2015. Building upon work begun in Phase I, Phase II continues to provide the evidence base for each proposed gene/phenotype pair by extending and modifying the Evaluation of Genomic Applications in Practice and Prevention working group methodology. This includes performing semi-quantitative assessments of the clinical actionability of gene/phenotype pairs for ClinGen. A proposal for Phase III of this work is under development for funding in FY2016.

Support Provided by the Clinical Monitoring Research Program

Developmental Therapeutics Branch

The overarching mission of the DCTD Developmental Therapeutics Branch (DTB) is to evaluate innovative anticancer compounds in early-phase clinical trials, while providing outstanding clinical care for patients with different types of cancer. An important focus is first-in-human clinical trials, particularly those that incorporate pharmacodynamic and pharmacokinetic endpoints, with the goal of informing subsequent clinical development. CMRP provides one senior nurse practitioner and three clinical research nurses to support these efforts.

During FY2015, CMRP hired a research nurse to replace the research nurse who resigned, and hired two additional new research nurses, for the DTB. CMRP staff supports 20 ongoing protocols and, more specifically, independently coordinates every aspect of the research efforts (e.g., coordinating patient visits to NIH; directing the patients to admissions; consenting the patients for screening; preparing patient calendars, which tell the patient what research activities will be taking place every month; acting as a liaison between the patient and the providers; and coordinating specimen pick-ups) for these protocols. Aside from patient recruitment efforts, the clinical research nurse reviews patient referral records, contacts potential research patients to evaluate their present health status, schedules patients for screening clinic visits, and coordinates the patient visits once the patients arrive at NIH. The senior nurse practitioner evaluates patients on all 20 protocols and takes care of their day-to-day medical care needs as they arise.

During FY2015, CMRP staff members assisted in initiating and implementing three new protocols: (1) 15-C-0086, Phase I Trial of the Combination of Nilotinib and Paclitaxel in Adults with Refractory Solid Tumors; (2) 14-C-0161, Phase I Trial of the Combination of Bortezomib and Clofarabine in Adults with Refractory Solid Tumors; and (3) 14-C-0150, Phase I Study of Ganetespib and Ziv-Aflibercept in Patients with Advanced Gastrointestinal Carcinomas, Non-Squamous Non-Small Cell Lung Carcinomas, Urothelial Carcinomas, and Sarcomas.

During FY2015, the CMRP staff has assisted in screening more than 100 patients for protocols and, so far, has enrolled 84 patients on the team's various protocols.

CMRP staff has been involved in various activities that promote knowledge transfer for effective and efficient undertaking of the team's research activities. For example, the CMRP research nurses gave in-service training sessions to 3NW (inpatient) nurses and 3SE (day hospital) nurses about the team's new protocols to better prepare the floor nurses for effective and efficient trial implementation. CMRP staff also manages two multi-site studies (CTEP 8875 and 8846) since the Developmental Therapeutics Clinic (DTC) is the enrolling site, runs the monthly conference calls for CTEP study 8875, and participates in the bimonthly conference call for CTEP 8846, in order to ensure effective coordination of those protocols. Additionally, CMRP research nurses are independently responsible for the coordination of CTEP study 9149, which is scheduled to go multi-site in the near future, with an estimate of up to 70 participating sites. One of the CMRP research nurses will run the conference calls and manage the multi-site aspect and another CMRP research nurse will manage the regulatory aspects of this trial.

Division of Cancer Prevention

Support Provided by the Applied and Developmental Research Directorate

The BioProcessing Laboratory provided support to five Division of Cancer Prevention (DCP) Phase III clinical trials for specimen processing, repository management, specimen data management, and meeting support. These studies are the Selenium and Vitamin E Cancer Prevention Study (SELECT), the Prostate Cancer Prevention Trial (PCPT), the PLCO Cancer Screening Trial, the 2003 DCP Consortia for Early Phase Prevention Trials, and the Alternatives in Women's Healthcare.

Biospecimen Processing and Repository Management

Study	Material	# of Aliquots	Activity
SELECT	Plasma	9,941	Receive and store returned aliquots from extramural investigator
SELECT	DNA	2,117	Extract, quantify, normalize, aliquot, store; distribute aliquot to extramural investigator
Early Phase Consortia	Multiple	5,678	Receive, data map, consolidate, and store specimens from consortia collections. Activity included creation of communication plans, distribution methods, and database enhancements for this new collection's future use. Collection includes seven material types to date.
EDRN	Multiple	48,105	Organize logistics for the acquisition of 318,105 specimens stored at another facility, of which 48,105 were received, data mapped, and stored in the last quarter of FY2015.
ALT	Multiple	30,358	Pull and discard plasma, PreservCyt, and slide specimens from the collection.
PLCO	DNA	1,362	Extract, quantify, normalize, aliquot, store; distribute aliquot to extramural investigator

Division of Cancer Treatment and Diagnosis

Office of the Director

Support Provided by the Applied and Developmental Research Directorate

Clinical Pharmacodynamics – Biomarkers Program

As part of the reorganization and consolidation of support to the Division of Cancer Treatment and Diagnosis (DCTD), the Phase I/II Sample Processing Laboratory, the Preclinical Assay Development and Implementation Section (PADIS), and the National Clinical Target Validation Laboratory (NCTVL) were grouped together under the umbrella of Clinical Pharmacodynamics – Biomarkers Program.

Preclinical Assay Development and Implementation Section

Assay development, transfer, and preclinical support

- A multiplex immunofluorescence assay (IFA) for use on formalin-fixed, paraffin-embedded (FFPE) biopsies and designed to assess the epithelial–mesenchymal transition (EMT) in tumors has completed demonstration of clinical readiness, and was deployed to analyze patient specimens from the MK1775 (P9350) and pazopanib (P8880) trials.
- The MET IFA fitness of purpose was demonstrated using SNU5 FFPE xenograft tumor samples from animals treated with increasing doses of crizotinib in vivo. Quantitative measurement by Definiens analysis of pY1235-MET and total MET in tissue regions of interest (ROI) showed 50 percent and 95 percent pY1235-MET inhibition, with 12.5 mg/kg and 25 mg/kg crizotinib, respectively. There were no significant changes in total MET by IFA. A high correlation (R = 0.899) was observed between the pY1235-MET/total MET ratio measured by IFA levels (expressed as the marker area/number of cells for pY1235-MET and total MET per ROI) and the pY1235-MET/total MET ratio determined by ELISA levels (pM/ug protein) in the validated quantitative sandwich immunoassay IA previously developed by PADIS. The MET assay was also applied and validated on FFPE tissues from SNU5 xenograft tumors treated with the VEGF inhibitor (pazopanib), the putative MET inhibitor (tivantinib; ARQ197), or the drug combination (Navas et. al., AACR 2014). Quantitative IFA assessment showed a significant increase in the percent pY1235-MET/total MET expression in pazopanib-treated tumors compared to the vehicle ($P < 0.007$ vs. vehicle), while a significant decrease in the percent pY1235-MET/total MET was observed in the drug combination group ($P < 0.0005$ vs. pazopanib). A high Spearman's correlation was also observed in the pY1235-MET/total MET ratio by IFA vs. ELISA levels (R = 0.52; P = 0.0112; N = 23).
- PADIS successfully applied the MET IFA on FFPE tumor samples from the CTEP 8880 clinical trial. We have shown specific membrane staining of pY1235-MET and total MET in two clinical specimens (ovarian and esophageal), both of which have been reported to have high pMET and total MET expression levels by the MET quantitative sandwich IA. The pY1235-MET IFA staining was specifically blocked by the pY1235-MET peptide, but not by the pY1234-MET or unphosphorylated MET peptide.
    - A multiplex assay of 13 apoptosis biomarkers developed earlier in PADIS on the Luminex platform was utilized to first identify, and subsequently validate, pharmacodynamic

biomarkers of novel combinations of drugs discovered at NCI (Holbeck et al., 2014), demonstrating superior efficacy in preclinical studies. Biomarker analysis performed supported two novel drug combinations that have advanced to Phase I clinical trials (NCT02211755 and NCT02379416). The goal of translational studies was to identify mechanistic biomarkers of drug efficacy and identify optimal timing of biopsy collection for Phase I studies to demonstrate pharmacodynamic modulation.

- PADIS supported the DCTD unexpected drug synergy program. This program has moved three drug combinations discovered as active in the American Recovery and Reinvestment Act of 2009 (ARRA) program into preclinical development, with the objective of filing IND applications and initiating clinical trials. PADIS developed evidence for the mechanism of action and provided a mechanistic biomarker to be employed in monitoring drug activity.
  - The first combination, now in a Phase I trial, is of bortezomib and clofarabine. Bortezomib (0.75 mg/kg, IP) with clofarabine (60 mg/kg, PO; abbreviated B+C) was tested in sensitive (HCT116, colon cancer) and non-responsive (M14, melanoma) xenograft models. A survey of apoptosis pathway components using the PADIS-developed Luminex multiplex assay in the HCT116 model treated with B+C showed an approximately 300 percent increase in the level of cleaved caspase-3, accompanied by a 35 percent lower survivin level and translocation of Bax from cytosol to the mitochondrial fraction at 6 hours and 24 hours post–dose five. In contrast, there was a complete lack of biomarker modulation in the non-responsive (M14) model treated with B+C. Sustained suppression of survivin was identified as a key regulator of B+C efficacy. PADIS examined the roles of clofarabine incorporation into DNA, the inhibition of DNA synthesis, and the inhibition of DNA repair by IFA analysis. The DNA damage repair markers γH2AX and pNbs1 increased in response to clofarabine alone and the drug combination treatment group, in a responsive model but not in a non-responsive model. At the six-hour time point, a higher induction of γH2AX was observed in the drug combination group compared to clofarabine alone in HCT116 models, which could indicate a potential synergistic action of clofarabine and bortezomib in sustaining the presence of DNA damage. Analysis of the mitotic marker histone H3 – pSer10 revealed reduced expression in the clofarabine only and combination groups, indicating cell cycle arrest in the responsive model only. Taken together, these data provide clear mechanistic evidence of DNA damage and cell cycle arrest that contributes to the efficacy of the bortezomib and clofarabine combination in a responsive model with attendant activation of the intrinsic mitotic pathway through suppression of survivin at its chromosomal localization. Based on our overall pharmacodynamic analysis, the six-hour time point was selected to be optimal for pharmacodynamic monitoring in an ongoing clinical trial (NCT02211755).
  - A second combination (abbreviated N+T) of nilotinib (50–100 mg/kg, QDx5, PO) was tested with paclitaxel (10 mg/kg, Q4Dx2, IV) in a breast cancer MDA-MB-468 model and with docetaxel (7.5–15 mg/kg, Q4Dx2, IV) in a glioma U251 model. IFA analyses of xenografts confirmed pHH3 activation consistent with the known mechanism of action of paclitaxel.
  - Both drug combinations (B+C and N+T) demonstrated tumor volume regression in responsive models. A survey of N+T-treated tumors in the U251 model showed reduced levels of the Mcl1—BAK heterodimer, which was accompanied by increased mitochondrial BAX and cytosolic cleaved caspase-3 levels. Validation of biomarkers for the N+T combination is under way.
  - In vitro analysis began for the combination cediranib+erlotinib, with the goal of identifying a pharmacodynamic marker of activity for the drug combination.
- Immuno-pharmacodynamics: PADIS initiated work on a program to identify pharmacodynamic and mechanistic markers of immune modulator therapies focused on identifying and validating key reagents and in vitro–mixed culture systems.
- Kinase signaling quantitative enzyme IA multiplex for profiling major intracellular signaling pathways was begun. Work is focused on generating prototype assays with a set of antibodies and calibrators generated under the ARRA program. Identification of additional critical antibodies and assay calibrators has begun.
- DNA repair pathway activation: In-house development has continued on multiplex assays to survey DNA repair pathway activation on pathology slides from tissue biopsies. The second multiplex of four DNA repair markers (phosphoS343Nb1s, γH2AX, pATR, and RAD51) has completed fitness-for-purpose testing in a mouse xenograft model and clinical readiness testing. Assay standard operating procedures and calibrators were completed and assay transfer to NCTVL was initiated in a modified form since NCTVL does not have the equipment to acquire and analyze focal image data from cell nuclei.
- ERCC1 stand-alone assay for assessment in clinical diagnostic testing, in collaboration with the Fox-Chase Cancer Center, was completed, and

retrospective correlation of nuclear ERCC1 levels with platinum resistance was confirmed.

- PADIS initiated the development of a new multiplex panel for biomarker measurement on patient biopsy–fixed sections. The panel is designed to report cell cycle status for use with the DDR2 panel that monitors molecular level responses to agents targeting DNA replication, repair, and cell division. Validated, clinic-ready markers to be included are pY15ckd1/2 and phosphohistone H3. Additional biomarkers are being identified and tested.

Clinical trials support

Clinical trials support continues to be a significant part of PADIS' activities. PADIS performs assays that cannot be readily transferred to other laboratories due to equipment availability (e.g., CellSearch® and Confocal Microscopy) or assays that are highly exploratory and require additional evidence of clinical utility before dissemination to the wider community (e.g., tests performed on skin biopsies). Specific accomplishments are outlined below.

- PADIS continued direct support of the NCI Clinical Center trial of indenoisoquinolines with quantitative, validated assays of γH2AX for pharmacodynamic in circulating tumor cells (CTCs).
- PADIS completed c-MET analysis of clinical biopsy specimens generated during the CTEP8880 trial of pazopanib, with the novel finding of inhibition of c-MET by pazopanib.
- PADIS provided direct support to the NCI Experimental Therapeutics (NExT) Program in domestic dogs with cancer (trial COTC007). Both pharmacodynamic endpoint assays (total Top1 and γH2AX) and research studies with the DNA repair multiplex panel DDR2 are being performed.
- PADIS implemented a specimen tracking system and reorganized all physical specimen banks to enable use of the new system. The section also implemented a centralized clinical sample accessioning and tracking function. All incoming pharmacodynamic samples are monitored and routed to the appropriate testing laboratory or for short-term storage in a secure biorepository. All relevant sample information is logged in an accessible SharePoint tracking system, and the lineage and location of sample derivatives are also tracked to ensure the appropriate sample workflow and the ability to deaccession all remaining materials and derivatives at the end of the trial according to Institutional Review Board (IRB) requirements.
- Other clinical trials supported are listed in the following table.

Clinical Trial	Clinical Center	Investigational Agent
P8282	CTEP/Pitt	ABT888
P8273	DTC	Indenos
P8351	DTC	FdC+THU Phase II
P8484	CTEP/Farber	888 + SCH727965 +/- Carboplatin
P8620	CTEP/Pitt	888 + Carbo + Paclitaxel
P8880	DTC	Pazopanib
P8811	CTEP/COH	888 + Carbo + Paclitaxel
P8813	JHU/Princess Margaret	IR + 888
P9127	DTC	FdC+THU Oral
P9235	DTC	TL32711 Birinopant
P9284	DTC	XL184 Cabozantanib
P9350	DTC	MK1775
P9362	JHU	MK8776+AML
P9430	DTC	LMP400, LMP776
P9483	DTC	TRC102+TMZ
P9510	DTC	BMN673
P9605	DTC	Ganetespib+Zif-Afibercept
P9659	DTC	Nilotinib+Paclitaxel
P9883	DTC	TdCyd

Preclinical drug development support of NExT Program agents

These are ongoing efforts for evaluating the pharmacodynamic activity of new compounds, employing assays already developed and validated by PADIS to support the development of agents for testing in Developmental Therapeutics Clinic (DTC) clinical trials.

- Analysis of the pharmacodynamic activity of 5-thiodeoxycytidine (TdCyd) established that TdCyd is active against solid tumor–derived cell lines in vitro and in vivo, and that it specifically attacks the enzyme DNA methyltransferase 1. Involvement continues with the design and validation of a clinical biomarker testing strategy for the agent in preclinical (xenograft) models, and measurement of p16 induction in CTCs from patients enrolled in the Phase I clinical trials.
- Aza-TdCyd activity is being explored in parallel with TdCyd in xenograft models.
- Mcl-1 inhibitor development: PADIS is currently providing assistance on the drug development project team working to develop Mcl-1-specific inhibitors.
- VX970: A single-agent xenograft model is being analyzed, as is the combination with cisplatin. These models will enable a three-agent model, with the addition of veliparib preparative, for a clinical trial at DTC.

- Vx984: In vitro studies were initiated to determine if a specific mechanistic marker of Vx984 inhibition of DNA-PKc can be identified, given the high degree of cross-talk between the three major DNA repair–initiating signaling molecules ATM, ATR, and DNA-PK.
- BMN673: Mechanistic biomarker studies are ongoing in xenograft models with BMN673 as a single agent in MX-1 (BrCa-) and BL0293 patient-derived xenograft (PDX) models.

The epitomics subcontract

Epitomics generates monoclonal antibodies targeting key pharmacodynamic biomarkers when commercially available antibodies are of insufficient quality or are unavailable. PADIS established a subcontract with Epitomics to provide antibodies as directed by task order.

- PADIS completed monoclonal antibody molecular cloning and research level production (15–50 mg) for pT1989ATR clone 7A7, anti-CD133 clones 47-10 and 133-3, and P15/16 clone 28.
- PADIS initiated monoclonal antibody generation to support targeted agent development for pS367 ATM, DNMT3, and DNA-PKc.
- PADIS continued work on demonstrating fitness for purpose of monoclonal antibodies generated to a set of transcription factors associated with EMT and drug resistance in solid tissue cancers.

CTC separation device development

System validation, assay validation, and clinical readiness of the CellSearch® 5 channel system for CTC analysis was completed, and the instrument will be brought online in support of a clinical trial of veliparib + Vx970, to begin in FY2016. This work was undertaken with the support of Janssen Diagnostics, which provided the upgraded detection instrument software at no charge. Knowledge gained from the application of the ApoStream® platform was translated back to the CellSearch platform in order to improve clinical utility and take advantage of the utility of the CellSearch platform for fixed specimens. Internal development of a CTC detection algorithm and incorporation of tumor marker antibodies and pharmacodynamic biomarker antibodies into the reported channels (i.e., generation of a home-brew testing kit) have increased the number of CTCs recovered by one to two logs and allowed the scale down of specimen requirements from 7.5 to 2 ml. An ApoStream system is in the process of being transferred to the specimen processing laboratory in Building 10 at the NIH Bethesda campus, for support of ongoing DTC trials.

Patient-derived xenograft program support

PADIS processed 290 blood specimens in the first six months of FY2015 to implant into non-obese diabetic SCID IL-2 receptor gamma chain knockout (NSG) mice as part of the PDX program (PADIS processed an average of 48 specimens per month). Live CTCs have been recovered from 4-mL blood specimens obtained from cancer patients enrolled in trials at the NCI Clinical Center and are being "cultured" in mice as xenografts. In support of this work, PADIS has developed a set of CTC phenotyping assays using four-color immunofluorescence and the Aperio scanner for data acquisition. Currently, PADIS is using the Definiens software to determine cell count and segregate subpopulations of interest based on biomarker expression analysis on the recovered cells. An extensive set of antibodies targeting key tumor markers was validated for this application, including CEA, MUC-1, PSA, PSMA, vimentin, pan-cytokeratin, γH2AX, CD45, ASPL-TFE3 types I and II fusion proteins, β-catenin, TLE1, EpCAM, and EGFR. Additional work is under way to determine optimal methods of maintaining CTC viability for cross-country shipment.

Assay community training and transfer

PADIS continued its support of the training mission. The section held one class on CTC training and another on poly-ADP ribose (PAR) immunoassays.

American Recovery and Reinvestment Act of 2009–related support

A variety of approaches have been advocated for the efficient isolation of CTCs from peripheral blood specimens, exploiting the differences in the biological and/or physical properties of CTCs and normal blood cells. Under this project, a microfluidic, antibody-independent CTC isolation technology called ApoStream, which can isolate live CTCs from epithelial and non-epithelial cancers, was developed, validated, and brought online to isolate CTCs from NCI patient clinical specimens, and assist in evaluating the pharmacodynamic effects of new anticancer agents. ApoStream works on the principle of dielectrophoresis field-flow fractionation (DEP-FFF), wherein dissimilar cells respond differently to an applied non-uniform electric field. Theory of device set up and operation, and performance validation across laboratories was also required for this project.

The most significant lesson learned through this project is that successful development of a new technology, which actually pushes the science forward, will then expose additional areas in which important technological advances have lagged, and, therefore, increase the level of effort needed to fully realize the potential for the new technology. In the case of this device, a key example was the inability to incorporate an in-line cell counter into the ApoStream device because there are no small detectors available that can count the low number of CTCs (generally less than 1,000) typically collected from a patient blood specimen. This will be an area of technical development left for future work. PADIS compensated for this challenge by developing an automated fluorescence microscopy system to characterize and enumerate the cells isolated by the ApoStream device.

National Clinical Target Validation Laboratory

The National Clinical Target Validation Laboratory (NCTVL) serves as a pharmacodynamic biomarker validation and testing center for DCTD, NCI, and is a key component for the NCI clinical biomarker program. NCTVL works closely with the PADIS, DCTD Project Management Office, and NCI clinicians, investigators, and staff. These collaborations focus on pharmacodynamic assay development, assay transfer, assay validation, and testing of clinical specimens treated with novel small-molecular agents targeting signal transduction and DNA repair pathways. The primary focus of the lab is to provide pharmacodynamic assay support to DCTD-sponsored clinical trials and to report assay results back to the trial sites, using the reporting instructions and report templates found in the particular assay standard operating procedures.

Significant Achievements

In FY2015, NCTVL has been supporting pharmacodynamic correlative studies for seven Phase I clinical trials, as listed in Table I. The validated γH2AX IFA is a microscope slide–based immuno-fluorescence assay analyzing tumor biopsies, tumor aspirates, and PBMCs. A 96-well plate–based homogeneous immuno-antibody capture sandwich assay is used for PAR and Top1 quantitation. In the case of the CTEP#9510 trial with BMN673, NCTVL successfully processed and tested pharmacodynamic biomarkers, including PAR IA and γH2AX- IFA. NCTVL also supported preclinical studies, including the treatment of BL0293 PDX tumors with various doses of BMN673 and other poly(ADP-ribose) polymerase (PARP) inhibitors, such as ABT888, AZD2281, and MK4827, and their combinative treatments. NCTVL-supported preclinical studies are listed in Table II.

For pharmacodynamic assay development, NCTVL successfully completed quantitative γH2AX IA using total γH2AX as the denominator and internal calibration of the biospecimen. This assay method and technology led to the filing of a U.S. patent application (number 62/110,764, Leydig, Voit & Mayer, ID number E-276-2014/0-US-01). PADIS also worked with the Small Business Innovation Research grantee to manufacture phosphorylated full-length γH2AX and further characterize γH2AX assay performance by comparing the synthetic peptide with recombinant γH2AX as quantitative standards. Using γH2AX IA to quantify DNA damage, NCTVL showed the synergic effect of treatments with drug combinations at dose- and time-dependent manners. The testing agents included inhibitors of Top1, PARP, and ATR, and their combination. Our data was presented at the 2015 American Society of Clinical Oncology annual conference at Chicago, IL.

To support pharmacodynamic assay transfer, NCTVL has been working closely with the DCTD Project Management Office and PADIS scientists. We have validated the final revisions of PAR-IA, Top1-IA, γH2AX IFA, and other biospecimen processing and pharmacodynamic testing standard operating procedures. We also assisted with community training to NIH-funded cancer center and testing labs in order to assist personnel with assay implementation. We assisted with hands-on laboratory training classes and supplied critical assay reagents. In terms of new pharmacodynamic assay transfer from PADIS to NCTVL, we have successfully set up the Luminex system for multiplexed bead–based immunoassays in NCTVL lab in Bethesda. Using the Luminex system, we are currently in the middle of assay transfer and validation of apoptosis panels in a total of 13 biomarkers.

Table I. NCTVL-supported Phase I Clinical Trials

PD Testing	Clinical Trial Protocol #	Agent	No. of Pts	Specimen Type	No. of Specimens
γH2AX Cytospin IFA	CTEP # 8282	ABT888	18	Tumor Biopsies	29
	CTEP # 7998	ABT888+ Cyclophosphamide	1	Tumor Biopsies	2
	CTEP # 8620	ABT888+ Irinotecan	11	Tumor Biopsies	20
	CTEP # 8273	LMP776, LMP400	2	Tumor Biopsies	3
	COTC007b	LMP776, LMP400, LMP744	47	Tumor Biopsies	173
			13	Tumor Aspirate	46
	CTEP # 8273	LMP776, LMP400	8	PBMCs	72
PAR IA	CTEP # 8329	ABT888+ Topotecan	3	PBMCs	30
	CTEP # 9510	BMN673	6	Tumor Biopsies	11
Top1 IA	CTEP # 8273	LMP776, LMP400	7	PBMCs	75
	COTC007b	LMP776, LMP400, LMP744	5	Tumor Biopsies	30
Total			121	Tumor Biopsies	491

Table II. NCTVL-supported Preclinical Model Studies

PD Testing	Preclinical Xenograft Models	Agent	No. of Mice	Specimen Type	No. of Specimens
PAR IA	MX1	PARPi/Irinotecan	40	Tumor Biopsies	72
	BL0293/PDX	PARPi/BMN673	72	Tumor Biopsies	288
HIF1α	5 Models for Baseline Studies	NA	76	Tumor Biopsies	76
	MX1/A375	PARPi/Irinotecan	184	Tumor Biopsies	216
γH2AX IA	BL0293/PDX	PARPi/BMN673	30	Tumor Biopsies	30
Total			402		682

Pharmacokinetic/Pharmacodynamic Specimen Processing Lab

DCTD collaborates with CCR to sponsor early clinical trials of new investigational agents. The Phase I/II Pharmacokinetic/Pharmacodynamic Support Lab handles biospecimen processing to the Early Clinical Trials Development Program, and is responsible for supplying uniform blood and other biospecimen processing core support as identified in the clinical trial protocol. This includes processing for pharmacokinetic/ pharmacodynamic components of clinical trials sponsored by CTEP. The group is located in the NIH Clinical Center, Bethesda, MD.

Significant Achievements

- The lab processed over 1,300 incoming biospecimens from 135 patients and outputted over 3,300 prepared samples to various labs. The lab also maintained work coverage throughout odd hours and weekends on a routine basis for time-sensitive samples.
- The lab worked on 16 active trials and launched 2 new protocols in 2014/2015, including nilotinib-paclitaxel and TCYD. The lab closed out 8 protocols working with various groups to share the data on hand.
- The lab provided increased support to the Clinical Center research team to ease the work load as the research team transitioned to a new principal investigator and brought on three new research nurses.

NExT Program Support: Chemical Biology Consortium Technical Project Manager

The NCI Experimental Therapeutics (NExT) Program is a cancer drug discovery and development pipeline established by the NCI Division of Cancer Treatment and Diagnosis (DCTD) in conjunction with the NCI Center for Cancer Research (CCR). Its vision is to bring promising drugs to patients more rapidly by streamlining NCI's anticancer drug discovery and development resources under a unified governance structure. The Chemical Biology Consortium (CBC), launched in 2009, is a component of NExT and its discovery engine, charged with facilitating the discovery of first-in-class drug candidates for preclinical and clinical development within NExT. Following the formation of the CBC, the Functional Biology Working Space (FBWS) was created within NExT to provide this NCI program with the biological expertise and capability to functionally decipher cancer-specific genomic aberrations discovered through various human genomics programs, such as The Cancer Genome Atlas (TCGA) and The Therapeutically Applicable Research to Generate Effective Treatments (TARGET), with emphasis on the discovery of novel druggable targets and the development of target-specific assays that may be adapted to drug screening. The CBC is an integrated network of centers selected from government, academia, nonprofit, and private sector organizations recognized for collective expertise in molecular oncology, therapeutic target discovery and validation, specialized biochemical and cellular assays, state-of-the-art high-throughput screening technologies, biophysics and structural biology, and medicinal and synthetic chemistry. Eleven of the twelve currently designated CBC Member Centers are Leidos Biomedical Research subcontractors. Leidos Biomedical Research is also a CBC participant.

The CBC Technical Project Manager (TPM) Group in the NExT Program Support coordinates and facilitates the applied biology and chemistry technical tasks related to drug target validation and drug discovery efforts within the NExT-CBC and FBWS, particularly in the areas of therapeutic target validation, high-throughput screening assay development and implementation, secondary and tertiary confirmatory assays, mechanism of action functional assays, structural biology, and medicinal and synthetic chemistry for iterative drug design and synthesis, leading to optimization and eventual drug candidate identification. These tasks are undertaken by competitively selected subcontractors, such as basic ordering agreement holders and contract research organizations. Once new CBC projects are approved to enter the NExT pipeline, the CBC TPM staff is tasked with developing the relevant technical documents required for project planning and implementation, evaluating and negotiating technical proposals submitted by subcontractors, and making recommendations on subcontractor selection. For the ongoing CBC projects, the TPM staff duties include monitoring and evaluating subcontractors' technical progress; communicating with the technical point of contact about the assigned tasks;

assisting with the resolution of technical problems encountered during performance; providing task management and task reporting for the project teams; and facilitating and managing project team access to the shared resources. In addition, TPM staff also serves on the NExT project teams. With the recent completion of the ARRA-funded FBWS initiatives, new NExT projects aiming to functionally validate therapeutic targets will be integrated into the CBC project portfolio. Significant achievements are summarized below.

CBC Compound Registration and Project Data Capture: The CBC Chemistry TPM Group continued to provide technical support to the NExT Program initiative on the CBC compound submission and registration system. The system has achieved significant enhancements in speed, convenience, and compliance by the CBC Centers for compound submission to the NCI-Chemotherapeutics Agents Repository. In accordance with NCI direction, the TPMs have led efforts to capture and streamline project data flow from the CBC Centers to NCI. In conjunction with this effort, the TPMs continue to refine and improve data-surfacing capabilities by using, and receiving training on, D360, a data retrieval and analysis tool that has been made available to the NCI staff and all CBC Centers.

NExT Program Support: The Biology and Chemistry TPM Groups have implemented a contractor performance review that allows comprehensive technical assessments of the CBC basic ordering agreement holders. The reviews are based on technical performance, science management, and business operations. The group has also assisted NCI senior management in identifying technical gaps within the CBC. This assessment was critical in formulating a plan for CBC version 2 (CBCv2). A significant endeavor is under way to develop a Request for Proposal (RFP) for the NExT CBCv2. The RFP for CBCv2 is a collaborative project between NCI, and the Leidos Biomedical Research NExT Program Support Group, Research Subcontracts, and Project Management Office.

NExT CBC Project Support: The Biology and Medicinal Chemistry TPM Groups have provided scientific and technical project management support for 10 active NExT projects (see Table III) that are operating at the various CBC Centers. During the reporting period, one new project was initiated (WDR5-MLL1).

Table III

	Project Name	CBC Centers	Project Stage	Status
1	AAA ATPase p97	UCSF, UPCDC	SDS & LI	Active
2	Artemis Endonuclease	SBP, SR, SRII, UPCDC	ESD	Active
3	ATG4B	SBP, UCSF, UPCDC, SR	ESD	Active
4	GBM-PPI	Emory, UCSF	TAF	Active
5	IDH1	NCATS, UNC	SDS & LI	Active
6	KDM5A/B	Emory, NCATS	ESD	Active
7	LDHA	NCATS, SR, VCDC	SDS & LI	Active
8	Mcl-1	VCDC, NCATS	SDS & LI	Active
9	Taspase1	UCSF, VCDC, SRII	FB-SDS	Active
10	WDR5-MLL1	VCDC, NCATS	SDS & LI	Active

CBC Centers: Southern Research Institute (SR); Sanford Burnham Prebys Medical Discovery Institute (SBP); SRI International (SRII); University of Pittsburgh Chemical Diversity Center (UPCDC); Emory University (Emory); University of California San Francisco (UCSF); National Center for Advancing Translational Sciences (NCATS); University of North Carolina (UNC); Vanderbilt Chemical Diversity Center (VCDC); Georgetown University (GU); University of Minnesota (UMN); University of Pittsburgh Specialized Applications Center (PSAC).

Project Management Office

The Project Management Office plays an integral role in supporting the drug discovery and development efforts at NCI by integrating standardized, business-focused project and portfolio management practices and tools into existing drug discovery and development programs. One of these programs is the NExT Program, which consists of drug discovery projects from the Functional Biology and Chemical Biology Consortia. The Functional Biology and Chemical Biology Consortia are major new drug discovery initiatives designed to increase the identification/validation of drug targets and the flow of early stage drug candidates into NCI's drug development pipeline. By working with the biopharmaceutical industry, academic centers, project leaders, and teams of scientists/clinicians from NCI, the Project Management Office supports the rapid discovery and development of small-molecule drugs and biological therapeutic agents (proteins and monoclonal antibodies) for the treatment of a variety of cancer types.

Significant Achievements

- The Project Management Office continued to provide project management and administrative support for NExT Program drug discovery and development projects, including monthly project meetings, biweekly Senior Advisory Committee (SAC) meetings, quarterly CBC Steering Committee meetings, portfolio reviews for quarterly Special Emphasis Panel meetings, weekly meetings for the

Clinical Pharmacodynamics – Biomarkers Program, and monthly meetings for the In Vitro Evaluation and Molecular Pharmacology Program.

- The office supported the review of 46 different applications from three review cycles in FY2015.
- The office oversaw completion of 13 projects and initiation of 15 new projects, with an overall increase in the NExT portfolio from 68 to 70 projects and with the number of project managers at five (the Developmental Therapeutics Program assigned two NCI employees at 50 percent effort each towards project management).
- The office continues to refine the NExT Portal (the DCTD SharePoint site for portfolio/project management collaboration and document/data storage/retrieval) and has initiated five cross-project initiatives.

Medical Writing Unit

The Medical Writing Unit (MWU) provides scientific writing and clinical protocol support to DCTD. Its primary functions are to write and submit clinical protocols and informed consent forms for Cancer Therapy Evaluation Program (CTEP) and NCI IRB review and approval, and to write and publish preclinical and clinical manuscripts arising from DCTD research activities. In addition, MWU prepares documents (abstracts, meeting summaries, PowerPoint presentations, pamphlets, posters, and notification letters) for the DCTD Developmental Therapeutics Clinic (DTC), the DCTD Pharmacodynamics Research Group, and the NExT Program. Specific activities are summarized below.

- MWU currently supports 29 Phase 0/I/II clinical protocols for DTC. In the past year, MWU efforts have resulted in four new protocol approvals, including the multicenter tissue procurement protocol to support the Patient-Derived Models Initiative. Three new protocols are undergoing regulatory review. Also submitted for CTEP/IRB approval were 26 protocol annual continuing reviews and more than 60 amendments.
- MWU provided scientific writing, data analysis, and editorial support for six published manuscripts, as well as five manuscripts that have been accepted for publication, four manuscripts that are in late-stage development, and two posters for the American Association for Cancer Research (AACR) and the American Society of Clinical Oncology (ASCO).

Cancer Diagnosis Program

Support Provided by the Clinical Research Directorate

Biospecimen Research Group

Genotype-Tissue Expression (GTEx) Scale-up Phase II

The Common Fund's Genotype-Tissue Expression (GTEx) program aims to study human gene expression and regulation in multiple tissues, providing valuable insights into the mechanisms of gene regulation and, in the future, its disease-related perturbations. Leidos Biomedical Research has provided project management and operational support to the GTEx project for four years. The GTEx Scale-up phase successfully met its final accrual goal of reaching 901 post-mortem cases, including 408 brain cases, by August 2015. The Biospecimen Research Group (BRG) supported GTEx Scale-up phase II in fiscal year (FY) 2015 through frequent detailed reporting, project management, subcontract management, pathology review and qualification of all tissue, and quality-directed audits of the collection sites at Roswell Park Cancer Institute and the National Disease Research Institute (NDRI). Publications on the Comprehensive Data Resource, pathology findings, and operations are being written. The GTEx program made the cover of *Science* on May 7, 2015, and many Leidos Biomedical Research employees were included in the authorship list. The NIH GTEx Symposium was held, and BRG gave a talk on the management and quality efforts of supporting GTEx.

In addition, the Ethical, Legal, and Social Implication (ELSI) Study continues to explore family decision maker comprehension of bio-banking research and areas where consent administrator training impacts recollection and consent rate. Another key part of the GTEx ELSI sub-study is community engagement, and the project includes input from two Community Advisory Boards, one of which focuses on issues affecting the Hispanic community. This research has already produced a manuscript, which was published in *Genetics in Medicine,* and three other manuscripts are planned in the future.

Genotype-Tissue Expression Encyclopedia of DNA Elements Project

The GTEx program team executed the GTEx Encyclopedia of DNA Elements (GTEx-ENCODE) project in FY2015, which entailed the collection of up to 26 tissue aliquots from up to 29 tissue types from four non-brain post-mortem donors procured from the Organ Procurement Organization setting through the BRG subcontractor NDRI. The tissue was frozen in liquid nitrogen vapor phase and then routed through the Comprehensive Biospecimen Resource at the Van Andel Institute for receipt at the Broad Institute. A full PAXgene-preserved GTEx case was also

collected from the same donors. The work was defined, subcontracted, and closed out on schedule in FY2015.

Biospecimen Pre-Analytical Variables Program

The Biospecimen Pre-Analytical Variables (BPV) program witnessed unprecedented success in achieving very aggressive goals for 2015. A systematic approach to annotating all possible deviations during tissue collection and processing at four tissue collection sites for different cancer types (kidney, colon, ovarian, and lung) created a sample bank with rich metadata. The sample bank was utilized immediately for downstream molecular analysis, and it ultimately uncovered the effects of pre-analytical variables on different analytes using a variety of analysis platforms, such as protein-based analysis using mass spectrometry and immunohistochemistry; DNA-based analysis using aCGH, exome sequencing, and methylation analysis; RNA analysis via transcriptome sequencing, miRNA sequencing, and nanoString technologies; and plasma-based research using Luminex and mass spectrometry. In addition, a thorough quality control analysis was conducted on nucleic acids extracted from tissue specimens that were subjected to various pre-analytical conditions. Contracts were executed to conduct metabolomics studies to evaluate the impact of pre-analytical factors on metabolite profiles in plasma samples. The findings from some of these studies were presented via multiple posters and podium presentations at American Association for Cancer Research (AACR) and International Society for Biological and Environmental Repositories (ISBER) annual meetings this year.

In addition, a successful on-site summit was conducted by the program to foster collaboration between cross-platform molecular analysis and biospecimen procurement teams, Leidos Biomedical Research, and NCI. The BPV program also included an ELSI sub-study that focused on donor comprehension and acceptance of biobanking research programs. This research has yielded surprising findings that should be an important contribution to the field. Preliminary results from one of the sites (Emory) have already been presented at the American Society of Clinical Oncology meeting. The research team is currently preparing a primary manuscript focusing on the data results, which is to be followed by a conceptual manuscript that contextualizes the groundbreaking results from the study.

Developmental Therapeutics Program

Support Provided by the Biopharmaceutical Development Program

Process Analytics

Process Analytics (PA) functions both as a method development laboratory that interacts directly with project scientists and customers during the feasibility and development phases of a project and as a current Good Manufacturing Practices (cGMP)–compliant testing laboratory for facility environmental monitoring, raw materials testing, in-process testing, non-clinical and clinical product QC testing. During this reporting period, PA processed approximately 8,050 samples from approximately 1,150 unique test requests. One lot each of lyophilized rhIL-15, Tetanus-CMV peptide, PVS-RIPO, and PVS-RIPO MVB manufactured under cGMPs were analyzed by PA during the reporting period. The PA group also continued to support serious adverse event (SAE) and product excursion testing for the rhIL-15 and HuMikβ1 studies, as well as supporting rapid stability testing for the ganitumab MAb project in response to Health Canada. During the reporting period PA conducted studies to re-certify bulk drug substances from external manufacturers (TA-CIN); continued to provide supplemental support for a Cooperative Research and Development Agreement (CRADA) with United Therapeutics Corporation (UTC) for monoclonal antibody ch14.18 which received FDA and EMA licensure approvals during the reporting period; and demonstrated the compatibility of products based on clinical administration protocols (HSV-C134, Panitumumab-IRDye, rhIL-15). During the reporting period, the PA laboratory staff supported the Lyophilized rhIL-15, Tetanus-CMV peptide, RLIP76, TA-CIN/GPI-0100, Panitumumab-IRDye800CW, PVS-RIPO second clinical lot and new Master Viral Bank (MVB), mrhIL-7, and HSV-C134 projects, in addition to ongoing stability testing of 47 clinical product lots.

PA staff members also continued to act as project scientists for several new and legacy projects. The PVS-RIPO, Lyophilized rhIL-15, ganitumab, Panitumab-IRDye800CW, Tetanus-CMV peptide, and RLIP76 projects have been the major focus of PA cGMP analytical efforts during this reporting period. In addition to testing and releasing four cGMP clinical drug products during the reporting period, PA scientists have developed several new analytical methods for pre-clinical development of RLIP76, including: SEC-HPLC, IEX-HPLC, RP-HPLC, SEC-MALS, DLS, imaged cIEF, Western blotting, gel analysis, peptide mapping MS/MS, activity bioassays, and a variety of other product characterization tests. The activity assay efforts with RLIP76 were extensive and included the de novo development of two cell-based Antioxidant Response Element (ARE) pathway methods, as well as a cell-based apoptosis assay for drug substance release testing. Analytical development efforts were also completed for the mrhIL-7 project, Tetanus-CMV peptide, TA-CIN/GPI-0100, and for the PVS-RIPO virus project, including the development of FDA-requested RT-qPCR and Illumina deep sequencing methods.

In order to support transfer of the PVS-RIPO viral manufacturing process to a third-party CMO, PA staff completed three Employee Invention Reports (EIRs), resulting in two US patent applications in 2015. PA also conducted early development activities for the RLIP76, MV-NIS, PTEN-long, EBV-Ferritin, and other

prospective new projects in addition to rapid analytical support activities required by the Tetanus-CMV project.

Product testing and certification during the reporting period. PA approved 15 assay profiles/master specifications, representing five projects, and 11 new or revised certificates of analysis (COAs), including the following:

New COAs for:	Revised COAs for:
Tetanus-CMV Peptide	Vero WCB
Lyophilized rhIL-15	PVSRIPO MC
PVS-RIPO MVB (New lot)	
PVS-RIPO Clinical (New lot)	
PVSRIPO Ref. Std.	

Operations

Because of the limited amount of labor resources available and in order to maximize those resources, Biopharmaceutical Development Program (BDP) operations comprises a pool of personnel available to perform a variety of operational tasks. Since the demands on different elements of technical operations (manufacturing, testing, and research and development) vary widely at any given time, the technical staff maintains broad expertise among the employees so that the expertise can be effectively utilized in a variety of capacities to meet the current demands of the NCI workload. The validation, environmental monitoring, water monitoring, and raw material testing duties are all performed by this labor pool. The same labor pool performs production operations, technology transfer, and scale-up, with specific personnel assigned duties based on individual skill sets. This approach presents significant planning challenges because a particular demand not only requires technical expertise for its performance, but also requires expertise in the support functions. Resources can be used more efficiently when these needs are properly balanced throughout the labor force At the same time, the organization continues to undertake a cross-training paradigm that provides maximum flexibility in adapting to NCI's changing needs. Other labor resources within the organization have been, and continue to be, cross-trained, so that each person's level of skill is appropriate for a given task. The cross-training gives BDP the ability to efficiently leverage labor resources at any given time, depending on the need for testing, development, or manufacturing activities. Noteworthy facets of this approach include:

- Establishing a framework for cross-training technical personnel in manufacturing, testing, and development activities to allow them to move seamlessly from one type of activity to another, providing maximum flexibility;
- Implementing automated systems to streamline processes and ease the burden of repetitive tasks performed by technical staff;
- Augmenting existing automated systems to improve information processing and retrieval;
- Establishing a framework for cross-training technical personnel in quality assurance (QA) activities, such as validation and auditing, to further diversify their skill sets and take full advantage of the available labor resources; and
- Utilizing new perspectives to enhance efficiencies, as people from different backgrounds are tasked with learning new skill sets.

The same can be said of the nontechnical side, though to a lesser extent, because the nontechnical side represents a smaller and more directed pool of expertise. Nonetheless, the same labor skill diversification paradigm has been applied. BDP is leveraging existing expertise available from support services on an as-needed basis, as opposed to maintaining in-house, dedicated expertise in a variety of areas. This approach includes:

- Working in concert with and relying on Facilities Maintenance and Engineering (FME) to perform more repetitive tasks, and simply overseeing these activities;
- Working in concert with and relying on Data Management Services (DMS) to perform more repetitive tasks, and simply overseeing these activities;
- Commissioning DMS to implement improved solutions for performing more repetitive tasks so that they require less intervention;
- Freeing up internal IT resources by off-loading routine IT tasks to an outside entity. This shift allows staff to focus on organization-specific tasks, thereby improving IT infrastructure rather than simply maintaining the status quo; and
- Cross-training staff where possible, to re-establish the redundancies lost by reducing dedicated in-house staff.

Development

Mammalian IL-7 development was conducted during this period via both transient and stable expression systems. In the former, the process for cell growth, transfection harvest, and downstream purification was optimized. The process has been scaled up, and a 100 mg (product yield) run will take place from July to September. For the latter, three stable clones have been brought forth, and stability assessment made up to 15 generations.

A PTEN-Long generated by a principal investigator was evaluated in-house. Because of the level of remaining endotoxin, it was decided not to proceed toward cell-based assays with this material. In-house work has been initiated toward *Escherichia coli* expression to be followed by generation of endotoxin free purified protein.

National Center for Advancing Translational Sciences project RLIP76 was conducted from March through August . A codon-optimized plasmid in a BL21AI host was put in fermenter, and the cell paste was taken

through a sequential purification process. The optimized downstream process was biochemically characterized. This phase of the work, designated as Milestone 1, was described in reports related to the process and characterization of the product.

Biopharmaceutical Quality Assurance and Regulatory Affairs

BDP maintains a quality system that is compliant with FDA requirements for manufacturing Phase I, II, and nonpivotal Phase III investigational products. QA responsibilities are distributed between the QA staff and the administrative and technical operations staff. We continue to evaluate our quality systems and investigate ways to improve efficiency while maintaining quality with significantly reduced resources.

The BDP is fully operational at the Advanced Technology Research Facility (ATRF). Because of resource limitations, the eight manufacturing suites are maintained but only those in use are monitored. It takes two to six weeks to ready a suite for GMP manufacturing.

Multiple products manufactured by the BDP are now in late-stage clinical trials and/or undergoing commercial licensure activities. The FDA approved the commercial licensing of ch14.18 (now known as dinutuximab, generic name, and Unituxin, brand name for UTC on March 10, 2015. The BDP was intimately involved with this project since 1997. Eleven lots of ch14.18 were manufactured at the BDP for preclinical and clinical studies. Both the BDP-supplied product and the assistance that BRB and BDP personnel provided to UTC were significant factors that led to FDA approval. The EMA has recommended approval. Upon the imminent agreement by the European Commission, dinutuximab will be commercially available in the European Union.

QA Auditing releases product for clinical and toxicological use, and provides compliance oversight of BDP cGMP production, testing, and support operations (including conducting internal audits to ensure compliance with cGMP), as well as external contract manufacturing and testing facilities.

QA Auditing approved product release documentation for four final vialed products for human clinical trials and one master viral bank for cGMP manufacturing use. To accomplish this, QA reviewed 8 master production records, 50 batch production records, 7 master specifications, and 11 COAs, and conducted 5 in-process audits of critical manufacturing operations.

QA processed approximately 2,000 documents to support various BDP cGMP, Good Laboratory Practice (GLP), and laboratory activities. QA continues to process and track more than 25 types of documents. Improvements in database systems continue to be evaluated to increase efficiency.

Products Manufactured and Released by BDP

cGMP Product	Lots	Vials
Panitumumab-IRDye FVP	1	292
IL-15 FVP	1	2,630
PVS-RIPO FVP	1	1,656
TET-CMV	1	628
PVS-RIPO MVB	1	53
Total	5	5,259

Quality Engineering and Validation

Quality Engineering and Validation (QE&V) oversight of facilities, utilities, equipment, and related supporting activities is performed by our quality engineer. This includes managing the equipment calibration program and ensuring that facilities, utilities, equipment, and supporting activities are suitable for use. Other QA and technical operations staff assisted with the calibration data review, environmental excursions, and authorship and execution of validation protocols to minimize the huge workload on one individual. Priority is given to those pieces of equipment and processes related to upcoming and critical operations. Requalification of systems is performed by the BDP. Utilizing shared resources for manufacturing and validation takes careful coordination.

QE&V has been instrumental in maintaining ATRF operability and validation. This requires coordination of BDP technical labor resources and FME staff for calibration, preventative maintenance, and repair. Qualification and validation for utilities and all classes of equipment have been executed. Quality monitoring of utilities has demonstrated that the facility and utilities operate in full conformance with FDA requirements.

Despite significantly reduced resources, the large workload was able to be scheduled and prioritized to allow production activities to proceed on schedule.

Regulatory Affairs

Regulatory Affairs (RA) provides regulatory agency submission documentation to describe the manufacture and testing of BDP products to meet regulatory requirements. Submission strategies and regulatory guidance are provided to expedite regulatory agency review and move products into clinical trials.

Regulatory support was provided for eight BDP products. Key documents were prepared for submission to regulatory agencies, including Chemistry, Manufacturing, and Controls (U.S. CMCs), Clinical Trial Application (CTA) CMCs (Health Canada), responses to regulatory agency questions, and related documents. Additional support for the tracking of stability data and annual reports was provided for 26 products.

Major achievements this year have included regulatory support for the ch14.18, ganitumab, panitumumab-IRDye, TA-CIN (HPV16 L2E7E6 fusion protein), and the PVS-RIPO projects. UTC

received marketing approval for ch14.18 by the FDA in March for the treatment of pediatric patients with high-risk neuroblastoma. Approval in Europe is pending. Investigational New Drug (IND) applications were cleared to start for panitumumab-IRDye (an intraoperative agent for the detection of EGFR-expressing head and neck squamous cell carcinoma) and TA-CIN (for head and neck cancer) in the U.S., and a CTA was cleared to start in Canada for ganitumab for the treatment of patients with Ewing sarcoma. CMC support and technology transfer are under way for the PVS-RIPO treatment for glioblasoma.

RA continues to maintain a facilities drug master file (DMF) that is on file with the FDA for the ATRF facilities. This document describes the facilities, utilities, and critical process flows used in the manufacture of BDP products.

Support Provided by the Applied and Developmental Research Directorate

Natural Products Laboratory

The Natural Products Support Group provides services to the Developmental Therapeutics Program (DTP), DCTD, NCI. The Extract Production Lab carries out all grinding, extraction, drying, and freeze-drying of plant, marine, and fungal biota specimens. The Fungal Metabolites Lab performs fermentations for screening, assures culture purity, performs cryo-preservation of fungal stocks, optimizes titration of bioactive metabolites, produces co-cultures to search for new compounds, and carries out scale-up fermentations for drug production. The Drug Processing Lab weighs pure chemicals and extracts; produces both 96-well and 384-well microtiter plates of extracts and pure drugs for anticancer screenings; ships and receives extracts, drugs, and plates; develops solubilization methods; and processes and delivers extracts and drugs for animal testing. The Natural Product Chemistry Laboratory provides analytical support; purifies compounds of interest for testing; identifies new natural products; makes chemical modifications of compounds with biological activity; and performs scale-up isolations of compounds of interest to DTP for further biological evaluation.

Extract production and drug processing

During FY2015, new extract production totaled 1,232 (34 plant, 304 marine, and 894 fungal extracts). Plating of new extracts gave 17 new plate maps, which increases the screening library to 2,492 unique plates. More than 1,500 microtiter plates were produced.

In support of the NCI-60 primary anticancer screen, sample preparation was 480 total test slots (one-dose equivalents) per week. Drug preparation support to in vitro anticancer testing totaled 1,241 compounds for multidose 60-cell testing and 11,943 compounds for one-dose 60-cell testing. Specialty plate production requests, such as combination studies (6 drugs in 12 combinations) decreased, and special requests, such as nonstandard vehicle or dilution sequence compounds, increased this year. Overall, there has been an increase in natural product testing, with more than 50 percent of capacity committed to testing natural product extracts and fractions for Biological Evaluation Committee (BEC) projects.

In support of DTP in vivo anticancer, there were 108 synthetic experiments (260 drugs tested in 7,207 dosing vials) and 1 natural product experiment (1 drug tested in 18 dosing vials) prepared. Solubility studies were conducted on 38 synthetic products and 1 natural product.

Fungal Metabolites Laboratory

The Fungal Metabolites Laboratory (FML) provided 536 microbial extracts from 180 organisms, resulting in over 400 liters of fermentation broth:

Routine fermentations: The laboratory produced 468 extracts from 156 organisms (351 liters of fermentation broth).

Special fermentation requests: Sixteen regrows were requested by Dr. Paula Watnick of Harvard Medical School; all were grown at 3 L each (48 L of fermentation broth). Twelve regrows were requested by Dr. Anna Mandinova of Massachusetts General Hospital; five will be regrown by the end of September 2015 at 2 L each (10 L of fermentation broth).

BEC-related large-scale grows: Three large-scale grows (35 L of fermentation broth) were conducted to support the isolation of biologically active microbial natural products for anticancer testing and mechanism studies.

Natural Products Chemistry Laboratory

The laboratory completed a prefractionation pilot study that involved the generation of more than 1,800 natural product fractions sourced from the NCI Natural Products Repository. The pilot study was part of a DTP/CCR proposal for a comprehensive natural products–based screening platform, with the aim of generating a library of 1,000,000 fractions available for high-throughput screening. The Natural Products Support Group pilot study involved representative examples of plant, marine, and fungal biota, examined nine different solid-phase extraction adsorbents with eight different solvent systems, and produced more than 1,800 natural product fractions.

The laboratory purified and delivered four grams of the natural product silvestrol in support of a DCTD NExT project. Starting from 60 kg of plant biota, over four chromatographic steps, 4 g of 98.5 percent pure silvestrol has been isolated in a single lot.

The laboratory investigated 33 natural product extracts for the isolation and identification of anticancer active natural products, as requested by the BEC.

In Vitro Evaluation and Molecular Pharmacology

In Vitro Screening Group

The In Vitro Screening Group comprises the NCI-60 Screening Lab and the Target Validation and Screening Lab. The NCI-60 Screening Lab is responsible for running supplied samples against 60 cancer cell lines to identify valuable compounds for development as anticancer agents.

NCI-60 cell line screen: The aim of the NCI-60 screen is to identify, for further evaluation, synthetic compounds and natural product samples showing selective growth inhibition or cell killing in specific cell lines in the NCI-60 cell line. The screen can also be used to evaluate drug combinations in order to identify those that produce an additive or synergistic effect on tumor cell line growth and survival.

The NCI-60 screen consists of a three-step testing process that starts with an initial single-drug dose screen against all 60 cell lines. Drugs that show activity in the one-dose assay are retested in a five-log-dose concentration test. The results of this assay are used to determine if the drug is selected for a second confirmatory five-dose assay. Specific achievements are summarized below:

- The NCI-60 Screening Lab performed testing on 2,304 drug plates containing either two five-dose samples or ten one-dose samples.
- The lab performed one-dose testing on more than 4,797 new synthetic compounds and 6,696 natural products. These assays also included more than 1,277 of the internal drug standard that is included in each one-dose testing plate.
- The lab tested more than 556 synthetic compounds, 485 natural products, 18 combinations, and 39 internal drug standards in the five-dose screen, with more than 92 compounds submitted for the confirmatory five-dose assay.
- The lab provided more than 81 lines and prepared 80 96-well plates with cells for use by other DTP support laboratories.
- The lab prepared more than 302 sample lines that are available for testing to verify the identity of cells.
- The lab prepared 54 vials for a new working seed stock for CAKI-1.
- The lab prepared and shipped one set of 60 cell lines of RNA and three flasks of viable cells to investigators approved by the DTP Molecular Targets Committee.

Target Validation and Screening Group

- The group undertook development of new in vitro models that may better predict the activity of compounds being screened and may improve the success rate for demonstrating the activity of these agents in vivo. The group also evaluated multiple platforms that could be used to develop multicellular tumor cell spheroids. These platforms included hanging-drop plates, microengineered plastic plates, and ultra-low adhesion plates and flasks. The ultra-low adhesion plates and flasks proved to be the most effective at producing spheroids in culture. The group utilized this approach to demonstrate the ability to form spheroid cultures for all of the NCI-60 cell lines. Many of the NCI-60 lines formed condensed spheroids with demonstrated necrotic cores, while others formed loose aggregates. To assist with these studies, the group acquired several instruments designed to perform 3D cell printing and high-content screening to allow imaging of the multicellular tumor cell spheroids in culture and after treatment with compounds of interest. The group utilized these new techniques to evaluate PDX cell lines for behavior in culture, both as tumor cells alone or in co-cultures with stromal cells. The group evaluated the drugs being used in the Metastatic Pancreatic Adenocarcinoma Clinical Trial (MPACT) on these models to determine correlations in results. Conditions have been defined that seem to provide excellent correlations between the data obtained with compound treatment of these tumors in vivo and the results observed with these spheroids in vitro. Over the next 12 months, efforts will continue to expand the observations across multiple PDX lines. To assist with these studies, a robotics high-throughput screening platform was recently installed that will allow for automation of the compound screens in standard assays using the spheroid cultures. The platform allows both end-point assays and HCS assays to be performed on the samples.
- The work in spheroid assay development, highlighting the pros and cons of each of the methods that the group had tested, was presented at the Society for Lab Automation and Screening in Washington, DC, in February in an invited podium presentation.
- A manuscript based on the sarcoma screening data generated by the group has been submitted for publication and is currently under review. A manuscript based on the data obtained from the small-cell lung cancer (SCLC) screening data is in preparation for submission. The data from the sarcoma cell line screen and the SCLC cell line screen will be available to external researchers via separate public-facing websites that are currently in development. External researchers will be able to use the data from the compound screens along with the genomics data to develop and test novel therapeutic hypotheses.

Molecular Pharmacology Group

The mission of the Molecular Pharmacology Group is to evaluate the molecular responses of well-annotated patient-derived model cancer cell lines (PDM lines) to specific regimens (i.e., MPACT drugs: trametinib,

everolimus, a combination of temozolomide and ABT-888, and a combination of MK1775 and carboplatin). Our mission is addressed by altering the expression of specific targets using cutting-edge techniques (i.e., clustered regularly interspaced short palindromic repeats [CRISPR]/Cas9) to identify the molecular pharmacology responses that determine sensitivity to specific therapeutic agents, and by analyzing signaling pathways in response to specific treatments in 2D and 3D cultures of original and edited lines. The laboratory has the ability to support validation and modulation of genes and target proteins when deemed necessary. The laboratory also has molecular biology experience and expertise in the cellular micro-environment, and with hypoxia and cell manipulation.

RNA-guided genome engineering using the CRISPR-Cas9 system has yielded an unprecedented ability to perform site-specific editing in a variety of genomes. Target-site recognition by Cas9 is programmed by a chimeric single-guide RNA (sgRNA) that encodes a sequence complementary to a target protospacer, but also requires recognition of a short neighboring sequence (PAM). The group is taking advantage of a lentiviral-based, doxycycline-dependent system to be able to introduce Cas9 in difficult-to-transfect lines and express Cas9 in an inducible fashion. Using this system, the group is creating plastic PDM platforms that are amenable to any editing of choice following the introduction of a specific sgRNA to the target of choice and the induction of Cas9. This process involves generating and characterizing clonal lines expressing Cas9 that resemble the original PDM model for growth and activation of signaling pathways of interest. These clones are then used to introduce the editing of choice. Editing of specific targets involves the in silico design of several sgRNA sequences using available algorithms; validation of sgRNA sequences in a reference line by measuring the formation of indels (insertions/deletions) in the targeted genomic loci; generation of lentiviral vectors harboring sgRNA sequences; and infection of PDM plastic platforms. At this point, Cas9 is induced by doxycycline treatment, and indel formation is assessed. PDM-edited pools are then cloned by limiting dilutions, and edited clones are identified and characterized.

Significant Achievements

- The group developed and characterized eight PDM plastic platforms (two PDM lines with either wild-type Cas9 or Cas9-nickase; two clonal lines per model/Cas9) that are ready for gene editing. Wild-type Cas9 is very efficient at creating indels, although these are random events and desired editing is not guaranteed. Cas9-nickase, on the other hand, is less efficient than wild-type Cas9 (since it needs two Cas9n–sgRNA complexes targeting different sequences to generate an edit), but it has shown less off-target edits and is more suitable for precise gene manipulation using donor DNA (i.e., introducing or repairing mutations).
- The group generated and validated four to six different sgRNA sequences in two lentiviral backbones targeting three genes of interest (ATM, ATR, and PRKDC). These sequences are specifically designed to generate kinase-dead variants of ATM, ATR, or DNA-PK. One of the PDM plastic platforms has been used to create ATR or ATM kinase-dead clonal lines in order to evaluate the relative contribution of these targets to specific regimens. Clonal lines are currently undergoing characterization.
- The group evaluated DNA damage responses in two PDM models following treatment with topotecan, UVC, or temozolomide. DNA damage response signaling was evaluated in parallel in 2D and 3D cultures (monolayers on plastic versus spheroids generated in ultra-low attachment (ULA), 96-well plates). 3D cultures generated using ULA plates give rise to very limited amounts of protein lysates for use in detecting targets of interest; therefore, the group took advantage of Simple Western (WES) by Protein Simple, a new technology that allows for the separation, blotting, and detection of proteins in a similar manner to traditional Western blotting, except that the blotting is performed in a capillary format and uses limited amounts of samples. Using this technology, the group was able to compare ATM, ATR, and DNA-PK protein expression and activation in 2D and 3D cultures following DNA damage.)

In Vivo Evaluation Group

The central mission of the In Vivo Evaluation Group involves developing a repository containing approximately 2,000 PDMs. These PDMs will encompass 75-100 cancer subtypes derived from patient biopsies/resections and circulating tumor cells (CTCs) isolated from blood samples. Ultimately, this repository will contain both tumor fragments and in vitro cell cultures (extending also to paired cancer-associated fibroblasts).

In order to scale material, first-generation xenograft tumors from patient material are re-implanted into at least 10 new NSG mice. The goal here is to bank at least 250 vials containing tumor fragments from each "xenopatient," to accommodate future demand from extramural investigators. Material is also either flash frozen or fixed in 10 percent buffered formalin or OCT media to accommodate hematoxylin and eosin staining/pathology and microarray/DNA/exome analyses. As a matter of routine, each model will (1) undergo histopathologic analysis relative to the original patient tumor; (2) be examined by PCR for the percentage of mouse tissue present; and (3) be screened for the presence of mycoplasma and mouse/human pathogens. Additionally, provided that the model has been delinked from patient identification information, samples will be subjected to cDNA microarray and NGS assays, along with confirmation of patient origin using short tandem repeat analysis.

With regard to establishing in vitro cultures for each model, several approaches are being evaluated in order to maximize viability and maintain heterogeneity. These include utilizing different matrix supports, growth factors, and media with serum or serum replacements. To establish primary cell cultures, tumor fragments are subjected to collagenase digestion, or a small piece of biopsy/resection is placed directly onto the Matrigel. In addition to isolating tumor cells, the In Vivo Evaluation Group also isolates and purifies corresponding cancer-associated fibroblasts. Flow cytometry using antibodies against human HLA-A, B, C, mMHC class I, CD9, mCD9, CD90, EpCAM, and CD24 provides initial information regarding the level of mouse contamination and, more importantly, the level of human tumor or fibroblast cells in the sample. Based on the flow cytometry data, appropriate fluorescently labeled antibodies are selected to label the cells of interest, and the cell mixtures are then sorted using a BD FACSAria cell sorter to purify the cell population(s) of interest. Depending on the level of purity, the initially sorted cells may require multiple rounds of sorting. Human cells (including both tumor and fibroblast populations) are then expanded and subjected to a further round of fluorescence-activated cell sorting (FACS) analysis to evaluate purity. Additionally, clonal populations of cells are established from the heterogeneous tumor cultures using a soft agar assay.

All purified cultures undergo QC before inclusion in the repository. QC involves FACS analysis, qRT-PCR (for mouse contamination and confirmation that the culture is a tumor or fibroblast), and short tandem repeat analysis (if delinked from the patient) to confirm identity. QC occurs following initial purification, at passage 10 and finally at passage 20.

Tumor cell culture contamination with as little as 0.5-1 percent fibroblast or mouse cells is sufficient for eventually outcompeting some tumor cultures. Thus, while early passage tumor cultures are frozen back, a representative sample is maintained in culture for 10 and 20 passages for QC analysis. If the sample is noted to contain mouse or fibroblast cells, the sample will then undergo sorting to remove the contaminant and, in some cases, purify the associated human fibroblasts. Since fibroblasts have a finite life span in culture, purified fibroblasts are grown for five passages, and a sample is sent for QC before the final freeze for the repository. If the culture fails QC, it is then sent for sorting and the process starts again. Note that all cultures, tumor or fibroblast, are frozen in the presence of Y-27632 (a ROCK inhibitor, also known as Y compound).

Cultures deemed pure then undergo further characterization for growth with or without the Y compound, for proliferation rate, and for ability to form spheroids. The cultures are also tested for rodent or human pathogens, mycoplasma, and sterility. For those tumors where it is difficult to determine a tumor from a fibroblast cell (e.g., sarcomas and mesotheliomas), a qRT-PCR array has been designed to examine cells for a fibroblast signature. All cultures are tested for their tumorigenic potential in vivo by implantation into NSG mice. Lastly, microarray analysis is performed. All information is then added to the PDM repository website and to the certificate of analysis for each sample. To date, there are certificate of analyses available for three JAX-mixed cell tumor cultures, three clones derived from one JAX tumor line, and three fibroblast lines derived from patient material received from IRB-approved sites.

The secondary mission of this group is the testing of potential anticancer agents in vivo. Agents are first evaluated in the hollow fiber assay and, if active, are further tested in appropriate human tumor xenograft models in nude or other immunocompromised mice, or in rodent tumor models. Along with these traditional models, this group also provides support to the Biological Testing Branch's (BTB's) efforts to develop and explore new, potentially more predictive rodent models for assessing experimental chemotherapy regimens.

Significant Achievements

- Assays developed in support of the PDX have undergone significant changes. Specifically, the preliminary FACS assay used to analyze PDX samples (in terms of mouse/human and fibroblast/tumor ratios) has been adapted to a plate format in order to improve sample throughput. The analysis pipeline has been improved so that more than 20 samples can be acquired and analyzed, and data can be reported in a single workday (a 50 percent improvement). In some mixed cultures, separation/identification of tumors remains a challenge (e.g., mesenchymal tumors that express both CD90 and CD9). To address this challenge, a qRT-PCR array, termed the surface scan array is under development. This technology interrogates 92 transcripts coding for cancer-associated plasma membrane proteins with available monoclonal antibodies. As such, samples can be rapidly screened to identify potential surface antigens that could be used in the context of cell sorting.
- From September 2014 through July 2015, the group implanted over 1,092 primary models from 747 patients. These specimens originate from the NCI Clinical Center and the 44 IRB-approved Cancer Centers, and include tumor biopsies/resections or CTCs isolated from blood (via ApoStream, Oncoquick, or a filtration method). The group also implanted five glioblastoma multiforme samples into mice. The group tested PDX models for growth in rats and implanted 45 models (9 completed and 36 in progress). In addition to receiving specimens from human clinical trials, material has been received from canine trials. The group currently has 12 canine-derived xenografts (from six "patients") growing in mice.
- The PDM repository currently contains 59 completed models derived from 34 patients from clinical sites

and 25 models from the material purchased from Jackson Laboratories (250 vials frozen for each). These models include 1 breast, 18 digestive/ gastrointestinal, 1 endocrine/neuroendocrine, 10 genitourinary, 4 gynecologic, 8 head and neck, 1 musculoskeletal, 17 respiratory/thoracic, 2 skin, and 2 unknown primary tumors.

- Drug efficacy studies using MPACT agents/combinations (trametinib, everolimus, temozolomide+ABT-888, and MK1775+carboplatin) are in progress in vivo for those PDMs evaluated to have actionable mutations of interest. To date, 21 studies have been completed, 3 are in progress, and 19 studies are in the queue.
- To date, five mixed cell cultures and three fibroblast cell lines have been deposited into the repository. This means that the distribution lots have passed the final QC, and tumorigenicity studies have been performed. All lots have now been distributed internally. A total of 70 additional mixed cell cultures and 151 fibroblast lines are at various stages of the characterization process, including growth with and without Y compound, clonal isolation (two rounds of soft agar cloning), FACS analysis, qRT-PCR, testing for spheroid formation in serum-free media, determining proliferation rates, microarray analysis, and short tandem repeat sequencing. During this reporting period, 56 tumorigenicity studies are either in progress or have been completed. There are now a total of 11 pairs of tumor and fibroblast cultures originating from the same patient material.
- The overall lack of success in growing CTCs in vivo and in vitro prompted studies to re-evaluate blood collection and CTC isolation methods. Normal human blood collected under multiple conditions was spiked with patient-derived tumor cells, and the blood/tumor cell mixture was stored for 24 hours (the time it normally takes to receive patient samples from the different cancer centers) at either room temperature or 4°C. Recovery and viability of the tumor cells were assessed via sorting on the FACSAria. Data from these studies showed that tumor cells stored in blood collected into EDTA vacutainer tubes (used by the clinical centers) had inferior viability as compared to heparin vacutainers. The centers have now been asked to change to heparin blood collection tubes. Next, several methodologies were evaluated for isolation of patient-derived tumor cells from blood. Two methods, a density centrifugation method and a filtration method, have been chosen for further evaluation in the isolation of CTCs from blood. These studies are currently in progress.
- During FY2015, over 94 xenograft studies using distinct tumor models were conducted to assess the antitumor activity of synthetic compounds, natural product extracts, and drug combinations. In addition, 155 synthetic compounds/natural product extracts were assessed for activity using the hollow fiber assay, and 119 synthetic compounds/natural product extracts were assessed for acute toxicity. Along with these, seven tumor growth assays, six tissue arrays, and five tumor target studies were performed.
- In-life support is also provided for multiple pharmacodynamic assays (19 performed during this reporting period), assessing the impact of several clinical and experimental agents on a variety of targets of interest to the clinical translation program. Additionally, 18 pharmacokinetic studies were performed for the pharmacokinetic group.

NCI Patient-Derived Models Repository

The overarching goal of the Patient-Derived Models (PDM) Repository is to develop more than 2,000 unique PDMs, including both patient-derived xenografts (PDXs) and in vitro patient-derived cell cultures (PDCs; tumor cultures and cancer-associated fibroblasts). Ideally, each common disease will be represented by 75–100 unique PDX models, representing the genetic landscape of that disease, to allow for in-depth molecular comparisons and efficacy studies. Starting material for model creation includes patient biopsies/resections and CTCs isolated from blood samples using ApoStream technology (PADIS), and novel techniques developed in the BTB. The repository will distribute all PDX and PDC models through a publicly available website, along with DNA, RNA, and protein pellets. The website will house a public-facing PDM database interface that will include extensive molecular characterization information, patient clinical history, and patient social history for all models. A key component of this repository is to make a set of standard operating procedures for all aspects of PDM creation, propagation, and quality control available to the public.

Significant Achievements

- The repository conducted bi-weekly operational meetings with NCI senior management, the BTB, and the Molecular Characterization Laboratory (MoCha) to discuss specimen tracking and analysis, coordinate preclinical trials using the models, and review progress towards creation of both PDXs and PDCs. To date, the repository has received 1,412 specimens from 957 patients (Figure 1A, Table I, see next page).
- The repository began receiving specimens through a Central Institutional Review Board (CIRB) Tissue Procurement Protocol (9846) [in addition to the DTC's Tissue Procurement Protocol (06-C-0213)]. This protocol opened in May 2015, and, through the recruitment of participating sites from the Experimental Therapeutics Clinical Trials Network and the NCI Community Oncology Research Program, there has been a greater than five-fold increase in monthly specimen intake (Figure 1B). Overall, a total of 15 Comprehensive Cancer Centers and 2 intramural clinics are recruiting patients through the 06-C-0213 protocol, and 23 lead academic organizations with

over 140 clinical centers are recruiting patients in the 9846 protocol. All centers are funded through NCI Administrative Supplements, and progress towards these supplements is tracked.

- The repository established a defined PDC workflow with key go/no-go definitions along the model development pathway. In addition, the repository worked with the in vitro group to establish how progress towards PDC development will be reported to NCI to improve transparency. The repository also instituted a master tracking sheet of all PDCs, and, in combination with the existing PDX tracking, progress towards creating both PDX and PDC models is easily reported.
- The repository completed preclinical modeling of the ongoing NCI-Molecular Profiling-Based Assignment of Cancer Therapy (NCI-MPACT) Clinical Trial in 12 PDX models, and modeling is ongoing in three more models. Models are assigned to one of four treatment arms (trametinib, everolimus, ABT-888+ temozolomide, and MK1775+carboplatin) based on the presence of actionable mutations of interest as defined in the clinical protocol; however, unlike the clinical trial, all treatment arms are run on every model for a full comparison of response. In addition, molecular characterization, including whole-exome sequencing and RNASeq, is carried out on the baseline models and at various points during the study to try to identify key pathways involved in response. To date, three models have had a complete response to ABT-888+temozolomide, and multiple models have had growth delays in response to several of the drugs. Analysis is ongoing by MoCha to try to identify commonalities in the models.

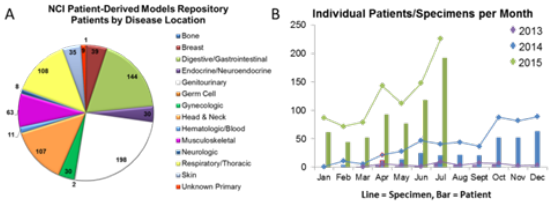


Figure 1. *(A) Representation of cancer diagnoses, divided by body location, that have been brought into the NCI PDM Repository. Numbers represent the total number of patients with the given diagnoses that have consented to provide specimens. (B) The line graph indicates the number of specimens (biopsy, resections, and blood) received monthly into the PDM Repository; bar graphs represent the corresponding number of patients enrolled. Both blood and tumor specimens can be collected from patients as part of the tissue procurement protocols.*

Table I

	# Specimens	# Patients
Overall	1,412	957
Since 9/1/2014	1,126	805

Patient enrollment and specimen (biopsy, resections, and blood) intake into the PDM Repository as of 7/28/2015.

Pharmacokinetics Laboratory

The Pharmacokinetics (PK) Laboratory supports the Office of the Associate Director, Developmental Therapeutics Program (DTP), and is responsible for providing information related to the preclinical chemistry and pharmacology of new anticancer agents identified by DTP. This information is then applied to developing methods for drug analysis that are used in the PK Lab to analyze samples from Phase 0 and Phase 1 clinical studies. Many of these clinical studies are first-in-human studies.

The analysis of drug candidates in biological fluids involves creating, applying, and validating a methodology for each drug candidate. Such efforts require extensive and specialized knowledge of analytical techniques, such as HPLC, LC-MS, LC-MS/MS, and LC-HRMS. Biological techniques covering metabolic processes (such as liver fractions, hepatocytes, and cell cultures) are employed to support in vivo findings.

Significant Achievements

- TdCyd (NSC 764274): The laboratory continued to improve and adapt methods of monitoring TdCyd and metabolites from a variety of sample matrices, including plasma, cell media, and DNA. Methods used to provide analytical support to various DTP branches/labs included the following: (1) the BTB, analyzing plasma and tumor samples in efficacy studies; (2) PADIS, analyzing in vitro samples, including determining global methylation status; (3) the Drug Synthesis & Chemistry Branch (DSCB), analyzing new analogues and metabolites (FtdU NSC 780926, ItdU NSC 780925, TdT NSC 776949, and TdU NSC 776952); and (4) Toxicology & Pharmacology Branch (TPB), analyzed samples and provided PK results from mouse, dog, and rat studies. These results were reported at working group meetings and used to support the IND filing of TdCyd for use in human trials. In addition to PK analysis and metabolism research, the laboratory conducted extensive cell studies on as many as 12 different cell lines, which provided information about optimizing doses, time of exposure, and toxicity of metabolites.
- *Methoxyamine and temozolamide combination trial (NSC 3801 and 362856):* The laboratory analyzed patient plasma and urine samples through seven dose escalations.
- *Paclitaxel and nilotinib combination trial (NSC 125973/747599):* The laboratory set up methods of analysis for paclitaxel and its major metabolites.
- *Rocaglamide project (NSC 326408):* The laboratory developed an analytical LC-MS method of analysis for determining and identifying rocaglamide and its metabolites in plasma and urine. The laboratory also conducted initial mouse PK studies and determined estimates of absorption, clearance, and modes of

metabolism, and analyzed samples from initial dog studies to determine clearance and modes of metabolism. These results were presented to team working groups and are being used to design further studies necessary for an IND filing.

- *Aza-TdC(NSC777586):* The laboratory developed a LC-HRMS method of analysis for Aza-TdC and its major degradation product. This method has been used to analyze Aza-TdC plasma levels in mouse studies, resulting in the discovery of good oral absorption and a lack of significant circulating metabolites. The method is being applied to determine Aza-TdC incorporation into DNA. Results from these studies have been presented to team working groups in order to further designs of studies aimed at an eventual IND filing.

Drug Chemistry Group

The primary objective of the Drug Chemistry Group is to provide the necessary medicinal and synthetic chemistry knowledge, expertise, and technical skill to support NCI's NExT Program as directed by the Division of Cancer Treatment and Diagnostics (DCTD), Developmental Therapeutics Program (DTP), and the Drug Synthesis & Chemistry Branch (DSCB).

NExT Program Support

Total synthesis of silvestrol: In a collaborative effort, NCI/DSCB and the Laboratory of Synthetic Chemistry (LSC) completed a total synthesis of silvestrol, a natural product derived from *Aglaia silvestris*. This is a high-priority NExT project and constituted a 28-step synthesis, with a reported overall yield of 1 percent. Numerous improvements in the synthetic yields and procedures were realized, resulting in the delivery of 3.5 g of material (with greater than 98 percent analytical purity) to support preclinical and clinical development needs. As a comparison, the isolation from natural resources required 60 kg of leaf and bark material to provide a similar amount.

Synthesis support of the Mcl-1 project: The group contributed to the project by providing synthetic support, which included constructing more than 5 g of intermediate that can be used to deliver the final drug material in 1–2 steps to support preclinical in vivo pharmacology experiments. A key finding is a Suzuki coupling that can be conducted using thermal conditions rather than the reported microwave conditions. Any future scale-up needs for advanced molecules will benefit from this discovery.

Developmental Therapeutics Program quality control analysis of compounds: The group established a blanket purchase agreement with Emoryville Pharmaceutical Services to facilitate the QC analysis of purchased investigational or approved clinical agents. To date more than 75 compounds have been evaluated. This is a significant cost- and time-saving effort in support of DSCB.

Analytical separations: A blanket purchase agreement was established with Averica to facilitate the separation of chiral intermediates. The service is a valuable asset that was utilized in the silvestrol project and facilitated the availability of a key intermediate. This is a significant cost- and time-saving effort in support of DSCB.)

Investigative Toxicology Laboratory

The mission of the Investigative Toxicology Laboratory (ITL) is to develop and implement mechanism-based predictive in vitro models to identify potential liability and elucidate the mechanisms of vital organ toxicity in support of the DTP within DCTD, NCI. In FY2015, ITL continued scientific qualification of new assays, protocol optimization of established assays, and providing support to NExT projects.

Significant Achievements

- *Validation of microelectrode array (MEA) platform to assess the proarrhythmic liability:* Drug-induced torsades de pointe (TdP) arrhythmia is a serious safety issue since it is the number one single safety liability issue that resulted in the most withdrawals of marketed drugs over the past decade, and there are increasing incidences of QT prolongation and TdP arrhythmia associated with targeted anticancer therapeutics, (i.e., nilotinib, sunitinib, dasatinib, and lapatinib). The current strategy to assess the risk of TdP arrhythmia, as outlined in International Conference on Harmonization (ICH) S7B/E14 guidance, largely relies on the detection of QT prolongation liability. Since QT is a sensitive, albeit non-inclusive surrogate marker, focusing on QT leads to unwarranted drug attrition, misclassification of hazard, and other risks. Hence, a comprehensive in vitro proarrhythmia Assay (CiPA), endorsed by the FDA, Cardiac Safety Research Consortium, and Health and Environmental Sciences Institute, has been proposed as a new testing paradigm. CiPA consists of three core components: (1) determining the effects on multiple key cardiac ion channel currents (i.e., IKr [hERG], INa, ICa,L and IKs); (2) plugging ion channel data into the computational ventricular action potential model to predict effects on action potential duration/ electrocardiogram (ECG); (3) and confirming the simulation output in stem cell–derived human cardiomyocytes using MEA or voltage-sensitive fluorescence imaging technology. Aimed at replacing the Thorough QT Study, CiPA employs a full characterization of proarrhythmic liability in vitro, while maintaining a link to human ECG endpoints. An MEA system measures the electric signal of cultured cardiomyocytes (ECG in a dish); thus, it is an ideal tool to bridge the in vitro–in vivo translation of cardiac electrophysiology. ITL established an impedance-based system (xCELLigence) in 2013 to detect arrhythmia in a dish directly. However, as this

system does not measure the electric signal, it is less informative in revealing the ionic/electrophysiological mechanisms responsible for observed arrhythmic events. An MEA system could complement a thorough interrogating of a drug's proarrhythmic risk through a more mechanistic-based approach. In FY2015, ITL acquired an MEA system (MED64) and applied it to induced pluripotent stem cell (iPSC)–derived cardiomyocytes in order to establish the in vitro proarrhythmic model. The scientific qualification of this model was completed with a set of cardiac ion channel and receptor modulators, including hERG (IKr) channel blocker E-4031, INa channel blocker tetrodotoxin (TTX), ICa,L channel blocker nifedipine, IKs channel blocker JNJ303, and β1-adrenoceptor agonist dobutamine. The xCELLigence and MEA systems have been utilized as the first-line assays in ITL for assessing both functional and structural cardiotoxicity of experimental anticancer drugs under development in the NExT program.

- *Implementation of the Wes™ platform for higher-throughput protein analysis:* Protein analysis is an indispensable aspect of the integrated approach to reveal the molecular mechanisms underlying the cardiotoxicity associated with anticancer drugs, and this approach particularly applies to the targeted anticancer drugs. However, the routine use of protein analysis is limited by the conventional SDS-PAGE gel-based Western blot (WB) platform due to its low throughput and requisite for a large quantity of protein samples. The Wes™ instrument works on the same principal as the conventional WB for protein separation and identification, but employs a novel nanofluidic or capillary electrophoresis technology, hence, only requiring 1/20 to 1/10 of the protein samples used for the conventional WB. In addition, Wes™ is a fully automated and higher-throughput system. It takes about three hours to complete a run to test up to 25 samples, or a day to complete 75 samples (3 runs) without manual attention, while the conventional WB assay platform involves multiple steps of manual processing and takes about 24 hours to complete a run. In FY2015, ITL acquired a Wes™ instrument and evaluated its performance. The evaluation data had confirmed the enhanced analysis efficiency, precision, and accuracy. At present, Wes™ is not only used routinely by ITL to support NExT projects, but also used heavily by the in vitro evaluation and molecular pharmacology group.
- *Assay characterization and protocol optimization:* In FY2015, ITL continued on model characterization and protocol optimization for established CD34+ bone marrow toxicity, rat dorsal root ganglion neurotoxicity, and hiPSC-cardiomyocyte cardiotoxicity assays.
- *CD34+ cell model:* Proliferation and differentiation of CD34+ precursor cells were further characterized using the bright-field image of the growth size, nuclear stains with DAPI, and fluorescence-activated cell sorting (FACS) analysis of dynamic expression of CD34, CD13, and CD11b at different time points in culture. Lipid-coated U-bottom plates were selected for obtaining the high-quality bright-field images, and the staining protocol was further optimized to improve the signal/noise ratio. The enhanced CD34+ assay was utilized to support the Mcl-1 inhibitor project. The manuscript detailing the CD34+ assay validation study has been submitted to a scientific journal for publication.
- *Rat dorsal root ganglion cell model:* A stain for neuronal-specific markers Tuj-1and NeuN, non-neuronal marker vimentin, and a cell-count marker DAPI were selected as standard biomarkers for testing drug effects on both neuronal and non-neuronal cells, and the 384-well plate was selected as a substitute for the 96-well plate in order to minimize the basal level variability of neuronal cell count. The manuscript describing the rat dorsal root ganglion cell model validations study has been submitted to a scientific journal for publication.
- *hiPSC-cardiomyocyte model*: Additional readouts and protocols have been developed to assess the mitochondrial respiratory function (with the Seahorse instrument); to separate cytosolic, nuclear, or mitochondrial fractions of lysates; to quantify the full panel of pro- and anti-apoptotic proteins; and to analyze the co-immunoprecipitates of Mcl-1 with other pro-apoptotic proteins. The manuscript summarizing the protocols developed by ITL for the hiPSC-cardiomyocytes has been published in Current Protocols in Chemical Biology, and the manuscript reviewing the application of impedance-based measurement with hiPSC-cardiomyocytes for evaluation of drug-induced cardiotoxicity has been published in Cardiovascular Toxicology.
- *Contribution to the CiPA initiative:* ITL leaders (Liang Guo [Leidos Biomed], Sandy Eldridge [NCI], and Myrtle Davis [NCI]) serve on the Health and Environmental Science Institute Technical Committee on Cardiac Safety. Specifically, ITL is actively involved in rechanneling the cardiac proarrhythmia safety paradigm. Drug-induced torsades de pointe (TdP) arrhythmia has been recognized as a serious safety concern in anticancer therapy, and the current strategy to assess the risk of this potentially fatal ventricular arrhythmia, as outlined in ICH S7B/E14 guidance, largely relies on the detection of QT prolongation liability. In FY2015, ITL played an important role in the pilot validation study of the CiPA initiative. In addition to conducting the experiment as one of 17 testing sites, ITL participated actively as a member of the core workgroup in designing the validation study and, with support from the NCI Drug Synthesis & Chemistry Branch and Chemotherapeutic Agents Repository group, blind-coding and distributing the test compounds to all participating sites.

- *Mcl-1 inhibitors:* The expression of the Mcl-1protein and its role in protecting the functional and structural integrity of hiPSC-cardiomyocytes were investigated thoroughly using multiple analytic platforms, including the siRNA knockdown, impedance, Seahorse mitochondrial respiration, conventional and Wes™ Western blotting, biochemical high-content imaging, and transmission electron microscopy. Mcl-1 knockdown exhibited a sub-lethal injury in hiPSC-cardiomyocytes, likely through altered autophagy activity. Two Mcl-1 inhibitors (NSC 782442 and NSC 782839) caused mitochondrial damage at high concentrations.
- *Silvestrol:* The precision-cut lung slice (PCLS) assay was conducted using two human and two dog lungs to test the lung toxicity of silvestrol. An immunohistochemistry protocol to stain the cleaved caspase 3 in lung slices was developed to evaluate the apoptosis activation by silvestrol. Studies conducted in human lung and additional dog lung slices reproduced the pulmonary injury observed in the previous PCLS studies.

Information Technology Support

The DTP Computer Center (DTPCC) provides computer support, including operations, technical support services, and software development, to DTP and DCTD. DTPCC provides core services for many aspects of DTP's information systems requirements, including data acquisition within the laboratories, data analysis, and web publication of experimental results. Computer support is provided for many functions of DTP, including identifying and scheduling compounds to test, preparing and handling the compounds, performing the experiments, and analyzing experimental results for activity.

Application servers hosted on the Microsoft Windows Server platform support the planning, analysis, and data storage tasks of the program. Windows servers are utilized as application development and deployment platforms, and, through web-based services, provide researchers with an interface to the DTP data and tool repository.

DTPCC support includes the administration of 118 servers. Operational support consists of maintaining all server platforms at the highest levels of availability and performance possible. This support includes performing system upgrades, and backup and recovery operations, diagnosing and resolving problems, and implementing and monitoring system security features. All system operations are completed utilizing practices that minimize system downtime and the impact on a global research community. System consultation and support to various software developers and scientists who use the system are also provided.

Core applications supported by DTPCC staff include both DTP in-house developed software and commercial-off-the-shelf data management and analytical applications. Among those applications are the ORACLE RDBMS, BIOVIA Pipeline Pilot, CambridgeSoft ChemBioOffice Enterprise, Microsoft SharePoint, StudyDirector, Accord, Spotfire, Certara D360, Apex, and Laserfiche. Operating system administration support includes Windows (2003, 2008, 2012, Hyper-V) and Linux.

Primary functional groups within the Developmental Therapeutics Program Computer Center

The Windows Server Support Group, provides support for Oracle, Windows, and Linux-based servers. The primary responsibilities in this area are applications and data storage management, performance tuning, data security, and RDBMS availability.

The Web Application Development Group is responsible for the creation and maintenance of program web pages and applications, as well as Java and Oracle development activities.

Significant Achievements

- Completed the migration of three Internet-facing servers to Center for Biomedical Informatics and Information Technology (CBIIT)– and FNLCR-secured networks. Servers that are Internet-facing are subject to higher security risks because they are frequently the target of network intrusion attempts (i.e., hacks). These three servers are used to distribute DCTD research information to the public. These servers were migrated to higher security networks in order to maintain server security and reduce the inherent risks of allowing public access. This migration increases server reliability and availability, while reducing the risk to other DCTD resources. In the event that these public-facing servers were compromised, the networks on which they reside are designed to allow very limited inbound access to other networked resources, preventing the spread of malware or disruption to mission-critical services.
- Integrated Pipeline Pilot web services into the CBC and DTP applications, enabling the use of Pipeline Pilot services with any DCTD web application, including those available to the public.
- Updated the Supplier Reports web application to enable users to easily see which National Service Centers (NSCs) are related to NSCs for which they have searched, and to add reports for these related NSCs to the report list. These new functions operate across all screening systems and greatly reduce the effort needed to produce reports for related NSCs.
- Implemented the GI50, TGI, and LC50 mean graphs in Pipeline Pilot for drugs tested in the cancer five-dose screening system. Implementation allows these graphs to be incorporated into other Pipeline Pilot applications and makes the mean graphs available as a web service. It also allows the user to see results averaged over all the experiments that tested a particular drug.

- The Structure Definition File batch-loading operation, a component of the CBC application process, was updated, incorporating molecular structure duplication detection. This update automates much of the workflow necessary for getting compounds that are registered with all CBC programs into the hands of the reviewers. As a result, less time is required for administrative overhead, increasing the time available for analysis.
- Completed the conversion of ORADIS Omnis7 libraries to Omnis Studio 6.1. This allows the Drug Information System to be run on 64-bit Windows machines, eliminating the previous 32-bit limit and increasing the available memory for applications.
- Designed and implemented a new web application for viewing, editing, and importing annotations for cell lines. Each annotation can store information about some aspect of a cell line, and any number of these annotations can be attached to each cell line in the database.
- Created a combined Natural Product Report for natural products tested in cancer one-dose experiments. The new report lists experiments, natural products, and any prior tests for which decisions were logged. A similar report for natural products tested in cancer five-dose experiments was created. Converted the In Vivo Detailed Graphs application to use Microsoft's Internet Explorer internal SVG rendering.
- Installed and deployed the BIOVIA Insight application suite. BIOVIA Insight is used for interactive searching, browsing, and visualizing of data within the BIOVIA Cheminformatics Suite.
- Created integrated data sources that define the DTP tables and columns available to the BIOVIA Insight data visualization and analysis software. Created numerous search and viewing forms in Insight that correspond to the current ORADIS standard queries and viewers.
- Worked with NCI/Information Technology Branch personnel to re-implement the current ORADIS compound registration processes in BIOVIA's Chemical Registration software. Assisted with the definition of data fields needed for the chemical registration form. Wrote Pipeline Pilot protocols to implement required Drug Information System customizations.
- Tested, validated, and deployed Quickfields, a document imaging and capture front-end for the Laserfiche Enterprise Content Management suite.
- Upgraded COMPARE Oracle databases from Oracle 10g to Oracle 11g and converted all servers from physical to virtual servers.
- Completed the migration of 12 Windows 2003 servers to Windows 2008 or 2012, improving system responsiveness and compliance with NIH security requirements.
- Completed the purchase and integration of significant storage resources (200 TB) for the DCTD-DTP-Laboratory of Human Toxicology and Pharmacology (LHTP) and DTCD MoCha laboratories.
- Completed the purchase and integration of a new DTP Fileserver, significantly improving researcher access speeds and resource availability.

American Recovery and Reinvestment Act of 2009–related projects

The Comprehensive IT Program for Facilitating Drug Discovery and Development (ARRA Order #9) was successfully concluded during FY2015.

Significant Achievements

- Completion of the Early Trials – Clinical Trials network SharePoint portal.
- Purchase of training for LHTP laboratory personnel in the use of Spotfire High Content Profiler Pro and the purchase of three High Content Profiler licenses.
- Successful execution of Perkin Elmer/CambridgeSoft contract, integrating specific DCTD Oracle data operations using CambridgeSoft application functions.

Software Licensing Support

At the request of DCTD, DTPCC coordinated the purchase of licenses and maintenance contracts for 14 groups within DCTD; 70 software packages were included. Additionally, the group transitioned ARRA-funded SharePoint services and other software maintenance contracts to the DCTD software cost center.

Computational Drug Development Group

The DTP Computational Drug Development Group (CDDG) supports the mission of the BEC decision process, the NeXT program, the CBC program, and CCR research (via the laboratory of Dr. James Doroshow, Developmental Therapeutics Branch) through the application of computational data modeling, which includes bioinformatics, chemoinformatics, molecular visualization, computational chemistry, molecular modeling, structure-based medicinal chemistry, and statistical data mining.

Significant Achievements

- Collaborated with the Peter Wipf laboratory at University of Pittsburgh on P97 lead mining in support of a NeXT proposal.
- Developed homology models of KDM5 enzymes, in the absence of X-ray crystal structures. Evaluated the binding modes of KDM5 inhibitors using

structure-based computational docking. Optimized several di-pyridine–KDM5B complexes with various substituents in both para and meta positions.

- Performed quantum calculation of HOMO-LUMO gaps to determine the stability of the KDM5B-inhibitor complexes in order to provide insight into observed activity data using tool compounds. Quantum calculations were used to measure the change in distance to the active site iron to determine the effect on chelation tendency with various substituents.
- Continued oxyphenisatin (NSC's 59687, 59814, 117186) modeling, data mining, and target analysis in support of BEC. The compound is active in MCF7 and OVCAR-3 xenografts, and other data is pending.
- Generated high-resolution models of NOX 1, 2, 4, and 5, and DUOX2 active sites. Docking studies with inhibitors have been used to optimize structure–activity relationship data generated by Dr. Doroshow's lab.
- Performed structural optimizations, using quantum chemical computational methods, for iodonium DPI and congeners (including NSC736322) for the NOX project. The structure was corroborated using the Cambridge Structural Database, and transition-state complexes with FAD were examined to further the understanding of the mechanism as it relates to the structure–activity relationship data generated by Dr. Doroshow's lab.

Additional ADRD Program Support to DCTD

ADRD's Clinical Support Laboratory (CSL) performed recertification testing to assess the bioactivity of clinical-grade interleukin-4 and interleukin-12 in support of the Biopharmaceutical Development Program. At total of 20 test plates were evaluated in testing these two drug products.

CSL also performed sequential flow cytometric analysis of cultured CD34 cells at the request of Dr. Liang Guo, Leidos Biomedical Research.

Cancer Imaging Program

Support Provided by the Applied and Developmental Research Directorate

Leidos Biomedical Research's Cancer Imaging Program (CIP) support included oversight of chemistry, clinical trials quality assurance support, medical imaging agent availability, regulatory affairs, and imaging informatics. Oversight of critical research subcontracts awarded to facilitate both preclinical and clinical research activities for imaging agents, as well as the specific chemistry management support provided to the radiopharmaceutical facilities in Frederick, has served to ensure wider availability of investigational agents for exploratory and Phase I–III clinical trials. Regulatory support has been focused on managing the life cycle of the CIP INDs, assisting with the advanced development of the CIP- and non-CIP-sponsored investigational imaging agents, supporting intramural and extramural clinical trials, and providing access to CIP imaging agents for additional researchers via several cross-reference mechanisms that have been implemented. Oversight of imaging informatics, including the teams' leadership in numerous informatics communities and imaging networking endeavors, has also been a key contribution. These efforts, through managing research subcontracts, providing regulatory and medical affairs expertise, and participating and leading imaging informatics communities, have served to support the mission and goals of CIP for the NIH intramural and extramural research communities, and high-profile NCI programs, such as the NCI Experimental Therapeutics (NExT) Program.

In addition to other NCI programs, CIP staff collaborated with NIH groups at the Clinical Center in Bethesda, MD, and in Frederick, MD; with networks including the American College of Radiology Imaging Network (ACRIN), American College of Radiology (ACR), and Society for Nuclear Medicine (SNM); and with other scientific and regulatory organizations, including the FDA. During the reporting period, interagency meetings were conducted with regulatory and medical counterparts in the FDA's Division of Medical Imaging Products. These efforts have supported CIP's goals of promoting the wider use of medical imaging in diagnosis, response to therapy monitoring, therapeutic drug development, and medical decision-making for cancer patients.

During the past eight years, CIP emphasis has shifted toward the development and delivery of a variety of imaging products, requiring new strategies, resources, and external outreach activities. The Phase 0 initiatives and the dissemination of short-lived tracer technology are two prominent examples of initiatives resulting from this shift in CIP focus. The NExT Program integrated the activities of several cross-institute imaging activities into two decision-making committees. CIP continues to be involved in NExT projects by providing support and guidance to the Radiopharmaceutical Chemistry group and the Leidos Biomedical Research Radiopharmacy. Current efforts have been maintained to support NCI DCTD through its scientific advisory committee (F-alpha-methyl-tyrosine, F-AMT [DTFFAMT]), and also through the NExT Program (NIR-panitumumab [NX194-104-131-001]), Lum015 (NX229-110-186-001), and DCFBC (Cl100-603-637-001). The F-AMT and NIR-panitumumab were the result of internally developed ideas requested through CIP, while the others are from extramural investigators (DCFBC originated from Johns Hopkins University and [18F]fluoroestradiol originated from the University of Washington). New efforts to support researchers in CCR are ongoing to make F-DHE, a reactive oxygen species tracer, for use in cellular imaging.

The CIP informatics team provides leadership, community management, infrastructure, and tools to support imaging research initiatives, enhance reproducibility in research, and support the NIH big data mission.

CIP continues to manage and expand The Cancer Imaging Archive (TCIA) research subcontract, which it leverages to provide support to the public clinical imaging research community, the CIP Quantitative Imaging Network (19 U01 grantee institutions), and four multi-institutional research groups focused on the novel field of imaging genomics. CIP leads the development of new technologies and methodologies for integrative data analysis, clinical imaging data de-identification and curation, and image processing, and has also provided leadership in developing organization and logistics for grand challenges designed to compare the performance of image analysis software.

Radiopharmaceutical Chemistry and Imaging Agent Research Subcontract Support

CIP's chemistry program primarily supports the goals of the Imaging Drug Group, providing development of new imaging agents and follow-up testing of currently administered agents. This groundbreaking work may lead to increased availability of types of agents for clinical trials. Maturation of this effort is documented by the fact that the original space designated for this work was transitioned to a United States Pharmacopeia (USP)–level radiopharmacy capable of delivering clinical-grade human doses for preclinical and clinical evaluation efforts by a certified nuclear pharmacist.

To date, the radiopharmacy has supplied 18 doses of [18F]-fluoroestradiol for administration to 11 subjects at the Clinical Center in Bethesda, MD, under CIP's IND; enrolled its first three subjects for 89Zr-panitumumab; and has enrolled its first 44 subjects for DCFBC, a new radiotracer for prostate cancer. During FY2015, the radiopharmacy was relocated to an alternative site in Frederick, MD. Planning meetings were successful, and newly occupied space (Building 459) has a better layout and is larger than the previously used space. To accommodate the move, the radiopharmacy was closed on May 15, 2015, and reopened on July 17, 2015.

Research subcontracts with extramural sites were coordinated to facilitate the formal clinical trials performed at the CIP Phase I and II NCI contract sites. In addition, efforts to make promising radiopharmaceutical agents available to the research community for clinical investigation have been significantly broadened. Because the PET tracers have no intellectual property associated with them, commercial entity investment is viewed as risky. CIP personnel were involved with negotiations with the three major suppliers of cyclotron-produced isotopes and radiopharmaceuticals for implementing fluoro-L-thymidine (FLT) tracer synthesis and applying for a DMF so the tracer could be supplied to NCI trials.

CIP provides selected PET radiopharmaceuticals to support both small early phase trials and larger trials. Through a research subcontract with the University of Pennsylvania, 5-fluoro-2'-deoxcytidine (5FdC) is the only additional tracer remaining to be investigated. Radiolabeled 5FdC has been identified as an imaging agent of special interest to DCTD as part of its Phase 0 Clinical Trial #8865 involving 5FdC with tetrahydrouridine (THU) for the treatment of head and neck, lung, bladder, and breast cancers. The drugs 5FdC and THU are being used in a cancer treatment study. Since researchers continue to investigate how 5FdC works in the body, researchers are assessing a modified form (radiolabeled 18F-5dC) using imaging studies to see how the drug reacts with the cancer. A new nonseverable research subcontract has been awarded to the University of Pennsylvania to provide 50 doses for 25 patients over the next four years.

Regulatory Affairs Support

During FY2015, comprehensive regulatory support was provided for CIP activities related to the IND and New Drug Application (NDA) development process for imaging agents. CIP facilitates the development of promising diagnostic agents, many of which are PET drugs that fall under special FDA oversight and regulation because their manufacturing often poses unique challenges and they may not be able to undergo the same amount of standard preclinical testing or early-phase clinical testing, as is required for more conventional drug development. A variety of regulatory mechanisms and strategies must therefore be kept in place at CIP as part of the life cycle of the CIP-sponsored imaging agents, and to enable others to cross-reference this information for their own research.

The following ten CIP-sponsored INDs and one NDA are currently managed and supported by the Regulatory Affairs staff:

1. IND 71,260 ([18F]-fluoro-L-thymidine), a proliferation agent
2. IND 68,556 (ferumoxytol), a blood-pool MR agent
3. IND 70,900 (ferumoxtran-10), a lymph node MR agent
4. IND 76,042 ([18F]-fluoromisonidazole), a hypoxia agent
5. IND 79,005 ([18F]-fluoroestradiol), an estrogen receptor agent
6. IND 100,429 [111In]-Herceptin, an Her2 receptor agent
7. IND 103,429 [18F]-NaF, a bone-scanning agent
8. IND 116,229 [89Zr]-panitumumab
9. IND 122,503 [18F]-DCFBC, a prostate-specific membrane-antigen agent
10. IND 70,651 hyperpolarized pyruvate (^{13}C) injection, an MRI agent
11. NDA 22-494 sodium fluoride, a bone-scanning agent

Multiple protocols are being conducted under each of the CIP-sponsored INDs that range from Phase 0 to Phase III, with Phase II having the most protocols and all having differing regulatory requirements. Twelve clinical trials were active and enrolling patients during this reporting period. Many of the trials have inherent regulatory complexities due to the involvement of multiple investigators, sites, local IRBs, and contract organizations located in the U.S., Canada, and other foreign countries. During this reporting period, CIP Regulatory Affairs issued approximately nine letters of authorization allowing independent researchers to cross-reference the materials in CIP INDs for their trials.

During the past year, increasing CIP regulatory and chemistry support has been required to guide the development of several INDs and NDAs by researchers within the NIH community. A new IND for hyperpolarized pyruvate was transferred for sponsorship by CIP. Additionally, CIP staff continues to work closely with federal staff to revise and update the hundreds of regulatory and production materials on the Cancer Tracer Synthesis Resources pages on the CIP website.

Per CIP guidance, the Regulatory Affairs group continues to provide regulatory support for the subsequent requirements of the [18F]-NaF NDA. Due to its FDA status as a reference-listed drug, this enables abbreviated NDAs to be submitted by drug manufacturers around the country.

Medical Affairs and Quality Assurance Support

The CIP support team works with NCI CIP medical officers, the NCI CIP Clinical Trials Branch (CTB) chief, Eastern Cooperative Oncology Group-American College of Radiology Imaging Network (ECON-ACRIN) program director, and ECOG-ACRIN senior staff to provide significant day-to-day oversight for the ECOG-ACRIN QA, monitoring, and audit programs. ECOG-ACRIN operational (QA monitoring and audit) reports are reviewed primarily by the Leidos Biomedical Research CIP Regulatory and QA support team. Audit tracking schedules are reviewed in advance and evaluated against actual audit performance. Preliminary audit reports are sent to the Regulatory and QA support team for review immediately post-audit, thus providing an early warning opportunity. Should prompt action be necessary, the Leidos Biomedical Research CIP Regulatory and QA support team work hand-in-hand with NCI and ECOG-ACRIN to define and implement a course of timely intervention to mitigate suboptimal site issues. Items requiring immediate action are brought to the attention of the ECOG-ACRIN program director and the CTB chief. Strategic support is still provided to ECOG-ACRIN to assist in improving regulatory, IRB, and protocol compliance.

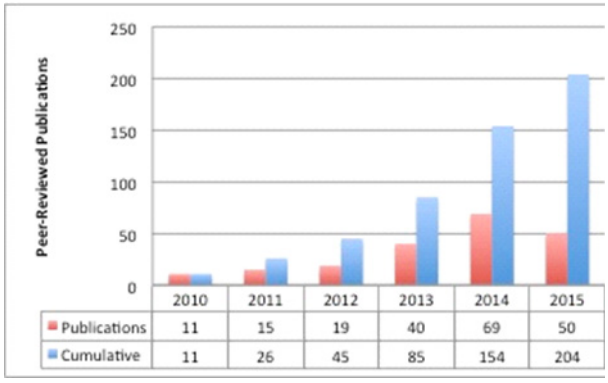
During the reporting period, staff supported upgrades to systems and processes for the receipt and tracking of adverse events (AEs) and auditing reports at CIP for the continuing ECOG-ACRIN legacy trials. Leidos Biomedical Research CIP staff completed modifications and evaluations of existing AE reporting systems designed for therapeutics, so that they now meet the needs of imaging clinical trials. Additional regulatory projects included: (1) ongoing co-monitoring of specific trial sites within ECOG-ACRIN to obtain information necessary to conduct a comprehensive process audit of the cooperative group; (2) supporting amendments to the cooperative group guidelines so that ECOG-ACRIN could be managed under the same policies as the other cooperative trial groups, and; (3) supporting the convergence of the National Clinical Trials Network (NCTN) and the Clinical Trials Monitoring Branch (CTMB) guidelines, and benchmarking ECOG-ACRIN to standardize imaging standard operating procedures.

The clinical trials administrator continued to work collaboratively with the CIP ECOG-ACRIN program director and medical officer, and other subcommittee/ working group/project members, to provide clinical insight and guidance to ensure that imaging-related content was included in NCI's processes, procedures, and working guidelines. These groups included the Clinical Trials Reporting Program; CTMB; NCTN; the Investigational Drug Branch/protocol review; the Cancer Trials Support Unit; the ECOG-ACRIN QA committee; and CTEP AE committees. Due to all AE monitoring and reporting switching over to CTEP in December 2014, members of the Leidos Biomedical Research CIP support staff are no longer required to support this effort.

The clinical trials administrator also continued to support the CTB by monitoring all Clinical Data Update Systems (CDUS) and Adverse Event Expedited Reporting Systems (AdEERSs) reporting for CIP imaging protocols. CDUS reports were compiled for review by the medical officer on a monthly basis. The reports were then presented quarterly at the CTB meetings. Many variables were regularly monitored for trend analyses, patient safety, and International Conference on Harmonization/ Good Clinical Practices (ICH/GCP) compliance, including treatment start date, monitoring method, imaging agent or Network Steering Committee (NSC) lead agent, protocol number, patient ID, institution, course ID, last changed date in the system, outcome grade, and AE toxicity. In addition, the AdEERS report (a reporting system for expedited and serious adverse events) was consistently monitored for such variables as site protocol compliance trend analyses, patient safety, ICH/GCP compliance, imaging agent protocol number, IND type, protocol name, patient identification, institution, NCI receive date, AE description and start date, imaging agent, attribution outcome, ticket number, and amendment. Each event was reviewed weekly with the medical officer and presented at the monthly CTB meeting. This information remains useful, in conjunction with annual reports, when filing NCI imaging INDs, continuing reviews for the Clinical Center IRB, and working on CTB ad-hoc projects.

Imaging Scientific Support

The Cancer Imaging Archive (TCIA): ADRD staff managed the TCIA project, including conducting monthly NCI Advisory Group meetings that set scientific priorities for new data collection and technological development activities. NIH director Francis Collins cited TCIA as a critical complement to The Cancer Genome Atlas (TCGA) program, as it provides critical phenome data to TCGA data sets. TCIA expanded TCGA data collection to include multiple sites in Canada. The program's impact was also evidenced by the receipt of increasing numbers of data-hosting requests. In partnership with NCI's Radiation Research Program, major imaging sets that include radiation therapy planning data have been collected. The complete annotated I-SPY1 clinical trial's imaging data was made available to researchers as a limited-access collection. Over 200 peer-reviewed publications now use TCIA-hosted data (see figure below).



NCI CBIIT imaging informatics: ADRD staff provided subject matter expertise to the Clinical and Translational Imaging Informatics Project (CTIIP), including archiving of pathology imaging, integrating challenge technology, and developing infrastructure and standards for co-clinical data sets. The team supported a review of the NBIA technology, with a view of re-factoring or replacing it with a more appropriate technology stack.

Imaging genomics: ADRD staff continued to build the TCGA-linked data set, with major collections coming from the MD Anderson Cancer Center and several Canadian sites. TCIA now hosts imaging data for almost 2,000 TCGA-linked cases.

Quantitative Imaging Network: ADRD staff provided leadership to multiple working groups, drove consensus on annotation and archiving, and managed research and challenge data sets on TCIA. Two members of the Leidos Biomedical Research team were included in an NCI Director's Award from former Director Dr. Harold Varmus.

FNIH Coding4Cancer: ADRD staff led a major data collection effort to provide additional low-dose CT screening data to the National Lung Screening Trial (NLST) data set for the Coding4Cancer challenge, which will leverage the TCIA.

NCI precision medicine trials: ADRD staff assisted in developing the imaging components in protocols for two major NCI precision medicine trials: M-PACT and Exceptional Responders. Both protocols use TCIA in their data collection and review components. Staff also developed strategies to maximize the imaging role in precision medicine to fast-track drug approval and increase the leveraging of imaging-genomics signatures as biomarkers.

Journals and research reproducibility: Dr. Philip Bourne, NIH associate director for Data Science, wrote an editorial appearing in the April 2015 issue of the journal *Radiology*, specifically calling out the significance of the CIP effort to support Digital Object Identifiers (DOIs) and encouraging the adoption of these identifiers by the imaging research community. The CIP team worked with major scientific journals, including *Scientific Data* and the *Journal of Digital Imaging*, to develop strategies for having imaging data published along with research papers, including journal recommendations, in submitter packets to leverage TCIA.

Community outreach: The CIP informatics team made presentations and conducted workshops at the Radiological Society of North America, SPIE, NIH Science of Data Sharing, the Medical Image Computing and Computer Assisted Intervention 2015 conference, and other venues, and developed several social media and feedback systems.

Cancer Therapy Evaluation Program

Support Provided by the Clinical Monitoring Research Program

The NCI's Cancer Therapy Evaluation Program (CTEP) utilizes CRADA funds to support correlative studies performed during sponsored clinical trials utilizing CTEP IND agents. This serves the extramural community by supporting critical correlative studies that are aligned with NCI-sponsored clinical trials being conducted under separate agreements between NCI and the clinical trial site. NCI has authorized the use of its CRADA funds to support research agreements that cover the cost of the approved correlative studies. The clinical trial site may receive CRADA funding to cover the costs of conducting correlative study activities, including assays and investigational imaging; appropriate and reasonable personnel efforts and supplies; direct patient care costs; specimen collection, processing and shipping; institutional direct costs; and protocol-mandated patient evaluations and /or sample acquisitions.

During the reporting period, support to CTEP included managing the complex acquisitions process to support the growing portfolio of clinical trials requiring correlative science funding. CMRP staff provided high-level administrative and research subcontract management support to more than 43 agreements awarded to more than 28 institutions, totaling approximately $544,000.

During the reporting period, CMRP staff supported active cost centers that were utilized to fund correlative science activities sponsored by the following seven drug companies: (1) AstraZeneca, (2) Genentech, (3) GlaxoSmithKline, (4) Millennium, (5) Bristol-Myers Squibb, (6) Merck, and (7) MedImmune. New support was provided to GlaxoSmithKline and Millennium, with the approval of correlative studies for either new or additional sites supporting CTEP protocols conducted at multiple participating institutions. Thirty-one Blanket Purchase Agreements (BPAs), three BOAs, three research subcontracts, and three TOs were approved, awarded, and/or modified.

An efficient purchase agreement process was further customized with additional cost control measures. Incremental funding of the agreements, along with monthly monitoring of deliverables, and quarterly progress reports and invoices provided consistent oversight that enabled the early identification of underperforming clinical trial sites. A streamlined, collaborative communication and funding process continued to be utilized, enabling the prompt funding of the NCI-approved, CRADA-supported correlative work.

Given the Operational Efficiency Working Group (OEWG) recommendations that were implemented in 2012 to increase the pace at which NCI-sponsored trials are initiated, CMRP staff continued to coordinate activities with Leidos Biomedical Research Contracts to identify and recommend the most efficient process for soliciting work and making awards.

Communication processes continued to be reviewed, and additional initiatives were added to disseminate information consistently to CTEP drug monitors, the PIs, and all stakeholders.

CMRP staff attended weekly CTEP/Investigational Drug Branch (IDB) meetings, coordinated monthly patient accrual deliverables with CTEP/IDB and participating institutions, and coordinated program teleconferences as needed.

In June 2015, CMRP began supporting the Brain Tumor Trial Collaborative (BTTC) in support of the NCI NOB. The BTTC includes a reimbursement process for trial accrual sites. The processes in place to support the CTEP activities were considered as the new BTTC work was initiated.

Support Provided by the Molecular Characterization Laboratory

Clinical Activities

The Molecular Characterization Laboratory's (MoCha's) Clinical Laboratory Improvement Amendments (CLIA)–certified clinical laboratory performs multiple analytically validated next-generation sequencing assays to support NCI Division of Cancer Treatment and Diagnosis (DCTC) clinical studies and precision medicine initiatives. To support the clinical trials, MoCha has built a strong group consisting of histotechnologists, molecular biologists, a quality assurance manager, bioinformaticians, a program manager, scientists, and a pathologist. MoCha aims to provide scientific evidence to improve patient outcomes by translating information from comprehensive characterizations of molecular alterations in patients' tumors.

MoCha established and manages a clinical assay development laboratory network (CADN) and specimen retrieval system (SRS) to support NCI's Clinical Assay Development Program (CADP). MoCha provided scientific and programmatic support to the CADP, CADN, and SRS by designing experiments; reviewing scientific data; troubleshooting experimental shortcomings; writing and reviewing statements of work (SOWs), statements of objectives (SOOs), and task orders (TO); approving purchase requests (PRs); evaluating responses to TOs; and scheduling meetings and coordinating efforts with subcontractors. Currently, the CADN has assisted in developing 8 assays in 11 competitively selected clinical laboratories to support assay development and validation.

MoCha coordinated the establishment of a next-generation sequencing (NGS) laboratory network that includes external subcontractors (Massachusetts General Hospital, MD Anderson Cancer Center, and Yale University) and MoCha's clinical laboratory. This network supports the NGS activities for the NCI-MATCH Clinical Trial (CTEP-EAY131). The NCI-MATCH NGS laboratory network will screen tumor biopsies from approximately 3,000 patients by performing the NCI-MATCH assay for enrollment in the clinical trial. MoCha led the effort to design, develop, and validate the NCI-MATCH NGS assays for the NCI-MATCH clinical trial using harmonized and locked standard operating procedures (SOPs). This is the first ever multi-laboratory effort to validate a complex NGS clinical assay using identical chemistry, the bioinformatics pipeline, and harmonized SOPs. The analytical validation study showed that the NCI-MATCH assay has a sensitivity of 97.4 percent, specificity of 99.9 percent, accuracy of 99.9 percent, and overall concordance of more than 99.9 percent. The validation report was submitted to the U.S. Food and Drug Administration (FDA) as a part of IND submission for the NCI-MATCH clinical trial. A favorable response to the submission was received from the FDA, and the agency deemed that the NCI-MATCH clinical trial was safe to proceed.

MoCha's clinical laboratory also supports NCI's Molecular Profiling-Based Assignment of Cancer Therapy (MPACT) for Patients with Advanced Solid Tumors Clinical Trial (CTEP Protocol #9149) using a custom NGS assay panel. This is a hypothesis-driven clinical trial that will screen approximately 700 patients to be enrolled in the MPACT clinical trial.

MoCha senior leadership has been sought after for participation in meetings, such as the AACR-NCI-EORTC International Conference on Molecular Targets and Cancer Therapeutics, the National Institute of

Standards and Technology (NIST) Genome in a Bottle consortium, the Advances in Genome Biology and Technology (ABGT) Annual Meeting, and the NCI Intramural Scientific Investigators Retreat, to share their experiences in clinical assay development, bioinformatics pipelines, formalin-fixed paraffin-embedded (FFPE) samples used in NGS assays, and NGS application/assay design in clinical trials and studies.

The director of MoCha received an NCI Merit Award for the planning and successful launch of the Exceptional Responders Study, and was recently invited to the White House for a discussion on precision medicine. The director of MoCha also serves as one of the principal investigators for both the MPACT and NCI-MATCH clinical trials. In addition, MoCha researchers are frequently invited to FDA/Center for Devices and Radiological Health (CDRH) workshops and roundtables for discussion of precision medicine and genomics. MoCha's research associate II was awarded a Certificate of Achievement for LFS101x: Introduction to Linux (December 2014).

MoCha frequently engages its reagent suppliers. These interactions have led the team to ensure lot integrity and monitoring of expiration dates, and have provided suggestions on kit configurations that would reduce reagent costs by approximately 14 percent and decrease reagent waste, thus providing sufficient savings. A majority of these efforts were spearheaded by MoCha's research associate III.

Recently, MoCha was requested to build its histology and pathology capacity to analytically validate selected immunoassays in the CLIA environment for patient selection, in support of DCTD clinical trials and programs. MoCha intends to perform tissue processing, sectioning, and staining, and image capture of tumor specimens. MoCha's histotechnology research associate I was awarded Histotechnician Certification (June 2015).

Research and Development Activities

The Research and Development (R&D) group of MoCha is involved with developing new technologies using next-generation technology, and has developed robust research assays to support genomic characterization in many different tissues and bodily fluids. MoCha's R&D group is directly involved in NCI's Patient-Derived Model (PDM) project initiated by Dr. James Doroshow, DCTD. MoCha is tasked with genomic characterization of all the patient-derived xenografts by performing RNA sequencing, whole-exome sequencing, and a variety of related clinical assays that are used to fully characterize PDM models. The MoCha histopathology group provides pathology support to the PDM project through morphological and immunoassay characterization of patient-derived xenografts from DCTD's programs.

The advantage of MoCha having both a CLIA-accredited clinical laboratory and an R&D laboratory is that research-grade assays can be easily converted into clinical assays for patient care. The group has led many collaborative efforts to understand the predictive biomarkers found in patient tumors after treatment in order to determine why a treatment was effective or ineffective in patient tumors. MoCha performed whole-exome sequencing on FFPE 30-year-archived ovarian cancer specimen blocks and found mutations similar to those reported in fresh tumors. As a quality control measure, MoCha has developed a PCR-based quality screen for determining the ability of a specimen to provide acceptable NGS data.

MoCha successfully demonstrated a method for cutting costs while increasing throughput using a combination of chemistries and assay techniques. MoCha staff members have participated in Biospecimen Pre-Analytical Variables (BPV) Program meetings to contribute their nucleic acid quality control assay results.

MoCha has interacted with NIST in developing clinical reference and control materials. MoCha has successfully developed 67 plasmids as reference materials and is working collaboratively via a CRADA with SeraCare to commercialize this approach for use in oncology NGS assays.

NIAID INTRAMURAL

Division of Clinical Research

Support Provided by the Applied and Developmental Research Directorate

AIDS Monitoring Laboratory

The AIDS Monitoring Laboratory (AML) performs sequential studies of immune function in patients with HIV disease or other emerging/re-emerging infectious diseases during treatment with a variety of antiviral and immunomodulatory agents. The results of this work aid in assessing the efficacy and mode of action of these agents, as well as determining optimal therapeutic strategies that may lead to restored immune function. AML is certified by the Department of Health and Human Services (HHS) and Centers for Medicare & Medicaid Services (CMS) to perform high-complexity testing on human specimens under the auspices of the Clinical Laboratory Improvement Amendments (CLIA) of 1988. Current CLIA-approved tests include white blood cell count, white blood cell differential, and lymphocyte immunophenotyping.

During FY2015, AML provided comprehensive immunological monitoring for 59 clinical research protocols conducted by NIAID's Division of Clinical Research (DCR). Support of these clinical studies resulted in the processing of 3,579 whole-blood specimens; 284 leukapheresis specimens; 10,701 sera specimens; 4,952 plasma specimens; 469 respiratory specimens; 269 urine specimens; and four cerebral spinal fluid specimens. AML performed 32,212 immune cell phenotype

determinations; 2,706 D-dimer assays; 48,363 cytokine measurements; 3,579 complete blood count/cell differentials; and 11 immunomagnetic-bead separations. AML cryopreserved 25,424 vials of patients' peripheral blood mononuclear cells (PBMCs); 21,096 vials of serum; 29,870 vials of plasma; 1,729 vials of urine; and 938 respiratory tract specimens. AML coordinated 147 shipments of patient specimens to investigators located at NIH and other domestic and international institutions. Specific efforts are identified below.

- In support to NIAID, the AML Clinical Flow Cytometry Group evaluated and performed validation testing of a new six-color, IVD-approved TBNK lymphosum monoclonal antibody cocktail and a new eight-color custom lyophilized activation marker panel to replace the existing four-color panel currently used for all clinical immunophenotyping. The transition to six- and eight-color immuno-phenotyping will result in two substantial benefits to NIAID. First, the six- and eight-color tests require a smaller volume of whole blood than the incumbent four-color test, thereby requiring less blood to be drawn from each patient. Second, switching to the six- and eight-color tests will reduce reagent costs by approximately $519,000 annually.
- In support to Dr. Irini Sereti, NIAID, the AML Clinical Flow Cytometry Group used a custom eight-color immunophenotyping panel to perform a detailed analysis of monocyte subpopulations in the blood of patients enrolled in two clinical trials: the PANDORA trial, a natural history study intended to evaluate the incidence, predictors, and pathogenic mechanisms of immune reconstitution inflammatory syndrome in HIV-infected adults; and the ECSTATIN trial, a study of the effects of statin therapy versus aspirin on immune activation in HIV-infected participants. Monocytes have been shown to be relevant in immune activation. In the setting of HIV infection, monocyte phenotypes correlate well with soluble biomarkers of clinical relevance, such as interleukin (IL)-6, CRP, and D-dimer. Monocytes have strong relevance in atherosclerosis, and monocyte changes are attractive targets for intervention and for study endpoints. During FY2015, monocyte subpopulations were analyzed in 167 patients.
- In support to Dr. Irini Sereti, NIAID, the AML Clinical Flow Cytometry Group continued to examine programmed death-ligand 1 (PD-L1) expression on the surface of monocytes and neutrophils in whole blood using a custom three-color immunophenotyping panel. PD-L1, also known as cluster of differentiation 274 (CD274) or B7 homolog 1 (B7-H1), is a protein that, in humans, is encoded by the CD274 gene. PD-L1 has been thought to play a major role in suppressing the immune system during particular events such as auto-immunity. In mouse models, activated monocytes have been shown to greatly upregulate PD-L1. PD-L1 has been shown to act as a positive co-stimulatory molecule in intracellular infection. During FY2015, AML analyzed PD-L1 expression in 167 patients.
- In support to Dr. Eric Meissner, NIAID, the AML Clinical Flow Cytometry Group continued to study CXCR3 and CXCR4 expression on memory and naïve T- and B-cell subsets using a custom five-color immunophenotyping panel. The chemokine receptor CXCR3 is expressed predominately on the surface of T cells; however, some B-cell and NK-cell subsets also express CXCR3. CXCR3 expression has been shown to be greatest following cell activation. The chemokine receptor CXCR4 has been found to be expressed on the surface of most immature and mature cell types, including T cells and B cells. HIV has been shown to use CXCR4 to gain entry into target cells. During FY2015, specimens from 50 individuals participating in the SYNERGY clinical trial were analyzed from three different study time points.
- Ebola virus disease projects. In response to the international public health emergency created by the recent Ebola epidemic in West Africa, AML rapidly mobilized resources to provide clinical laboratory support for two high-priority Ebola vaccine clinical trials sponsored by NIAID.
    - In support of a vaccine clinical trial based in the U.S., AML quickly established procedures to receive, test, and store blood specimens collected from volunteers participating in a Phase I trial of an experimental VSV-ZEBOV Ebola vaccine. To date, AML has received and processed blood specimens from 39 volunteers.
    - In support of NIAID's global efforts against Ebola disease, AML staff assisted with establishing a new clinical laboratory at Redemption Hospital in Monrovia, Liberia, in order to provide laboratory testing for patients who participated in the Partnership for Research on Ebola Vaccines in Liberia (PREVAIL) study. PREVAIL is a Phase II/III randomized, double-blind, placebo-controlled clinical trial of two experimental vaccines to prevent Ebola virus infection. AML swiftly helped to identify and procure the required equipment and supplies for the set up and operation of the laboratory in a resource-limited setting. In January 2015, Adam Rupert, associate scientist, traveled to Liberia to help set up the lab in preparation for start-up of the trial. Rupert received accolades from Dr. H. Clifford Lane, clinical director, NIAID, for his invaluable assistance with helping the lab become operational in time for the start of the trial. Redemption Hospital completed enrollment at 1,500 participants on April 30, 2015, and month-six follow-up visits are currently under way.

- Biomarker Testing. The AML Functional Immunology Group continued to perform ELISA tests and electrochemiluminescent multiplex assays to measure a wide range of biomarkers in support of multiple NIAID-sponsored clinical trials and research projects. Testing activity included:
  - In support to Dr. Virginia Sheikh, NIAID, the laboratory measured lipopolysaccharide (LPS)-binding protein levels in 78 plasma specimens from individuals with idiopathic CD4 lymphocytopenia.
  - In support to Dr. Caryn Morse, NIAID, the laboratory measured 24 biomarkers in specimens collected from 160 HIV+ individuals who participated in the TRANSAM clinical trial.
  - In support to Dr. Irini Sereti, NIAID, AML measured a panel of 20 biomarkers in 741 plasma specimens and assayed interleukin-7 levels in 427 sera specimens collected from patients with immune reconstitution inflammatory syndrome.
  - In support to Dr. Marta Catalfamo, NIAID, the laboratory determined levels of P-selectin and D-dimer in plasma obtained from 36 healthy volunteers.
  - In support to Dr. Irini Sereti, NIAID, a panel of 13 biomarkers was measured in 80 cell culture supernatants.
  - In collaboration with Dr. Irini Sereti, NIAID, and the University of California, San Francisco, AML measured six biomarkers in 90 plasma specimens and seven biomarkers in 99 plasma specimens collected from HIV+ patients.
  - In support of Dr. Frank Maldarelli, NIAID, the laboratory measured a panel of six biomarkers in 140 plasma specimens obtained from HIV-infected individuals.
  - In support to Dr. Irini Sereti, NIAID, AML evaluated levels of D-dimer and C-reactive protein in 22 plasma specimens collected from HIV-infected individuals who participated in the Bone Biomarker Project.
  - In support to Drs. Maura Manion and Irini Sereti, NIAID, AML measured levels of sCD14 and sCD163 in 18 cell culture supernatants.
- AML Research Flow Cytometry Group. The AML Research Flow Cytometry Group provides flow cytometry support to DCR, NIAID (Drs. Anthony Fauci and H. Clifford Lane). During FY2015, this support included 54 sterile cell sorts, 64 carboxy-fluorescein succinimidyl ester (CFSE)/cell proliferation assays, 17 apoptosis assays, 217 RNA/DNA analyses, and 64 cell-cycle analyses. In addition, the following flow cytometric determinations were performed: two thirteen-color, 87 ten-color, 52 nine-color, 430 eight-color, 233 seven-color, 247 six-color, 159 five-color, 641 four-color, 34 three-color, 422 two-color, and 10 single-color. Specific efforts are listed below.
  - Dr. Marta Catalfamo, NIAID. The laboratory developed a nine-color immunophenotyping panel to examine protease-activated receptor-1 (PAR-1) expression in CD4+ and CD8+ T-cell subsets, monocytes, B cells, and NK cells. This assay will be used to study the effects of vorapaxar treatment on PAR-1 expression in patients with HIV infection who participate in the Attenuation of D-dimer Using Vorapaxar to Target Inflammatory and Coagulation Endpoints clinical trial.
  - Dr. Irini Sereti, NIAID. The laboratory continued to perform complex seven- and eight-color immunophenotypic analysis to investigate memory and naïve subsets of CD4, CD8, and T-reg cells in patient specimens collected from the Immune Reconstitution Inflammatory Syndrome clinical trial and the interleukin-7 (CYT107) Treatment of Idiopathic CD4 Lymphocytopenia: Expansion of CD4 T Cells clinical trial. A total of 99 patient specimens were analyzed during FY2015.
  - Dr. Irini Sereti, NIAID. The laboratory performed eight cell-sorting experiments to obtain ultra-pure populations of CD4-positive and CD4-negative cells in support of a project to study the effects of tuberculosis/HIV co-infection on long-term HIV reservoirs in HIV-infected individuals.
  - Dr. Mary Wright, NIAID. In order to study long-term T-cell memory in anthrax survivors, the laboratory utilized a CFSE-based flow cytometry assay to measure in vitro T cell–proliferative responses to anthrax-recombinant protective antigen. Specimens from 36 individuals were analyzed during FY2015.
  - Dr. Colleen Hadigan, NIAID. The laboratory continued to perform complex five-color immunophenotypic analyses of blood specimens in support of the Clinical Outcomes in Persons with HIV Acquired Early in Life clinical research protocol. Seven patient specimens were analyzed during FY2015.
  - Dr. Hiromi Imamichi, NIAID. The laboratory performed a variety of immunophenotypic determinations and cell-sorting experiments in support of several HIV proviral DNA sequencing projects.
  - Dr. Tomozumi Imamichi, Leidos Biomedical Research. The laboratory continued to perform a variety of cell cycle and cell surface marker assays to study the mechanism by which

interleukin-27 inhibits HIV-1 replication in T cells, macrophages, and dendritic cells in vitro.

- Dr. Richard Lempicki, Leidos Biomedical Research. The laboratory supported various research projects by analyzing RNA molecules using advanced multiparameter flow cytometry and by performing several cell-sorting experiments.

- Biorepository support to NIAID. AML continued to serve as the central biospecimen repository for several domestic and international clinical trials conducted by the NIAID Influenza Research Collaboration (IRC) group and the NIAID International Network for Strategic Initiatives in Global HIV Trials (INSIGHT) group. Specific biorepository projects are identified below.
  - IRC001B: A Pilot Study for Collection of Anti-influenza A (H1N1) Immune Plasma. During the past year, AML received, inventoried, processed, and stored approximately 300 plasma samples per week from three community blood banks: Mississippi Valley Regional Blood Center, Davenport, Iowa; Memorial Blood Centers, Saint Paul, MN; and Gulf Coast Regional Blood Center, Houston, TX. The specimens were processed and screened for high levels of anti-influenza antibodies in order to use that information for future influenza A (H1N1) immune plasma treatment studies or in the manufacture of high-titer H1N1 intravenous immunoglobulin. AML processed approximately 6,000 plasma specimens during the 2014/2015 influenza season.
  - IRC002: A Multicenter Study of Anti-influenza A (H1N1) Immune Plasma for the Treatment of Influenza A (H1N1) Infection. The laboratory received, cataloged, and stored approximately 1,787 specimens (sera, endotracheal aspirates, nasal swabs, and oropharyngeal swabs) from patients treated at multiple clinic sites in the U.S. Clinical specimens were also processed and forwarded to the Virus Isolation and Serology Laboratory for anti-influenza antibody testing, and forwarded to the Laboratory of Molecular Cell Biology for influenza virus detection.
  - IRC003 and IRC004: International, Multicenter Influenza Treatment Studies. During the past year, AML coordinated the receipt, inventory, and storage of approximately 13,830 IRC003/IRC004 biospecimens (sera, oropharyngeal swabs, and nasopharyngeal swabs) collected from patients treated at 41 U.S. clinic sites and 15 international clinic sites. The laboratory also shipped 1,577 specimens to the Naval Health Research Center, San Diego, CA, for protocol-mandated virology testing. AML collaborated with the IRC003/IRC004 study teams and Frontier Sciences on several projects, including the review and revision of study protocols, study manuals of operations (U.S., Mexico, Argentina, and Thailand), study-specific import documentation, the NIAID IRC Portal, and proposed study changes to increase site/participant enrollment and shipping compliance. AML represented Leidos Biomedical Research on the IRC Study Team, providing logistical/repository support on the IRC combination/operational and team/site teleconferences. AML played a key role in collaborating with Social & Scientific Systems, Inc. (SSS), to devise a Shipping Procedures Overview document for IRC-003 domestic sites. This document was created to rectify shipping concerns at the site level, summarizing shipping resources and shipment preparation for site staff. AML collaborated with IRC-003/IRC-004 study teams and Frontier Sciences to devise weekly reports for the study team denoting clinical specimens collected and received at Leidos Biomed. These reports provide direct access for study team review, and AML staff plays a key role in reviewing the reports, and communicating the identification of data queries and the documentation of sample collection/processing/receiving/virology testing concerns. AML collaborated with SSS to evaluate standardized packaging to be supplied for IRC-003 domestic sites shipping to the central biospecimen repository for the upcoming influenza season. This will be advantageous in streamlining the shipping process across sites, and protocol-specific packaging will help ensure consistency during transport.
  - INSIGHT FLU002 and FLU003: International Observational Studies of Patients with Influenza. During the past year, AML coordinated the receipt, inventory, and storage of approximately 43,739 FLU002/FLU003 biospecimens (sera, plasma, oropharyngeal swabs, nasopharyngeal swabs, and lower respiratory tract specimens) collected from patients in 18 countries. AML also coordinated the shipment of 26 INSIGHT FLU specimens to study investigators in support of various influenza projects. AML continued to represent Leidos Biomedical Research on the INSIGHT Laboratory Procedures Group and INSIGHT FLU Protocol Teams, reviewing clinical protocols, case report forms, lab manuals, and proposed use of specimens.
  - INSIGHT FLU006: Anti-Influenza Hyperimmune Intravenous Immunoglobulin Clinical Outcome Study. AML was selected to serve as the central biospecimen repository for a new, international, randomized double-blind placebo-controlled trial of anti-influenza

hyperimmune intravenous immunoglobulin (IVIG) in individuals hospitalized with influenza A or B, to determine whether, when added to standard of care treatment, IVIG helps reduce the severity and duration of flu symptoms. In preparation for this study, AML developed new programming and workflows necessary to receive, inventory, and store sera, plasma, and nasopharyngeal swabs collected from clinical sites in nine countries.

- Yellow Task 14-099. NIAID DCR requested Leidos Biomedical Research and AML to assume control and management of legacy and future biospecimens collected from several INSIGHT studies, including, but not limited to, ESPRIT, SMART, STALWART, and CPCRA IL-2 clinical trials. The legacy biospecimens, numbering approximately 330,000 vials, were previously stored at Advanced BioMedical Laboratories, LLC (ABML), under a contract held by the NIAID Division of AIDS. AML collaborated with NIAID DCR and Leidos Biomedical Research's Research Subcontracts department to establish a new subcontract with ABML that provides for the continued management, inventory, and storage of the biospecimens.

In May 2015, the NIAID Repository Projects laboratory moved from Building 434 to newly renovated laboratory and administrative space in Building 469. The move was accomplished with no interruption to the shipping and receipt of clinical trial specimens or to study team support.

Virus Isolation and Serology Laboratory

The Virus Isolation and Serology Laboratory (VISL) provides services to the Laboratories of Immunoregulation, Clinical Investigations, and Host Defenses, and the Division of Intramural Research within NIAID.

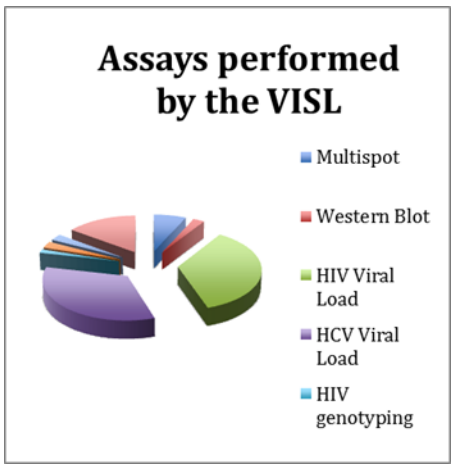
The primary mission of the VISL is to perform sequential serologic, virus detection and quantification, and genotyping studies. The results of these studies provide information for the further development of research and support the ongoing drug efficacy and epidemiology studies of the NIAID/Laboratory of Immunoregulation.

Significant Achievements

- Viral load. HIV and hepatitis C virus (HCV) viral loads continued to be the bulk of our workload. We produced 3,122 HIV viral loads and 1,756 HCV viral loads. Dr. Henry Masur at NIH has assumed the HCV protocols we monitor. We continue a collaboration with Dr. Alice Pau on her DOTCOM protocol, which involves both HIV viral load reporting and HIV genotyping.
- Influenza studies. We continue to support two large IRC)studies: the IRC001 plasma collection protocol and the IRC002 treatment protocol. Both protocols involve testing for H3N2 and H1N1, and IRC002 includes influenza B testing as well.
- Serology. Elsewhere in the serology department, we performed 591 multispot assays and 153 Western blots. In addition, we continue to pursue development of the LIPS (luciferase immunoprecipitation system) assay in our lab when time permits.
- Genotyping. During the course of the year, we have produced 100 HIV genotypes and 53 HCV genotypes for the eighth floor clinic. Our continued support of NIH is thanks to our successful transition to a new, more complex method of HIV genotyping.
- Technology Transition. We continued collaboration with the ADRD Laboratory of Immunopathogenesis and Bioinformatics in our successful quest to find a replacement for the now-retired Trugene assay manufactured by Siemens that we used for HIV genotyping. It was necessary to hire a new person to assist with this time-intensive endeavor. We are in the process of tweaking the MiSeq assay to provide even more HIV genotype information to NIH customers. Our goal of producing clinician-friendly resistance reports for the eighth-floor clinic, while providing value-added information for researchers interested in more in-depth analysis of patient samples, has been accomplished in part with the assistance of SmartGene, which continues to generate reports.
- International Studies. This is the final year for the Phidisa Project, an international collaboration with South Africa that has aimed to facilitate a treatment program for members of the South African military and their dependents. Over the past 10 years, our participation included sub-study and scientific steering committee teleconferencing every month, manuscript review, and travel to various study sites in South Africa.

A new international endeavor has been support of the PREVAIL study. We traveled to Liberia in January to help establish a lab for the first phase of the project in which participants were enrolled for vaccination against Ebola. Then, in June, we traveled again to Monrovia to assist with lab monitoring for the third phase of the trial in which Ebola survivors and their contacts were enrolled for study.

We will continue to explore new ways to meet the ever-changing needs of the clinical research community at NIH, and the challenging task of HIV/AIDS, hepatitis C, and influenza management.



Multispot	473
Western blot	168
HIV viral load	3,122
HCV viral load	1,756
HIV genotyping	100
HCV genotyping	53
HAI (NIH)	36
HAI (IRC)	1,036

Laboratory of Molecular Cell Biology

Testing for influenza viruses: The Laboratory of Molecular Cell Biology is one of two central laboratories that conducts testing on influenza samples for an international epidemiological study. The lab has tested 1,867 nasal, oral, and endotracheal swab samples for the presence of pandemic influenza, seasonal H1, H3, and influenza B viral RNAs. Samples that were indeterminants were grown in culture and retested for the influenza A and B viral RNAs. During this review period, this laboratory also tested samples from the IRC002 protocol. A total of 509 nasal swab, oral swab, and endotracheal aspirate samples were tested for the presence of pandemic influenza, AH1, AH3, and influenza B viral RNA, and then the virus present was quantitated by real-time PCR.

Quantitation of donor cells in a recipient infused with lymphocytes: A method developed in-house was used to detect and quantify the presence of unmarked donor lymphocytes in a recipient infused with allogeneic lymphocytes. Cells transfused into a recipient from a donor were successfully monitored by allele-specific PCR for a clinical protocol.

T-cell receptor excision circles (TREC) analysis: TREC levels in 33 PBMC samples were quantitated by real-time PCR. Enumeration of the number of cells harboring TRECs is considered to be a direct measure of newly matured T cells coming from the thymus. TREC data from this analysis have been used to assess whether thymopoiesis following rhIL-7 contributed to the T cell increases. A manuscript containing these TREC data has been submitted for publication.

Detection of HIV DNA and quantitation of gene-modified cells in patients' samples: DNA samples from patients enrolled in different clinical trials were tested for HIV DNA by amplifying gag, envelope, and LTR regions of HIV. Patient samples from three different clinical trials were monitored for the presence of gene-modified cells by quantitative PCR. Data show that some patients maintain a significant number of gene-modified T cells in their blood for more than 20 years after the infusion of those cells.

The sodium/iodide symporter (NIS) gene detection: The sodium/iodide symporter (NIS) is involved in iodide uptake and has been used as a sensitive and non-invasive imaging reporter for gene- and cell-based therapies. We have established an assay to detect the NIS reporter gene in macaque cells for a study on in vivo imaging of adoptively transferred hematopoietic cells in macaques. NIS levels in 110 samples were quantitated in macaque and human cells for a NIAID investigator, in order to optimize the conditions for gene transduction methods.

HIV replication in macrophages: Monocytes from human PBMCs were isolated and differentiated into macrophages to study the effect of compounds that induce cellular stress response on HIV replication. Data showed that a compound that induces interferon-induced genes inhibited HIV replication.

Progress report on the study of innate immune and stress pathways activated by thyroid hormone: Earlier results from this lab have shown that supraphysiological concentrations of thyroid hormone (T3) induce the expression of interferon-stimulated genes, activation of PKR, induction of integrated stress-response (ISR) pathways, and inhibition of vesicular stomatitis virus (VSV) replication. To understand the mechanism of this inhibition, a panel of *ISR* genes was explored, and we have identified that endoplasmic reticulum stress-response genes, *GADD34*, *CHOP*, and, *XBP1*, are significantly induced by T3. Further investigations show that GADD34 inhibitors guanabenz (GBZ) and sephin-1 (SPH) inhibit VSV replication. Future studies will explore in detail the mechanism of ISR pathways and the importance of growth arrest and DNA damage-inducible protein (GADD34), C/EBP homologous protein (CHOP), and X-box binding protein 1 (XBP1) in regulating VSV and HIV-1 replication. A manuscript containing some of these data has been submitted for publication.

Laboratory of Human Retrovirology

The Laboratory of Human Retrovirology (LHR) has evaluated potential anti-HIV activity in novel reagents and investigated the mechanism of the antiviral effect. The primary goal of the research is to develop potent anti-HIV therapies for HIV-infected patients who have virologically or immunologically failed in clinical therapy at NIAID. In the course of studies, we have found a broad

antiviral effect in IL-27 and discovered novel micro-RNAs possessing potent antiviral activity.

Characterization of the mechanism of DNA-mediated IFN-λ1 induction: LHR previously demonstrated for the first time that cytosolic foreign DNA (e.g., transfected DNA or DNA from an infected DNA virus) induces interferon lambda 1 (IFN-λ1), a potent anti-HIV cytokine, rather than IFN-β from primary macrophages, dendritic cells, and monocytes. We discovered that the IFN-λ1 induction is mediated via Ku70, a protein related to DNA repair; however, the precise mechanism of the IFN-λ1 induction remains unclear. In this period, we have investigated the signal transduction pathway in the Ku70/DNA-mediated IFN-λ1. Utilizing an immunoprecipitation assay, knock down by siRNA, and CRISPR-mediated gene editing, we found that IFN-λ1 induction involves the STING/TBK1 pathway and induces activation of IFN-regulatory factors. Currently, a manuscript is in preparation.

Evaluation of anti-HIV effect in a combination of a novel delivery system and an antisense oligo: LHR has investigated the efficiency of the anti-HIV effect using a combination of an antisense oligo against HIV and OncoImmunin's patented delivery system. The system allows delivery of any nucleotide sequence of oligos (up to 30 nt) into any cell type within 10 minutes at 100 percent efficiency. Utilizing the system, LHR has succeeded in suppressing HIV replication by more than 99.9 percent in T cells, macrophages, and PBMCs, without any cytotoxicity. The delivery system also suppressed multiple drug-resistance virus strains by more than 99.9 percent. These results indicate that the delivery system may be a useful technology in anti-HIV therapy for patients who fail from current anti-HIV regimens. LHR will continue to evaluate the impact of the delivery system on nonhuman primate models.

Neutrophil Monitoring Laboratory

The Neutrophil Monitoring Laboratory (NML) performs studies of phagocytic cell function on cells isolated from patients with recurrent bacterial, mycobacterial, and fungal infections (chronic granulomatous disease, Job's syndrome, leukocyte adhesion deficiency, IFN-γ receptor deficiency), as well as from patients with abnormal inflammatory responses (PAPA syndrome). During the past year, the NML received 1,340 samples from patients and normal volunteers, a 36 percent increase over the previous year. Among these are 246 samples that were received by overnight express mail. Analysis of samples by overnight express prevents the costly expenses incurred for patient travel and housing. The NML performed 7,031 assays of neutrophil function ($O_2^{\bullet-}$ generation, staphylocidal activity, adherence to plastic/coated surfaces, chemotaxis, degranulation, and surface-antigen expression by flow cytometric analysis). The NML work scope also includes analyzing cytokine production (up to 10 cytokines) using multi-array cytokine analysis of stimulated PBMCs. An extensive panel of cellular stimuli, including many toll-like receptor ligands, is used to determine the integrity of specific ligand–receptor cell signaling that may be associated with specific immune dysfunction. Over the past year, 1,419 assays of cytokine production by cultured PBMC were performed. In the performance of the above work, the NML has determined 27,656 analytes (cytokines, lactoferrin, gelatinase, defensins, and other immunoregulators) by multiplex array and ELISA.

Characterization of patients with chronic granulomatous disease

Diagnosis of chronic granulomatous disease (CGD): CGD is a rare genetic immunodeficiency that is caused by mutations in *CYBA*, *CYBB*, *NCF1*, *NCF2,* and *NCF4,* encoding for $p22^{phox}$, $gp91^{phox}$, $p47^{phox}$, $p67^{phox}$, and $p40^{phox}$ of the NADPH oxidase enzyme complex (NOX2). CGD is characterized by a failure of phagocytes (neutrophils, monocytes, macrophages and eosinophils) to generate superoxide and other related reactive oxygen species (ROS), leading to recurrent infections, granulomatous complications, and premature death. To diagnose CGD, the NML offers several assays that assess ROS production by patient neutrophils. Once a diagnosis of CGD is established, the NML performs immunoblotting of neutrophil extracts to characterize the specific protein deficiency in patients with CGD. Using only one vial of frozen neutrophils (5×10^6 cells), the NML can perform four separate Western blots that are developed with antibodies provided by the Laboratory of Host Defenses. In the past year, the NML analyzed human polymorpho-nuclear neutrophils (PMNs) from 19 patients and normal volunteers, and identified the following defects:

- p47phox defect (immunoblot negative) – 4 individuals
- gp91phox defect (immunoblot negative) – 12 individuals

Based on the identity of the defective protein by immunoblotting, the NML forwarded DNA and RNA samples to the Genomics Laboratory, Leidos Biomedical Research, for genomic and cDNA sequence analysis. In the past year, the following mutations have been determined:

- $gp91^{phox}$ (X-linked CGD) – 29 patients, carriers, or kindred
- $p22^{phox}$ (autosomal CGD) – 1 patient
- $p67^{phox}$ (autosomal CGD) – 1 patient
- $p40^{phox}$ (autosomal CGD) – 2 patients or kindred

Sequence analysis of patients with $p47^{phox}$ CGD: CGD is caused by defects in any one of five subunits of the phagocyte NADPH oxidase, including $p22^{phox}$ (less than 5 percent of CGD patients), $p47^{phox}$ (approximately 30 percent of CGD patients), $p67^{phox}$ (less than 5 percent of CGD patients), $gp91^{phox}$ (approximately 65 percent of CGD patients), and $p40^{phox}$ (one reported case). CGD neutrophils, monocytes, macrophages, and eosinophils

fail to generate sufficient ROS, leading to recurrent infections, granulomatous complications, and premature death. In general, identification of the specific genetic defect in $p22^{phox}$, $p67^{phox}$, $gp91^{phox}$, and $p40^{phox}$ can be easily obtained by traditional Sanger sequencing. However, identification of the specific genetic defect in patients with $p47^{phox}$ CGD (*gene NCF1*) is complicated by the presence of two highly homologous (greater than 98 percent) pseudogenes that are thought to have arisen through gene duplication. The wild-type *NCF1* gene has a GTGT at the start of exon 2, while the pseudogenes (*NCF1B* and *NCF1C*) contain a GT deletion (ΔGT) (see Figure 1).

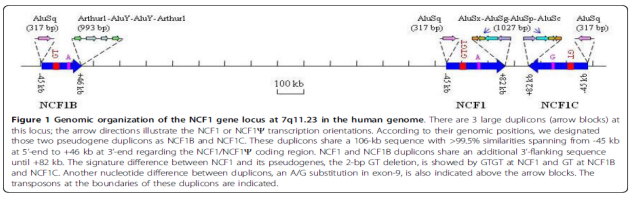


Figure 1 Genomic organization of the NCF1 gene locus at 7q11.23 in the human genome. There are 3 large duplicons (arrow blocks) at this locus; the arrow directions illustrate the NCF1 or NCF1Ψ transcription orientations. According to their genomic positions, we designated those two pseudogene duplicons as NCF1B and NCF1C. These duplicons share a 106-kb sequence with >99.5% similarities spanning from -45 kb at 5'-end to +46 kb at 3'-end regarding the NCF1/NCF1Ψ coding region. NCF1 and NCF1B duplicons share an additional 3'-flanking sequence until +82 kb. The signature difference between NCF1 and its pseudogenes, the 2-bp GT deletion, is showed by GTGT at NCF1 and GT at NCF1B and NCF1C. Another nucleotide difference between duplicons, an A/G substitution in exon-9, is also indicated above the arrow blocks. The transposons at the boundaries of these duplicons are indicated.

Figure 1. *Brunson et al., BMC Genetics, 2010 11:13 doi:10.1186/1471-2156-11-13*

Unequal crossing over between the wild-type *NCF1* gene and these highly homologous pseudogenes is thought to account for the majority of mutations in $p47^{phox}$-deficient CGD by inserting the pseudogene-derived ΔGT into *NCF1*. Because of the high degree of homology between the wild-type gene and pseudogenes, standard Sanger sequencing has proven to be inadequate for assigning a specific genetic mutation in these patients. We have developed a protocol using droplet digital PCR that can differentiate those patients with the ΔGT mutation from patients with other mutations in *NCF1* (see Figure 2). Using this analysis, we can accurately segregate the populations into those CGD patients (red circle, 86 percent of all $p47^{phox}$ CGD patients) and CGD carriers with ΔGT mutations (purple circle), and those patients (blue circle) and carriers (green circle) with mutations other than the ΔGT mutation. The dotted lines represent the theoretical predicted values for one copy of GTGT/six total copies of NCF1 and its pseudogenes (= 0.17), two copies of GTGT/six total copies (= 0.33), etc. Moreover, this assay can accurately determine the carrier status of other kindred within CGD families. This single assay eliminates the need for further analysis in 120 of 144 (86 percent) $p47^{phox}$ CGD patients, carriers, and kindred.

It is interesting to note that among the normal subjects tested, a significant number exhibited more than the expected two copies of GTGT, with sixteen individuals showing three copies (11.5 percent of subjects tested) and four individuals exhibiting four copies (3 percent of subjects tested). These data suggest that while unequal crossing over can lead to insertion of the ΔGT into the *NCF1* gene, it can also lead to the unequal distribution of *NCF1* and its pseudogenes in daughter cells.

In the past year, 251 DNA samples have been analyzed for *NCF1* and copy number variation by droplet digital PCR. These samples include DNA from 137 normal subjects segregated into four ethnic groups—Caucasian, Asian, African American, and Hispanic—to confirm ethnic differences in copy number that have been reported by other investigators. Thus far, we have not been able to confirm those differences.

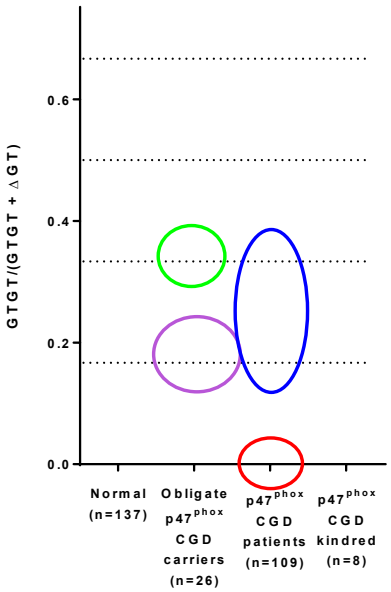


Figure 2. *Droplet digital PCR determination of the number of copies of GTGT vs. ΔGT in normal subjects, obligate $p47^{phox}$ CGD carriers, $p47^{phox}$ CGD patients, and $p47^{phox}$ kindred. The dotted lines indicate one GTGT of six total copies (= 0.17), two of six (= 0.33), three of six (= 0.5), and four of six (= 0.67).*

Development of luminol-enhanced chemiluminescence to monitor ROS production in neutrophils: Luminol-enhanced chemiluminescence can be used as a sensitive, peroxidase-dependent measure of ROS, detecting both intracellular and extracellular ROS production, though it may not detect them with equivalent efficiency. This versatile assay, in addition to its quick and easy setup, offers the capability of testing several different subjects and stimuli on the same plate, using reduced amounts of cells and providing high sensitivity. Results from normal subjects and patients can be assessed simultaneously and monitored kinetically or using the area under the curve (AUC). The NML has developed this assay to complement its other assays of ROS production. The NML has established normal ranges for both soluble (fMLF and PMA) and particulate stimuli (opsonized zymosan) shown in Figure 3. In addition, the NML has begun performing luminol-enhanced chemiluminescence studies on patients with CGD and carriers of CGD for comparison with other established measures of ROS production such as superoxide dismutase-inhibitable ferricytochrome c reduction.

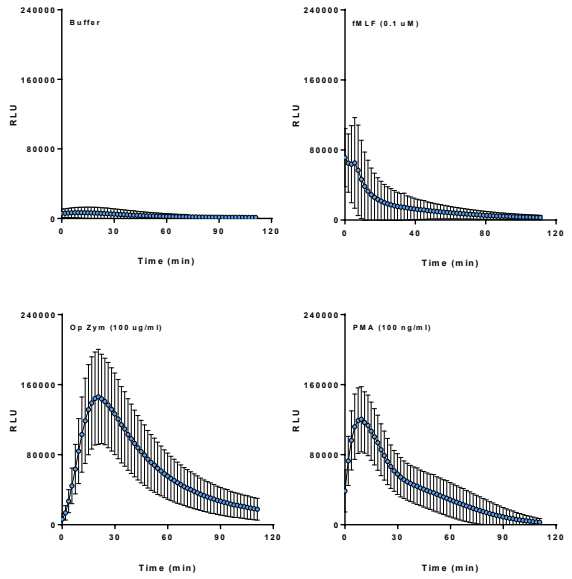


Figure 3. *Detection of ROS production by luminol-enhanced chemiluminescence and determination of the responses of neutrophils isolated from normal subjects (mean ± SD, n = 58).*

Development of new assays to characterize patients with other primary immunodeficiencies

Development of assays to assess neutrophil extracellular trap (NET) formation: PMNs are the most abundant nucleated cells in circulating blood (2–8 x 10^6 per ml). They have a characteristic multi-lobed nucleus that may predispose them to NET formation. If activated, PMNs may extrude their DNA and form NETs; release the contents of their granules, which can be associated with the NETs; produce inflammatory mediators and ROS; and engulf microbes through phagocytosis. In vivo, NET formation is stimulated by bacterial and fungal infections, and NETs are found in abundance at sites of infection. To undergo NETosis, a unique form of cell death, neutrophil DNA undergoes de-condensation, a process mediated by peptidyl arginine deiminase, type IV (PADI4). PADI4 catalyzes the conversion of peptidyl arginine to citrulline, particularly on histones 3 and 4, reducing the cationic nature of the histones, reducing histone:DNA compaction, and eventually forcing extrusion of DNA from the cell. The activity of PADI4 is Ca^{2+}-dependent (binds up to five Ca^{2+}), and the protein is activated during PMN activation. PMNs from patients with type I and II diabetes showed increased NET production when stimulated with ionomycin, compared to PMNs from healthy subjects. Wound healing in diabetes patients may be delayed due to the cytotoxic effects of NET production. Similar cytotoxic effects observed in the lungs of patients with cystic fibrosis have been attributed to NET formation. NETs have also been shown to be involved in the pathogenesis of preeclampsia, rheumatoid arthritis, and lupus.

In order to develop a better understanding of the signaling pathway, the mechanisms, and the contents of NETs, we have begun to develop and optimize assays to quantitate NET formation in neutrophils using fluorescent DNA probes that only bind to extracellular DNA (Figure 4).

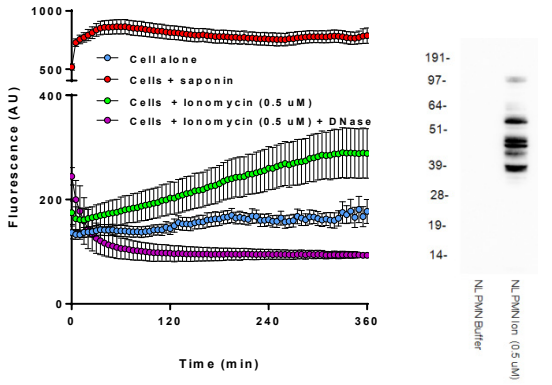


Figure 4. *NET formation in peripheral blood neutrophils. The panel on the left represents the temporal release of DNA after treatment with the buffer (blue circles) or with the Ca^{2+} ionophore, ionomycin (0.5 uM, green circles). The data represent the mean ± SD, n = 5. The panel on the right depicts the citrullination observed in neutrophils after treatment with ionomycin for two hours.*

Treatment of cells for six hours with ionomycin induces a significant release of DNA from normal neutrophils compared to untreated neutrophils, a process that was completely abrogated by adding DNAse. Adding the detergent saponin yields a maximum fluorescence response. Initially, we have focused on agonists that are Ca^{2+}- mediated, such as ionomycin and thapsigargin, but we plan to extend these studies to other agonists, such as PMA, IL-8, LPS, and LPS-activated platelets. In addition, we plan to monitor PADI4 activity by immunoblot analysis of neutrophil proteins using anti-citrulline antibodies (shown in the right panel of Figure 4). We have identified several patients with damaging mutations in PADI4. We plan to investigate the impact of these mutations on the pathophysiology of the disease process in these patients.

Quantitation of neutrophil spreading: Cell spreading is a vital process in the innate immune response of human neutrophils to invading pathogens. In peripheral circulation, neutrophil rolling along the endothelium is mediated through transient associations with selectins on the endothelium. Chemical signals heralding the presence of invading microbes induce the spread of neutrophils on the endothelium, resulting in neutrophil integrin activation and a firmer attachment to the endothelium. This serves as a prelude to transendothelial migration of neutrophils into the infected tissue. These dramatic changes in cell morphology require rearrangement of the actin cytoskeleton. Defects in the actin polymerization: depolymerization pathway lead to disruption of neutrophil spreading. Neutrophil spreading can be mimicked in vitro. In suspension, neutrophils are primarily spherical.

However, as they settle onto a glass slide, they undergo a morphological change to a spread "fried egg" appearance. Using time-lapse photomicroscopy to collect the images and imaging software to analyze the images, the area of individual cells was determined in sequential images obtained from t = 0 to t = 10 minutes. As shown in Figure 5, neutrophils from normal subjects undergo a rapid two-fold increase in area within 3 minutes, followed by a prolonged slower increase through 10 min. Patients with a defect in actin interacting protein 1 fail to exhibit normal spreading of their neutrophils.

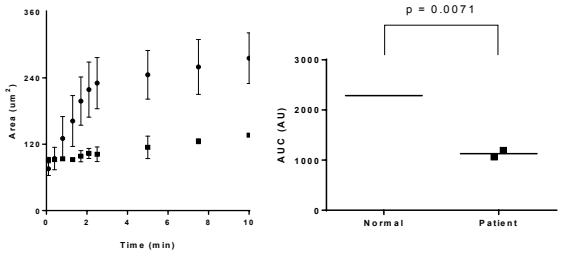


Figure 5. *Cell spreading of neutrophils is defective in neutrophils isolated from patients with mutations in actin-interacting protein 1 (AIP-1) compared to neutrophils isolated from normal subjects. The panel on the left represents the temporal change in area of neutrophils isolated from normal subjects (n = 7, solid circles) and from patients with mutations in AIP-1 (n = 2, solid squares) undergoing spreading on a glass slide. The panel on the right represents the area under the curve (AUC) for the normal subjects and in the patients depicted in the left panel. An unpaired t-test shows a significant difference in the AUC between the normal subjects and the patients.*

Genetic analysis of other immunodeficiencies: In addition to providing sequence analysis for identification of the genetic defect in patients with CGD, the NML provided sequence analysis for Crohn's disease, leukocyte adhesion deficiency, WHIM (warts, hypogamma-globulinemia, infection, and myelokathexis) syndrome, and other neutrophil disorders. In the past year, the NML has isolated and forwarded 262 DNA samples to the Genomics Laboratory for genetic analysis associated with specific immune deficiencies.

- CXCR4 (WHIM disease) – three individuals
- ITGB2 (leucocyte adhesion deficiency) – two individuals
- WDR1 (AIP-1) – one individual
- PADI4 – five individuals

Expansion of the NML into Building 310, Room 106

The relocation of the Laboratory of Immunopathogenesis and Bioinformatics to Building 469 afforded an opportunity for the NML to expand into vacated adjoining laboratory space. The NML redesigned its existing lab space and the new space to increase the efficiency of sample processing within the laboratory. It is anticipated that the modest renovations to the space will occur in the fall of 2015, with a planned occupation of the new space by the end of 2015.

Repository of biological samples for NIH investigators

The NML serves as a repository for patient biological samples collected under specific protocols by investigators at NIH. In the past year, 14,346 vials of plasma, serum, mononuclear cells, and neutrophils were stored in the Central Repository for future use. The NML has cultured an additional 306 EBV-transformed B cell lines, cryopreserving 2,715 vials. All cell lines were tested for mycoplasma contamination to ensure that cell lines being forwarded to other investigators were contaminant free. These cell lines have proven to be a valuable source of DNA and RNA to confirm genetic mutations in CGD. In the past year, the NML has established 21 primary fibroblast cultures from punch biopsies; 235 vials of fibroblasts have been cryopreserved. The NML prepared 187 shipments, totaling 1,178 samples (DNA, RNA, EBV cell lines, plasma, cells), for further analysis. The shipments were forwarded to other Leidos Biomedical Research laboratories, physician investigators at NIH, and outside testing facilities.

Immunological Monitoring Laboratory

In support of the Laboratory of Clinical Infectious Diseases, the Laboratory of Host Defenses, and the Laboratory of Infectious Diseases, NIAID (APO/H 88-020), the Immunological Monitoring Laboratory (IML) has performed immune function studies on patients in a wide variety of protocols. The IML is continuing its involvement with a clinical trial for the treatment of Crohn's disease using the anti-IL-12 antibody, ustekinumab. In collaboration with Drs. Lesia Dropulic and Jeff Cohen, the IML has completed 89 percent of the first human herpes simplex virus 2 (HSV2) vaccine protocol designed to prevent genital herpes disease. The vaccine is ACAM-529, a live attenuated HSV viral strain backed by Sanofi Pasteur that has not yet been tested in humans. As the HSV529 protocol winds down, the IML will now enter into a pilot study directed by Dr. Dropulic to evaluate safety and estimate disease frequency after human challenge with wild-type recombinant respiratory syncytial virus A2.

Significant Achievements

- In the past 12 months, PBMCs, plasma, and serum from 882 patient blood samples were isolated and cryopreserved, representing a 27 percent increase from last year. The IML isolated 6,031 vials of cells (a 43 percent increase over last year); 1,793 vials of plasma and 4,155 vials of serum (a 41 percent increase over last year; 835 vials of whole blood; 183 vials of RNA or DNA; and 373 frozen DNA lysates from these patients and volunteers.
- Having completed the Fas–autoimmune lymphoproliferative syndrome (ALPS) protocol, the IML is now continuing its collaboration with the newly formed Clinical Genomics Unit, Laboratory of Immunology, NIAID, headed by Dr. Koneti Rao.

This section will continue to evaluate patients with ALPS-like symptoms who do not have mutations in genes usually associated with this syndrome (Fas or Caspase mutations). Other patients with novel genetic disorders not presenting like the ALPS syndrome will also be studied under the purview of this new initiative.

- The IML, along with Drs. Warren Strober and Ivan Fuss, have engaged in a new clinical protocol looking at the mechanisms associated with ustekinumab anti-IL-12 antibody treatment of common variable immune deficiency in patients who have associated GI involvement. Our aspect of the protocol will involve assessing the level of RNA activation of 14 cytokine and chemokine markers usually associated with the elevation of autoimmune symptoms associated with this syndrome. The Quantigene kits from Affymetrix that are necessary for quantifying the RNA level of these markers have been ordered, and patient recruitment is under way.
- In cooperation with Dr. Adriana Marques (Laboratory of Clinical Infectious Diseases, NIAID) and the NCI at Frederick Central Repository, the IML has been directing the re-labeling over 5,000 vials in its possession that have been labeled over the last 20 years using patient identifiers. The labels will now be transferred to Dr. Marques' protocol, and the vials will be labeled with a single repository code number, with Dr. Marques and the IML having the codes in protected databases. This will reduce the cost of storage from the IML budget, eliminate patient information on these old vials, and make retrieval of these samples much easier and less time consuming.
- The IML is continuing two rhesus monkey vaccine protocols in collaboration with Drs. Jeff Cohen, Sarah Valencia, and Wei Bu in the Laboratory of Infectious Diseases: the LID 31#1 CMV vaccine study and the LID 12 EBV vaccine study. These new experiments are now in the early stages of examining new protocols for assuring that the challenge of the monkeys with the virus will indeed infect the control animals. Therefore, we are continuing to isolate the viral DNA from urine and throat-wash samples from the monkeys in the early stages of these protocols, and then using RT-PCR to determine the CMV and EBV viral gene copy levels in these tissues. The IML will continue to perform RT-PCR studies on the throat-wash and urine samples from the EBV vaccine protocol, looking for the viral gene, BAM-H1, that was determined to be a more sensitive marker of infection since there are seven copies of this gene in the EBV genome.
- The IML assayed 11 cytokines from patients having persistent EBV infections associated with mutations in the IRAK4 gene. The patients' PBMCs were stimulated in vitro in our lab with stimulators associated with the activation of TLR 1 through TLR 9. The TLR mutation patients showed several differences in the degrees of responsiveness to several of the TLR stimuli that may help explain the mechanism behind the persistence of the EBV infections in these patients. A similar study is also in the planning stages for a patient with a mutation in the TRA3 gene.

The IML has processed the blood products from 89 percent of the HSV529 vaccine protocol volunteers. This protocol enrolled 60 volunteers that will be vaccinated three times with the ACAM-529 live-attenuated HSV strain over a six-month period, with blood samples harvested at ten key intervals over a one-year period. At every interval, PBMCs and serum samples have been frozen and stored, with cell lysates having been produced and stored for every PBMC sample. Seventy-five percent of the PBMC samples destined for distribution to Drs. David Koelle and Nancy Hoskin at the University of Washington have been sent in six batches via our LN2 cryoshipper. The cells processed by our laboratory are now being used by Drs. Koelle and Hoskin in ELISPOT and viral activation assays at the University of Washington. Over 90 percent of the samples used by Drs. Koelle and Hoskin showed greater than 90 percent viability 24 hours post-thaw, with the rest of the viabilities in the high 80-percent range. PBMC and serum samples that are to be distributed to the Center for Human Immunology, Autoimmunity and Inflammation (CHI), a trans-NIH initiative, will be sent when the harvesting portion of the protocol has been completed, which is anticipated to occur in December. The ADRD courier group was instrumental in delivering these time-sensitive samples as quickly as possible after they were obtained from the volunteers. The delivery speed of these samples was a condition mandated by our CHI collaborators to ensure that data from samples processed in our lab will yield similar results to those processed by the CHI.

Division of Clinical Research Office of the Director Project/Program: Research and Laboratory Support (Radiochemistry)

ADRD provides staffing in Building 21 in Bethesda, embedded in the laboratory of Dr. Chaig Paik, head of the Radiopharmacy Section, Clinical Center. The Leidos Biomedical Research senior scientist primarily provides support to Dr. Michele Di Mascio, chief, AIDS Imaging Research Section. Project support included the following:

- Provided support to a longitudinal SPECT imaging study using Tc-99m-labeled F(ab')2 CD4 to evaluate lymphocytes in tissues in real time following whole-body irradiation and reinfusion of vector-transduced, autologous CD34+ cells.
  - Prepared radiotracers for more than 15 doses in rhesus macaques, including fragmentation of antibodies to prepare and purify F(ab')2.
  - Performed conjugation and radiolabeling with Tc-99m.

  - Prepared radiotracers and performed testing of test subject plasma samples to detect the production of antibodies to F(ab')2 CD4 using cell-binding incubation and size-exclusion high-performance liquid chromatography.
- Provided support to a study to evaluate myocardial fibrosis detection in rats and dogs using non-invasive microPET imaging, including performing binding kinetics using multiple platforms:
  - ELISA and flash plate
  - Biolayer interferometry (Blitz and Octet)
  - Surface plasmon resonance (Biacore)
- Developed a radiolabeling method for duramycin for use in mPET imaging in rats.

Laboratory of Parasitic Diseases

The Clinical Support Laboratory (CSL) provides dedicated staffing to perform clinical sample processing for the Laboratory of Parasitic Diseases, including isolation of serum and plasma, cell isolations by density gradient separation, and immunomagnetic bead separation to isolate purified eosinophils. During FY2015, CSL received samples from 15 clinical protocols, with receipt of samples from 451 patient visits. CSL performed approximately 105 eosinophil isolations and prepared 5,820 aliquots of clinical materials for return to NIAID investigators.

Laboratory of Molecular Microbiology

CSL provides dedicated support to Dr. Malcolm Martin, Laboratory of Molecular Microbiology, for processing blood samples obtained from macaques and other nonhuman primates involved in simian immunodeficiency virus (SIV) vaccine studies. The laboratory received approximately 1,420 blood samples for separation of mononuclear cells and plasma, and generation of cell pellets for DNA extraction. Approximately 4,600 aliquots of mononuclear cells, 115 cell pellets, and 13,000 vials of plasma were produced for storage in the NCI at Frederick Central Repository or return to the investigators as requested. The laboratory also prepared shipments of samples for return to Bethesda.

Additional ADRD Program Support

Data Management Group

The Data Management Group (DMG) was formed in 1990 to meet the needs of the Clinical Services Program (CSP) scientific and administrative staff. The DMG currently supports over 125 users and 300 equipment items, including network servers, workstations associated with scientific equipment, administrative and scientific staff workstations, and mobile IT devices. The DMG has been instrumental in the development of CSP program-specific database tracking systems and scientific computer programs. The group constantly evaluates the computer needs of the CSP. Administrative and laboratory functions are analyzed to determine where procedures can be automated to save work hours. Workstations and networking equipment are monitored and upgraded to fit the growth of scientific data processing and storage. The group makes a consistent effort to provide the latest technology in networking and computer programming, and ensures compliance with security requirements to protect data and patient confidentiality. The DMG consists of two sections: Programming Support and the Network Office.

NIAID: The DMG currently supports NIAID users and equipment items, including network servers, workstations associated with scientific equipment, administrative and staff workstations, and mobile IT devices. The DMG has also been instrumental in the development of CSP program-specific database tracking systems and scientific computer programs. Significant achievements are listed below.

- AML Six-Color Flow Program – The DMG designed and wrote a new program used by the AML Clinical Flow Cytometry Group for the extraction of six-color lymphosum monocloncal antibody testing result data used for clinical immunophenotyping. The program processes patient data in batches, eliminating many man-hours of manual data extraction and calculations. In addition to performing all the necessary flow analysis calculations required for reporting clinical data to NIH, the program extracts the data and performs quality control checks for the generation of QC reports.
- AML Eight-Color Flow Program – The DMG designed and wrote a new program used by the AML Clinical Flow Cytometry Group for the extraction of antibody testing result data for a new eight-color custom-lyophilized monoclonal antibody panel. The program processes patient data in batches, eliminating many man-hours of manual data extraction and calculations. In addition to performing all the necessary flow analysis calculations required for reporting the clinical data to NIH, the program extracts the data and performs quality control checks for the generation of QC reports.

CSP Administration: CSP Shared Services Program – The DMG designed and wrote a new financial system used by the ADRD associate director and CSP financial staff to track laboratory labor and supplies, courier services, sample processing costs, and other miscellaneous charges incurred on a monthly and yearly basis. Laboratory and administrative personnel enter their costs directly into the system for real-time access and processing of laboratory costs and charges. This system replaces an obsolete system by providing better tracking of shared services costs based on new financial charge codes. The program is used for generating internal financial reports and files that are used for cost

verification before monthly CSP financial data is sent to the Leidos Biomedical Research Finance Department.

Laboratory of Cell-Mediated Immunity

- In response to CSAS-17049, the laboratory performed three sets of three- and six-day proliferation assays to evaluate the proliferative response of cells from normal monkeys against the mitogen phytohemagglutinin, pokeweed, and a pool of allo-stimulator cells in a mixed lymphocyte culture, in the presence and absence of bone marrow stromal cells at multiple concentrations. A total of 174 tests were performed.
- LCMI performed 1,289 proliferation, ELISPOT, and ^{51}Cr-release assays at the request of Dr. Doug Kuhns, Leidos Biomedical Research, in support of CSAS-16922 and CSAS-16923.
- LCMI performed 48 ELISPOT tests at the request of Dr. Ven Natarajan, Leidos Biomedical Research, in support of CSAS-17659.

Clinical Support Laboratory

In support of Dr. Michele Di Mascio, CSL performed analysis on approximately 275 blood samples, for a total of 1,150 tests, obtained from rhesus monkeys infected with SIV or from controls to evaluate lymphocyte subsets as part of a whole-animal imaging study. Plasma was also prepared and frozen from these samples. The samples were primarily received from a NIAID-supported animal facility in Poolesville, MD.

In support of Dr. Marta Catalfamo, CSL provided flow cytometry support to a nonhuman primate study of IL-15 and anti PD-L1 in SIV. The immunophenotyping panel evaluated changes in lymphocyte subsets, including memory and effector T-cell subsets, as well as activation and proliferation markers. A total of 36 nonhuman primate samples, for a total of 336 tests, were analyzed. Blood samples were also processed for isolation of PBMCs that were cryopreserved for future immune function analysis, and plasma was recovered and stored. In addition, the laboratory performed three assays on a total of 21 samples to evaluate if monkeys developed antibodies to IL-15.

CSL provided sample processing support to Dr. Michail Lionakis of the Fungal Pathogenesis Unit for Protocol 13-I-0187. Approximately 25 whole-blood samples were received for Ficoll separation and QIAzol-treated aliquot preparation, with 240 aliquots stored in the NCI at Frederick Central Repository.

Support Provided by the Clinical Monitoring Research Program

Clinical Consulting and Support

The Clinical Consulting and Support (CCS) group was established in the fall of 2004 to support NIAID's special initiatives and projects. CMRP provides specialized management, logistics, administrative, and programmatic support for various NIAID Division of Clinical Research (DCR) and Division of Intramural Research (DIR) initiatives, including establishment and maintenance of research subcontracts; financial management; travel, conference, and meeting coordination; building management; and overall administrative support. CCS consists of 13 staff members, three of whom provide part-time support.

During FY2015, CCS assisted in recruiting and hiring 60 positions; established and maintained 120 research subcontracts and consulting, blanket order, and direct pay agreements; prepared 128 international and 185 domestic employee and non-employee travel packages, as well as obtained 113 urgent foreign visas from the embassies of Liberia, Sierra Leone, and Guinea; coordinated arrangements for nine conferences, seminars, retreats, and training sessions; coordinated 24 domestic shipments and five international shipments of clinical research material; printed and shipped 3,000 plasma labels; coordinated the preparation and printing of one poster; completed 520 courier runs; and provided acquisitions support, including purchasing and property.

The current reporting period also included a high volume of support to the Ebola response. This involved urgent procurement and shipping of supplies to Liberia, Sierra Leone, and Guinea; recruitment assistance for new positions; preparation of urgent travel packages; additional courier runs to the embassies of Liberia, Sierra Leone, and Guinea, as well as to the U.S. State Department; and delivery of medical supplies from the NIH Clinical Center Pharmacy Department to Fort Detrick. Additionally, CCS provided NIAID DCR with logistical support for the new Partnership for Research on Ebola Vaccines in Liberia (PREVAIL) vaccine clinical trial in Monrovia, Liberia. Many hours and long days were dedicated to ensure PREVAIL I could successfully launch as planned in late January 2015. Efforts are underway for PREVAIL I to begin in Guinea during FY2015. The CCS group also provided the same operational support to meet the urgent start date of PREVAIL II, an Ebola treatment study in Liberia, Sierra Leone, and Guinea, as well as the study initiation for PREVAIL III, an Ebola natural history study of survivors in Liberia in June 2015.

CCS provided conference support for U.S. Ebola protocol meetings, DSMB meetings, and on-site protocol and operation meetings in Liberia. Also in response to the urgent Ebola effort, CCS created and maintained a comprehensive tracking system to track orders from creation, receipt, shipment, and receipt in-country. Daily communications are sent to project teams to keep all parties abreast of the latest status of project requests. A revised tracking system has been created with storage via a SharePoint site to streamline access by project personnel, thereby reducing e-mail communications to seek information regarding purchases.

The Clean Sweep initiative was also supported by CCS. The scope of this urgent project included a comprehensive search for potentially hazardous biological materials in assigned spaces, both government-owned and leased facilities. Each directorate was responsible for documenting that the search was completed for its assigned spaces. CCS staff provided the logistical support to complete the initial sweep of CMRP buildings and coordination for the independent verification review.

An overview of the specific support services provided by the CCS group during the past year follows.

Research Subcontracts Management

The CCS group administers and oversees the establishment of research subcontracts in support of specific international and domestic NIAID research efforts. Activities include preparing Statements of Work (SOWs), overseeing research subcontractor progress; monitoring budgets, and collaborating with NIAID project officers to ensure the SOW objectives are met in a timely and efficient manner.

During FY2015, a consolidated Excel spreadsheet was utilized to compare the information in each of the managed agreements with the SharePoint site and Cognos financial management applications. The spreadsheet, which is shared with the CMRP director, allows for a better understanding of the status of each agreement and ensures that the information is consistent between the executed agreements, the Cognos applications, and CMRP's Research Subcontracts SharePoint site.

An Excel file was also utilized as a research subcontract tracking tool; it includes separate spreadsheets for each agreement and provides up-to-date detailed information regarding each agreement. The tracker information is updated daily and cross-referenced with the executed agreement documents and the Cognos applications, which helps to highlight any discrepancies. The spreadsheet has been shared with other staff members managing agreements and has now been implemented on a wider scale.

The CCS group continued to collaborate with CMRP colleagues regarding CMRP's Research Subcontracts SharePoint site, to include ways to manage the new project ID account numbers and perform audits to confirm the integrity of the information within the CMRP Research Subcontracts SharePoint site.

Throughout FY2015, the CCS group supported research subcontracts and agreements as follows:

- Managed research subcontracts with PPD, Inc., which include a Basic Ordering Agreement (BOA) and multiple task orders (TOs) for continued clinical monitoring efforts in support of ongoing international clinical trials. To date, there are a total of 10 TOs with PPD supporting various international clinical trials.
- Managed three research subcontracts in support of the Phidisa Project in South Africa: (1) a BOA with Bioanalytical Research Corporation (BARC), which was maintained in the event there was a need to support close-out activities at BARC; (2) a research subcontract with Dr. Sean Emery to provide support to the Phidisa Project and other international efforts; and (3) a research subcontract with Mr. Nicolaas Pool.
- Managed research subcontracts with Ms. Ellen Cull to provide support for leadership and organizational development for the NIAID Office of Planning and Operations Support (OPOS).
- Managed a research subcontract with the Turner Consulting Group to provide data governance and management in support of the Integrated Research Facility (IRF).
- Managed a consulting agreement with Ms. Gillian Morgan to provide a variety of strategic planning and organizational development services for DCR.
- Managed a blanket order agreement with Progenitor Cell Therapy, LLC, for the processing of peripheral HIV and blood stem cells for the protocol titled, Immunologic and Virologic Response in HIV-Infected Progressors after Infusion of Lymphocytes from HIV-Infected 'Elite' Long Term Non-progressors.
- Managed a BOA and two TOs with Knovex, LLC, in support of the DCR Leadership Development initiative.
- Managed a research subcontract with Martin Michael in support of the Barriers to Clinical Research initiative.
- Managed a research subcontract with the HIV Resistance Response Database Initiative (RDI) for modeling various antiretroviral therapy responses.
- Managed research subcontracts and blanket order agreements with Digital Infuzion, Iron Mountain, Palladian, ALL-Shred, and Fisher BioServices in support of the Office of Clinical Research Policy and Regulatory Operations (OCRPRO).
- Managed a research subcontract with Biologics Consulting Group, Inc., in support of DCR's research and development initiative for the recombinant human interleukin-15 (IL-15) study.
- Managed a research subcontract with Matthews Media Group to provide Institutional Review Board (IRB) meeting materials in support of OCRPRO.
- Prepared and managed a research subcontract with Professional Education Services Group (PESG) to provide accreditation services for Intramural Clinical Management and Operations Branch (ICMOB) clinical staff.
- Prepared and managed a new research subcontract with Delphine Yamadjako to provide clinical monitoring services for international clinical trials in West Africa.
- Awarded a new agreement with PPD to provide clinical trial monitoring services for a Phase II randomized, double-blind, placebo-controlled study of the safety and immunogenicity of two doses of the LID/NIAID live attenuated tetravalent Dengue

vaccine (TV003) administered six months apart to healthy adults, adolescents, and children in Thailand.

- Established a new agreement with Khon Kaen University, located in Thailand, to continue follow-up visits with subjects enrolled in an ongoing clinical study titled, Mycobacterial and Opportunistic Infections in HIV-Negative Thai and Taiwanese Patients Associated with Autoantibodies to Interferon-γ (NIAID Protocol Number: 09-I-N060). Although the study supports the Division of Intramural Research (DIR), PPD is the clinical monitor for this study under an agreement in support of DCR.

During the reporting period, assistance through the acquisition process was provided to the training group to expand the current scope of work of Professional Educational Services Group (PESG) to allow PESG to provide accreditation services for a training event being held for DCR clinical research professionals. The acquisition process proceeded through obtaining a quote; however, the acquisition was cancelled as a decision was made to perform the accrediting services in-house rather than to have it outsourced. Ongoing management of approximately 22 active agreements of various types continued through the reporting period. These agreements included services for clinical trials monitoring support as well as repository and consulting services for program support.

Financial Management

The CCS group provides support to the CMRP Financial Management group with budget preparation and spending predictions utilizing the CMRP Financial Management SharePoint site. During the reporting period, close-out of the FY2014 DCR annual budget was completed, as well as four rounds of spending predictions for FY2015. Budget preparation for FY2016 also occurred.

Travel, Conference, and Meeting Coordination

The CCS group provides travel coordination for nongovernment and CMRP employees involved in major NIAID initiatives. The group coordinates international and domestic meetings, conferences, and training for nongovernment participants collaborating on many long-term clinical research initiatives. The services include arranging visits by domestic and/or foreign scientists and officials to various national and international locations to attend meetings, conferences, planning sessions, and program discussions; developing detailed travel itineraries; providing guidance to U.S. and foreign travelers in obtaining passports and/or visas; arranging ground transportation as necessary; arranging hotel or other lodging accommodations; making direct contact with the host and the traveler to ensure all arrangements are mutually understood; and providing reimbursement upon receipt of an expense statement for appropriate expenses relating to travel.

Building Management

The CCS group provides support to a leased building in Frederick, MD. This facility houses CMRP employees working in support of NIAID, DCR. CCS staff guides and coordinates all areas of lease oversight, facilities maintenance, facility renovation and design, staff relocations, issue troubleshooting, preventive maintenance schedules, and coordination with outside vendors. Over the last year, several facility projects required extensive support, including the transition of the existing phone system and infrastructure to Voice over Internet Protocol (VoIP).

Administrative Support

The CCS group's administrative staff services include managing program schedules, coordinating meetings, preparing agendas and disseminating meeting minutes, making conference arrangements (local and international), scheduling guest speakers, coordinating training sessions, preparing domestic and foreign travel packages in accordance with all applicable government guidelines, tracking action items related to branch initiatives and project milestones, coordinating with project teams to compile and distribute information as directed, monitoring program operational plans, developing progress reports, and coordinating and overseeing all aspects of the U.S. Department of Health and Human Services (HHS) Efficient Spending Policy.

During FY2015, CCS administrative staff continued to support the new Leidos Biomedical Research Enterprise Resource Planning (ERP) system, which is made up of four new systems: CostPoint for purchasing, Corcentric for invoicing and credit cards, Deltek Time and Expense for travel and expense authorizations, and Cognos for financial reporting. The ERP implementation presented many challenges. The ERP Task Force continues to meet as needed to collectively gather feedback, convey lessons learned among staff members via a weekly CMRP ERP News e-mail, and share experiences to help reduce time spent navigating the new systems. Several CCS staff members have stepped in to serve as leads and/or subject matter experts (SMEs) for each of the systems. The new ERP system also necessitated reviewing and cross-referencing data to confirm that the migration of data from the old system to the new system was correct and accurate. Monitoring of information in the new ERP system is still ongoing to ensure data completeness.

Repository Support

The CCS group's program manager and senior program coordinator provide support and management oversight for a subcontract with Fisher BioServices. This subcontractor provides the storage and shipment of clinical research material to domestic and international locations in support of DCR and the DIR Laboratory of Infectious Diseases (LID).

Technical and Scientific Support

CCS provides operational leadership and technical and scientific support to the Collaborative Clinical Research Branch (CCRB) and its oversight of NIAID's special projects and initiatives, and plays a key role in disseminating research information to the clinical community.

A physician and a clinical project manager support CCRB activities by providing high-level technical expertise for the implementation and management for research strategies, by developing and teaching sound clinical concepts related to infectious disease research, and by presenting and publishing information that is valuable to the research community. These specialized personnel provide project and program management for DCR special projects, coaching and mentoring to the next generation of clinical researchers, as well as clinical and scientific consulting services for NIAID's portfolio of mission-critical clinical research initiatives.

The physician serves as a clinical attending on the inpatient infectious diseases consult service at the NIH Clinical Center. In this capacity, the physician engages in patient care and teaches medical students, residents, and fellows. The physician coaches the incoming NIH clinical fellows on clinical research design and mentors the fellows to enhance their clinical research capacity. The physician also attends a biweekly journal club and instructs fellows and research staff on design, analysis, and interpretation of clinical research studies.

The physician serves as a mentor and co-investigator with NIAID and NIH clinical fellows on various research efforts, including: (1) evaluation of patients' experiences with fever, with the NIH Clinical Center nursing department; (2) evaluation of fungal clearance as a surrogate endpoint in cryptococcal meningitis, with NIAID fellows and attending staff; (3) evaluation of natural history and outcomes of bacteremic patients in the Clinical Center population, with NIAID fellows and attendings; (4) performance of discordant minimum inhibitory concentration analysis as a measure of drug effect, with the NIAID biostatistics department; (5) systematic review of brucella arteritis, with NIAID fellows; and (6) evaluation of consent forms for clinical trials of antibiotics, with the NIH nursing department.

The physician continues to teach the Uniformed Services University (USU) introduction to clinical research course annually, delivers several lectures on clinical research design, and has also been asked to present at journal clubs and provide lectures specific to clinical research methods for USU medical students.

The physician is a member of several national and international committees, bringing knowledge of current clinical research topics to the CCRB. The physician participates in these committees in varying capacities, including as: (1) member, Foundation for NIH (FNIH) working group on endpoints for skin infections, community-acquired pneumonia, and hospital-acquired pneumonia; (2) chair, International Society for Pharmacoeconomics and Outcomes Research (ISPOR) Clinician Reported Outcome task force (received award from U.S. Public Health Service); (3) adviser, World Health Organization (WHO) Advisory Group on Integrated Surveillance of Antimicrobial Resistance (AGISAR); (4) member, Data Safety Monitoring Board (DSMB) for two Division of Microbiology and Infectious Diseases (DMID) protocols on randomized double-blind trials evaluating older generic drugs (clindamycin and trimethoprim-sulfamethoxazole) for skin infections and skin abscess; and (5) full member, Department of Veterans Affairs, and Cooperative Studies Scientific Evaluation Committee (CSSEC).

The clinical project manager (CPM) provides operational leadership, overall management, and coordination of multiple special projects in support of the DCR research portfolio. The CPM's high-level technical expertise contributes to the development, implementation, and management of project strategies, including developing goals and objectives, formulating and monitoring operational metrics, and identifying risks and mitigation strategies. Working collaboratively with the CCRB and CMRP program and project leadership, the CPM helps to set operational standards, identify and address project barriers, establish project communication strategies, direct study teams and drive accountability, and identify process improvements. The CPM participates in organizational development activities, including strategy management and operational planning, as well as routine review and evaluation of goals and performance metrics to ensure mission alignment.

During the current reporting period, at the request of CCRB, CMRP recruited and hired the new CPM to support CCRB's multiple and complex special projects. The CPM quickly established rapport with NIAID/DCR staff and has played a progressive role in advancing CCRB's project needs. The CPM is actively involved in several special projects, including the Southeast Asia Infectious Disease Clinical Research Network (SEAICRN), Indonesia Research Partnership on Infectious Disease (INA-RESPOND), and PREVAIL programs. In conjunction with CMRP senior leadership, the CPM recruited and hired a technical project manager to oversee the subcontracting responsibilities for NIAID's INA-RESPOND clinical research network. Additionally, the CPM served as a member of the source evaluation group (SEG) that was convened to select a qualified vendor to provide in-country support to the INA-RESPOND clinical research network. The CPM contributed to the agendas for the SEAICRN and INA-RESPOND annual meetings and executive team/steering committee meetings, and also attended those meetings. In addition, the CPM, along with the SEAICRN medical officer and in-country team, visited clinical research sites in Vietnam, Thailand, and Indonesia. The site visits were to assess the capacity at the site level and to build relationships.

The CPM has helped to develop and deploy several surveys for the INA-RESPOND network to assess the future needs of the network steering committee and the secretariat. The CMP continued to work closely with the

clinical research associates and NIAID clinical research oversight manager to review and provide input to the monitoring reports. For the PREVAIL project, the CPM supported the in-country teams for the Ebola vaccine study and the natural history study. This entailed taking a leadership role to facilitate activities to ensure the study staff had the necessary supplies, facilities, and support. Over the past five months, the CPM spent more than seven weeks in Liberia to assist with PREVAIL logistics and operations. The Ebola natural history study (PREVAIL III) will include an ophthalmology sub-study with a principal investigator from the National Eye Institute (NEI). The CPM escorted the investigator during her visit to Liberia and provided on-the-ground logistical support. Activities entailed visits to several clinics and hospitals in Monrovia, as well as participation in meetings with hospital directors, Ministry of Health representatives, and non-governmental organization (NGO) representatives such as SightSavers, which is providing support to the ophthalmology clinics in Liberia. The assistance allowed the NEI investigator to make productive use of her time in the country.

The CPM has participated in the NIAID and CCRB team assessments and strategy planning meetings for the SEAICRN network to help develop a plan for the support from NIAID for this effort. This is an ongoing initiative to plan for the network through FY2016.

Office of the Director

Support Provided by the Clinical Monitoring Research Program

Emerging, Re-emerging, and Related Respiratory Diseases

Influenza causes significant worldwide morbidity/mortality and presents challenges to global health security because many foreign nations, especially less-developed countries, may not have preparedness plans and/or the capabilities/capacity to respond to the pandemic. For these reasons, NIAID's DCR requested that CMRP provide support in the following areas: (1) associate investigator activities, including development, management, and oversight of the conduct of these studies; (2) clinical trials management and support; (3) regulatory support, including clinical monitoring, safety reporting, and IND management; (4) clinical site preparation and study/trial operational assistance; (5) handling of clinical specimens; (6) training; (7) data management; (8) management and oversight of several task orders, including more than five multimillion-dollar research subcontracts; (9) general logistical and administrative services, such as conference planning, specimen shipping, invoice tracking and processing, travel planning, meeting planning and organization, and financial analyses; (10) protocol development and review; (11) website development and maintenance; (12) personnel; and (13) biostatistics.

CMRP currently provides scientific and technical management and oversight for multiple efforts for the DCR Emerging, Re-emerging, and Related Respiratory (ERRR) Diseases initiative, including the NIAID Influenza Research Collaboration (NIRC), the Mexico Emerging Infectious Disease Clinical Research Network (La Red), and the Symptoms Scale initiatives. In addition, inpatient and outpatient influenza observational studies, as well as interventional studies administering intravenous hyperimmune immunoglobulin (IVIG) are being performed through the International Network for Strategic Initiatives in Global HIV Trials (INSIGHT). These initiatives are of critical importance in the development of a prepared global clinical research community poised to respond to the next emerging influenza or influenza-like challenge.

NIAID Influenza Research Collaboration

The NIAID Influenza Research Collaboration (NIRC) is a NIH/NIAID-sponsored clinical trials network dedicated to finding new treatments for seasonal and pandemic flu. There are currently four ongoing NIRC studies supported by Leidos Biomedical Research:

IRC 001B: Anti-influenza Plasma Collection at a Community Blood Bank: Anti-influenza plasma, previously obtained from academic blood banks, is used in both a treatment study and manufactured into intravenous immune globulin. In an effort to increase plasma collection and to lower the costs of plasma units to the U.S. government, plasma collection was transitioned from donor-directed (screening a population to find appropriate donors, then collecting plasma from those donors) to screening units collected as routine at community blood banks to find units that meet the study requirement of high-titer anti-influenza antibodies. This program started with Mississippi Valley Community Blood Center (MVRBC) in Iowa. During FY2015, this program was also performed at Gulf Coast Regional Blood Center in Texas and Memorial Blood Bank in Minnesota. Slightly more than 2,000 units of plasma have been collected through this mechanism to date. At the end of the influenza season, 1,044 plasma units, totaling approximately 300 L of plasma, were identified and shipped to Emergent BioSolutions for the intravenous immune globulin (IVIG) manufacturing.

IRC 002: H1N1 Plasma Therapy Study: This research evaluates the safety of using human plasma containing high-titer antibodies in addition to standard care (antiviral medications) in treating subjects with severe influenza. Launched in December 2010, the protocol completed enrollment in March 2015, reaching an enrollment/randomization number of 98 (with a goal of 100 infused subjects). Site monitoring was initiated in order to conduct close-out visits; plasma recall was also completed, with sites returning all unused units to the repository. An Investigators Meeting was held in June 2015 to review the study data and discuss next steps. As a result, a concept for a follow-on study was developed. The study will be titled IRC 005 and will be initiated during FY2016.

IRC 003: Combination Therapy Study: This study focuses on enrolling subjects who are at risk of developing severe influenza based on criteria set by the Centers for Disease Control and Prevention (CDC). The purpose of the study is to evaluate whether combination therapy with three antivirals (compared to the standard, one antiviral) will help symptoms resolve faster and with fewer complications. The IRC 003 protocol was launched in January 2011 in the U.S., followed by Australia in August 2011 (closed in FY2014), Mexico in February 2012, Thailand in June 2012, and Argentina in July 2012. During the 2014–2015 flu season, 276 subjects were enrolled and 221 were randomized in the U.S., bringing the total number of subjects enrolled to 362 and randomized to 265. With the inclusion of the international sites, the total enrolled is 588 to date, with 396 randomized. Additional sites were sourced in the U.S. and added to the IRC 003 study site roster. Two data safety monitoring board (DSMB) meetings also took place during FY2015.

IRC 004: Tamiflu (Oseltamivir) Versus Placebo Study: This research seeks to understand whether subjects on Tamiflu show decreases in the amount of virus detected in the nose or throat, and to understand whether the change in the amount of virus is associated with changes in symptoms. Subjects at low risk for developing complications will be randomized to receive either Tamiflu or a placebo. The IRC 004 protocol was launched in January 2012 domestically, followed by Thailand in June 2012 and Argentina in July 2012. During this reporting period, four sites in Thailand were actively participating in IRC 004, as all other study sites have been closed. These sites have enrolled a total of 222 participants, with 219 randomized as of April 2015, bringing the total number of subjects enrolled to 393 and randomized to 290 across all sites that have participated in the U.S., Argentina, and Thailand. There were two DSMB meetings during the reporting period.

Responsibility for the management and oversight of the IRC 001/002 studies, initially funded via a NIAID subcontract, was transferred to Leidos Biomedical Research, which previously only provided technical leadership to the initiative.

The CMRP medical affairs scientist functions as lead associate investigator for implementing all the treatment studies at the NIH Clinical Center and provides ongoing technical leadership to the projects. Activities included meeting with principal investigators (PIs), revising protocols, serving as the COTR on several research subcontracts, and providing scientific guidance related to study procedures, subject enrollment/inclusion/exclusion criteria, and global influenza status. The medical affairs scientist also oversaw the process redesign for plasma ordering in the IRC 002 study.

The secretary managed the administrative aspects of the program, including producing meeting minutes; generating purchase requests; overseeing the acquisition process flow; pre-processing vendor invoices; managing and updating clinical site lists for international shipping and CDC import permits; tracking biospecimen shipments and notification lists; organizing and maintaining electronic study files; compiling invoicing spreadsheets; and navigating the new Leidos Biomedical Research Enterprise Resource Planning (ERP) system.

The clinical project manager was heavily involved in the day-to-day administrative management of several research subcontracts, routinely reviewing and approving monthly reports and invoices, research subcontractor travel requests and trip reports, as well as monitoring budgets, budget modifications, expenditures, and end-of-year forecasting.

The clinical project manager oversaw the importation of IRC 003 study agent kits from Mexico to the United States and the transfer of the IRC 004 study agent from Argentina to Thailand. The clinical project manager organized and managed the annual stability testing, retest date extension, and completion of the overlabeling process of the IRC 003 study agent on a global scale, coordinating efforts with the testing laboratory and four different study agent depots to complete the process. Due to production issues with the expiry labels, enrollment screens were closed at all sites near the end of March 2015 while the overlabeling process was pending, and as sites completed this task, the enrollment screens were re-opened. Additionally, a new lot of IRC 004 was manufactured under the clinical project manager's oversight.

Due to low numbers of IRC 003 study agent inventory, a process was developed to transfer study agents between sites within the U.S. This process allows for redistribution of study agents from lower-recruiting or closing sites to new or higher-recruiting sites. The importation of study agents from Mexico increased inventory levels, returning distribution operations to normal.

An IRC 003 Investigator Meeting was held in Argentina in May 2015, prior to the onset of influenza season, to provide refresher training to current investigators and whole-protocol training to staff from four new sites. During this meeting, an extensive discussion was held between program and site staff regarding recruitment strategies and sites' needs in order to foster success for the southern hemisphere influenza season. Refresher training sessions were also held in Mexico and Thailand prior to their respective influenza seasons.

In an effort to reduce costs and utilize funds efficiently, several IRC 003 clinical sites were closed during the reporting period due to lack of subject randomization. Additionally, the U.S. clinical sites' budget for IRC 003 was modified to emphasize subject randomization rather than screening and recruitment. The subcontract for IRC 003 was incrementally funded to provide resources for the increased enrollment activities without obligating excess funds. Two funding modifications were completed during the reporting period.

The CDC import permit for the biospecimen repository required an annual update and was completed in early 2015. Once the updated permit was received, the team worked with the clinical research organization (CRO) to post the new permit to the shipping portal for use by all sites. In addition, the international shipping requirements changed in FY2015 to no longer require U.S. Department of Agriculture guidelines memo or documents, and instead required only the CDC import permit and labels. The Dangerous Goods label for dry ice (Class 9) was modestly revised as well. All changes were incorporated into the international site *Manual of Operations* (MOP) and posted to the shipping portal for use.

During FY2015, one new position, laboratory operations manager, was filled to support the growing needs of the NIRC program. The objective was to enhance program operations by relying less on subcontractors and more on internal resources. The laboratory operations manager scrutinized the data tables for plasma inventory to ensure accuracy for potential site shipments. Any errors identified with identification numbers or influenza designation were reported to NIAID immediately for correction/resolution. In addition, the reports tracking IRC 003/004 samples were reviewed weekly for missing/erroneous data by the laboratory operations manager and in conjunction with the repository and customer. Several report revisions have been engineered by the subcontractor due to the discrepancies noted. The lab operations manager created a master query file that is updated weekly, to include new queries for site resolution as well as documentation of all resolved queries for historical tracking purposes. This process is extremely labor intensive; however, working toward the goal of obtaining a more timely resolution to data discrepancies is forthcoming, as the team communicates about the issues at least weekly and strives to improve data fields, formats, and site communication. Subcontractor to team communications have greatly improved and responsiveness has been increased.

The blood banks (IRC 002) experienced many extensive shipping delays using Federal Express during FY2015. These delays were at the highest during the winter season and could cause unit loss or damage, which led the team to research shipping alternatives. For two of the blood banks, alternate couriers were utilized to transport materials—Adcom World Wide and MNX. With these couriers, we experienced excellent tracking support, no delays, and no lost units.

In addition, many site-shipping errors occurred during FY2015, including documentation, packaging, and labeling, which prompted the laboratory operations manager to instruct the CRO to provide instructional memos to each site prior to shipment. The laboratory operations manager also provided comments/reminders to be included in the monthly newsletters.

With completion of the IRC 002 enrollment, a strict schedule was developed to identify, pull, document, and mass ship over 1,000 plasma units to Emergent BioSolutions for IVIG production. During weekly meetings, the team assessed scheduling, timelines, and progress to ensure that each goal was achieved without issue. No delays were encountered, and units were shipped according to schedule in April 2015.

Mexican Emerging Infectious Disease Clinical Research Network – La Red

In March 2009, a new influenza virus caused an increase in reports of influenza-like illnesses (ILIs) in North America. In late April 2009, the Mexican Ministry of Health (MOH) responded to the public health threat by implementing a series of non-pharmaceutical interventions, which have been widely credited with halting the first wave of the outbreak in Mexico. In September 2009, the Mexican MOH and NIAID signed a letter of intent to develop a coordinated international effort to conduct clinical research on influenza and other respiratory diseases.

The Mexican Emerging Infectious Disease Clinical Research Network (La Red) conducted five clinical studies in Mexico: ILI002 (completed FY2015); ILI2014; NTZ-SARI; FLU-PRO (completed FY2015); and IRC 003. Below is a brief description of each study:

- ILI002 – An observational study to characterize adults and children with influenza-like illnesses.
- ILI2014 – An observational study with the goal of determining the causes of, and identify increases in, influenza-like illnesses.
- NTZ-SARI – A study to evaluate the safety, effectiveness, and tolerability of nitazoxanide (NTZ), in combination with standard care, in treating severe acute respiratory illness (SARI) in hospitalized patients.
- FLU-PRO – A three-stage study to develop a symptom scale that provides a standardized and comprehensive evaluation of influenza.
- IRC 003 – A study to evaluate whether combination therapy with three antivirals (compared to the standard, one antiviral) will help symptoms resolve faster and with fewer complications.

For the purposes of this report, the IRC 003 study activities are discussed at length in the prior NIRC section, and the FLU-PRO activities are discussed in the FLU-PRO (Symptoms Scale) section on the following pages.

In FY2015, CMRP added a new associate clinical project manager position (ACPM) to transition the overall day-to-day administrative management and oversight of the research subcontracts for studies being performed within the La Red network from the clinical project manager to the ACPM. The ACPM reviewed and approved monthly reports and invoices, travel requests submitted by subcontractors, and travel reports, as well as monitored budgets, budget modifications, expenditures, and end-of-year budget estimates. In addition, the clinical project manager and ACPM assisted with the successful

importation of IRC 003 study drugs from Mexico to the U.S. and the relabeling process of study drugs currently being used for the NTZ-SARI and IRC 003 protocols.

Evaluating the Safety, Effectiveness, and Tolerability of Nitazoxanide in Addition to Standard Care for the Treatment of Severe Acute Respiratory Illness in People Who Are Hospitalized (NTZ-SARI): During FY2015, CMRP staff provided management and oversight to NIAID DCR's non-influenza respiratory viruses initiative in the form of technical and scientific leadership, project/procurement management and logistics, and subcontract administration, as well as regulatory, safety, and clinical trial monitoring services. The NTZ-SARI study is expected to screen 500 subjects in order to randomize 290 subjects who are being hospitalized with severe acute respiratory illness (SARI). Subjects are randomized to treatment with standard care, or standard care plus nitazoxanide (NTZ), a compound with broad antiviral properties. The study is being conducted in its entirety in the La Red network in Mexico.

During the reporting period, five of the six sites were open to enrollment for the NTZ-SARI study. As of July 2015, over 300 patients were pre-screened and 81 subjects were enrolled. In addition, the subcontract with the clinical research organization (CRO) was modified to include providing full statistical support to the data safety monitoring board (DSMB). This activity was essential to ensuring that the DSMB was able to evaluate the study properly, and provide direction to the sites and the Network Coordinating Center (NCC). CMRP worked closely with NIAID, CRO, and NCC to find solutions for the lagging enrollment numbers.

Overlabeling of the NTZ adult formulation occurred twice during the fiscal year—once in the fall and again in the spring. The overlabeling was necessary to extend the expiration date based on stability data provided by the manufacturer. A second lot of the pediatric formulation was received to replace the lot that expired in June 2015. Sites performed destruction of the expired lot study agent kits.

Strategically, CMRP continued to use several mechanisms to provide rapid deployment of clinical trials management services for this time-sensitive initiative. CMRP's research subcontract with a qualified CRO allows for the provision of the following: clinical trials management and operational support; protocol implementation and staff training at six clinical sites; administrative and programmatic support; laboratory and specimen collection kit manufacturing, management, and distribution; data management; statistical support to the DSMB; and monthly progress reports. CMRP also has an established project agreement for the storage and distribution of investigational study product in Mexico City, Mexico. Additionally, CMRP executed a new project agreement for the new lot of pediatric formulation NTZ.

Representatives from the NCC, various sites, and the CRO met to discuss the possibility of adding new sites to the NTZ study, and decided to add a site in Durango, Mexico, to the La Red network.

The sites responsible for implementing the study have struggled to enroll patients at a rate that would achieve the desired number of participants (500 screened and 290 enrolled) within a reasonable timeframe. Obstacles to enrollment have included the following: (1) travel to and from the site is expensive and difficult for patients; (2) patients are being seen at local primary physicians prior to coming to the site and, therefore, are not within the required days of onset of symptoms; and (3) the study requires pediatric patients to have both parents present to sign specific study-related documents. Leidos Biomedical Research, NIAID, the CRO, and the NCC met to discuss these issues. As a result of these discussions, the CRO has begun to provide patients with debit cards loaded with money to offset the cost of the travel expense. The CRO has also developed posters and other literature for display at the study sites and distribution to the local primary physicians to assist in increasing the exposure of the study. One site was unable to obtain protocol approval from COFEPRIS, the authority that controls and regulates drug products and health care services in Mexico, during the reporting period, resulting in a decision to close the site and discontinue NTZ-SARI study participation.

ILI002 and ILI2014: In response to the outbreak of H1N1 in 2009, Leidos Biomedical Research was tasked with providing support to NIAID DCR, and contracted with Westat to perform basic and applied research to develop and evaluate therapeutics, vaccines, and diagnostics. Westat has provided rapid deployment of technical, administrative, and clinical trial management services to this mission-critical effort. Westat utilized the La Red network in Mexico to conduct the ILI002 and ILI2014 studies.

ILI002 is an observational study to characterize adults and children with influenza-like illnesses (ILIs). ILI002 has been ongoing since 2011. The ILI2014 study launched in this fiscal year; it is an observational study with the goal of determining the causes and identifying increases in influenza-like illnesses. As a part of ILI2014, the investigators will identify substudies that will be covered under this scope of work.

The CMRP medical affairs scientist provided technical leadership to the projects. He provided scientific guidance related to study questions, served as the TPM for two subcontracts, met with the PIs, and assisted in the review of the protocols, providing feedback as needed. The clinical project manager (CPM) and associate clinical project manager (ACPM) were involved in the overall administrative management of the subcontracts. They participated in regular status calls with the subcontractor and government customer; reviewed and approved monthly progress reports and invoices, travel requests submitted by the subcontractor, and travel reports; and monitored the budget and end-of-year budget estimations. During the reporting period, the administrative oversight of this project was transitioned from the CPM to the ACPM, who now serves as the primary administrative point-of-contact for these subcontracts.

CMRP staff continued to provided technical and scientific leadership, management and oversight, as well as regulatory, safety, and clinical trials monitoring services to the ILI002 study. The ILI002 study ended in FY2015; in total, 5,662 patients were enrolled in the study. Final data collection, reconciliation, and analysis were completed, and a data set was delivered to NIAID DCR. CMRP completed all close-out activities.

During the reporting period, the ILI2014 study began enrollment within the La Red member sites. The staff at each site received protocol-specific training. A data management plan was finalized and implemented. By the end of May 2015, 239 participants were enrolled into the ILI2014 study.

A meeting was held in June 2015 with the protocol team leadership and staff from several sites in order to develop ILI002 manuscripts and discuss the development of ILI2014 substudies to be implemented in FY2016.

Network Coordinating Center: A Network Coordinating Center (NCC) assists La Red in conducting the highest-quality research in support of multiple protocols through different funding sources. The NCC has established standard research procedures as directed by the Network Steering Committee, provides training on these procedures, and ensures the clinical research sites are in accord with these shared procedures; it also supports all other operational and administrative functions to maintain the network. The NCC currently supports four studies within the La Red network: ILI002, ILI2014, IRC003, and NTZ-SARI. These studies are currently being administered at six sites within the La Red network. The ILI2014 study is new this reporting period, and the NCC was heavily involved with the site-initiation visits required for the study.

During this contract year, CMRP staff administered research subcontracts for the oversight and management of NCC, including the maintenance of existing staff (i.e., the network director, data/IT manager, clinical research associate, clinical operations specialist, and clinical research assistant/IT support). NCC has been very active in coordinating several face-to-face meetings for the various studies managed within the La Red network.

The NCC staff assisted clinical study sites with materials and supplies acquisition, specimen courier services, travel coordination, data management, technical support, meeting coordination, annual reports, invoice processing, and equipment ordering. The NCC staff also coordinated the import of a new lot of NTZ-SARI study agent kits of the pediatric formulation.

The CMRP medical affairs scientist provided ongoing technical leadership to the projects, which included serving as project lead, meeting with principal investigators, revising protocols, serving as the technical project manager on several research subcontracts, and providing scientific guidance related to study procedures and subject enrollment/inclusion/exclusion criteria. The clinical and associate clinical project managers were involved in the overall administrative management of the subcontracts. They participated in regular status calls with the subcontractor and government customer; reviewed and approved monthly progress reports and invoices, subcontractor travel requests, and travel reports; and monitored the budget and end-of-year budget estimates.

Manuscript submissions by the La Red network continue to be challenging. In FY2015, NCC assisted various investigators who were in the process of authoring manuscripts, providing data tables and continual support to assist the authors with finalizing drafts and submitting manuscripts for publication. The La Red network worked on the following eight manuscript topics throughout the year:

- Adult ILI
- Pediatric ILI
- Association of ILI and GI symptoms
- Predictive model of severe ILI
- Influenza research post-H1N1 pandemic of 2009
- Respiratory syncytial virus
- Chronic obstructive pulmonary disease and asthma in patients with ILI
- Flu vaccine effectiveness

FLU-PRO (Symptoms Scale)

In support of DCR's overarching ERRR initiative, Leidos Biomedical Research is developing a standardized measure of influenza symptoms for use in clinical studies involving adult and pediatric patients.

The Influenza–Patient-Reported Outcomes (FLU-PRO) Symptoms Scale is a standardized and comprehensive evaluation of influenza symptoms. To date, there are no properly developed and evaluated symptom scales for influenza. Prior scales either lacked patient input (in terms of relevant symptoms), and were therefore incomprehensive, or they did not undergo formal evaluation in terms of measurement properties.

The goal of the FLU-PRO initiative is to provide a standard measurement of symptoms that can be directly assessed from patients on a daily basis. FLU-PRO can be used in epidemiological studies of the natural history of influenza, in the evaluation of outcomes for interventions for treating or preventing influenza, and in combination with other variables to develop a standardized severity index for influenza.

To date, severity indices for influenza have been based on admission to a hospital or an intensive care unit. Criteria for admission can vary between geographic sites, resulting in a lack of standardization in such measures. A standardized measure of symptoms would decrease variability, increase validity, and enable comparisons between studies on a similar scale.

The development of a standardized Patient-Reported Outcome (PRO) measure such as FLU-PRO consists of three stages. To date, two of these stages are complete, and enrollment in stage 3 is also complete; stage 1 was the elicitation of symptoms by direct interview of patients with influenza. Patients older than six years of age were

interviewed to determine the types of symptoms associated with influenza, utilizing a draft symptom questionnaire of 37 questions clustered by body system. During stage 2, a second set of subjects with documented influenza was interviewed to evaluate the comprehensiveness and understandability of the questions in order to develop a questionnaire in both English and Spanish. The information gathered from both stages was outlined in a draft manuscript and was reviewed by a collaborative team composed of representatives from the various study contributors. Stage 3 is the application of the final questionnaire with a third set of subjects with documented influenza, in order to evaluate the testing properties, item-to-item correlations, and clinical meaningfulness of score changes on the questions.

The work on stages 1 and 2 has been performed in NIAID-sponsored networks in collaboration with the U.S. Department of Defense (DoD) at military sites (Infectious Disease Clinical Research Network [IDCRP]) and the La Red Network in Mexico. Stage 3 was initiated in the northern and southern hemispheres in approximately 15 sites, with the goal of collecting questionnaires from 250 influenza-positive subjects. Through various subcontracting mechanisms, stage 3 was implemented in the La Red and INSIGHT networks. Additional funding was acquired from the DoD and the Biomedical Advanced Research and Development Authority (BARDA), allowing for more streams of enrollment through Johns Hopkins University and the IDCRP Network.

During the current reporting period, protocols were drafted for necessary sites/networks, and IRB approval was received for all sites. The team successfully modified a research subcontract with Evidera (formerly known as United BioSource) for the purpose of developing and maintaining an Interactive Web Response System (IWRS) to administer the FLU-PRO questionnaire. The IWRS is available in both English and Spanish.

During the northern hemisphere 2014–2015 influenza season, sites enrolled a total of 537 patients, of whom 283 were influenza positive. The La Red network enrolled 103 patients, which yielded 35 influenza-positive results. INSIGHT activated a total of three sites in Argentina during the southern hemisphere 2014 influenza season and enrolled five subjects, which yielded three influenza-positive results. INSIGHT sites in the U.S. and the U.K. enrolled 79 participants, of whom 26 were influenza positive. IDCRP sites enrolled 157 participants, of whom 113 were positive; Johns Hopkins University enrolled 63 patients, all of whom were influenza positive.

By February 2015, 283 flu-positive participants were identified, exceeding the 250 flu-positive goal for stage 3 and completing the study more than two months ahead of schedule. All data queries from all sites have been resolved, and all diagnostic testing has been completed. The statistical analysis plan has been completed, and electronic data for all 537 participants has been downloaded from the FLU-PRO website. The subsequent final report, including analysis outcomes and recommendations, and was completed by September 2015.

In addition, Leidos Biomedical Research copyrighted the FLU-PRO instrument and licensed its use to Gilead Sciences for a respiratory syncytial virus (RSV) clinical study, to MedImmune for RSV and influenza studies, to Nanotherapeutics for influenza studies, and to WCCT for influenza challenge studies. This effort aims to validate the FLU-PRO instrument for a different disease with similar symptoms.

Leidos Biomedical Research leveraged internal resources to reduce the funding needed to complete the FLU-PRO project through a direct subcontract. The senior medical scientist underwent qualification to train the clinical sites' staff on the protocols and the IWRS, resulting in a cost savings of approximately $10,000. Leidos Biomedical Research staff also leveraged cost savings from stage 1 and stage 2 of the contract with Evidera, and applied those savings to stage 3.

Additionally, many of the data management and site monitoring functions were transferred to Leidos Biomedical Research personnel. Through negotiations with IDCRP, BARDA, and FDA, the senior medical scientist was able to procure additional funding for this project, allowing for continuous operations through the end of the 2014–2015 northern hemisphere influenza season. IDCRP established a research subcontract with The Henry Jackson Foundation (HJF) to procure services through Evidera, keeping operations in place past the point where funding was available through Leidos Biomedical Research.

The FLU-PRO project encountered many challenges during the reporting period. The IWRS was developed so that patients could log into the system and input their own data on each day of enrollment. In working with the La Red team during project implementation, it was determined that the majority of the subject pool would not have regular or reliable access to the Internet. Leidos Biomedical Research worked with the IWRS developer to put a system in place whereby call center staff could have access to individual patient diaries within the IWRS and input data directly on behalf of the patient. A call center was established in Mexico for this purpose, and Mexico was able to enroll 123 patients in stages 1–2 and 103 patients in stage 3 utilizing this mechanism. The call center model was subsequently used in Argentina.

There were significant delays in receiving DoD command approval for the IDCRP sites, resulting in a lack of English patients being enrolled during the 2013–2014 northern hemisphere influenza season. Since the instrument must be validated in English, IDCRP agreed to fund the services needed to operate and manage the collection of data in the 2014–2015 northern hemisphere season.

Because subjects presenting with influenza-like illnesses are enrolled in FLU-PRO prior to confirmation of infection, the individual's influenza status is unknown at the time of randomization. The study assumptions included an estimated positive-to-negative ratio of 50 percent. The positivity rate in the 2013–2014 northern hemisphere was approximately 28 percent, which was less

than projected. In order to mitigate this finding, collaborations were sought with other groups, such as BARDA and the NIH Clinical Center's ongoing influenza natural history study to provide additional English-speaking subjects. This collaboration resulted in little to no cost to the project, as these groups were currently enrolling subjects in influenza or influenza-like illness studies, which can serve as a foundation for conducting the FLU-PRO study. Subjects were enrolled in these collaborative studies during the 2014–2015 northern hemisphere influenza season.

International Network for Strategic Initiatives in Global HIV Trials

NIAID has requested for Leidos Biomedical Research to facilitate the conduct of clinical trials through the International Network for Strategic Initiatives in Global HIV Trials (INSIGHT). Leidos Biomedical Research awarded a Basic Ordering Agreement (BOA) to the University of Minnesota to allow for multiple ILI/emerging infectious disease task orders.

During the reporting period, NIAID continued to fund the following four initiatives for the INSIGHT network under the University of Minnesota BOA: (1) continuation of three FLU protocols; (2) Intravenous Immunoglobulin (IVIG) Pilot Study; (3) Intravenous Immunoglobulin (IVIG) Outcome Study; and (3) FLU-PRO study. Updates regarding the FLU-PRO study are provided in the ERRR section of this report.

FLU Plus Protocols: CMRP staff worked with Leidos Biomedical Research Contracts and Acquisitions Directorate staff to execute an option year with the University of Minnesota for the continued administration of three clinical protocols: (1) an international observational study to characterize outpatient adults with influenza (FLU 002 Plus); (2) an international observational study to characterize hospitalized adults with complications of influenza (FLU 003 Plus); and (3) INSIGHT 004, a genomics study that is a sub-study of qualifying INSIGHT FLU studies. The FLU 002 and 003 protocols were revised to allow for enrollment of participants with other targeted non-influenza (TNI) respiratory viruses of public health concern, and were renamed FLU 002 Plus and FLU 003 Plus.

During the reporting period, the following numbers of participants were enrolled: 1,700 participants in FLU 002 Plus; 600 participants in FLU 003 Plus; and 1,900 participants in INSIGHT 004.

To best utilize the data collected from the INSIGHT influenza studies, CMRP executed a subcontract with Sage Analytica, LLC, in January 2015. The sub-contractor is providing scientific expertise, and working collaboratively with INSIGHT investigators and other influenza investigators to generate study concepts and submit them for review to the network and the NIAID Scientific Steering Committee (SSC). The SSC approved the following concept, which will be developed into a manuscript and submitted for publication during the reporting period: using INSIGHT data to rapidly assess key clinical and epidemiological characteristics of a future pandemic. Additional concepts are being developed for review approval.

Intravenous Immunoglobulin Pilot: The INSIGHT network's Anti-Influenza Hyperimmune Intravenous Immunoglobulin Study (IVIG pilot) completed enrollment and finalized data during this reporting period. This study was conducted at clinical sites in the U.S. to compare the percentages of patients who died or who remained hospitalized at seven days between patients assigned the flu IVIG and those assigned a saline placebo. The results from this study were analyzed and used to create the IVIG outcome protocol.

As an extension of the concept of polyvalent immunotherapy that underlies the IRC 002 plasma therapy study, NIAID has an interest in studying the therapeutic efficacy of purified anti-influenza immuno-globins. Plasma collected from IRC 001 and IRC 001B that was not used in the plasma therapy study was manufactured into IVIG by Emergent BioSolutions (formerly Cangene) via a separate contracting mechanism.

Intraveneous Immunoglobulin Outcome Study: During the reporting period, with the support of CMRP and NIAID, INSIGHT completed site assessments, trained site personnel, and initiated 15 sites to participate in the global INSIGHT 006, FLU-IVIG: Anti-Influenza Hyperimmune Intravenous Immunoglobulin Clinical Outcome Study (IVIG Outcome Study). Enrollment began in January 2015; at the time of this report writing, 35 participants are enrolled. The IVIG Outcome Study is a double-blind, placebo-controlled randomized Phase II trial of flu IVIG and standard of care (SOC), versus placebo and SOC, in patients 18 years of age and older who are hospitalized with influenza, to compare the percent of patients who died or who remained hospitalized at day seven, for patients assigned the flu IVIG versus a saline placebo.

Human plasma units with high titers for anti-influenza antibodies that are collected as part of an influenza treatment study are being used to manufacture concentrated IVIG. To ensure that the appropriate plasma units are being used to manufacture IVIG, an influenza hemagglutinin inhibition assay (HAI) is conducted. The HAI testing needs increased by 100–200 specimens per week due to this study, so CMRP is managing a subcontract to provide a laboratory technician to perform this testing at the Naval Medical Research Center. Once the NIH and Leidos Biomedical Research study team reviewed the HAI testing results, plasma units with the highest influenza antibody titers to the relevant circulating influenza strains (which can change each season) were identified and shipped to Emergent BioSolutions for the manufacture of IVIG.

Through a research subcontract, CMRP provided administrative oversight, and scientific and technical leadership for producing a second lot of IVIG for the IVIG outcome protocol. This support included providing technical management of the research subcontract;

establishing manufacturing, drug substance, and drug product parameters and release criteria; establishing stability testing; and providing the necessary regulatory support to use this product in the treatment study. CMRP collaborated with key staff at the Vaccine Research Center (VRC) to provide cGMP expertise. Specifically, the VRC provided assistance and input for the quality agreement and the statement of work, which outlined technical GMP standards and requirements for the IVIG for Emergent BioSolutions. The VRC also reviewed all manufacturing batch records (in-process and control records, out-of-specifications results, environmental monitoring deviations, and investigations/supporting documentation of all observation/comments made) to ensure that the IVIG lot complied with standards.

There were several challenges in executing the contract with Emergent BioSolutions. Leidos Biomedical Research requires any agreement over a certain monetary ceiling to be done via subcontract, and Emergent BioSolutions felt that the agreement should have been a "fee-for-services" agreement. Therefore, there were a lot of negotiations regarding the terms and conditions by both parties, which Research Contracts diligently addressed; however, the process meant a delay in the execution of the Emergent BioSolutions contract. This delay made it challenging to procure all the plasma required for a manufacturing run of IVIG. Originally, half of the required one liter of plasma was to be provided by Emergent BioSolutions, but with the long negotiation period, this was not possible. Leidos Biomedical Research contracted with Emergent BioSolutions to do a smaller manufacturing run of only 500 mL of IVIG, and we procured the required specimens from the unused plasma collected from IRC001 and IRC 001B.

Phidisa Project

CMRP staff continues to be part of the U.S. team collaborating with NIAID DCR, the South African National Defence Force (SANDF), and the U.S. Department of Defense (DoD) to conduct high-quality clinical research for the Phidisa Project.

The Phidisa Project is an extension of the Masibambisane Program, a cooperative initiative to help prevent the transmission of HIV/AIDS among South African military and civilian employees, and their families. Phidisa was initially designed to conduct clinical research within SANDF and its network of clinics, sick bays, and hospitals. The intent was to build important biomedical and public health research capacity for future efforts to address health issues of critical importance for military force preparedness. As a result of the Phidisa Project, information has been, and will continue to be, generated to assist SANDF in its decisions about how best to manage the HIV/AIDS epidemic in military settings, to advise SANDF on combat readiness, and to expand knowledge regarding the best way to treat HIV infections.

A major focus for the Phidisa Project over the years has been on implementing a five-year strategic plan collaboratively with SANDF, the South African Military Health Service (SAMHS), the DoD, NIAID DCR, and Leidos Biomedical Research colleagues. The three major strategic goals of the project were to: (1) integrate Phidisa more effectively into SAMHS/SANDF/South Africa Department of Defence (SA DoD) as a clinical infectious diseases research component; (2) build the capacity for sustainable clinical research within SAMHS/SANDF/SA DoD; and (3) conduct high-quality clinical research.

In 2013, the Phidisa Project was modified and the focus of the U.S.–South African teams became centered on the strategic plan's third goal, which is the one most relevant to the primary mission of Phidisa. Accordingly, a series of research projects, derived from existing data and biospecimens, were identified by the Scientific Steering Committee and approved by the Phidisa Management Committee and the Executive Committee. CMRP is actively involved in the planning of these projects, and much of the work will be accomplished by October 2015 through research subcontracts; project teams are being established by South African members of Phidisa.

We extended consulting agreements with Nicolaas Pool and Dr. Sean Emery to allow continued support to the Phidisa program through September 25, 2015. Nicolaas Pool completed work by the project's close-out timeline, and CMRP performed agreement close-out activities. Dr. Sean Emery provides support to other NIAID programs under his agreement, so close-out activities were unnecessary related to his agreement. The Basic Ordering Agreement (BOA) with Bioanalytical Research Corporation South Africa (BARC) to provide repository and laboratory services continued in the event that a task order was required to support Phidisa activities; however, no new task orders were issued during the reporting period. Per NIAID's request, maintaining and managing the repository services (provided by BARC under task order 1) concluded at the end of FY2014; these tasks were transferred to another institution. During this reporting period, the technical project manager provided administrative support by reviewing and approving final invoices, and collecting all progress reports associated with the work performed under the BARC task order.

The CMRP director continues to be an active participant of the Phidisa Laboratory Working Group. The clinical trials director and the CMRP director continue their involvement as active participants of the Phidisa Regulatory Working Group, which is of notable importance. This group provides expert advice on regulatory and clinical trials management issues, such as DSMB, SAE reporting, ICH/GCP, and South African GCP guidance related to accessing study files and general monitoring issues. The clinical trials director continues to work with the group on a possible follow-up publication to the benchmark paper written in 2008.

Additional activities conducted by CMRP staff during the fiscal year included: reviewing site re-consent tables, participating in discussions on satellite closure and subject follow-up visit strategies at the lead site, and reviewing monitoring visit reports.

Genomic Studies

A NIAID Yellow Task was processed at the end of FY2013 for CMRP to complete a genomic study using samples previously collected and stored from subjects under NIAID's Phidisa Project Ia—a prospective, cohort study of HIV infection (both treated and untreated) and risk-related co-infections in the South African National Defence Force. The goals are to identify novel variants in a population of individuals of South African ancestry and host genetic factors associated with: (1) susceptibility or resistance to infection by HIV, hepatitis B (HBV), hepatitis C, gonorrhea, syphilis, and many other diagnosed active infections; (2) disease progression rates; (3) various clinical parameters (e.g., blood cell counts, viral load, liver function tests, lipids, glucose); (4) therapeutic responses; and (5) virus genotype or phenotype.

The initial work on the Phidisa genomic study has not yet come to fruition due to the political climate in South Africa. Leidos Biomedical Research staff continues to discuss various options for future genomic studies with NIAID DCR.

Once the study commences, CMRP will: (1) provide semiannual status reports detailing research activities and progress; (2) provide programmatic updates related to milestones achieved under studies, research activities, and budget status; (3) provide data reporting and analysis; and (4) manage research subcontract activities. Additional genomic studies may also be performed per the Yellow Task statement of work and Leidos Biomedical Research's response. As such, a purchase order was established with Advanced Biomedical Laboratories, LLC, during this reporting period to perform double DNA extraction on approximately 2,600 samples from the INSIGHT network's Strategic Timing of AntiRetroviral Treatment (START) study. The goal is to investigate the optimal time to begin antiretroviral therapy in over 200 sites around the globe; work is ongoing and anticipated to be completed in FY2016.

Recombinant Human Interleukin-15

CMRP continues to provide support to the Recombinant Human Interleukin-15 (IL-15) Project. CMRP's administrative support group provides project management support to oversee coordination with a research subcontractor (Biological Consulting Group) and Smithers Avanza Laboratories (formerly Avanza Laboratories) to perform pharmacodynamic and pharmacokinetic studies.

Since October 2014, the CMRP technical project manager and the assistant technical project manager have overseen a new research and development study, and coordinated the conclusion of two animal clinical studies: (1) Study 2078-11422, Good Laboratory Practices (GLPs) Study of Human IL-15 in Rhesus Monkeys Chronically Infected with SIV; and (2) Study 2078-12649, a research and development pilot study, Blockage of PD1/PDL-1 Ligand Interaction to Enhanced SIV-specific CD8 T Cell Effector Function in SIV Infection Using Anti-PDL1 in Rhesus Monkeys.

CMRP completed the final report for the GLP Study 2078-11422 and coordinated the final disposition of all data, documents, blocks, slides, and tissue samples, which were archived in GLP storage. In addition, CMRP assisted with two requests for additional histology of samples from all stored blocks.

Upon completion of the research and development pilot study (2078-12649), NIAID DCR terminated any follow-up on research efforts and requested that all animals be necropsied to obtain simian immunodeficiency virus (SIV) viral loads in blood and tissues; NIAID DCR also asked for fluorescence-activated cell sorting (FACS) analysis and histology. These items were not part of the original protocol. Expeditiously, CMRP staff amended the subcontract and protocol within one month, allowing for the timely completion of the additional work.

With the requirement to support future studies, CMRP, in collaboration with the Biopharmaceutical Development Program (BDP), released a GMP lyophilized lot of 2,580 vials of rhIL-15 cytokine to NIAID DCR during FY2015.

Recombinant Human Interleukin-27

NIAID DCR requested that Leidos Biomedical Research facilitate the rapid deployment of management services in support of DCR's Research and Development Initiatives. DCR's preliminary approach to this effort was to launch an initial study involving recombinant interleukin-27 (IL-27), a heterodimeric cytokine, which preferentially inhibits HIV-1 replication in monocyte-derived macrophages (MDMs), one of the suspected reservoirs for HIV infection. In addition, studies of similar cytokines are anticipated, as promising scientific findings have been revealed in this initial study. IL-27 significantly induces interferon-related antiviral genes in MDMs and has been shown to be capable of inhibiting simian immunodeficiency virus (SIV) infection in nonhuman primate (NHP) MDMs.

The Research and Development Initiative project aligns with DCR's mission to provide multidisciplinary trans-NIAID services, facilitating clinical research and managing special projects as directed by NIAID leadership. CMRP supports IL-27 through a number of activities, including: (1) providing the analysis of IL-27 or similar cytokines to be measured in up to thousands of patients and controls as part of the initial evaluation of the utility of IL-27 or similar cytokines; (2) establishing a research subcontract with a Contract Manufacturing Organization (CMO) for producing compounds, agents, and/or diagnostics; and (3) establishing a research subcontract with an animal research facility for testing in vivo activity

in an NHP model for HIV infection or other animal models specific to infectious diseases. This support is expected to continue through 2018.

During FY2014, laboratory work was conducted to identify the active component of IL-27 that could be used as the drug product for this project. Based on preliminary data, the subunit of IL-27 showing the observed anti-HIV activity had been identified as Epstein-Barr virus–induced gene 3 (EBI-3; also known as interleukin-27 subunit beta [IL-27B]). Upon further evaluation, laboratory test results showed that the EBI-3 obtained from the vendors was contaminated with interferon-alpha, which is already known to have anti-HIV activity in humans. Interferon-alpha has previously been targeted by researchers as a potential treatment for HIV infection. This discovery halted the evaluation efforts on EBI-3 as a potential anti-HIV drug, and redirected the project to revisit IL-27 as the potential drug product. Subsequently, due to manufacturing issues and concerns related to cytokine production, the NIAID clinical director requested that the evaluation of IL-27 be placed on an indeterminate hold.

During this reporting period, new laboratory evaluations continued in order to find a new cytokine or similar compound capable of showing anti-HIV activity. While conducting these evaluations, the principal investigator (PI) found a new drug delivery system that could potentially be used to deliver a cytokine. This finding allowed the PI to revisit IL-27 against HIV. In vitro tests are currently being conducted to determine the feasibility of using this delivery system for IL-27 or other elements downstream of the IL-27 intracellular signaling pathway, and regenerating the possibility of using this cytokine or its downstream elements as an anti-HIV drug. Recent laboratory results have indicated that a specific micro-RNA obtained from IL-27-treated cells possessed strong anti-HIV activity; this discovery has prompted the submission of an invention report by the PI. Pending the laboratory results, CMRP plans to establish a research subcontract with a vendor to produce compounds using the micro-RNA, in preparation for testing in nonhuman primates. The goal is to begin a GLP pharmacokinetic study in healthy NHPs in FY2016.

Per recent in vitro test results, CMRP prepared a statement of work for the production of a micro-RNA/ delivery system, patented by OncoImmunin. With support from Research Subcontracts, we issued the request for proposal (RFP) for a sole-source agreement to OncoImmunin. The cost proposal was not acceptable so the RFP was rescinded.

Utilizing the patented platform, the PI will evaluate the anti-HIV property of sRNAs and ASOs in vitro, followed by in vivo using NHPs. Based on the findings, clinical trials will potentially be conducted with HIV-positive patients and those who failed current clinical therapy under antiretroviral therapy (ART) due to selection of multiple drug-resistant strains, in order to test suppression of ongoing viral replication.

The project team has leveraged CMRP's past knowledge, experience, and internal resources from the preclinical development of IL-15, a cytokine also being studied for HIV treatment, for the evaluation of IL-27. This approach has provided the government customer with valuable insight and allowed for more informed decisions when considering the long-term vision of the overall research and development initiative.

Southeast Asia Initiative

The Southeast Asia Infectious Disease Clinical Research Network (SEAICRN, or "the Network") was established in 2005 to address avian influenza, although it has increased its scope to include other emerging infectious diseases in the region. This research collaboration is of the highest priority for HHS, NIH, and NIAID, and is one of several special projects for NIAID DCR that fosters international, collaborative clinical research. In FY2013, CMRP facilitated a competitive solicitation and awarded several multimillion-dollar research subcontracts to Family Health International 360 (FHI 360) under a Basic Ordering Agreement (BOA). The research subcontracts established the operational infrastructure to support SEAICRN's research portfolio, and provided technical support and administrative assistance to the network and site management for the clinical research sites in Thailand and Vietnam. CMRP focused resources on addressing and resolving the logistical challenges of conducting international clinical research; these challenges include: complying with the multiple and varying regulations of different countries; identifying and improving unequal levels of readiness to conduct research among sites; and overcoming language barriers.

Leidos Biomedical Research, FHI 360, and the SEAICRN partners worked to initiate the Sepsis Study by staffing the Network Operations Center; finalizing the protocol and informed consent/assent documents; creating study-specific CRFs and a central repository for study data; identifying, assessing, and subcontracting with 11 study sites in Thailand and Vietnam; finalizing necessary protocol-specific documents (e.g., *Manual of Operations*, SOPs, and data/management plans) and training staff on these documents; and identifying and contracting with a biospecimen repository in each country. The clinical project manager, CMRP director, and other CMRP senior staff members have provided valuable expertise and input into the development and implementation of the Sepsis Study designed for SEAICRN.

FHI 360, in conjunction with CMRP and NIAID, continued enrollment in the Sepsis Study in Thailand and Vietnam; currently there are 1,250 patients enrolled. The team also supported the Indonesia Research Partnership on Infectious Disease (INA-RESPOND) in preparing four sites in Indonesia to participate in the Sepsis Study; currently 30 people are enrolled. Enrollment in all three countries will end by December 31, 2015 to provide ample time for data analysis and study close-out. An ongoing challenge with managing the Sepsis Study is

ensuring that enrollment is even across seasonal variations and during local holidays. To ensure that the enrollment target of 1,500 participants will be fulfilled in Thailand and Vietnam by December 31, 2015, the study team has decided to allow increased enrollment through November 2015. Starting December 1, 2015, enrollment will be competitive across all sites within the country to ensure that the enrollment target is met. FHI 360 will continue to closely monitor enrollment and provide support, when needed, to ensure each site is successfully enrolling their target numbers.

SEAICRN held its annual meeting in June 2015 in Jakarta, Indonesia. Nearly 100 people participated in the successful two-day event. In addition to updates from the Sepsis Study, scientific updates on current studies from network members and updates on new and emerging diseases in the region were provided. The annual meetings are an important forum for forming collaborations among the area investigators and providing information on possible new studies for SEAICRN after the Sepsis Study concludes.

The FHI 360 biostatistical team conducted an interim analysis on the data for the first 340 study participants and presented the data during the June meeting, which sparked good discussion about analysis options and possible follow-on studies and/or analysis.

FHI 360 continued maintenance of the network SharePoint site for housing all documents. This included managing access issues for all network personnel. The documents housed on the SEAICRN SharePoint site include historic documents from previous network studies, as well as current documents, Sepsis Study–related documents, and future study concepts and information.

An additional task order was executed with FHI 360 for operational tasks to support SEAICRN and the network PIs. This allowed FHI 360 to hold a meeting to discuss a protocol for EV71; assist in protocol development for several possible network studies (Randomized Controlled Trial of IVIG Use in Severe Hand, Foot, and Mouth Disease [EV71], and Genotype Replication of Genetic Variants Associated with Severe Influenza [EXOM Study]); and assist Indonesia with planning to participate in the Sepsis Study. FHI 360 has also taken on hosting two additional Executive Committee meetings per year and supporting the EXOM study utilizing specimens from SEA001. EXOM support has included finalization of protocol, monetary support for blood draw of control specimens, and paying ethical submission costs for four sites.

Through coordination with FHI 360, Oxford University Clinical Research Unit (OUCRU) and other SEAICRN members are assisting Indonesia's reference laboratories with obtaining the necessary control material to validate the following tests that are not currently done in Indonesia: viral respiratory panels (adenovirus; enterovirus; RSV A & B; human metapneumovirus; rhinovirus; parainfluenza virus 1, 2, 3, and 4; coronavirus 229E/OC43/HKUI/SARSCoV/NL63; parechovirus; and bocavirus); bacterial respiratory panels (*Legionella pneumophila*; *Mycoplasma pneumonia*; *Chlamydophila pneumonia*; *Chlamydophila psittaci*; and *Bordetella pertussis*); diarrheal panels (norovirus; adenovirus; and astrovirus); and encephalitis panels (Streptococcus suis, Parechovirus PCR, and enterovirus). This control material will improve the laboratory testing capacity in Indonesia, and provide more varied testing for both clinical and diagnostic testing.

FHI 360 continued to assist Oxford personnel with maintaining the new network website. SEAICRN hopes that the updated website and increased visibility will bring additional collaborators and funding to the Network.

In the interest of cost saving, the CMRP clinical project manager attended meetings of less than two days' duration through teleconferencing. This option was also extended to FHI 360's project manager living in the U.S. Whenever possible, the Southeast Asia–based project manager would attend the face-to-face meetings, which reduced travel and labor costs by nearly $25,000.

Indonesia Ministry of Health

Research supported and conducted by NIAID strives to understand, treat, and ultimately prevent the myriad of infectious, immunologic, and allergic diseases that threaten millions of human lives. NIAID DCR supports clinical research to control and prevent diseases caused by virtually all infectious agents. This includes basic and applied research to develop and evaluate therapeutics, vaccines, and diagnostics.

NIAID's DCR, the National Institute of Health Research and Development (NIHRD) Ministry of Health (MOH) in Indonesia, and a number of Indonesian research sites formed the Indonesia Research Partnership on Infectious Disease (INA-RESPOND), with the purpose of bringing together clinical and academic medical institutions to develop a robust collaborative infectious disease research network. The aim of the INA-RESPOND Network is to conduct basic and clinical research, increase the understanding of the pathogenesis of diseases, and prevent and treat infectious diseases based on the concerns of the country and in alignment with the priorities of the Indonesian MOH. This beneficial collaboration allows both countries to partner in research and study infectious diseases that affect Indonesia, the surrounding region, and the global community.

As the primary U.S. government institute for HIV/AIDS research, NIAID is committed to conducting research necessary to successfully end the fight against HIV/AIDS. The overall prevalence of HIV in Indonesia is estimated to be less than 1 percent; however, there are provinces where the prevalence is as high as 2.5 percent. The Indonesian MOH is concerned about the steady incidence rate in the country, which is at about 21,000 new cases per year based on reported data. To target this, the Indonesian MOH is in the concept development stage to begin a test-and-treat HIV research initiative in approximately eight of the country's 33 provinces. These eight provinces will receive testing for approximately

1.2–1.8 million individuals in high-risk groups (e.g., pregnant women, prisoners, and homosexual individuals). NIAID will provide support to this research effort for a subset of sites across the various provinces.

NIAID requested that CMRP provide project management and oversight for the completion of at least one HIV study that assesses the impact of testing for, and treating, HIV in Indonesia. CMRP understands the scope to include the evaluation of two approaches to HIV treatment and prevention in Indonesia. One approach, as noted above, will be implemented in eight provinces by the MOH and compared to a second approach that will be implemented in other selected provinces that follow the current standard of HIV care and prevention. The intent is to help in the evaluation of a strategy to curb the incidence of HIV/AIDS and curtail the course of what could become a highly prevalent disease. To facilitate the completion of this work scope, CMRP will establish research subcontracts with qualified vendors to provide the necessary support on the ground and will provide the programmatic oversight necessary to complete this initiative.

A new clinical project manager was hired in January 2015 to manage the overall Indonesian initiative. CMRP provides other subject matter experts and clinical project managers to support the overall execution of this initiative, build network relationships, and establish appropriate research subcontracts.

Efforts continue with NIAID and NIHRD to determine the scope of the project, statement of work activities, and project deliverables. In February 2015, Leidos Biomedical Research prepared and released a Request for Proposal (RFP) for full and open competition in order to award a new research subcontract for the implementation of research support services by September 2015. Leidos Biomedical Research held a bidders teleconference in March 2015 for the Source Evaluation Group (SEG) to address questions raised by potential offerors. Proposals from a total of three offerors were found to be complete by Leidos Biomedical Research's Research Subcontracts group and were forwarded to SEG members for evaluation. Best and Final Offer (BAFO) questions were sent to each vendor after the SEG convened. The proposal review process prompted NIAID and the Network Steering Committee chair to rethink the current approach for the services and support provided to INA-RESPOND due to challenges and inefficiencies occurring at the ground level with the current subcontractor. The SEG re-evaluated the existing operational approach in use by the subcontractor currently supporting the network via NIAID, and began to strategize on a new approach that would leverage Leidos Biomedical Research's services and expertise to more fully support INA-RESPOND.

To set the foundation for improved communication and project expectations, Leidos Biomedical Research created and implemented project management tools (e.g., RACI Chart, Core Management Diagram) defining stakeholders' roles and responsibilities, and the lines of communication between the vendors, Leidos Biomedical Research, NIAID, and NIHRD. Based on the new approach, Leidos Biomedical Research's Research Subcontracts group informed the offerors that the RFP was withdrawn. Leidos Biomedical Research and NIAID plan to subsequently contact the current subcontractor and an Indonesian Contract Research Organization (CRO) to negotiate sole-source agreements that are in line with the revised approach to provide services and support to the INA-RESPOND Network. The goal is to award new subcontracts with two vendors by September 2015.

To gain knowledge and understanding of INA-RESPOND's current infrastructure and the dynamics within, project team members from Leidos Biomedical Research and NIAID traveled to Jakarta, Indonesia, on multiple occasions during FY2015. The team members had face-to-face meetings with the INA-RESPOND network's Steering Committee chair, an in-country Leidos Biomedical Research consultant, and other network staff, and also visited study sites participating in this clinical research network. To reduce unnecessary repeated costs, one of the Leidos Biomedical Research project team members obtained a multi-entry visa that is renewable annually for multiple travels to Indonesia, as opposed to obtaining individual 30-day visas for each trip. When possible, the Leidos Biomedical Research project team members obtained reduced airfare for flights to Indonesia by departing from their current travel location as opposed to returning to their home location prior to flying to Indonesia.

HIV Replication Study

Toward the end of FY2014, NIAID DCR requested that CMRP provide clinical trials management, regulatory, and safety support service for the HIV Replication Study. The goal of the study, which will be approximately three years in duration (since the funding will expire in three years), is to look for HIV replication in privileged compartments (i.e., the brain) that cannot be safely studied in living individuals (i.e., looking at a population of deceased individuals with HIV/AIDS, whose disease was suppressed and who died of other causes).

CMRP provides programmatic oversight and general overall direction for any research subcontracts determined to be necessary to complete this initiative.

Limited support has been provided to this project during the current reporting period, as NIAID leadership dedicated high attention to the Ebola response team efforts. Once the HIV Replication Study reaches higher priority, Leidos Biomedical Research will be prepared to support this activity and will engage members of the team supporting the Genotype-Tissue Expression (GTEx) project, which has similar components.

Mali Clinical Research Program

With the overarching goal of developing sustainable research programs in geographic areas of high infectious disease burden and enhancing the capacity of research

sites throughout Africa to perform clinical research in accordance with ICH/GCP guidelines and applicable U.S. government–mandated regulatory requirements, NIAID DCR planned a partnership initiative and requested CMRP to facilitate and manage the program.

Specifically, CMRP was asked to provide support for building the clinical research infrastructure necessary in Mali to carry out the Strategic Timing of Antiretroviral Treatment (START) study; research the pathogenesis of TB and its intersection with HIV; and study emerging infectious diseases with hemorrhagic viruses in the region. To accomplish this, CMRP is providing management and oversight for the establishment of the University Clinical Research Center (UCRC) infrastructure and resources, as well as strengthening research capacity for ongoing University of Sciences, Techniques, and Technologies of Bamako (USTTB) research platforms. A subcontract with USTTB is serving as one facet to facilitate development of coordinated clinical research programs in Mali; enhance the existing clinical research program and facilitate growth and sustainability; stimulate clinical research in West Africa that is guided by international standards and principles; and develop an excellent research environment that will attract researchers worldwide and foster collaborations.

The key activities undertaken by the CMRP Mali project team during FY2015 have been related to the planning elements required to create the University Clinical Research Center (UCRC). The process began by initiating a number of strategic planning meetings to first define the vision, mission, and objectives of the UCRC. The next steps were to determine the governing structure of the UCRC, define the core capabilities needed to operate it, identify who would lead the UCRC, and select a location where UCRC clinical trials would be housed. Activities also included establishing a subcontract with USTTB to manage on-the-ground events for UCRC and the biosafety level 3 lab (BSL-3) functions, which fall under the umbrella of UCRC. During the course of the year, six trips were taken by the CMRP Mali project team members to Bamako, Mali, to provide oversight to the planning and implementation process.

Following a very productive strategic planning meeting in Bamako at the end of FY2014, the CMRP team created the UCRC. In November 2014, NIAID DCR and CMRP members traveled to Mali to participate in a second UCRC strategic planning meeting, which was held in conjunction with an Ebola scientific meeting. The UCRC Strategic Plan was developed during this meeting. Subsequently, team members spent a substantial amount of time outlining the specific goals and objectives of UCRC and detailing how the center will operate. The UCRC Strategic Plan documents the core values, governance and organizational structure, and the administrative management and operational structure. The plan has been reviewed by NIAID DCR and endorsed by the Malian UCRC team. The plan development process helped the team determine the need to establish the UCRC Governing Board.

Three new staff members were hired by CMRP: a clinical project manager to provide overall operational and project management functions, including oversight of the new UCRC subcontract; a special projects administrator to provide logistical support, including research subcontract invoices, high-level procurement and budget assistance, and meeting coordination; and an administrative assistant to provide overall administrative support, including various international logistics such as travel coordination, procurement, shipping, and budget tracking. An additional clinical project manager is also part of the CMRP Mali project team to provide high-level oversight.

Steps were taken to hire a UCRC director. The UCRC Planning Committee prepared the job description for the position and provided it to the rector of USTTB. In January 2015, the rector officially appointed an interim UCRC director who is now actively involved in managing the UCRC.

In February 2015, the first official UCRC Board Meeting was held in Mali to formally create the UCRC Governing Board (GB), launch UCRC, and validate the strategic plan. During the meeting, board members developed the terms of reference for the board members, further expanded on the roles and responsibilities of the Executive Committee, and discussed how often they would meet, in addition to determining when the first Executive Committee meeting would be held. While in Bamako for the GB meeting, NIAID DCR members and CMRP staff took the opportunity to visit buildings on the Point G hospital campus that could potentially be renovated and utilized as the UCRC headquarters.

The first UCRC Executive Committee meeting was held in May 2015. This meeting brought together the members with a scientific background who would review the UCRC protocols. The Executive Committee members discussed managerial, administrative, and logistical aspects of how the Executive Committee would function. The interim UCRC director outlined the key elements UCRC should focus on during the first year and a proposed strategy for accomplishing those goals. The Executive Committee members and interim UCRC director agreed on a way forward and a strategy implementation process is under way. CMRP and the NIAID DCR Mali project operational team held several meetings, including a kick-off meeting with the project stakeholder representatives (NIAID DCR, CMRP, UCRC director, UCRC SEREFO lab team, the Mali Service Center [MSC], and The Mitchell Group [TMG]). The team also met separately with MSC to discuss the financial and administrative procedures for managing the UCRC project funds. High-level meetings were held with the hospital administrator as well as an architect to continue discussions on the potential building renovation.

One of the ongoing work efforts of UCRC is to renovate the building where the UCRC clinical research activities will be housed. An architect was hired to prepare the blueprints of the current state of the building as well as a blueprint of the proposed future layout of the UCRC clinical research site. Work is under way to

determine the cost of the renovations and to hire a general contractor to start the renovation. UCRC is also in the process of building a team of staff members; UCRC is on track to fill key positions, such as the administrative assistant and project manager, by the end of the year. In parallel, the BSL-3 lab completed the MODS protocol in July 2015, with 135 patients enrolled, and has screened 308 patients for the MAL02 protocol. The UCRC team and Executive Committee members continue to research and review proposals of potential protocols for studies that may be conducted by UCRC.

CMRP took steps to engage a subcontractor in providing a mechanism to support the salaries of staff members and the project activities of UCRC. There were some initial challenges, as CMRP had planned to engage TMG for this subcontract component, but, after several discussions with, and the involvement of, the Contracts Offices of NIAID, NIH, it was determined that TMG could not hold the subcontract due to its relationship with the Mali Service Center (MSC), which is the financial arm of the university mandated to manage the funds for the subcontract work. CMRP also had to obtain further clearance from the NCI Contracts Office to pursue establishing a subcontract with a partner in Mali because there was an incorrect statement in the partner's response to how it would perform the task requested by NIAID DCR.

CMRP successfully collaborated with the MSC Advisory Board, through the support of NIAID DIR, to develop a funding mechanism that made it possible for CMRP to engage USTTB as the in-country partner. This engagement allows TMG to still provide oversight to MSC in support of the UCRC project, without the perception of playing a dual role on the project. The pre-award letter was signed in April 2015 to support the UCRC expenses during the period of April and May. The subcontract with USTTB was fully executed in June 2015.

Emerging/Re-emerging Viral Hemorrhagic Fevers and Other Emerging/Re-emerging Infectious Diseases

Research supported and conducted by NIAID strives to understand, treat, and ultimately prevent the myriad of infectious, immunologic, and allergic diseases threatening the health of millions of people in the U.S. and around the world. Against a background of established infections, epidemics of new and old infectious diseases periodically emerge. This threat has been increasingly recognized over the last decade. Emerging and re-emerging diseases (ERIDs), such as viral hemorrhagic fevers (VHFs), Ebola hemorrhagic fever, Lassa fever, and Marburg hemorrhagic fever, are of particular concern given the potential for significant morbidity and mortality. This concern fosters the overall goal to better understand the diseases and therapeutic options, and to improve medical outcomes for afflicted patients.

CMRP has developed and is managing a portfolio of international clinical research studies that serve as a comprehensive research platform allowing DCR to effectively respond to VHF and other ERIDs through anticipation, early reaction, disease characterization, treatment, collaboration, and flexibility.

In early FY2015, CMRP launched a concentrated effort to respond to the high-priority initiative of addressing the Ebola epidemic in Liberia, Africa. This included mobilizing staff members across various groups to facilitate the conduct of a Phase II/III study, beginning with assembling an advanced team to travel to Liberia for an information-gathering visit in late October 2014 to understand the logistical issues that required attention to successfully launch the studies. The team assessed potential sites and resources, sought details about local government approval requirements and IRB processes, discussed staffing issues and hiring mechanisms, and met with in-country representatives and agency collaborators. During the next few months, a series of meetings were held with U.S. and Liberian technical team advisors to map out strategies and manage ambitious timelines.

Planning efforts for the Partnership for Research on Ebola Vaccines in Liberia (PREVAIL) I study (Phase II/III randomized, double-blind, placebo-controlled, 3-arm trial of two Ebola virus disease (EVD) vaccines, each compared against a placebo arm) were initiated, and infrastructures related to conducting the study were established. In addition to completely creating and renovating laboratory and clinic space, several clinical research elements necessary for conducting clinical trials were implemented. These included designing innovative methodologies associated with patient recruitment and monthly follow-up of approximately 28,000 subjects; establishing a manual of operations; providing regulatory oversight and Data Safety and Monitoring oversight; offering logistical shipping, meeting, and travel support; awarding research subcontracts; determining efficient procurement mechanisms; providing on-site training; establishing pharmacy, laboratory, and repository operations; and providing overall project management.

Due to the diligence of the Regulatory Affairs group, the IND and CTAs were cleared/approved to proceed within three months, allowing for the initiation of the PREVAIL I study in late January 2015; study enrollment began in early February 2015. Of the total sample size, the first 600 participants will be part of a Phase II sub-study. Enrollment for the sub-study was completed in April 2015.

Two additional studies (PREVAIL II and PREVAIL III) have also been initiated and supported by CMRP resources.

The PREVAIL II study (Phase II/III randomized, blinded, safety and efficacy study of putative investigational therapeutics in the treatment of patients with known Ebola infection) was initiated, and infrastructures related to conducting the study were established. These efforts included establishing a manual

of operations; providing regulatory oversight and Data Safety and Monitoring oversight; offering logistical shipping, meeting, and travel support; awarding research subcontracts; determining efficient procurement mechanisms; providing on-site training; establishing pharmacy, laboratory, and repository operations; and providing overall project management. This study is being conducted in the U.S., Liberia, and Sierra Leone, and was recently expanded into Guinea.

CMRP's Regulatory Affairs group worked quickly to ensure the protocol would be cleared/approved to proceed, allowing initiation of PREVAIL II (Medical Counter Measures Study) in February 2015. Study enrollment began in March 2015 and currently has 51 patients enrolled across all the countries.

To initiate the Ebola natural history study, PREVAIL III (Ebola Virus Disease Survivors: Clinical and Immunologic Follow-up) infrastructures related to the study conduct were established. In addition to completely creating laboratory space and renovating clinical facilities, the team was involved with designing innovative methodologies associated with patient recruitment and follow-up of subjects; establishing a manual of operations; providing regulatory oversight; offering logistical shipping, meeting, and travel support; awarding research subcontracts; determining efficient procurement mechanisms; providing on-site training; establishing pharmacy, laboratory, and repository operations; and providing overall project management. The study began enrollment in early June 2015.

Three subcontracts were pre-awarded, allowing work to get under way pending execution of the final agreements: one provides professional advice and deploys rapid on-the-ground business operations; another oversees the administration and disbursement of local resources (i.e., in-country hiring, construction, and logistics); and the third provides statistical and trial operational support, including feasibility assessments and data management, as well as expertise to support protocol development and implementation. Additional subcontracts were executed to address the social mobilization needs within the country to help educate, engage, and communicate with the local communities about Ebola and the clinical trials supported by NIAID.

CMRP hired the following staff members to support in-house and on-the-ground efforts for the project: four clinical project managers (varying levels), two program managers, two medical affairs scientists, two secretaries, one administrative assistant, one financial analyst, one patient care coordinator, one shipper/packer, and one shipper/receiver.

Launching PREVAIL has involved a broad team effort among CMRP to meet customer expectations. In addition to the routine regulatory and clinical trials management services, the project management support services are spread across multiple CMRP staff members to oversee travel logistics, including acquiring expedited visas from the embassies of Liberia, Sierra Leone, and Guinea, providing information for electronic country clearances, securing hotel reservations, and establishing meeting/office space in the U.S. Embassy compound in Liberia and other office locations in Sierra Leone and Guinea. CMRP procured equipment and supplies and managed the shipping/delivery process. Staff continues to provide on-the-ground oversight and support, maintaining an active presence in Liberia, Sierra Leone, and Guinea from the project development through the study initiation phase, and will continue until study completion.

CMRP logistics support is an operational priority of the PREVAIL effort. Logistics support to the Ebola epidemic in West Africa can be defined by the supply throughput of material to Liberia, Sierra Leone, and Guinea—the nations simultaneously impacted by the health care emergency. The CMRP team is made up of dedicated and adjunct support professionals working across supply networks, leveraging experience and expertise to procure strategic and essential commodities. This support includes procurement, contracting, freight handling, warehousing, and in-country logistics and operations.

Order management and distribution of materials and supplies ranged from facility hardware and IT components for infrastructure build-out and growth, to specialized medical and laboratory equipment, as well as medications for treatment, vaccine, and natural history studies. From December 2014 through June 2015, more than 45 commercial shipments of materials and supplies were sent to Liberian sites for the PREVAIL studies. The logistics team was responsible for procurement and shipment of more than 77,836 kilos of material transported via commercial carrier during that time, and it is projected that the latter half of FY2015 will exceed the previous period in procurement and shipment activity as study locations are added and expanded under PREVAIL I, II, and III.

Procurement planning, execution, and distribution of multiple classes of supplies, including hazardous materials, perishable freight, and sensitive equipment, are conducted by the logistics team. Inventory, storage, and flow of supplies from port of entry to the medical facilities and Emergency Treatment Units (ETUs) is coordinated by on-the-ground support, including local support staff and the U.S. Embassy for customs clearance, transportation, warehousing, and distribution.

Efficient supply chain support in this global operation is neither without challenges nor milestone successes. CMRP's agile team provides near real-time response to procurement needs and urgent requests requiring collaboration with U.S. Embassy staff, freight forwarders, industry suppliers, and on-the-ground operational staff.

The logistics team supports service requests and is a facilitator in obtaining translation services and ensuring that translated documents are provided to the PREVAIL team in Guinea. To date, more than 12 documents (protocols, consent forms, regulation documents) have been translated. The average time from request to delivery of a translated document is three days.

Data Safety Monitoring Board (DSMB) support is part of the logistics team function; it is provided on a monthly basis or more frequently as the studies necessitate. The role includes meeting coordination, documentation distribution, and direct support to the DSMB.

The CMRP Ebola support team has worked to address several challenges associated with this complex project. A brief summary of the overarching challenges and solutions is outlined below.

Lack of site infrastructure/in-country resources: The two potential facilities to initiate the study, JFK Medical Center and Redemption Hospital, lacked laboratory infrastructure and required renovations to create functioning laboratory space. CMRP responded rapidly to contractor proposals. The Redemption Hospital renovation was complete in time for the vaccine study initiation, and JFK renovations continued, with the goal of opening a secondary site. CMRP handled procurement of all necessary laboratory equipment and supplies, and arranged for charter flight shipments to ensure timely deliveries. The U.S. Embassy has been acting as a customs agents to help obtain clearances for receiving the shipments and ensuring transportation to the sites.

Rapid initiation: Due to the complex nature and seriousness of the Ebola outbreak in West African countries, and international concerns about the disease's spread, study objective timelines were established with an ambitious schedule. The fast pace of finalizing the protocol, coordinating the planning logistics, and collaborating with multiple partners was further challenged by beginning a study in a country where CMRP did not have established clinical research projects. Working with the U.S. Embassy and our in-country partner (The Mitchell Group), CMRP facilitated logistical planning for study initiation and hiring needs to staff the laboratory, pharmacy, and clinic with local Liberians. Additionally, CMRP used an "all hands on deck" approach and garnered resources from various groups to efficiently and effectively manage study objectives and timelines.

High visibility: The high-profile nature of the Ebola response effort puts the study under an extra degree of scrutiny that layers an additional level of pressure on staff members. Key staff members continue to provide project management and oversight on all aspects of the project. The medical affairs scientists are helping with community outreach and social mobilization to ensure community support and encourage study recruitment/enrollment.

While assisting with building the laboratory and clinic infrastructures in Liberia, CMRP has also facilitated the training of local Liberian pharmacy, laboratory, and clinical staff to ensure standard procedures for filling syringes, obtaining informed consents, aliquotting and processing samples, vaccinating and monitoring participants during the post-vaccination period, and tracking participants.

Office of the Chief Scientist, Integrated Research Facility

Support Provided by the Clinical Monitoring Research Program

The mission of the Office of Chief Scientist, Integrated Research Facility (OCSIRF), is to manage, coordinate, and facilitate the conduct of emerging infectious disease and biodefense research for the development of vaccines and medical countermeasures, and improvement of clinical outcomes for patients. OCSIRF executes the biodefense research needed to understand clinical disease processes associated with the severity of microbial-induced disease. Central to its core mission is the use of hospital tools, including endoscopy, cardiac telemetry monitors, computed tomography (CT), magnetic resonance imaging (MRI), single-photon emission computed tomography (SPECT), and positron emission tomography (PET) imaging, to evaluate the pathogenic processes and disease trajectory in animal models exposed to microbes.

CMRP provides programmatic support and management oversight for research subcontracts to support OCSIRF initiatives. A research subcontract with Turner Consulting Group, Inc. (TCG), is maintained to facilitate high-level computing, and administrative and scientific design, and to provide subject matter expertise (SME) for the Integrated Research Facility (IRF). TCG serves as SME in the areas of data management and governance.

TCG continues to support the core objectives, which include implementing and adopting the LabWare Laboratory Information Management System (LIMS) application modules across all IRF core support laboratories. Efforts involve extending the LIMS framework, establishing the study portal structure in the electronic document and records management system (EDRMS), and leveraging the use of Tableau and SharePoint capabilities to deliver dynamic data reporting and self-service business intelligence capabilities.

TCG continued extension of LIMS functionality and completed the modules for immunology and molecular biology workflows. Improvements to the clinical sample workflows have been released, allowing specific functionality for the tracking and accountability of specimens under the select agent program. EDRMS deployment continues with the use of EDRMS to automate the submission, review, and cataloging to animal study plans. The configuration and use of EDRMS in establishing document workflows for the submission review of study plans, as well as a structured reposition for the information artifacts to be generated by that study, are also in the final stages of development. The study calendar and data browsers that communicate study plans and assay results using nightly extracts of the LIMS database and Tableau visualizations have been deployed. A data management site was created as part of the IRF SharePoint environment, from which assay and study information are disseminated. TCG leveraged the use of

SharePoint for assay scheduling and resource management for events not captured in the LIMS study design process. The two deliverables completed during the reporting period were the electronic data management systems presentation, and the strategic plan review and budget discussion meeting summary.

Biodefense Initiative

CMRP provides administrative and programmatic support services for the facilitation and coordination of scientific workshops and conferences for NIAID's biodefense research initiatives. CMRP has facilitated the logistics and planned the provisions for several workshops and conferences both locally and nationally, arranged international travel, and coordinated with large conference facilities. The workshops and conferences bring together experts from various areas of scientific and clinical research, as well as multidiscipline research professionals, to share and disseminate information and research outcomes. These efforts directly align to the DCR strategic goal to "facilitate the generation of new knowledge and insight from research."

In past years, CMRP staff planned and coordinated several meetings for the NIAID Integrated Research Facility (IRF) and other NIAID/NIH biosafety level 4 (BSL-4) laboratories. The information shared and outcomes generated from these meetings have supported current research efforts that align with NIAID Planning for the 21st Century, Research Resources, Priority 2, to "build and maintain safe and secure containment research facilities for working with highly infectious pathogens, and ensure appropriate training for workers in these facilities."

During the current reporting period, efforts have been focused on strategic planning for future activities, which could include the coordination of meetings centered on research related to NIH imaging efforts, and the launch of a series of meetings referred to as the Concept Incubator. The Concept Incubator will serve as the forum for the review and prioritization of research efforts for the IRF at Fort Detrick in Frederick, MD. CMRP continues to support DCR's commitment to fostering knowledge sharing and promoting the dissemination of new research findings to the clinical community by providing comprehensive administrative and programmatic services for these mission-critical initiatives.

Intramural Clinical Management Operations Branch

Support Provided by the Clinical Monitoring Research Program

The Intramural Clinical Management and Operations Branch (ICMOB) oversees the logistical management of clinical research and related clinical operations for the following NIAID intramural laboratories: the Laboratory of Immunoregulation (LIR); the Laboratory of Immunology (LI); the Laboratory of Host Defenses (LHD); the Laboratory of Clinical Infectious Diseases (LCID); the Laboratory of Infectious Diseases (LID); the Laboratory of Parasitic Diseases (LPD); and the Laboratory of Allergic Diseases (LAD). ICMOB manages one inpatient unit and two outpatient clinics at the NIH Clinical Center. The CMRP team is responsible for clinical protocol review and approval, assurance of scientific quality and human subject protection, the quality of care delivered to NIAID patients, and the quality of professional performance of the health care providers.

The intramural portfolio constantly expands as new research initiatives and projects are identified to help further NIAID's research agenda. CMRP is actively involved with these mission-critical projects through the provision of clinical staff resources, such as clinicians, study coordinators, and administrative support personnel, as requested by NIAID.

CMRP provides five nurse practitioners who function as clinicians, managing acute and chronic diseases that are studied through NIAID protocols in both an inpatient and outpatient setting. Eleven protocol nurse coordinators provide direct protocol management, ranging from recruitment and patient consent, to collection and recording of research-driven data and handling of regulatory reviews. Twelve case managers provide nursing care to an assigned caseload of patients, utilizing the nursing process to assess, plan, intervene, and follow up on disease-related features as outlined in the clinical protocol. These staff members also coordinate and schedule patient visits to meet the required protocol procedures and data collection time points. Two clinical research nurses gather clinical information for prospective and current patients, in addition to helping with case management and monitoring activities pertaining to clinical protocols, including patient recruitment and retention; trial progress; and the need to extend or renew ongoing clinical trials. Two patient care coordinators organize the complex and comprehensive logistical needs of NIAID protocol patients by coordinating follow-up visits, diagnostic tests, and travel arrangements. One physician serves as lead associate investigator on several protocols and provides outreach to a community clinic; a physician assistant and one physician extender support clinic efforts by performing protocol-mandated initial and follow-up medical histories and physical examinations. A physician provides consultation in the area of infectious disease for a transplant program studying chronic granulomatous disease, in addition to supporting protocol and clinical operations. Collectively, the group ensures the conduct of high-quality clinical research through quality assurance activities and adherence to human subject protection guidelines; updates clinical staff on patient care, protocol process, and progress; and provides ICH/GCP and QA education, while providing support to more than 60 protocols.

In addition to the credentialed clinical support staff, CMRP also provides patient education/recruitment expertise. The patient educator/recruiter manages the

placement and tracking of media advertising, medical chart reviews, phone screening, and community outreach, and serves as the major conduit through which referrals of prospective patient and normal volunteers will enter the clinical trials network. One research technician and one clinical research associate are responsible for collecting data, updating logs, and categorizing and preparing infectious and noninfectious tissue specimens for shipments derived from clinical research trials.

CMRP provides clinical nurse administrator support to ICMOB leadership and its core team. The clinical nurse administrator serves a quality role by reviewing documentation for those currently receiving inpatient care to ensure that all requirements are fulfilled for admissions and discharges. The clinical nurse administrator is also responsible for identifying and addressing any medical record delinquencies with appropriate NIAID-licensed independent providers, and communicating directly with ICMOB staff to ensure that any necessary follow-ups are addressed in a timely fashion.

While HHS is responsible for maintaining a living document that provides federally approved HIV/AIDS medical practice guidelines, a number of CMRP staff members are providing technical writing and logistical support services to the HHS Panel on Antiretroviral Guidelines for Adults and Adolescents. This HHS panel has standing meetings that are conducted via teleconference, with one annual face-to-face meeting that, to minimize costs, is coordinated to coincide with the Annual Conference on Retroviruses and Opportunistic Infections. Several NIAID ICMOB staff members provide key leadership to the HHS panel. The work of the HHS panel affects NIAID's domestic and international HIV protocols, and the clinical staff members benefit from the panel's summary, which, in turn, benefits the HIV patients. CMRP directs the necessary resources to support all aspects of conference planning for the face-to-face meeting of the HHS panel. This support includes managing the necessary government approvals, planning and overseeing the budget, coordinating travel, facilitating hotel and meeting room arrangements, and providing on-the-ground support during the meeting. CMRP also provides oversight of a research subcontract for technical writing services for the HHS panel. These services include the provision of qualified personnel who have the necessary editorial and technical skills, as well as knowledge of scientific and medical terminology, to prepare minutes for the HHS panel teleconferences and the face-to-face meeting.

ICMOB is responsible for the quality of care delivered to NIAID patients and is accountable for the professional performance of the NIAID clinical staff. There continues to be a critical need to provide both NIAID and Leidos Biomedical Research clinical staff that support NIAID with a mechanism to more efficiently earn continuing medical education (CME) credits to maintain required licensure and NIAID credentialing. CMRP oversees a research subcontract that provides accreditation management services for issuing CME credits. The primary objective of this effort is to plan, develop, and implement an educational initiative focused on important topics in both patient care and research areas as related to the work of physicians, nurses, and pharmacists at NIAID, and to provide, monitor, and manage a comprehensive, online CME Program Management System tailored to the specific needs of NIAID. It is expected that approximately 40 sessions will be completed by the end of FY2015. This initiative provides an on-site/at-work option for clinical staff to obtain the necessary CME credits to maintain their professional licenses and avoid costly travel to off-site venues and lengthy out-of-office instances.

Laboratory of Allergic Diseases

The Laboratory of Allergic Diseases (LAD) conducts basic and clinical research on immunologic diseases, with an emphasis on disorders of immediate hypersensitivity, which include the spectrum of classic allergic diseases. The LAD scientific agenda is composed of basic and translational research aimed at elucidating events in mast cell–dependent, IgE-mediated allergic inflammatory reactions, including anaphylaxis, systemic mast cell disorders, and physical urticarias. Research efforts are focused on the role of mast cells, basophils, eosinophils, and T lymphocytes, and their cytokines in these disorders.

During FY2015, LAD will be seeing patients who have autosomal-recessive hypomorphic loss-of-function mutations in phosphoglucomutase 3 (PGM 3). These mutations have been shown to result in a novel congenital disorder of glycosylation (CDG), presenting with a hyper-IgE clinical phenotype. The goal is to understand how glycosylation defects result in atopic diatheses and immune dysregulation, providing novel insight into their immunopathogenesis. Developing successful therapies in these patients may further provide novel targets or approaches to the treatment of allergic diseases in the general population.

The Natural History of Genetics of Food Allergy and Related Conditions protocol began enrolling patients in summer 2015. Affected participants will have a clinical history of an IgE-mediated food allergy, and be sensitized to food allergies but clinically tolerant to those foods, or have a known or suspected genetic or congenital disorder potentially associated with a food allergy. Unaffected relatives and other healthy volunteers will also be recruited. This is an exploratory natural history study to evaluate the genetic, cellular, biochemical, microbial, immunologic, and nutritional factors that contribute to the pathogenesis of an IgE-mediated food allergy.

CMRP provides clinical support staff to assist in the conduct and facilitation of LAD's primary research objectives. Due to the high demand for support to facilitate high-quality clinical research, the LAD case managers are often sought after to provide support to other research labs within the Division of Intramural

Research (DIR). Currently, one CMRP case manager provides clinical support and assists with facilitating the LCID's primary research objectives in the study of *Borrelia burgdorferi* (Lyme disease), as directed by Dr. Adriana Marques. The practice of leveraging clinical expertise from other laboratories maximizes the utilization of resources across DIR.

The registered nurse case management support services that CMRP provides to LAD include management of eight protocols that study various aspects of allergic and inflammatory diseases, atopic dermatitis, urticarial syndromes, and systemic capillary leak syndrome (SCLS). One nurse case manager provides dedicated support to the natural history protocol studying diseases of allergic inflammation, focusing on subjects with moderate to severe atopic dermatitis, or with suspected genetic or congenital disorders associated with allergic inflammation. In support of this protocol, the nurse case manager conducts allergen skin prick testing, provides patient teaching for inpatient wet wrap therapy, educates all protocol patients about the Eczema Management Plan, and serves as the point-of-contact for all protocol patients, fielding questions and concerns, scheduling post-treatment visits to obtain information regarding health status, and scheduling follow-up visits, as well as assisting with the coordination of travel and lodging arrangements. The nurse case manager maintains data collection and entry responsibilities for the quality of life questionnaires for all protocol patients.

Serving an active role in protocol and laboratory program activities, the nurse case manager participates in regular protocol meetings and upholds a leadership role by spearheading communications to the various team members regarding information related to protocol patients.

In the past year, protocol expansion has included an additional arm focused on the genetics patients, specifically observing elevated tryptase families, implementing skin biopsies to look at differences in the MAST cells in the electronmicroscopy, and looking at the constellation of symptoms that seem to be associated with elevated tryptase. In addition, vibratory testing has been implemented to study the reaction to vibrations that some patients are experiencing. For the atopic dermatitis patients, infrared imaging and cooling cuff testing has been initiated in collaboration with The National Institute of Biomedical Imaging and Bioengineering to search for changes with inflammatory cytokines related to temperature.

Two CMRP nurse case managers in LAD provide direct nursing care to an assigned caseload of patients, utilizing a well-defined nursing process for assessing, planning, intervening, and following up on disease-related features as outlined in the assigned clinical protocols. The nurse case managers also provide procedural support using various techniques for skin punch biopsies, allergen-antigen skin prick testing, and pulmonary function testing with impulse oscillometry. These clinical professionals operate with a unique combination of knowledge and abilities requiring not only nursing skills, but also an expert ability to coordinate a complex set of logistical and clinical variables unique to each protocol and patient.

Of the protocols supported by CMRP staff, the five noted below are supported by one nurse case manager and have enrolled 28 new patients. This nurse case manager facilitated 185 patient visits, with more patient visits anticipated during FY2015.

- 02-I-0055: Evaluation, treatment, and follow-up of patients with Lyme disease
- 96-I-0052: A comprehensive clinical, microbiological, and immunological assessment of patients with post-treatment Lyme disease syndrome and selected control populations
- 09-I-N017: Research use of stored human specimens and/or data
- 09-I-0126: Pathogenesis of physically induced urticarial syndromes
- 09-I-0184: Studies in the pathogenesis of systemic capillary leak syndrome

The two protocols noted below are supported by another CMRP nurse case manager. The 10-I-0100 study closed to accrual in April 2015; the 10-I-0148 has enrolled 597 patients since its inception, 96 of which have been accrued to date during the current reporting period, and it is projected that 30–40 more subjects will be enrolled by the end of September 2015.

- 10-I-0100: Pilot study of the use of Anakinra in severe refractory atopic dermatitis
- 10-I-0148: Natural History of Atopic Dermatitis (NHAD) and other genetic/congenital diseases associated with allergic inflammation

The nurse case manager who supports protocols 02-I-0055, 96-I-0052, 09-I-NO17, 09-I-0126, and 09-I-0184 is also tasked with a variety of responsibilities in support of the Outpatient 11 (OP11) clinic. These include maintenance, troubleshooting, and operations for patient testing, as well as oversight of the safe environment of care for allergy testing, which includes managing the secure storage of NIAID LAD and National Institute of Biomedical Imaging and Engineering instrumentation, and ensuring that all equipment is properly disinfected and inspected by NIH biomed services for safe use during direct patient care.

The nurse case manager performs the skin prick testing (SPT) procedures, including complete change-out of the allergen extract skin prick panel trays. Procedural responsibilities include the transport, maintenance, and storage of the allergen extracts as ordered by LAD principal investigators to ensure the LAD allergy consult physicians have immediate access to allergen testing supplies and on-the-spot patient testing. In addition, all allergen extracts are secured in the OP11 cold-chain storage facility. The nurse case manager is enrolled in Project Immune Readiness, a program supported by the U.S. Army Medical Department, as an online training student to ensure clinical expertise and safe conduct of

practice. Furthermore, he has attained certification from the University of Pittsburgh Medical Center Health System with the National Institute for Occupational Safety and Health (NIOSH–approved spirometry course completion.

This nurse case manager also maintains specialized training and skills to perform aeroallergen sampling data entry and microscopic identification of sampled aeroallergens obtained from Burkard and RotoRod air-sampling devices. This training includes hands-on instruction related to serial dilutions and quality checks of allergen extracts for fulfillment of U.S. Army Centralized Allergen Extract Laboratory (USACAEL) customer order sets for testing and immunotherapy. Safe environment of care has been attained to 100 percent in the conduct of nurse case manager direct patient care mission activities and procedures employing conscious sedation (i.e., esophagogastroduodenoscopies with biopsies).

As a credentialed health care provider with certificates from the Defense Health Agency (DHA), in May 2015, this nurse case manager completed the Immunization Program Leaders Course (in-classroom, two-day instruction course). Additionally, he is heavily involved in contributing to various knowledge-sharing efforts fostered by the LAD investigators, including contribution to manuscripts.

Another nurse case manager provides dedicated support to two protocols (i.e., 10-I-0100 and 10-I-014 noted above). The NHAD protocol focuses on subjects with moderate to severe atopic dermatitis or with suspected genetic or congenital disorders associated with allergic inflammation. The nurse case manager conducts allergen SPT and provides teaching for inpatient wet-wrap therapy, as well as administers the eczema management plan. For both protocols, the nurse case manager serves as the point of contact for all protocol patients, fielding questions and concerns, scheduling post-treatment visits to obtain information regarding health status, and scheduling follow-up visits, as well as assisting with the coordination of travel and lodging arrangements. The nurse case manager is also responsible for data collection and entry for the quality-of-life questionnaires for all protocol patients.

Maintaining an active role in protocol and laboratory program activities, the nurse case manager participates in regular protocol meetings and upholds a leadership role by spearheading communications to the various team members regarding information related to protocol patients.

Both nurse case managers leverage various professional development opportunities to maintain and enhance the knowledge and skills necessary to support the LAD and LCID research efforts. These opportunities include participating in online training, attending lectures sponsored by NIAID LAD at the NIH Clinical Center, and obtaining cardiopulmonary resuscitation and pediatric advanced life support certifications.

Laboratory of Clinical Infectious Diseases

NIAID's Laboratory of Clinical Infectious Diseases (LCID) conducts clinical and basic studies of important human infectious and immunologic diseases, focusing on mycobacterial, bacterial, viral, and fungal infections, as well as the acquired and congenital immune disorders associated with infection, susceptibility, and resistance. Staff members supporting LCID are involved in the study and treatment of a wide spectrum of diseases, including primary immunodeficiencies, hyper IgE syndrome, herpes simplex virus, tick-borne infections, and autoimmune lymphoproliferative syndrome, as well as the identification of novel viruses.

CMRP provides a variety of clinical professionals, including three nurse practitioners, one clinical research nurse, four protocol nurse coordinators, three nurse case managers, and one patient care coordinator to support the development and conduct of LCID protocols.

Selected areas of clinical focus include: (1) the natural history and therapies of bacterial, mycobacterial, fungal, or viral infections; (2) the natural history and therapies of immune defects; (3) immune responses to infections and vaccines; (4) the identification of novel bacteria, mycobacteria, viruses, and fungi; (5) the diagnosis and treatment of Lyme disease; and (6) treatment-related protocols, such as Arikace and sildenafil.

CMRP clinical staff supports 24 protocols, with more than 950 patients involved. Support activities include direct patient care; protocol implementation; data management using the Clinical Research Information System (CRIS) and Clinical Research Information Management System of NIAID (CRIMSON); regulatory management; safety data monitoring; and FDA correspondence for Single Patient Exceptions (SPEs).

CMRP provides additional direct clinical support by coordinating patient activities, including clinical assessments to determine study eligibility, medication compliance, and general health. CMRP staff members also schedule and coordinate study visits, conduct post-visit follow-ups, and serve as a points of contact for study patients by fielding questions and concerns.

A CMRP protocol nurse coordinator remains actively involved in the coordination and scheduling of numerous LCID Science Symposiums, which are held weekly and attended by the clinical nursing team. These symposiums provide a forum for the nursing team to stay current on developing protocols, new and current research findings, and other important topics related to the management of patients enrolled on LCID protocols.

CMRP clinical support staff members remained very active during the year. The natural history study, Detection and Characterization of Host Defense Defects, Protocol 93-I-0119, enrolled 142 subjects during the reporting period, bringing the study's total enrollment to 475 patients. The subjects had diagnoses of chronic granulomatous disease (CGD); GATA 2 deficiency; thymoma; STAT 1 gain-of-function; IRAK-4 deficiency; X-MEN syndrome; FOXP-3 mutation; IgG4 deficiency; Sjogren's

syndrome; leukocyte adhesion deficiency; PI3K deletion; CTLA-4 dysfunction; X-linked agammaglobulinemia; nocardia brain infection; tuberculosis; disseminated aspergillosis; *Cryptococcus meningitis*; disseminated coccidioidomycosis; and *Mycobacterium marinum* infection (rarely diagnosed). Ongoing follow-up, as part of this natural history study, has enabled the study team to gain knowledge about new mutations, and to characterize and manage clinical complications, such as coccidioidomycosis and nocardia. The investigators are currently focusing the research on correlating specific infections with specific immune defects, such as fungal infections in CGD and with anticytokine autoantibodies.

Another active study, the Detection and Characterization of Infections and Infection Susceptibility (screening study), enrolled 140 subjects during FY2015, and screened 184 patients over the last six months of the reporting period. This study had several disease-related discoveries, including the first patient with disseminated coccidioidomycosis due to a mutation of IL-12 receptor beta 2; the first patient with aspergillosis and CARD9 mutation; and cases of progressive multifocal leukoencephalopathy (PML) associated with STAT1 gain-of-function mutations. Diagnoses for patients seen in this study included: GATA 2 mutation; GATA 3 mutation; PI3KRI mutation; CTLA 4 mutation; PI3Kp85 mutation; STAT1 GOF; RAG 1 mutation; CGD; PNTM; hyper IgE; FUO; hypogammaglobulinemia; Mounier-Kuhns syndrome; *Burkholderia cepacia bacteremia*; and Alpha-1 anti-trypsin deficiency. Three amendments were also made during this period, adding intramural and extramural collaborators, and expanding the scope of investigation to include state-of-the-art functional genomics and molecular diagnostic techniques.

The active procedural protocol Research Respiratory Tract Procedures allows for the collection of specimens during bronchoscopy, nasal mucosal sampling, and induced sputum from patients and healthy volunteers to support bench research investigations of collaborating investigators. The bronchoalveolar lavage specimens, bronchial brushings, nasal mucosal scrapes/brushings, and sputum are being used to study the mechanisms of disease pathogenesis and susceptibility. One disease of interest is Alstom's syndrome, in which the patient may be blind and deaf. The study team consented 60 patients, several of whom are legally blind and/or children. With these patient characteristics, the consenting process was more complex. A bioethics consult was facilitated by the study team to ensure that appropriate human subjects protection was in place and followed.

The major goals of the Lyme Disease Research Program are to develop better means of diagnosing, treating, and preventing this disease. To accomplish these objectives, the NIAID research portfolio includes a broad range of activities designed to increase the understanding of Lyme disease, encompassing basic and clinical research studies conducted by extramural and intramural investigators. The CMRP nurse practitioner for LCID assists in reviewing potential candidates for the Lyme Disease Research Program by reviewing data that accompanies study participation requests to determine eligibility. After reviewing the data, the nurse practitioner contacts the potential future candidate to conduct a telephone interview to obtain more detailed clinical information. The nurse practitioner then presents the clinical case at weekly Lyme Disease Research Program meetings and sees eligible patients in the clinic for a history and physical exam.

During FY2015, the nurse practitioner conducted approximately 10 case reviews of potential candidates; performed history and physical exams for nearly 20 new patient visits; conducted about 80 follow-up visits for currently enrolled patients; and performed procedures such as lumbar puncture skin biopsies. The work of the nurse practitioner has significantly increased since the time of the last reporting, as the study team is actively ensuring that all protocol timelines for return visits are being met. To efficiently manage the process of multiple patient visits per day (i.e., seeing the patient and reporting findings to the principal investigator before proceeding to the next scheduled patient), the nurse practitioner designed a table that included pertinent history (e.g., previous physical exam findings, lab results, and the agreed upon treatment plan). This table is readily available for each patient prior to their arrival for scheduled visits, decreasing the amount of time needed to refer to previous visit notes and increasing efficiency when seeing multiple patients in one day.

A new multicenter protocol is managed by a protocol nurse coordinator. This recently approved study, 15-I-0131 Xenodiagnosis after Antibiotic Treatment for Lyme Disease Phase II Study, is preparing for recruitment at four study sites.

CMRP clinical staff members have expanded and enhanced consenting procedures to accommodate several international patients in critical need of medical care. In the past year, study teams obtained consents in Lao, Thai, Hindi, Korean, Amharic, Chinese, Khmer, French, Italian, Arabic, Spanish, Greek, Portuguese, Urdu, Vietnamese, and Turkish. All subjects were consented in the language they were most comfortable with and could read. The study teams go to great lengths to ensure that the culture of the patient and his or her family is respected, and human subjects' protections are applied appropriately.

During FY2015, the study teams faced admitting critically ill young adults for life-saving treatments. These patients are cognitively unable to sign an informed consent upon their arrival at the NIH Clinical Center. The study teams have developed a collaborative relationship with the NIH Bioethics Office to ensure timely responses to these critically ill patients, and three 'ethics consults' were conducted during this period.

CMRP clinical staff members are very involved in the facilitation of Material Transfer Agreements (MTAs). During the current reporting period, new MTAs have been completed, which include collaborations with researchers in the United Kingdom and Taiwan, and

intramural collaborations with the National Human Genome Research Institute. CMRP staff members have developed the necessary network within NIH to efficiently and effectively execute these agreements with both international and domestic parties.

CMRP staff remained flexible when asked to provide support in the absence of available LCID resources on several occasions. Most recently, CMRP supported two LCID protocols for a clinical research nurse on medical leave and covered multiple responsibilities in the nurse's absence. A protocol nurse coordinator went on medical leave and was able to prepare two continuing reviews early in anticipation of her absence. CMRP clinical staff members routinely provide coverage, which can range from consenting on other studies, to submitting an amendment or stipulations, or screening patients. This support allows workflows to continue uninterrupted.

The CMRP clinical staff continues to support knowledge-sharing activities, such as Science with Steve and Friends, a seminar presented by the LCID researchers to the nurses on a weekly basis. This forum brings the science of the lab to the nurses on the floor/clinic. The seminars began in 2009 and have continued every Thursday; CMRP staff members contact the speakers, set the calendar, and coordinate meeting room logistics.

As a result of previous involvement of a CMRP study coordinator in the Association for the Accreditation of Human Research Protection Programs' (AAHRPP) accreditation interview (detailed in last year's report), the CMRP study coordinator continues to participate in the CRIMSON Study Coordinator Overview Committee, which is helping to integrate AAHRPP requests into CRIMSON.

Laboratory of Host Defenses

The Laboratory of Host Defenses (LHD) studies the immune functions essential for the host's defense against infection. LHD also studies the genetics and patho-physiology of inherited primary immune deficiencies. These abnormalities may be associated with recurrent infections and/or dysfunctions of immune homeostasis, which the lab investigates through clinical protocols.

LHD clinical investigations aim to develop new diagnostic and therapeutic approaches to the management or correction of immune dysfunction in patients. CMRP provides a variety of clinical staff to support LHD, including protocol nurse coordinators, nurse case managers, a clinical research nurse, and a physician. The major areas of research for LHD include the study of gene therapy, inflammatory bowel disease (IBD), common variable immune deficiency, granulomatous disease, allogeneic transplantation using hematopoietic stem cell grafts, and acute and chronic graft-versus-host diseases.

The protocol nurse coordinators support LHD by reviewing activities related to screening and enrolling new subjects, in addition to performing continuing protocol reviews and protocol amendments. One protocol nurse coordinator currently oversees four protocols and serves as the LHD liaison for the electronic regulatory binder program. The protocol nurse coordinator has enrolled 27 new subjects and has had two site visits.

The clinical research nurse is responsible for screening, and has enrolled more than 110 patients and conducted one site monitoring visit during the reporting period.

A protocol nurse coordinator has been heavily involved in the NIAID Nursing Education Committee. This committee was created to streamline the orientation process for new nursing staff within NIAID. In addition, she is also working with CRIMSON, the NIAID research database, to improve processes to query information within the computer program. The clinical research nurse has been instrumental in the protocol development and implementation of a new LHD Protocol 15-I-0113 titled NIAID Clinical Center Genomics Opportunity Protocol. The clinical research nurse continues to collaborate with NCI to streamline care for patients affected by dedicator of cytokinesis 8 (DOCK8) immunodeficiency.

The LHD nurse case managers work closely with team members to successfully bring patients to the NIH Clinical Center. The nurse case managers serve as the point-of-contact for the study patients, often fielding questions and concerns, as wells as scheduling and coordinating study visits and post-treatment follow-ups. One of the protocol nurse coordinators identified challenges with scheduling patients for lodging/travel who require special consideration pertaining to their medical condition. She has been working with the NIAID travel team to improve this process, thereby eliminating the potential for patients to have to find other means of lodging upon their arrival to NIH.

The clinical research nurse and protocol nurse coordinator developed a workflow tool for case managers to use in caring for the complex patients that are seen in LHD. This collaborative tool will streamline visit appointments and patient management, thereby eliminating errors when ordering protocol-driven tests and procedures. During the reporting period, a protocol navigator was hired but subsequently chose not to continue with the position shortly into the orientation period. Efforts are being made to replace the vacancy with an additional protocol nurse coordinator position.

CMRP provides a physician to support protocols and clinical operations initiated by LHD. The patient population is complex, and includes children and adults with congenital immunodeficiencies, such as CGD of childhood, XL-SCID, and X-linked agammaglobulinemia. Since these conditions predispose these patients to complex, recurrent, and chronic infections, an infectious diseases physician is a major asset to their care. LHD also supports a transplant program for CGD and XL-SCID, and is currently involved in gene therapy for XL-SCID, CGD, allogeneic transplantation using hematopoietic stem cell grafts, and acute and chronic graft-versus-host diseases. The physician supports the primary care, infectious disease consultation, and transplant-related activities related to new immunodeficiencies such as DOCK-9, PASLI, and WHIM syndrome. The physician

continues to participate in in-house and distance consultation (for patients not yet enrolled or those enrolled, but receiving care at outside facilities) for patients with congenital immunodeficiencies beyond the scope of transplantation infectious diseases. Other new responsibilities are related to the transition to the LHD of patients previously seen in NHGRI with Wiskott-Aldrich syndrome and ADA-SCID, some of whom received transplants.

The physician now is active as the vice chair of the IRB for NIAID, assuming responsibility for protocols from a selection of the NIAID laboratories and serving as chair of the board.

The physician provides consultation support in the pre-transplantation evaluation, and the care related to complications that may occur during and/or after the transplant. In addition, the physician participates in the infectious diseases practice at the NIH Clinical Center by being involved in the care provided by the infectious diseases consult service, and in the education of students, residents, and infectious disease fellows. To facilitate the consistent practice of transplant infectious diseases medicine, the physician has leveraged the opportunity to observe and provide consultation in the NCI Experimental Transplantation and Immunology Branch (ETIB) program. These efforts are directly related to improving the consistency of care at the NIH Clinical Center associated with the management of the infectious complications of transplantation. Additional responsibilities and opportunities have arisen that are related to transplantation and post-transplant care for patients with other complex immunodeficiencies. Experience with this broader population provides additional information and increases interaction with the NIH transplant community, which is vital in understanding the alternative approaches to infectious and noninfectious diseases associated with transplantation.

The physician continues to participate in multiple infectious disease services, provides continuity of care by working weekends and on services that are in addition to mandated responsibilities, and collaborates with outside investigators on microbiological studies related to the care of LHD patients, including the study of Burkholderia, a major pathogen in CGD, and Campylobacter/ Helicobacter/Flexispira, a pathogen in Bruton's agammaglobulinemia patients.

The physician's participation in larger, clinical center–wide transplant activities has led to a significant broadening of responsibilities in the LHD transplant program, and that experience was a direct contributor to the development of new transplant protocols within the LHD for haplo-identical transplantation using post-transplant cyclophosphamide as a graft-versus-host disease prophylaxis, with the first successful transplant completed in late 2014. In addition, the physician's presence has added sufficient supervisory capacity to improve LHD's continuity of care in providing ongoing treatment of the large cohort of immunodeficiency and post-transplant patients so that LHD care is reviewed on a weekly basis with LHD staff.

Dr. Mark Parta received the 2014 Clinical Center Director's Award for "exceptional collaboration in planning and implementing the clinical care provided to CC patients exposed to or infected with Ebola virus."

Laboratory of Immunology

The major research activities of the Laboratory of Immunology (LI) are related to the basic genetics, molecular biology, cell biology, and cellular immunology of the immune system. The research scientists are interested in how dysregulation of the immune system results in autoimmune and lymphoproliferative diseases, and what strategies might be valuable for vaccine development.

CMRP staff supported the Autoimmune Lymphoproliferative Syndrome (ALPS) Unit, which had been in LI since 2012 but moved to the Laboratory of Clinical Infectious Diseases (LCID) halfway through FY2015. The ALPS Unit focuses on gaining a better understanding of the clinical and genetic characteristics of people with ALPS and related disorders. By identifying the genes responsible for symptoms, NIAID researchers not only help affected families, but also increase the understanding of how the immune system works. Whole-genome sequencing is one of the tools the investigators are using to address these research questions. Ultimately, they hope to develop safe and effective treatments targeting the genetic defects in children with ALPS and related disorders. Due to the laboratory transition during the reporting period, some of CMRP's support activities are reported here and others are reported in the LCID section of this Annual Report.

The volume of work decreased somewhat due to the lack of referrals during the transition between labs and the seven-week absence of the CMRP clinical research nurse due to surgery. However, referrals are expected to increase as the result of a recent publication by LI's multidisciplinary team in *Blood* [30 April 2015, *Blood* (125) 18: JMML and RALD (Ras-associated autoimmune leukoproliferative disorder): common genetic etiology yet clinically distinct entities]. The clinical research nurse works extensively with the patients and referring physicians to obtain records, pathology material, and radiology CDs prior to the first visit and for interim visits.

In FY2015, the clinical research nurse coordinated intake referrals with outside physicians and handled new referrals for patients considered eligible for a study by sending out screening kits and consents to patients. The clinical research nurse is responsible for ensuring informed consent is obtained before any screening tests are done, logging the signed consents (signed by a patient/guardian, a witness, and the investigator who communicates with the patient/family) into CRIMSON and sending a copy back to the patient, enrolling the patient on the study in CRIMSON, and ensuring specimens are sent to the appropriate locations for testing.

The clinical research nurse provides support to the ALPS team primarily at the direction of the ALPS study coordinator. During the reporting period, the following activities were accomplished: 20 new patients were referred for consideration; records of 270 active and new patients were loaded into CRIMSON; 12 blood, 22 saliva, and 10 buccal send-in samples were processed; 19 pathology slides were processed; 26 research reports were filed in secure electronic files; 177 old files were converted to secure electronic files; and assistance was provided to the study coordinator with setting up tracking mechanisms for tracking compliance of study staff for an upcoming protocol sponsored by Novartis that will begin recruitment in FY2015.

The nurse practitioner provided support to the ALPS team at the direction of the ALPS principal investigator and study coordinator. She also referred new patients for study consideration; loaded records of active and new patients into CRIMSON; processed pathology slides; filed research reports in secure electronic files; and spent approximately 120 hours assisting the study coordinator in compiling/organizing research data. Additionally, the nurse practitioner spent approximately 40 hours in radiology training; processed imaging findings for patients; and saw patients in clinic for history and physical exams.

A new protocol approved in October 2014 (14-I-0206, Novel Genetic Disorders of the Immune System) was designed to evaluate patients with suspected or identified novel immune disorders, with a focus on abnormal immune homeostasis potentially due to defects in activation or apoptosis. Blood relatives of enrolled patients will also be evaluated. Affected individuals may have Mendelian gene defects involving mostly single or, occasionally, multiple genes. These patients may have signs and symptoms suggestive of clinically significant lymphocyte homeostasis disorders. However, some selected patients manifesting autoimmunity, autoinflammatory conditions, end-organ dysfunction, Epstein-Barr virus (EBV) and cytomegalovirus (CMV) viremia, frequent infections, allergies, or laboratory abnormalities consistent with immune defects of research interest may also be studied under this protocol at the discretion of the investigators. The clinical research nurse is involved primarily in the data sample collection. After review, the nurse practitioner will be an active member of the team, seeing patients in the outpatient/inpatient units.

Laboratory of Infectious Diseases

The Laboratory of Infectious Diseases (LID) has a long history of developing vaccines and identifying new agents of viral diseases. LID is noted for undertaking high-risk, high-reward programs that require extraordinary time and resource commitments, such as programs to develop vaccines for viral hepatitis, severe childhood respiratory diseases, and viral gastroenteritis. Clinical studies complement LID's major areas of research, including testing candidate vaccines in clinical trials, a human challenge study with influenza to study pathogenesis and immune correlates for protection against the virus, and studies of severe virus infections in persons without known immune deficiencies.

The CMRP nurse practitioner provides support to the LID team at the direction of the principal investigator and lab chief. During FY2015, her activities included seeing nearly 90 patients in clinic for history and physical exams, and reviewing the medical histories of five patients who are interested in participating in the clinical trial.

The nurse practitioner identified inconsistencies in clinical data reported in patients' charts, an issue partly attributed to an inadequate amount of time set aside for nursing to give verbal and written patient data directly to the patient provider. The nurse practitioner developed a systematic means of accurate information transfer from the nurse to the patient care provider to prevent this from happening in the future.

Laboratory of Immunoregulation

The Laboratory of Immunoregulation (LIR) investigates the cellular and molecular mechanisms regulating the human immune response in health and disease. A major component of these efforts is the study of the immunopathogenic mechanisms of HIV infection and disease progression. Developing a thorough understanding of how to prevent and treat HIV infection requires an understanding of how HIV destroys the immune system. Several important aspects of this process are under intense investigation, and CMRP plays a significant role in providing the clinical support resources needed to drive progress and maintain the stamina needed to achieve success.

CMRP provides study coordination; case management; patient recruitment; and laboratory, clinical (nursing and provider-level), pharmacist, and research support to LIR. During the current fiscal year, LIR supported over 55 active protocols. In addition to mission-sensitive, HIV-related research, LIR placed great emphasis on domestic and international Ebola research efforts, and also wrapped up a successful clinical trial evaluating an interferon (IFN)-free hepatitis C treatment protocol for hepatitis C mono-infected and hepatitis C/HIV co-infected individuals.

CMRP staff members are highly responsive to the needs of the laboratories in which they serve and have demonstrated flexibility in responding to shifting NIH priorities. Study coordinators and the OP8 recruiter collaborated to conceive, execute, and fully enroll a Phase I Vesicular Stomatitis Virus (VSV) Ebola Vaccine trial at the NIH Clinical Center in record time. The OP8 pharmacist and research technician volunteered to serve as WatSans to assist providers in donning and doffing personal protective equipment at the NIH Clinical Center; they also served as facilitators in WatSan "train the trainer" courses to enhance WatSan capacity at the clinical center. In addition, the OP8 pharmacist travelled to Liberia to support in-country Ebola research efforts.

CMRP staff members have been equally responsive to meeting the shifting needs of the hepatitis C research team. With the identification of a successful IFN-free hepatitis C treatment regimen, research priorities are shifting to focus on community-based treatment and long-term follow-up. CMRP staff supports all aspects of hepatitis C research, and increasingly collaborates with the DC Partnership for HIV/AIDS Progress and the University of Maryland to achieve research priorities.

NIAID cost savings have been achieved through continued paper reduction and increased electronic transmittal of documents. The use of the electronic, secure e-mail system for communication with patients results in savings on postage, which amounts to approximately $600 per year.

During FY2015, the patient recruiter continued to work with the Office of Communications and Government Relations (OCGR) in a coordinated effort to understand the use of listservs and social media in the recruitment process, and for the dissemination of information related to clinical trial availability. In addition, the patient recruiter expanded the reach of NIH recruitment by successfully utilizing new recruitment platforms like ResearchMatch.

Laboratory of Parasitic Diseases

The Laboratory of Parasitic Diseases (LPD) conducts basic and applied research on the prevention, control, and treatment of a variety of parasitic and bacterial diseases of global health importance. Research efforts are largely focused on the identification of immunological and molecular targets for disease intervention. LPD also conducts research related to the role of eosinophils and eosinophil activation in disease pathogenesis, with the ultimate goal of developing novel diagnostic tools and treatments for hypereosinophilic syndromes and other conditions with marked eosinophilia, including helminth infections. Additionally, LPD has a clinical group that conducts patient-centered research at the NIH Clinical Center. CMRP provides physician assistant support, nurse case management support, and study coordination services to LPD.

Collectively, the clinical support staff for LPD coordinates patient schedules, data collection, and nursing care. Staff members order protocol-mandated tests, labs, and procedures, and alert the physician to adverse events (AEs), abnormal outcomes, and/or problematic trends. Clinical staff participates in the development of protocols, procedure manuals, and case report forms (CRFs). Additionally, clinical support staff members oversee protocol operations to ensure study compliance, trouble-shoot possible protocol violations, and interface with the IRB to ensure proper and timely filing of SAEs, amendments, annual reports, and other regulatory documents, including biweekly safety reports. These CMRP staff members play an active role in providing updates to clinical teams on patient care and protocol progress.

The clinical support staff assists in maintaining 18 actively enrolling protocols. During the reporting period, 110 new subjects were enrolled; 22 site visits occurred; and one initial submission, 19 continuing reviews, and nine amendments were completed.

The protocol nurse coordinators, who serve as associate investigators on the active protocols within LPD, assisted investigators in collecting and analyzing retrospective data for patients with eosinophilia. These efforts led to a manuscript publication, acceptance of an abstract, and submission of poster abstracts.

During the FY2014 period, LPD started five new protocols, three of which are IND studies. As a result, the overall work efforts of the protocol nurse coordinators in FY2015 have increased greatly to screen and recruit patients for these new studies as well as the existing protocols. The number of patient visits has also increased with the advent of these new studies, increasing the volume seen by the nurse case managers. In addition, the new IND studies have required frequent safety monitoring by the protocol coordinators for various regulatory groups. The protocol nurse coordinator, who oversees the protocol 14-I-0191 titled Longitudinal Study of Immune Responses to *Mycobacterium tuberculosis* (Mtb) in Subjects with Latent Tuberculosis (TB) Infections (LTBI) with or without Concomitant Helminth Infection, has been working closely with the Maryland IRB and a local, state-run health clinic to recruit subjects.

During this fiscal year, LPD underwent staff changes. In mid-September 2014, a new protocol nurse coordinator was hired. In October, both of the nurse case managers resigned, leaving LPD without staff to cover clinic patient visits. As a result, the protocol nurse coordinators had to manage the regulatory responsibilities for LPD protocols as well as the scheduling of all patient appointments. A new case manager was hired and started in January 2015. The second case manager started in April 2015. During this transition period, staff members from other areas of the Clinical Center were used to cover clinic visit for the patients. In addition, a patient care coordinator from another CMRP division was hired to assist with patient travel. This additional staff support was instrumental in creating a seamless environment for the patients in order to ensure that protocol requirements were met.

New strategies are currently under consideration to create better guidelines for patient travel to cut down on expenses for local travel.

The protocol nurse coordinators and case managers worked closely with a patient care coordinator from ICMOB to assist with patient travel. LPD was used as the pilot group for training the patient care coordinator and has been instrumental in incorporating its work efforts into other NIAID labs. As potential pitfalls were identified, LPD worked with the CRIMSON team and the patient care coordinator to identify methods to streamline the process and make it more beneficial for staff and patients alike. Additionally, the protocol nurse coordinators have been working with physicians from other NIH institutes to arrange consults and procedures.

By working with a select group of physicians, this has allowed for continuity of care across the various protocols for patients with eosinophilia.

Pharmacy Support

CMRP staff includes a clinical pharmacist who provides pharmacologic support to NIAID's clinical operations. This support includes patient education, inpatient and outpatient clinic services, research-related support, and pharmacologic guidance and expertise. The clinical pharmacist works with patients to ensure their understanding of antiretroviral therapies, opportunistic infection (OI) treatment, HIV pathophysiology, and treatment goals. Hospital inpatient and outpatient clinic services include discharge counseling; continuity-of-care between inpatient and outpatient settings; support to rotating medical residents involving inpatient HIV patients; support to NIAID fellows while on HIV clinic assignments; and support to NIAID HIV attending and clinic physicians involved with antiretroviral regimens and OI treatment/prophylaxis. Specifically, the clinical pharmacist assists with entering orders for take-home medications and verifying accuracy of orders; serves as a liaison to the NIH Clinical Center pharmacy staff; assists residents with coordinating orders for patients receiving directly observed therapy and therapeutic drug monitoring at the NIH Clinical Center; follows up on labs and medication orders for HIV patients, and provides recommendations accordingly; provides pharmacologic expertise involving dosing, drug interactions, and side effects of antiretroviral, anti–hepatitis C, and concomitant medications; and provides follow-up to address adherence barriers to therapies. Medication adherence support includes coordination with the outpatient pharmacy, pillbox teaching, and communication with caregivers and assisted living staff. All services are provided to ongoing natural history protocols for HIV, the CONQUER (hepatitis C, April 2014), DOTCOM (HIV drug resistance, January 2014), and PANDORA (HIV treatment, May 2014) studies, and will be incorporated into upcoming hepatitis C treatment studies (STOPCO, liver transplant candidates, 2015; and HCV retreatment study, 2015).

The clinical pharmacist acts as an observer on the HHS panel, provides drug interaction tables for the HHS HIV guidelines annually, and conducts literature reviews upon request. The clinical pharmacist also provides logistical support for annual meetings. Additionally, this staff member serves as a mentor for pharmacokinetics research fellows, provides lectures to the NIAID fellows on HHS guidelines and antiretroviral therapy, and provides nursing education on antiretroviral therapy.

Research Subcontract Support

CMRP manages and administers a research subcontract with Professional Education Services Group (PESG) for accreditation services for seminars and other training type events attended by clinical staff. During this reporting period, the PESG agreement was extended to cover services through FY2016. Additionally, the acquisition process to issue a modification expanding PESG's scope of work to include a one-off training event for DCR clinical research professionals was initiated; however, after receiving and evaluating PESG's proposal for the work, a decision was made not to modify the PESG agreement to include the expanded scope.

CMRP also manages and administers a Blanket Purchase Agreement (BPA) with Palladian Partners, Inc., to provide specialized science, medical, and public health communication support. Services provided by Palladian Partners include scientific writing and editorial support, quality assurance expertise, transcription, translations, and meeting support. Under the BPA, Palladian Partners provides the services of Dr. Frances McFarland Horne.to support the NIAID/ICMOB/Office of AIDS Research Advisory Council (OARAC) Panel for Antiretroviral Guidelines for Adults and Adolescents. The Palladian Partners BPA period of performance has been extended to continue through December 2015.

Collaborative Clinical Research Branch

Support Provided by the Clinical Monitoring Research Program

Infectious Diseases Clinical Research Program, Department of Defense

Since 2005, CMRP has worked with NIAID to establish and maintain a collaborative effort between CMRP, NIAID, and the Department of Defense (DoD) within the Infectious Diseases Clinical Research Program (IDCRP). With a CMRP physician serving as the team leader for the project, the overarching goal of this collaboration has been to facilitate high-priority, translational clinical research to address infectious disease problems of military relevance. Additional objectives include building research capacity, developing infrastructure, facilitating efficient clinical research, and leveraging scientific expertise within and outside of NIH.

The CMRP physician continues to facilitate the development of research capacity by aiding IDCRP staff in developing and implementing protocols, assisting with prioritizing research protocols within the network, and developing research areas of prime importance to the network. RCHSPP staff has helped IDCRP develop an informed, independent staff for regulatory and monitoring functions. Under this mentorship, IDCRP staff members now monitor several of their own protocols and have developed quality assurance (QA) and quality control (QC) standards for IDCRP.

Currently, 88 IDCRP protocols are in various stages of development (ongoing, planned, or completed). There are 30 ongoing studies (17 HIV and 13 non-HIV), 41 completed studies (24 HIV and 17 non-HIV), and 17 new studies planned (one in HIV and 16 in non-HIV). The new protocols include studying skin infection in

submarines, chlamydia and gonorrhea screening in asymptomatic women, and an exploratory study to evaluate immune responses to anthrax vaccination. In addition, the CMRP physician is working with IDCRP staff to develop a study to evaluate various interventions in the treatment of diarrhea in military personnel in Europe, Africa, and the Middle East.

The physician serves as the chair of the IDCRP Scientific Review Board (SRB), reviewing all new and amended research protocols for scientific design and validity, and chairing the review groups for each protocol. The physician also serves as an ex officio member of the IDCRP Steering Committee, a member of the Senior Science Group, which evaluates new research concepts before proceeding to protocol development, and is a member of the Senior Advisory Group, which meets weekly to review program operational progress and address challenges.

CMRP staff members have also helped develop research capacity by acting as points-of-contact for clinical research questions and standards, such as NIAID-specific protocol templates and SOPs. The CMRP physician holds regular biweekly meetings regarding the function and vision of the IDCRP program with NIAID staff members to keep them up-to-date on the progress of the program. Additionally, the physician has lectured groups of principal investigators (PIs) and has mentored individual PIs to enhance their scientific understanding, and has worked closely with IDCRP staff to reorganize the data collection and analysis branch.

During FY2015, the CMRP physician aided DoD staff in developing an infectious disease–specific IRB and continued work with IDCRP staff on development of a study to evaluate various interventions in the treatment of diarrhea in military personnel in Europe, Africa, and the Middle East. RCHSPP staff provided protocol pre-review for regulatory compliance and protocol monitoring, when appropriate, per GCP regulations.

During this reporting period, the CMRP physician continued assisting NIAID with completing the annual interagency agreement (IAA) to provide annual funding for the program. The IAA between NIH and IDCRP is renewed yearly and requires modifications that reflect changes within the organization. The CMRP physician is responsible for ascertaining any changes, working with NIAID's DCR to obtain appropriate approvals as needed, and ensuring that funds have been advanced as required by contract.

The CMRP physician continues to guide this project, often assisting and advising on the structure of new projects and guiding military physicians on the conduct of high-quality science, along with providing lectures to scientific groups and young investigators. The continuation of weekly and monthly meetings keep CMRP staff informed of potential changes and ongoing needs for assistance and support. The CMRP physician reports updates and changes to, and discusses them with, the NIAID clinical director.

Biostatistics Research Branch

Support Provided by the Clinical Monitoring Research Program

The mission of the Biostatistics Research Branch (BRB) is to develop collaborative relationships with intramural and extramural researchers and to conduct independent research in statistical methodology. CMRP staffs four biostatisticians to support this effort.

The CMRP biostatisticians provide statistical and mathematical support, as well as data management, programming, and statistical data analysis to many intramural clinical research protocols. These staff members also analyze novel, high-dimensional immune assay data collected through the Phase I vaccine studies conducted at NIAID's Vaccine Research Center (VRC), including vaccine efficacy and studies of malaria and HIV. In addition, CMRP biostatisticians help develop and test novel statistical methods for researchers, assist in safety evaluations, and prepare DSMB reports.

During the reporting period, the biostatisticians were involved in a wide variety of projects, from developing analysis plans to performing complex statistical analyses, writing reports, and co-authoring manuscripts. Some of the projects supported by BRB included tuberculosis (TB) fingerprinting, influenza-like-illness, Project Phidisa, H1N1 flu epidemiology, childhood malaria, drug safety and mitotoxicity, and various vaccine studies. The biostatisticians also conducted various statistical tests, from descriptive statistics to regression models, graphs and reports for several VRC studies (e.g., VRC 207, 601,) and vaccine trials.

A biostatistician provides statistical and mathematical programming support and aids in analyzing a broad range of clinical and laboratory studies, while being directly involved in performing research experiments, data collection, processing, and assisting with the experimental imaging of simian immunodeficiency virus (SIV)/simian/human chimeric immunodeficiency virus (SHIV) in rhesus macaques.

Additional activities during FY2015 included: (1) analyzing data from noninvasive in vivo single-photon emission computed tomography and positron emission tomography imaging of SIV/SHIV-infected non-human primates, (2) studying the levels of tissue penetration and intracellular delivery of antiretroviral drugs by formulating into cochleates, (3) studying the in vivo recovery of the immune system of healthy monkeys that underwent total body irradiation, and (4) designing in vivo studies targeting a cure for HIV.

The CMRP biostatistician II received the NIH Merit Award in November 2014, given to the GATA2 discovery group in recognition of outstanding clinical and basic research leading to the discovery and characterization of GATA2 deficiency.

Office of Planning and Operations Support

Support Provided by the Clinical Monitoring Research Program

The mission of the Office of Planning and Operations Support (OPOS) is to provide services and innovative solutions to optimize the facilitation of NIAID clinical research and special projects. CMRP provides executive leadership and management oversight for a variety of programmatic and administrative resources in support of this mission. OPOS has developed and maintained an innovative portfolio of services, which CMRP staff directly supports and facilitates. These services include strategic and operational planning, learning and professional development, technical solution support, and research subcontract management and oversight.

A variety of experienced CMRP staff members support the portfolio of services offered by OPOS. A program manager administers and applies project management principles and concepts, focusing on strategy implementation and performance management. A clinical training manager and clinical training specialist serve as the primary resources for facilitating and conducting learning and professional development activities supported by OPOS. A special projects administrator acts as the point of contact in the Technical Solution Groups, providing technical support to the branches and offices of NIAID DCR. These resources provide a breadth and depth of experience and knowledge that is leveraged division-wide.

CMRP provides management oversight to several research subcontracts in support of OPOS program operations and major initiatives. These research subcontracts supply technical resources that provide facilitation experts for OPOS's ongoing organizational development and strategic implementation initiatives, as well as leadership coaching services to support DCR's division-wide leadership enhancement initiative.

CMRP staff coordinated a consulting agreement to obtain a management and organization consultant to facilitate strategy development and implementation for several of DCR's special projects. Consultant services were utilized for the University Clinical Research Center (UCRC) initiative, a collaborative partnership between the Mali Minister of Health and Public Hygiene; the Mali Minister of Higher Education and Scientific Research; the Rector, University of Sciences, Techniques and Technologies of Bamako, Mali; and the NIAID Division of Clinical Research. The UCRC planning meeting in November 2014 yielded a review of potential Ebola studies to be considered by UCRC, and also resulted in the following: finalization of the draft UCRC governance model and operating structure, discussion of UCRC challenges identified during the stakeholder meeting held in FY2014, review and agreement on the draft objectives needed to achieve the goals in the strategic plan, finalization of the draft UCRC guiding values, identification of the location and scope of UCRC capabilities, and definition of the next steps and action items.

A governing board meeting was held in February 2015 with the following objectives: review principles of UCRC governance, discuss governing board considerations, present the UCRC strategic plan, appoint the executive committee, and endorse the budget and partner contributions.

CMRP manages another organizational development consultant who provides support to the Strategic Management in Clinical Research Networks effort in collaboration with the subcontractor Jerry Lassa, Inc. (referenced in the Performance Measures section and in the Clinical Consulting and Support Sections of the CMRP Annual Report) and other special projects initiatives. CMRP support to other subcontracts is also outlined in the Clinical Consulting and Support section of the CMRP Annual Report.

Project Management Support

OPOS provides strategy and operational management for the DCR branches, offices, and special projects that ultimately further NIAID's clinical research agenda by setting and monitoring strategic goals and initiatives aligned with NIH priorities. CMRP provides a program manager to support the Organizational Effectiveness Group (OEG), Strategic Planning Group (SPG), and Special Projects Group for OPOS. The program manager, in collaboration with the OPOS groups, provides strategy and operational and project management support to NIAID's DCR.

In FY2015, the program manager assisted with the finalization of two operational plans, co-facilitated two strategy management sessions, developed three new strategy management tools, created a service offerings brochure, and completed progress reports for five branches/offices and two special projects, for a total of 19 reports.

In addition to supporting OPOS's strategy management activities, the program manager is responsible for assisting with DCR's workforce alignment efforts. Utilizing a performance management mapping tool that was created by the program manager in FY2013, metrics and data for FY2015 were easily identified, which resulted in simplified mid-year and year-end evaluation processes. Brainstorming sessions were held with key staff members to identify DCR projects, initiatives, and activities to be considered for inclusion. Based on information gathered during the sessions, a matrix with options and recommendations was presented to DCR leadership, allowing for an informed decision-making and prioritization process.

The program manager continues to establish, implement, and maintain a flexible reporting system for monitoring the progress of operational plans, which requires facilitating the ongoing review and maintenance of five DCR operational plans and two special project operational plans, and progress reports for each branch/office/special project's leadership on an agreed-upon basis.

During this reporting period, quarterly progress reports were prepared for OPOS, the Office of Clinical Research Policy and Regulatory Operations (OCRPRO), the Program Planning and Analysis Branch (PPAB), and the Intramural Clinical Management and Operations Branch (ICMOB). Two semi-annual reports were prepared for the Indonesia Research Partnership on Infectious Disease (INA-RESPOND), and an annual report was prepared for the Biostatistics Research Branch (BRB). In addition, the program manager prepared the first progress report for the University Clinical Research Center (UCRC) in Mali.

As part of a new strategy management process piloted by OPOS in FY2014, the program manager co-facilitated strategy review sessions with two branches (PPAB and OCRPRO). Collaborating with members of the SPG, the program manager assisted in the development of presentations and consulted with the branch/office on task/metric development, refinement, and alignment to DCR/NIAID/NIH goals. This process included reviewing survey data as well as incorporating staff feedback and initiative changes. After the sessions, the program manager met with the branch/office chief and select staff to finalize its strategy for 2015; this included reviewing new and revised tasks, metrics, and target recommendations that are cascaded to the branch/office operational plan, progress report, and dashboard. In addition, the program manager assisted with two informal strategy review sessions with ICMOB and project leadership for INA-RESPOND.

To assist OPOS with its strategic plan renewal, the program manager participated in the OPOS staff strategic planning meetings and all operational planning meetings with OPOS's functional teams (Financial Management, OEG, Learning & Professional Development, Technical Solutions Group, and Special Projects Group). The program manager assisted with formatting OPOS's new strategy map, ensured updates to tasks and metrics throughout the process were accurately documented, and worked with staff to identify target years for each task.

The program manager also oversaw the development of an Organizational Effectiveness Services brochure that outlines OPOS's services offerings. This brochure was created to inform DCR branches, offices, and special projects on how OPOS can assist with their office, branch, and special project needs. As part of the development process, the program manager organized an OPOS group photo shoot, formatted and designed the brochure, and worked with the Leidos Biomedical Research publications group to review the copy. The program manager also liaised with NIH's Division of Medical Arts to discuss its printing capabilities, file requirements, and production timelines, and oversaw the print production process. Due to the effectiveness of the brochure, the OPOS director requested that the brochure be turned into a poster for internal use and distribution. In addition, three large poster versions of the brochure were printed to display on the 4th and 5th floors at Fishers Lane and one at Industry Lane.

To assist with DCR's knowledge-sharing efforts, the program manager collaborated with the Strategic Management Research Project Team to develop an engaging PowerPoint presentation of team findings, which was presented at the Science of Team Science conference. The presentation referenced known strategy management methodology and included customized graphics to illustrate their process.

At the request of the OPOS director, the program manager continued to provided project and strategy management support for the Phidisa project to assist with close-out activities for the project's conclusion in October 2015. The program manager oversaw the Phidisa substudy tracker to monitor progress from concept approval to publication, collected updates on each of the 17 substudies, and cited/filed evidence-based documents for archival purposes. The tracker was routinely shared with the Phidisa Management Committee (PMC), Phidisa Scientific Steering Committee, and the DCR director.

To develop a NIAID-specific transition plan for the Phidisa close-out, the program manager scheduled, organized, and facilitated seven close-out strategy sessions with U.S. PMC members, support staff, and Phidisa contractors. Working with the Phidisa project team lead, the program manager gathered relevant information, developed presentations, and led sessions for the following functional areas: NIAID Contractual Requirements, Site Closure Requirements, Regulatory and Monitoring Requirements, PI Requirements, Lab Requirements, and Government Furnished Equipment. During these sessions, the program manager asked participants to identify action items, owners, timelines, potential risks and barriers, and develop risk mitigation strategies. The information was used to coordinate development of a NIAID transition project plan. The program manager currently manages the plan to track progress against the milestone timeline.

To support DCR's efforts in rapidly responding to the Ebola outbreak in West Africa, the program manager worked with colleagues in another branch to develop a travel workflow process for contractors traveling to Liberia to obtain electronic country clearance. This workflow designates who is responsible for each step in the process and what must occur to ensure the traveler is allowed embassy access.

CMRP assisted the newly formed University Clinical Research Center (UCRC) in its strategy management efforts by co-facilitating a half-day session with other SPG colleagues and Mali project team leads to share DCR's best practices in strategy management with the interim director of UCRC. The program manager presented guidelines and distributed a sample set of strategy management tools for the network's use. After the session, the UCRC interim director had a better understanding of how to effectively implement and manage the network's strategy. Throughout the year, the program manager continued to support the UCRC's operational efforts by assisting in the finalization of the

operational plan, participating in bimonthly operational meetings, and creating dashboards and progress reports as requested.

To encourage workforce alignment, the program manager assisted OPOS and OCRPRO office directors with aligning operational expectations for FY2015 with the respective branch/office strategy (that ultimately cascades to HHS's strategic plan) and collected associated data to report progress towards operational expectations. To meet the deadlines established by the Office of Workforce Effectiveness and Resources (OWER), the program manager completed three branch-level progress reports. The program manager also supported other branch chiefs in this effort by reviewing branch goals, assessing how well those goals aligned with senior leadership and NIAID/NIH goals, then making recommendations as needed to ensure compliance.

Learning and Professional Development

A clinical training manager and a clinical training specialist provide learning and organizational/ professional development support for the Office of Planning and Operations Support (OPOS) by serving as members of the Learning and Professional Development (L&PD) group. The three primary areas of support are: (1) identifying/developing training resources to address client-identified training needs, (2) providing training and professional development subject matter expertise, and (3) participating in professional development to ensure that staff members maintain their subject matter expertise.

Support to the NIAID Nurses Onboarding Program involved the development, review, approval and deployment of an online training program with 38 training units, plus job aids, as well as design of a feedback collection process for each unit as it is completed. L&PD also solicited programmatic feedback from participants after 90 days and 180 days of employment, and facilitated annual review of each individual training unit.

Based on the customer's request to offer IACET CEUs for completion of each of four separate units of the OnlineGCP course, L&PD conducted a thorough review of the American National Standards Institute (ANSI) standard to determine which parts of the standard apply to "durable training materials." The process also included guiding this course through a rigorous content review by current subject matter experts (SMEs), establishing methods of capturing participant data in accordance with ANSI standard requirements, and ensuring competency assessment data and assessment validation data complied with government guidelines.

Support to the Partnership for Research on Ebola Vaccines in Liberia (PREVAIL) pre-travel training involved facilitating sessions every two weeks by preparing binders and a sign-in sheet. So far, we have facilitated nine sessions, involving 31 participants. L&PD continues to solicit feedback from each participant upon return from travel, then collates it and provides it to the government leads.

As part of the Human Capital Planning (HCP) initiative, L&PD created an extensive coverage and back-up matrix of 11 OPOS staff positions for the branch chief. This tool listed the OPOS positions and responsibilities, and identified where similar responsibilities of individual positions could be utilized to provide coverage and/or back-up in the event of staff absence or position openings.

PPAB requested support in developing their biannual customer satisfaction and staff satisfaction surveys. This involved designing two surveys that specifically addressed performance metrics in their operational plan. L&PD facilitated discussions with the staff to ensure that the metrics being evaluated reflected their understanding of their critical success factors, both in customer service and staff satisfaction. After multiple sessions, the content was solidified and the surveys configured and distributed. Once the data were collected, L&PD analyzed the data numerous ways, presented it to the branch chief and then provided it to the staff at a half-day retreat.

The CCRB project focused on the development of functional job specifications (FJS) for eight positions, identifying NIH competencies based on the responsibilities of the position, and using these data to create a comprehensive competency matrix that identified CCRB core competencies (i.e., the ones that were indicated for all staff based on the tasks that they identified for themselves). The first step of this project was to create a customized data collection tool for each CCRB staff member to document his/her individual responsibilities specific to their position. From that information, an individual FJS was created for each position; the FJS was then reviewed, edited, and approved by each staff person. The NIH Competency Dictionary was used to identify competencies for each responsibility in the FJS. From the list of competencies for each position, an organizational competency matrix was developed for CCRB and the common competencies for all eight positions were identified. The competency matrix was then compared to OWER's competency listing, a list of the 12 common CCRB and OWER competencies were identified, and a visual diagram of the competency comparison was created.

At the request of OPOS, the clinical training manager participated in the assembly of a competency model to address the new NIAID job function, the "Collaborative Clinical Trials Professional." This competency model involved identification of non-technical competencies, of which nine were selected, and technical competencies, of which eight already existed and six more needed to be drafted, reviewed, and approved. These competencies were selected in addition to the six NIAID core competencies. The model was then presented to the DCR deputy director of operational management.

During FY2015, the L&PD group provided the services listed below to OPOS and their customers.

Identify/develop training resources to address client-identified training needs

Most training requests within OPOS were initiated by the following offices and branches in the Division of Clinical Research (DCR): the Intramural Clinical Management Operations Branch (ICMOB), the Program Planning and Analysis Branch (PPAB), and OPOS. This year, L&PD supported the Partnership for Research on Ebola Vaccines in Liberia (PREVAIL) initiative by facilitating pre-travel training sessions for the federal staff serving in Liberia. In addition to facilitating these training sessions, L&PD collected evaluative feedback on the sessions when the participants returned, and provided it to the DCR customer.

L&PD continued to support the NIAID Nursing Education Committee in the development, deployment, and evaluation of a NIAID-wide onboarding program for all NIAID nurses (described below).

At the time this report is being written, L&PD is responding to ICMOB's request to configure an innovative, interactive training program (topic to be determined) for the Fall 2015 retreat.

In response to a request from the Clinical Research Oversight Manager (CROM), L&PD developed a process that allows continuing education units (CEUs) to be awarded at the completion of each unit of OnlineGCP, a computer-based training program that covers topics about the different aspects of Good Clinical Practices (GCPs).

Provide training and professional development subject matter expertise

The Human Capital Planning (HCP) initiative was completed for OPOS staff with delivery of a comprehensive backup/coverage matrix to the OPOS branch chief. The process involved L&PD's creation of a data collection tool that was populated with position responsibilities identified in job descriptions and input from staff, reviewed for accuracy, then used to develop functional job specifications and identify position responsibilities with similar characteristics. The final matrix, which covers 11 OPOS staff and contractor positions and their corresponding responsibilities, can be utilized by the OPOS branch chief to help with planning back-up/cross coverage in the event of an employee absence.

L&PD also completed an HCP initiative for the Collaborative Clinical Research Branch (CCRB) this year with the delivery of eight functional job specifications, a corresponding responsibility competency chart for each functional job specification, and a comprehensive organizational competency matrix that represented CCRB's competencies as a group.

L&PD provided competency development expertise to the DCR Collaborative Clinical Research Scientific Professionals (CCRSP) Competency Model.

During this fiscal year, L&PD offered support to PPAB on several projects. These included: identification of potential journals for the PPAB branch chief, who hopes to publish an article of the PPAB leadership culture initiative; assistance with the design, delivery, data analysis, and data interpretation of customer services and staff job satisfaction surveys; and facilitation of the PPAB retreat, at which the survey data were presented, interpreted, and discussed.

To support the third phase of the PPAB leadership culture initiative, L&PD engaged a coach with a specialty in the Hill's Team Leadership Model to optimize the dynamics of the PPAB leadership team. This resulted in the development of a shared leadership team development plan, as well as individual leadership team development plans that support the shared team.

The clinical training manager and the clinical training specialist continued to support the Organizational Effectiveness Group (OEG), this year focusing on optimization and operational planning of strategy management, learning and professional development, special projects, and the role of the new deputy director of operations and management in DCR.

The clinical training manager became more involved as a technical project manager on research subcontracts for OPOS, including one with Knovex related to the PPAB leadership team dynamics initiative and one with Professional Educational Services Group to grant continuing medical education (CME) credits for grand rounds and other approved learning events.

L&PD collaborated with the Office of Workplace Employee Relationships (OWER) to evaluate a potential OWER offering on mindfulness and to evaluate their current "Art of Leadership" offering.

Participate in professional development to ensure that staff members maintain their subject matter expertise

This year, the clinical training manager gave two presentations on influencing without authority: (1) at the Society of Clinical Research Associates (SoCRA) national conference in Denver, CO in September 2015, and (2) at the Western Virginia local Association of Clinical Research Professionals (ACRP) chapter's conference in November 2014. She also presented "Managing Up" to the local chapter of the International Association of Administrative Assistants in Frederick, MD in December 2014.

The clinical training manager and the clinical training specialist both attended courses on qualitative evaluation and evaluability assessment provided by The Evaluator's Institute of George Washington University's Graduate School.

Based on a need identified by OPOS for a robust knowledge management system in DCR, the clinical training manager conducted extensive research on behalf

of the work group and attended the Annual Knowledge Management Conference and pre-conference workshop in Houston, TX.

The clinical training specialist completed Excel level 2 and SharePoint training sessions; she also attended the Association for Talent Development (ATD) International Conference & Exposition in Orlando, FL in May 2015.

Of specific note, Barbara van der Schalie, the clinical training manager, received a NIAID Merit Award in October 2014 for her contribution to the DSMB online training.

Technical Solutions

The Technical Solutions Group (TSG) within OPOS works closely with the Office of Cyber Infrastructure and Computational Biology (OCICB), the Center for Information Technology, the Office of the Director (OD) Property Office, and other partners to provide high-quality enterprise and innovative solutions to the Division of Clinical Research (DCR) offices and branches. A CMRP special projects administrator assists TSG with managing the technical, information, and data challenges encountered in a clinical research environment.

During this reporting period, the special projects administrator supported the semi-annual Clinical Research Information Management System of the NIAID (CRIMSON) contract award fee reviews to assess research subcontract performance against the metrics outlined in the statement of work. Throughout each review period, the special projects administrator extracted data from the CRIMSON project manager's monthly status reports and placed it into Microsoft Excel spreadsheets that are used for comparative purposes; the special projects administrator also created dashboards for the review documentation packet. The special projects administrator wrote a summary for the current review period and assembled it, along with the dashboards and scoring form, into a review packet that was disseminated to panel members prior to the scheduled scoring/rating meetings.

The special projects administrator maintains scores, spreadsheets, meeting comments, and documentation packets for all reviews conducted since 2008. In addition, the special projects administrator finalizes the award memo for the contracting officer.

The special projects administrator is the central point of contact for property information in DCR, helping users resolve any outstanding issues and liaising with the OD Property Office to coordinate property transfers, surplus, life cycle replacements, and property passes. In conjunction with the OD Property Office, the special projects administrator consistently maintains the NIAID goal of greater than the 80 percent of user verification of property among the users located at 5601 Fishers Lane.

The special projects administrator plays an integral role in the Acquisition Management and Operations Branch (AMOB) annual inventory of equipment, which was conducted in February 2015. This effort required the special projects administrator to collaborate with the inventory team to reconcile property records and research the locations of missing and/or at-home equipment. More than 646 pieces of equipment were inventoried. In addition to the AMOB inventory, the special projects administrator also supports the Leidos Biomedical Research annual equipment inventory.

The special projects administrator served as the central point of contact for ordering all technical equipment (e.g., laptops, desktops, monitors) upgrades and replacements. This activity involved determining hardware and software specifications/requirements and coordinating any specialty software purchases, providing IT support, and following through to user satisfaction. In addition, the special projects administrator assisted in creating and managing the central computer annual budget, which is reconciled monthly with DCR financial reports.

The special projects administrator is responsible for 30 external CRIMSON users, maintaining their VPN and CRIMSON access, distributing security tokens, and keeping current records on accounts and returned tokens.

The special projects administrator has also become the point of contact for DCR's SharePoint updates and maintenance, a responsibility previously fulfilled through a subcontract arrangement. Since October 2014, there have been an average of 12 monthly updates, and the special projects administrator completed all requested updates within the 24-hour turnaround goal for seven DCR branches.

In response to the DCR's initiation of an Ebola research program in Liberia, the special projects administrator became responsible for prioritizing, ordering, porting, and distributing phones and laptops for core FTE travelers and new support personnel. The special projects administrator assisted in compiling a projection of mobile telecommunication device (MTD) international service costs through the remainder of FY2015. The projection of costs was submitted to the NIAID deputy director for an exception and approval to use Ebola appropriations money for these services and equipment related to the Ebola research projects in West Africa. The exception was approved and the special projects administrator will compile monthly reports, by user/traveler, of MTD international service costs, and also track computer equipment costs associated with the projects.

Performance Measures

At the end of FY2012, NIAID's DCR requested support for a DCR initiative to ascertain performance measures to provide data-driven progress reports for the individual branches within NIAID. DCR is a heterogeneous and unique organizational entity, encompassing both intramural and extramural functions in the domestic and international arenas. DCR tracks changes in health practices and policies, research capacities of domestic and international clinical research networks, the development of new mathematical models to describe the biology of infectious diseases or immune responses, and applicable

regulations to ensure compliance with GCPs during clinical trials. DCR's goals are to: (1) develop and maintain a leadership culture that advocates the priorities of NIAID; (2) facilitate the generation of new knowledge and insight from research; and (3) evaluate clinical research processes to optimize efficiency and effectiveness.

DCR is made up of seven branches and/or offices that provide critical support for expanding the clinical research enterprise. DCR facilitates state-of-the-art clinical research within NIAID and in global settings through: (1) oversight and management of intramural clinical research; (2) coordination of NIAID clinical research policy development and implementation; (3) regulatory monitoring and compliance; (4) statistical consultation; (5) operation of a state-of-the-art biosafety level 4 (BSL-4) facility; and (6) capacity building in domestic and international settings. To build capacity in a domestic or international setting, it is important to develop the appropriate performance measures (i.e., metrics) that contribute to the mission and goals of the DCR and that capture the complexity and nuances of the interwoven, multifactorial, collaborative productivity that DCR's individual branches contribute the facilitation of clinical research in other entities.

At the end of FY2013, CMRP staff worked with Leidos Biomedical Research Contracts and Acquisitions Directorate staff to establish a research subcontract with Quality Science International (QSI). QSI was tasked with providing advice and assistance to DCR for establishing appropriate performance measures/metrics that provide data-driven, objective assessments of performance and productivity in NIAID's DCR. Ultimately, the data derived from the performance metrics may help DCR achieve better outcomes and higher productivity. The goals of the project are to: (1) develop and/or enhance key performance indicators (KPIs) for each branch within DCR; (2) identify comparison measures against which program performance can be compared; (3) employ a solid mixed-methods (quantitative and qualitative) approach to develop and validate performance metrics that can be used for quantifying performance, evaluating outcomes, capturing program processes, and assessing quality; and (4) review potential dashboard systems and database features.

In January 2015, QSI dissolved and transferred the work under this subcontract to Jerry Lassa, Inc.; the same essential staff remained under the subcontract with Jerry Lassa, Inc. Over the past year, QSI/Jerry Lassa, Inc.: (1) worked with OPOS to review the effectiveness of strategy measures, provide recommendations for data collection, and incorporate measures into work to support strategy achievement; and (2) provided assistance to the Strategic Management Research Project Team (SMRPT) to continue exploring what enhances or inhibits successful strategy management in clinical research networks by developing K-N scoring framework and tools, conducting consultant interviews for the Mexico Emerging Infectious Disease Clinical Research Network (La Red), and developing a standardized interview guide. QSI presented results of the work at the June 2015 Science of Team Science meeting in Bethesda, MD. In addition, QSI/Jerry Lassa, Inc. provided focused support on data tools for measures and assessed ways to automate the collection and analysis of measures, including "scorecard" and/or "dashboard" systems. Dashboards for OPOS and Ops Plan are in development.

Barriers to Clinical Research

CMRP provides support to DCR's Barriers to Clinical Research (BTCR) initiative through the maintenance and expansion of the web-based International Clinical Research Regulatory Matrix (ICRRM), also known as ClinRegs. CMRP has provided subcontract management and oversight to the ClinRegs website initiative through the research subcontract awarded to SRA International (SRA) in February 2014; there are four option years through September 2018.

The ClinRegs website contains clinical research regulations from around the globe, providing a database of country-specific information that allows users to explore regulations and compare requirements across countries. The website serves as a central resource for persons involved in planning and implementing international clinical research. ClinRegs also provides useful links to official regulations and other key resources, promoting an efficient and effective way to research clinical regulations. The following information is included on the website: competent authority oversight, ethics committee oversight, clinical trial lifecycle, sponsorship, informed consent, investigational products, and specimens.

The ClinRegs website obtained permanent Authority to Operate (ATO) from the NIAID chief information officer in January 2015. To attain this authority, the IT team worked with NIAID's Office of Cyber Infrastructure and Computational Biology (OCICB) to obtain all necessary security scans and documentation, such as a security assessment report, security plan, NIST system categorization, and E-authentication threshold analysis.

In coordination with NIAID and the ClinRegs working group, the country priority list for content to be added to the website in FY2016 was finalized. The group analyzed the current and future countries where NIAID has been or will be conducting clinical trials and the overall budget for the projects. Using this information, the committee provided the list of priority countries, which was reviewed and approved by DCR's deputy director for clinical research and special projects.

During FY2015, the subcontractor developed content and updated current content for 15 countries. SRA researched regulatory information details via the Internet and directly contacted resources within and beyond NIH to obtain and/or update applicable information. When necessary, this regulatory information is translated into English, which is a challenging aspect of the project because obtaining reliable translations for the regulatory documents can involve costly translation services. The

team has relied on free web-based translations and sought assistance from individuals with appropriate language proficiencies who could critique or polish the translations, thus providing an invaluable service and cost savings. Prior to uploading information to the website, it is reviewed for both technical content and editorial accuracy.

Office of Clinical Research Policy and Regulatory Operations

Support Provided by the Clinical Monitoring Research Program

Since January 2002, CMRP has played a major role in developing and maintaining a regulatory environment that supports the research priorities of the NIAID Intramural Research Program. CMRP established and managed the Office of Clinical Research Policy and Regulatory Operations (OCRPRO), formerly known as the Regulatory Compliance and Human Subjects Protection Branch (RCHSPB), which included development of the Regulatory Affairs (RA) group, Clinical Trials Management (CTM) team, Clinical Safety Office (CSO), Protocol Navigation/Protocol Development Program (PN/PDP), and the necessary support teams including Document Control (DC), Information Technology (IT), Learning and Professional Development (L&PD), and Program Management. This infrastructure continues to support and manage a portfolio of more than 200 protocols.

The primary objective of OCRPRO is to maintain and enhance technical and programmatic support services for: (1) comprehensive clinical research management, regulatory compliance, and clinical safety oversight encompassing clinical trial monitoring and oversight; (2) Investigational New Drug (IND)/Investigational Device Exemption (IDE)/ Drug Master File (DMF) application development and management; (3) compliance with https://clinicaltrials.gov/ reporting requirements; (4) safety surveillance; (5) Adverse Event (AE) and safety reporting; (5) protocol and informed consent development and review; (6) investigational product oversight; (7) Data Safety Monitoring Board (DSMB) and Safety Monitoring Committee (SMC) management; (8) protocol logistics and development services; (9) Institutional Review Board (IRB) support; (10) IT systems development and maintenance; (11) QA compliance; (12) essential documents and records management; and (13) learning and professional development. These efforts ensure that NIAID-sponsored clinical protocols are conducted in accordance with HHS, FDA, and NIH regulations, and International Conference on Harmonization/Good Clinical Practices (ICH/GCP) guidelines. Additionally, OCRPRO provides scientific and administrative oversight to the establishment and maintenance of research subcontracts, domestic and international logistical needs, as well as project management infrastructure and operational support to a variety of clinical projects.

Part of CMRP's mission is to provide regulatory and clinical research support to PIs for meeting the Standards of Clinical Research requirements established by NIH in 2000. Before OCRPRO existed, PIs managed all of the regulatory/monitoring oversight for their individual clinical studies. With the establishment of OCRPRO, the regulatory compliance, clinical monitoring, and safety surveillance aspects of clinical research are now efficiently and effectively supported, allowing PIs greater opportunity to focus on the main objectives of mission-critical research protocols.

Clinical Trials Monitoring

The Clinical Trials Monitoring (CTM) team is an integral part of RCHSPP and plays a key role in cutting-edge clinical research for non-IND and Phase I and Phase II IND/IDE trials sponsored by the OCRPROC/NIAID Intramural Research Program at NIH. CTM staff consists of a clinical trials director, 3 clinical project managers, 11 clinical research associates, a clinical data analyst, and a program coordinator.

The CTM team's main focus is to facilitate and oversee clinical research studies. Responsibilities include monitoring studies to ensure that the rights, safety, and well-being of human subjects are protected; ensuring that the reported study data are accurate, complete, and verifiable from source documents; ensuring that the study conduct is in compliance with the IRB/ethics committee–approved protocol, with ICH/GCP guidelines, and with all other applicable regulatory requirements; detecting, reporting, and assisting with site quality management planning and resolving discrepancies that occur during the study period; and communicating all site-monitoring reviews and observations to PIs and clinical research oversight managers. The team also ensures that the sites maintain study agent(s) and devices in compliance with study protocols and FDA regulations that are under an IND or IDE.

Currently, the CTM team is involved with the management and monitoring of more than 194 active NIAID-funded clinical research studies conducted at sites throughout the U.S. and in several foreign countries. The types of studies vary and include Phase I/II IND and IDE studies, natural history studies, pediatric studies, and research studies that are noninvasive and not under an IND/IDE. During FY2015, the team conducted more than 38 study initiation visits; 190 interim monitoring visits; 10 audit visits, and 59 study close-out visits. Two audits were conducted for the Partnership for Research on Ebola Vaccines in Liberia (PREVAIL) study: Clinical trials monitoring was conducted at various international clinical sites across the world, including those in Argentina, Cambodia, China, India, Korea, Mali, Sierra Leone, Thailand, and Vietnam, and those in Liberia, Mexico, and South Africa. The CTM team and designees also conducted audits and study start-up site visits at locations in Argentina, Liberia, Mali, Mexico, South Africa, Thailand, Uganda, and Vietnam.

Involvement with NIAID Networks

The CTM team continues to provide sponsor-related clinical trials management for several established NIAID networks, including the IRC Network, an Intravenous Immunoglobulin (IVIG) study, the INSIGHT network, South East Asia (SEA), and the Mexico Flu networks. The team also continues to support studies in the Washington, D.C., area that are part of the District of Columbia Partnership for HIV-AIDS Progress (DC-PFAP) program and the Department of Defense Infectious Disease Clinical Research Program (IDCRP).

Mexico Network

The CTM team has been involved with the monitoring aspects of studies conducted under Mexico's Emerging Infectious Disease Clinical Research Network (La Red) since January 2010. There are five study sites actively recruiting subjects and, based on enrollment, the CTM team conducted on-site monitoring for four of these sites. Security issues in one area of Mexico prohibited on-site visits, and CTM was challenged with devising an alternative monitoring plan for that site. The CTM team implemented a risk-based, remote monitoring approach focusing on the site's QA/QC process, which allowed the CTM team to monitor the quality of submitted data in real time, identify potential protocol deviations and missing and/or inconsistent data, and signal systematic errors in data collection. However, the CTM may discontinue the remote monitoring approach and begin on-site monitoring in FY2016. During a visit to Mexico in February 2015, the CTM staff assisted in training the in-country network monitor who was assigned to the non-IND studies; provided the network with SOP samples and report templates; and reviewed all of the network draft SOPs as they became fully operational.

Influenza Research Collaboration Network

For the Influenza Research Collaboration (IRC) Network, the CTM team manages the sponsor's essential document files, as required by FDA and HHS, for more than 40 domestic participating sites, plus 20 international participating sites, including Argentina, Thailand, and Mexico, across the NIAID Influenza Research Collaboration (NIRC) and the International Network for Strategic Initiatives in Global HIV Trials (INSIGHT), and conducts sponsor-site audits. During FY2015, the team expedited the initiation of 21 new domestic a sites for the IRC 002 and IRC 003 influenza studies, and conducted approximately 35 close-out visits. Cost-saving measures established in collaboration with the OCRPRO clinical research oversight manager and the CTM director included the elimination of annual site-monitoring visits for IRC study sites that did not have any subjects randomized. As a result, the clinical trials director worked with the clinical project managers and clinical research associates of each affected study to create the required documentation for the site(s) and the sponsor's master documentation file. In addition, several IRC study visits were combined in order to cut costs.

As another cost-saving measure, close-out visits for IRC sites that did not enroll any subjects were conducted via teleconference. During FY2015, approximately 30 close-out visits were conducted in this manner, eliminating the need for costly travel.

In addition, a clinical project manager reviewed adequate investigator responsibilities, safety and AE documentation, and maintenance of investigational study agents during presentations to the domestic and Argentina Investigators Meetings held for the IRC studies.

The CTM team worked with the IRC protocol chair and Social and Scientific Systems, Inc. (SSS) to help make the protocol registration and activation process more efficient for the fall 2015 flu season. In addition, a clinical project manager and the clinical trials director worked with a contract vendor to improve the site selection by minimizing payments to underperforming sites for the 2014–2015 influenza seasons and to implement recycling of unused supplies from closed sites to new sites.

During the influenza season, the study agent required stability retesting prior to approval of continued use. A clinical project manager and the clinical trials director worked with members of the IRC 003 protocol team to ensure appropriate retesting and notified all affected sites. The clinical project manager developed memos to inform the study teams of the changes, worked with SSS to develop and distribute instructions for relabeling, and ensured completion of processes before allowing sites to enroll any additional subjects or distribute the study agent.

Southeast Asia 50 Study

CTM team continues to provide oversight of Pharmaceutical Product Development (PPD), Inc., for monitoring functions that are carried out in China, Korea, and Southeast Asia. During this past year, the 11 sites in the Southeast Asia 50 study (SEA050) have continued to enroll, and PPD has monitored the protocol accordingly.

A new Dengue study based on clinical trials conducted at the Johns Hopkins Center for Immunization Research began in Bangkok, Thailand, in late FY2014, and vaccinations continued at the site in FY2015. The site has been monitored twice during this reporting period. Many of the studies conducted in Korea have drawn to a close, yet one study remains and will be monitored by PPD into FY2016. A study in China that utilized PPD monitoring will be drawing to a close in FY2016. Three other studies being conducted at sites across Thailand will continue into FY2016. A new study involving several sites in South Africa and one in China began in late FY2015. For the study conducted in China, the CTM team is also utilizing PPD's monitoring services. CTM staff will continue to work with NIH staff and the PPD clinical research organization to ensure that additional studies are executed in a timely manner and within all applicable guidelines.

Africa

The clinical research associate who travels to Mali continues to provide GCP training to Malian study teams, with typically more than 30 staff members attending the training sessions that include instruction on adequate source documentation, proper informed consent form completion, AE/SAE reporting, and other pertinent clinical research conduct topics. This staff member organized an Informed Consent Form (ICF) training session, attended by many study team members, at the request of a NIAID PI in Mali. This session was very well received, and the PI has indicated she may request that this training be presented to future study team members, to ensure all parties are current on regulations.

A clinical research associate located in Benin, West Africa, continues to provide clinical trials monitoring support. This clinical research associate travels approximately one week each month to Bamako and works closely with CMRP staff to ensure that NIAID clinical trials are effectively monitored, and that the rights, safety, and well-being of human subjects are being protected. The clinical research associate also ensures that the reported study dates are accurate, complete, and verifiable from source documents; ensures that the study conduct is in compliance with the protocol, ICH/GCP guidelines, and applicable regulations and standards; and detects, reports, and resolves discrepancies that occur during the conduct of the study. A Transfer of Regulatory Obligations (TORO) is currently in place to allow the RCHSPP clinical research associate to monitor an IND study on behalf of a pharmaceutical study sponsor. Though the U.S. Department of State issued various travel warnings last year due to political instability in Mali, close communications between NIAID and the U.S. Embassy in Bamako confirmed that contractor travel may take place with certain limitations. CMRP continues to monitor the travel warnings and consult with NIAID for the coordination of travel to perform on-site monitoring activities.

Johns Hopkins University

During this reporting period, a multitude of trials continue to be run at the Johns Hopkins University Center for Immunization Research (JHU CIR). The trials include Respiratory Syncytial Virus (RSV), Influenza, West Nile, and several related to the Dengue virus. Many of the studies are also being run at the University of Vermont (UVM) site. Four new studies have started during this reporting period, with three of them utilizing both the JHU CIR and UVM sites and one being run only at the JHU CIR site. The RCHSPP group has supported the site initiation visits and continues to monitor these protocols along with several ongoing trials at the sites.

One of the studies being conducted at the UVM site was subject to an FDA audit during this reporting period. The RCHSPP team worked with the site remotely in order to prepare them for the visit, and as a result, the audit went well.

The Laboratory of Infectious Diseases (LID) has also continued to conduct studies at the University of Rochester Medical Center (URMC). One new study began at the URMC during the reporting period, and one study went through a close-out visit. Two other studies are still open at the site and continue to be monitored.

Department of Defense Infectious Diseases Clinical Research Program

One new multicenter study was initiated in FY2015: IDCRP-080 (Prevent TD). The CTM team conducted site-initiation visits at three Department of Defense (DoD) sites and provided QC guidance for international sites. Additionally, CTM is providing ongoing guidance to a multinational study conducted by Infectious Diseases Clinical Research Program (IDCRP; TreatTD). As part of this collaboration, CTM reviews IDCRP QA reports to align monitoring efforts with QA findings and to ensure consistency in recommendations to the sites. The CTM team continues to review all protocol amendments that affect the activated DoD/IDCRP general infectious disease and HIV studies. Also in FY2015, RCHSPP worked to close the IDCRP-045-01(FluPro) study and transition the IDCRP-037 (TravMil) study to IDCRP for QA/QC as the study will no longer enroll pediatric subjects.

D.C. Partnership for HIV/AIDS Progress

The CTM team continues to support studies in the Washington, D.C., area that are part of the DC-PFAP program, specifically the SYNERGY study.

Protocol and Informed Consent Form Reviews

The team reviewed clinical research protocols and informed consent forms, providing commentary to NIAID, IDCRP, and PIs at JHU, UVM, and the University of Rochester. The group also reviewed and revised IDCRP protocols, source documents, and case report forms (CRFs) on new and previously activated studies.

Overall, CTM reviewed approximately 23 initial clinical research protocols/informed consent forms, 70 amendment reviews, five site-specific informed consent forms, and 13 navigational initial reviews during this reporting period.

Data Systems Support

The CTM team continues to utilize FrameMaker/DataFax to create electronic Case Report Forms (eCRFs). Capabilities for providing remote data monitoring will be further investigated during FY2016. The creation of eCRFs using FrameMaker/DataFax has continued to prove effective. To date, the CTM team has worked on approximately 25 CRF sets. Several steps are included in the creation of CRFs; after finalization of the forms, the database setup can often take several weeks. In two instances, delays in the study team review of forms

resulted in studies having to start before the final set of coded forms was available. RCHSPP CTM responded by creating temporary source documents for the sites to use until the database setup was finalized. This enabled the protocols to start on time and still ensured key data points were captured.

Designees from CTM are continuing to also work with the Clinical Research Information Management System of NIAID (CRIMSON) staff and OCRPRO clinical research oversight manager to develop CRIMSON to allow electronic monitoring of NIAID studies, reducing the need for the database reports supplied by study coordinators, saving time, and reducing overall costs to our customer. Members of the CTM team continue to meet with the CRIMSON staff on a monthly basis to work on this project. CTM has been instrumental in guiding the CRIMSON IT developers in the monitoring process and in current documentation practices. Several demonstrations of the electronic monitoring function have been given, and CTM has provided advice for the development of this new platform. A working group is currently testing the system for implementation in FY2016.

Presentations

A clinical research associate presented a poster entitled, "Risk-Based Monitoring and Quality Management Plans: An Interdependent Relationship and Factors Influencing Plan Development," at the 2015 Association of Clinical Research Professionals (ACRP) conference in Salt Lake City, UT. The poster compared current risk-based monitoring data to historical non-risk-based monitoring data. A similar presentation was given by a clinical project manager at the Cambridge HealthTech Institute Clinical Trial Oversight Summit in Boston, MA, in June 2015. This presentation compared current risk-based monitoring data to historical non-risk-based monitoring data and also to FDA inspection data from 2014.

A clinical project manager and two clinical research associates were invited to present at an IDCRP Brown Bag session which focused on the definition, use, and completion of source documentation and case report forms, and the use of case report forms as both source and data collection forms. A clinical project manager was invited to IDCRP to provide an overview of the roles and responsibilities of CTM to new IDCRP managers. The team has been invited to provide more presentations in the future.

Essential Document Initiatives

In collaboration with OCRPRO, CTM helped develop and launch an electronic binder for protocol-specific essential documents for NIH site/labs. Several studies have transitioned to this new binder, and several other new studies will solely use the electronic system. As part of a monitoring visit, CTM completes a review of an electronic regulatory binder for a study and is working to finalize procedures for monitoring the system. This electronic initiative also presents an opportunity for cost savings to RCHSPP, as it eliminates the cost for the large binders provided to the sites to maintain and organize the documents. CTM anticipates that the NIAID labs/teams will also implement e-regulatory binders to maintain documents required for studies. Previously, this documentation was all paper based; the electronic versions will result in a cost savings by eliminating paper and reducing the binder size.

The tracking of protocol-essential documents in the TrackWise system instead of an Excel document was also implemented by CTM. This has saved time for the clinical research associates, as entering this information into TrackWise is more efficient since it is user-friendly and it reduces the amount of typing required to enter data. CTM designees selected new studies, activated since October 1, 2013, to be transitioned to TrackWise for tracking documentation. The TrackWise Essential Documents Transition Plan and Form were developed to aid the clinical research associates with the transition process, and a QC process was implemented to ensure a complete and accurate transition.

The OCRPRO Monitoring Guidelines were also updated and implemented in September 2014. The guidelines included updates to reflect the NIH changes in SOP-16, Framemaker and Datafax services provided by the team, and to include the TAPC definition CTM refers to when monitoring the subject consent process. (TAPC = (1) **T**ime to read and review the consent form; (2) **A**nswer any questions; (3) **P**rocedures not done prior to consent; and (4) **C**opy of the signed informed consent form offered to the subject.)

Ebola Efforts

Following the Ebola outbreak, clinical project managers, clinical research associates, and the clinical trials director developed a small Ebola working group. The CTM work group provided support via regulatory documents, expedited site activations, development of QA processes, development of flow sheets for clinical staff, and guidance for the teams in Sierra Leone and Liberia. The CTM work group also developed site training for remote locations and assisted in the training of the staff in Liberia.

Document Control

The Document Control (DC) group is at the center of RCHSPP's quality system. The DC group is tasked with the maintenance of critical documents that are required both from a contractual and a regulatory standpoint for all open protocols, as well as the archiving of documents associated with closed protocols. DC offers many services to assist the various RCHSPP groups, including: (1) establishing and maintaining RCHSPP SOPs; (2) establishing and maintaining CMRP SPs; (3) processing annual reviews of policies, SOPs, reference guides, SPs, and associated forms; (4) scanning and archiving documents; (5) training staff on the DC system and the various electronic documents maintained within the system; (6) assigning project codes; (7) overseeing the off-

site archiving and retrieval of documents stored at the Iron Mountain records storage facility; (8) generating audit reports and auditing regulatory and administrative documents; (9) generating and managing version-controlled documents; (10) establishing procedures for issuing, tracking, and reconciling all documentation; (11) maintaining the various locked drives, including, but not limited to, the shared drive (which houses current protocol documents, completed protocols, and current and historical CVs), the regulatory drive (contains locked IND folders), and the clinical safety drive; (12) developing and maintaining secure filing systems for all hard and electronic documentation; (13) establishing and maintaining RCHSPP protocol reviews; and (14) creating compact discs (CDs), various tracking tools, and logs.

During FY2015, DC managed files for more than 250 active protocols and 87 active INDs/IDEs/DMFs. To date, the DC group has processed more than 150 protocol reviews (31 PI reviews, 92 amendment reviews, 9 site-specific Informed Consent Form (ICF) reviews, 15 navigational pre–Institutional Review Board (IRB) reviews, 1 "other" document review, and 3 navigational amendment reviews).

DC has assigned 56 new project codes and processed 38 paper regulatory submissions; 23 regulatory annual reports; 7 non-FDA submissions; 42 non-FDA correspondence notices; 24 regulatory correspondence documents; 1 regulatory CD submission request; and 1 regulatory CD. The DC group additionally processed 160 regulatory electronic Common Technical Document (eCTD) submissions; 42 regulatory eCTD annual reports; 16 new eCTD IND regulatory submissions; 6 pre-IND eCTD meeting requests; 144 regulatory eCTD correspondence documents; 2 FDA eCTD meeting minutes; 220 eCTD CD requests; 12 eIND submissions; and 430 eCTD CDs. DC also processed regulatory master file submissions; regulatory annual reports; IDE regulatory submissions; IDE FDA meeting minutes; IDE regulatory correspondence requests; IDE eCopy CD requests; and IDE eCopy CDs. DC also processed and stored 13 DSMB randomization codes for the CTM group; posted 50 non-IND and 42 IND documents on CMRP's shared drive; scanned 293 CVs; processed 71 DSMB summary reports, 10 DSMB navigational summary reports, five Safety Monitoring Committee (SMC) meeting minutes, and 34 SMC conflict of interest forms; and managed 41 bucket requests. DC creates labels for each bucket that contains documents for each group serviced. Bucket requests from CTM are constant, and additional room for new protocols is critical. Each bucket is labeled with column and row information, including the protocol number.

There are currently more than 528 boxes, equaling approximately 634 cubic feet of documents, stored at Iron Mountain, a contracted off-site storage facility. During this reporting period, 34 new boxes were added, 81 boxes were refiled, and 91 boxes were requested from Iron Mountain. In addition, DC has 57 boxes containing approximately 259 paper files in the DC group's suite. These files include DSMB conflicts of interest, acceptance letters, navigational DSMB summary reports, DSMB summary reports, and meeting minutes.

DC also scanned new SAEs for the CSO, and processed new document requests, initial reviews, final reviews, final directorate reviews, and signature cycles of policies, SOPs, reference guides, SPs, and associated forms. In addition, DC completed annual reviews of SOPs, forms, policies, reference guides, SPs, and related forms.

The Service Contract Agreements (SCAs) were updated for the following filing cabinets maintained by DC: Cabinet 1–Kardex Remstar (C131573); Cabinet 2–Megastar (C126022); Cabinet 3–Megastar (S062586); Scanner–FUJITSU (C127364), Datum–(C128323), located within the DC suite; and Cabinet 4–Kardex Remstar (C129616), located within the Information Technology (IT) suite.

One of the challenges DC faces is being aware of what is contained within each cabinet as well as staying abreast of the space and volume remaining. Each shelf must be balanced and equally weighted for the cabinet to function properly. All groups needing access must do so via DC, as it has the only set of keys for each cabinet (to ensure proper control of all regulatory documents). DC must maintain constant level and weight control, and assist all groups in locating an appropriate open spot for documents. At various times throughout the year, DC has had to rearrange the rows to keep the shelves balanced. Therefore, DC organized the cabinets by labeling each bin and created a chart to verify all rows remained equally balanced. Additionally, DC created a diagram to indicate where each row and column is located within each file cabinet.

During the reporting period, a member of the DC group assisted with the Ebola initiative in Monrovia, Liberia, by providing an array of inventory management and support functions, such as (1) recording incoming and outgoing supplies; (2) creating an inventory tracking spreadsheet; (3) creating an inventory order list; (4) programming mobile phones for staff use; and (5) unloading supplies that arrived in Liberia. The DC staff member also attended Ebola project–related meetings, coordinated with incoming staff to assign duties and answer questions, assisted with audio conferences, assembled equipment, updated phone lists, and assigned mobile phones.

Document Control is working with the SOP management system developers on 44 Redmine tasks regarding system improvements and enhancements. DC handles the tasks on a priority basis and continually reviews the list through completion of the tasks. The DC group has created monthly status reports to assist other groups in managing their documents within the SOP system by listing outstanding tasks by group. DC compiles the reports monthly and sends a report to each manager to disseminate within their group. The DC group became the originators of the two reference guides used by all RCHSPP staff and new onboarding employees. DC will compile all new and updated definitions and

acronyms to ensure the reference guides are current and applicable on an ongoing basis throughout the year.

The SOP management system saves time, work hours, and resources, and DC is the point of contact for completing all requests entered into the system; formatting all documents; troubleshooting problems, and creating signature fields for all document PDF digital signatures.

Institutional Review Board Support

The RCHSPP Institutional Review Board (IRB) administrator provides administrative and programmatic support to NIAID's IRB. Working in collaboration with the Office of Clinical Research Policy and Regulatory Operations (OCRPRO), the IRB administrator efficiently and effectively processes documents for IRB submission. Support efforts include processing protocol actions for IRB meeting reviews through the iRIS database; generating templates for agendas and meeting minutes; preparing meeting packages; tracking protocol submissions from initial submission through the approval phase; preparing tracking reports; and maintaining protocol-specific records. These efforts facilitate the conduct of research within the NIH Intramural Research Program.

In FY2015, the IRB administrator supported the following ongoing IRB-related activities: processing incoming submissions and submission approvals, including review of submission components, identification of deficiencies, and providing administrative stipulations and guidance to investigators to assist them in successfully completing submissions; processing final approvals from the Office of Protocol Services (OPS), including logging and filing; updating the manual logs of protocol submissions and renewals; responding to inquiries and providing advice to investigators and study staff; participating in regular staff meetings, IRB meetings, and study coordinator updates; contributing to procedure discussions regarding new and/or changing NIH policies that affect the NIAID IRB; writing meeting agendas and minutes shells; preparing IRB meeting packets, which included generating quorum sheets, printing labels, and reviewing the collated packets for accuracy; preparing electronic meeting packets for IRB members who use an iPad during meetings; and attending IRB meetings in person throughout the year.

During the reporting period, the IRB administrator took on new projects related to knowledge sharing and dissemination of information. These projects included coordination of the September 2014 study coordinator update and one-on-one presentations for new individuals. The purpose of the study coordinator update was to discuss the role that OPS plays within the NIH Human Research Protection Program (HRPP). Topics covered the history and background of OPS, current workload and staffing of the office, procedures for sending submissions to the study teams from the NIAID IRB Office, and the study team's role with clinicaltrials.gov. As part of the NIAID IRB Office, the IRB administrator received a NIAID Merit Award in recognition of outstanding organizational leadership in implementation of new requirements of the NIH Office of Human Subjects Research.

The IRB administrator also provided support to special projects, including the utilization of iMedRIS (iRIS) web-based IRB submission software by serving on the iRIS development work group, which collaborates with developers to identify and troubleshoot methods for optimal use. The IRB administrator took the lead for ensuring that the NIAID IRB website remained up-to-date with regards to documents, links, and contact information. Additionally, the IRB administrator worked with IRB staff and the iRIS trainer to identify and correct issues with the updated iRIS applications that were impacting their ease of use. These efforts support OCRPRO's strategic priorities by directly aligning to the OCRPRO goals to "evaluate services and solutions and apply process changes as needed," specific to the objective, and "develop policies, guidance, documents and processes consistent with the spirit and intent of federal requirements that are focused on facilitating effectiveness of the research enterprise."

Additionally, the IRB administrator assisted in ensuring that priority IRB submissions, namely for new Ebola research, were efficiently processed from submission through approval.

During the reporting period, the IRB administrator continued assistance in the implementation of updated NIH SOPs and Conflict of Interest (COI) policies. RCHSPP continued to implement the use of new iRIS applications, relevant documents, and policies from updated NIH IRB SOPs, while identifying areas of concern. This effort involved meeting with the iRIS trainer to troubleshoot changes to iRIS applications specific to initial reviews, continuing reviews, and emergency INDs. In late November 2014, the iRIS system went down unexpectedly for over two weeks. The IRB administrator assisted in ensuring that the IRB Office could still accept submissions and processed them manually. This required creating a method for accepting submissions via e-mail to prevent study expirations and delays in critical research efforts. In addition, efforts have been focused on developing quality management standards by identifying process improvement opportunities.

Information Technology

The RCHSPP Information Technology (IT) group provides software development, computer, network, application, and backup/disaster recovery support services for NIAID initiatives. Staff members include one IT manager, two programmer analysts, one systems administrator, one network specialist, and one secretary.

Design, development, testing, and implementation of over 60 new TrackWise system service and product requests have been completed, including the tracking of a new application protocol type. Expanded Access is a different type of protocol and FDA category that is used in emergency situations to provide investigational drugs to patients when other mechanisms are inappropriate.

Two additional protocol activities were added to support the Protocol Navigation/Protocol Development Program (PN/PDP) team. A navigation-lite option was added to track activities when the PN/PDP's talent is used on an ad hoc basis, whereby an investigator chooses the level of support needed. An "other" option was also added to track tasks when the investigator returns for assistance after the protocol has already been through the NIAID IRB approval process. Additionally, the IT group enhanced TrackWise to include notifications to the DSMB executive secretary when an adverse event is recorded and added new time points to indicate when a trial site was last monitored.

The TrackWise platform itself was also enhanced. IT staff reviewed and executed a statement of work with Sparta Systems, Inc. in order to provide staff augmentation services for core modifications to the TrackWise production, development, and testing environments. The services were composed of tasks in support of the implementation associated with upgrading the environments to the new product suite version 8.7.2, and included performing configuration modification, testing, and validation exercises, and the modification and deployment of Crystal Reports templates. The upgrade provided the necessary support of the Internet Explorer 10 browser and the Tomcat 7 application server, which hosts TrackWise. Functionality changes included adding the ability to sort records by project type or record state in the TrackWise project hierarchy, enabling data to be found more quickly, providing an enhanced "see as you build" query tool, and introducing a "favorites" area to store frequently run reports and queries.

The IT group, in conjunction with the CMRP Learning and Professional Development (L&PD) group, continues to support the deployment of TrackWise Training Manager for tracking and managing training records for every program employee, from noncurricular group training to individualized curricular training. To date, more than 12,000 noncurricular and 6,300 curricular records have been entered and managed through the system. Last year, IT staff enhanced the TrackWise Training Manager configuration to meet the guidelines set by IACET in order for CMRP to be eligible to become a certified provider of continuing education units (CEUs). A curricular mapping report was also developed for managerial staff to track the SOP and individual curricular training sessions for their perspective groups. The report pulls the data directly from the TrackWise application, eliminating the need to track this information manually through Excel spreadsheets.

The integration of the OpenText Enterprise Content Management suite, also known as Livelink, and TrackWise to manage content for clinical protocols undergoing an initial or amendment review by RCHSPP continues to be a successful blend of two systems and is used extensively within the program.

The IT group provided ongoing technical support to the eCTD system for the submission of regulatory documents to FDA through the FDA's electronic submission gateway. Ongoing support of the eCTD publishing system included the installation of several product service releases, reallocation of the publishing software from two dedicated kiosks to individual Regulatory Affairs (RA) staff members' workstations, and timely responses to support inquiries from the RCHSPP RA group for the Omnicia eCTD publishing system and Verisign digital ID certificate, which are used for submissions to FDA through the electronic gateway. The IT group also continues to serve as a technical liaison for the RA group to ensure that software interoperability exists with United States Government Configuration Baseline group policies and security updates.

The IT group provided survey support for DCR. Since September 2014, the IT group has developed seven surveys on the following topics: use and design of technology resources, quality of training materials, document design services satisfaction, and employee satisfaction.

Several desktop and environmental enhancements were completed to improve efficiencies and optimize the computing platforms, including: implementation of a Network Access Control (NAC) application to monitor to prevent unauthorized devices from gaining access to the NIAID network; lifecycle replacement of all mobile devices over two years old; upgrade and management of software for workstations; and facilitation of the release of an upgraded Citrix environment for remote access for program users.

Ongoing core IT functions provided to CMRP span a broad spectrum of technologies and service offerings, including: (1) application of whole-disk encryption to all new laptop computers, encryption key recovery services, and audits to ensure continued compliance with the Office of Management and Budget/DHHS directive for protection of sensitive information; (2) evaluation, specification, acquisition, integration, and management of computer hardware/software; (3) system administration, technical support, and backup/disaster recovery services for program staff in both domestic and international settings; (4) standardization of government-furnished Microsoft Windows personal computers in compliance with the United States Government Configuration Baseline mandate via technical analysis and review of federal policies and procedures, establishment of project plans, analysis of software impact, dissemination of communications to program staff, categorization of resources into applicable security containers, development and submission of waivers, and generation and allocation of secondary administrative accounts; (5) installation and monitoring of McAfee ePolicy Orchestrator for the management of site antivirus and related security software and BigFix for hardware inventory and software patch management; (6) collection, evaluation, design, and implementation of change requests for TrackWise, the quality and process tracking system for the program; (7) development, unit testing, and maintenance of custom Crystal reports for correlative analysis, qualitative and quantitative process/data measurements, and end-of-month/quarter/year summaries from TrackWise; (8)

participation in RCHSPP strategic planning sessions, working groups for Section 508 compliance, TrackWise, and Livelink, and FDA inspection readiness teams; (9) evaluation, procurement, and deployment of encrypted USB keychains to staff in adherence with HHS policies; (10) development of IT training materials and presentation at new employee orientations; (11) provision of management, maintenance, and support services to the core site network and data services infrastructure; (12) design, development, hosting, integration, and maintenance of a Microsoft SharePoint Services platform; (13) participation as a member of, and key contributor to, several technology-related project teams, including the Leidos Biomedical Research Technology Review and Advisory Committee, Microsoft Active Directory Working Group, HIPAA/HITECH committee, and CMRP Leadership Advisory Group; (14) provision of video-conferencing and video collaboration support services for both local and remote locations; and (15) provision of services to ensure compliance with smart card authentication requirements and standards set forth by the Homeland Security Presidential Directive 12 Act of 2004 (HSPD-12) and associated Federal Information Security Management Act regulations, Office of Management and Budget memoranda, and NIH policy.

In collaboration with OCICB, the RCHSPP IT and Document Control groups were successful in the production release of an electronic SOP system to provide the following capabilities to members of the program: ability to utilize automated forms and work flows to manage cyclic SOP review/approval processes; ability to store SOP documents in an audited and version-controlled electronic repository; and ability to apply digital signatures to electronic documents.

To help mitigate the risk of data loss due to fluctuations in power, the IT group has deployed and supported the use of uninterruptible power supply units to computer workstations. In the event of a power outage, the units will support operation of the computer to provide enough time for data to be saved. As batteries are a consumable part, the IT group has actively replaced the units deployed in prior years to ensure all workstations at the site are properly protected.

In the previous reporting period, the IT group began the design of a new application to store and track IT equipment data. The design process was completed and featured items such as automatic notifications for purchase requests; financial approval and automatic transmission of custodial change approval notifications; real-time tracking of custodial information; property history tracking; tracking of new equipment as it is received; tracking of loaner inventory; and reporting that includes the ability to track budgets by forecasting property lifecycles of computer equipment and the collection of equipment from employees on their out-processing date. Testing on the design has been completed and approved for implementation. To date, over 1,400 pieces of decaled equipment, 40 of which are designated as loaner inventory, have been loaded and tracked by the application. The tracking of loaner inventory provides a real-time availability view of existing equipment, enabling more efficient allocation and lifecycle management of devices. The implementation of the property tracking system converted a mostly paper process into an electronic system to more efficiently collect, store, and report on data.

The IT group has been active in continuing to promote and encourage the use of communication technologies, including Microsoft Lync, Skype, Citrix GoToMeeting, and Cisco WebEx for collaboration with colleagues. These technologies have helped bridge barriers to communication, as virtual web meetings with integrated audio and video are available to reduce travel times and increase attendance at meetings with staff stationed at remote locations. Further benefits include cost savings, as domestic and international phone calls placed by program staff on travel can be replaced by lower-priced Skype, Vonage, or Lync calls, and the establishment of the technical framework to facilitate the implementation of the federal Telework Enhancement Act of 2010.

To accommodate a mobile workforce while promoting enhanced real-time communication and collaboration with internal and external partners, the IT group added Skype and Vonage to the portfolio of mobile IT service offerings. These tools allow staff participating in site visits and regulatory or operational support activities at remote client sites to seamlessly interact and collaborate with others. To further support this initiative, lifecycle replacement of devices occurred at no cost, with many users moving from Blackberry to iPhone model devices. This required a coordinated effort among the group and user community, as the old devices had to undergo an electronic sanitization process while the new devices required individualized configuration and end-user instructions on operation and maintenance.

To comply and best integrate with current NIAID OCICB standards for network infrastructure, several networking components at the Industry Lane location in Frederick, MD, were identified as candidates for replacement. Some of these devices had been in operation for more than 10 years, and if replacement was not performed properly, network service interruption to the site could occur. To minimize these issues, equipment acquisition and configuration were performed in advance and the installation event was planned for an after-hours time period. The components were successfully installed and tested in this time period, and all network operations resumed as expected.

To best facilitate the deployment of a new NIAID Citrix remote access environment to program staff, the IT group provided information in advance of the release as well as individualized instruction on using the new environment. These efforts helped ensure a seamless transition from the old to the new environment. After the go-live date, the IT group provided prompt local and remote customer support to users, addressed questions and issues that were discovered, and prevented any disruptions to remote telework operation activities.

The IT group worked closely with members of NIAID OCICB to develop, test, and implement a new NIH security policy requirement, Network Access Control (NAC). This policy requires that all devices that attach to the NIAID network be identified and adhere to a common set of security and configuration baselines. To determine the best strategy for implementation, a stakeholder team, composed of technical team members within the IT group and OCICB, was formed, and weekly meetings were scheduled to promote sharing and discussion. This resulted in the development of use cases and testing models that could be evaluated with little to no disruption to the user community. An iterative approach to the release was taken, with tuning of the NAC parameters occurring based on feedback from the IT group. As a result of this collaboration, NIAID OCICB was able to successfully deploy NAC to all network nodes on June 15, 2015.

Learning and Professional Development

Learning and Professional Development (L&PD) support for the Regulatory Compliance and Human Subjects Protection Program (RCHSPP)/Office of Clinical Research Policy and Regulatory Operations (OCRPRO) is provided by a clinical training manager, a training specialist/instructional designer, and an administrative support staff member.

L&PD continues to offer courses that are eligible for the International Association for Continuing Education and Training (IACET) CEUs while expanding processes to include training sessions provided by third-party vendors and access to "durable training materials."

Currently, the SOP Document System does not have an alert mechanism to notify supervisors and managers when their SOPs have been implemented. The L&PD group is working with the Document Control group to create an automated process to notify L&PD when an SOP goes into effect so that training requirements can be addressed in a timely fashion.

A few cost-saving initiatives and customer support activities to highlight for FY2015 include: L&PD purchased an FDAnews webinar training pass, which allows our clinical groups to view past, current, and future webinars for one fixed price instead of paying a per-webinar fee; L&PD created Safety Essentials computer-based training for the clinical research public; and the L&PD group developed a process for granting CEUs for competency-based courses provided by third-party vendors.

L&PD support falls into the categories detailed below.

Identify/develop training resources to address client-identified training needs

The L&PD group facilitated the following training presentations: a one-day workshop on the fundamental concepts of medical device regulations; a three-session workshop on statistical reasoning for clinical trials; a seminar on core concepts of clinical immunology; and a workshop on dealing with difficult people.

The one-day workshop on the fundamental concepts of medical device regulations was offered to our Regulatory Affairs group. Provided in webinar format and hosted by the FDA, this workshop featured five sessions: (1) Investigational Device Exemption (IDE) Program; (2) 510(k) Program; (3) de novo; (4) Corrective and Preventative Actions (CAPA); and (5) Electronic Medical Device Reporting (eMDR). Each session consisted of a presentation followed by a question-and-answer period with a panel of experts.

A three-session, competency-based workshop on statistical reasoning for clinical trials provided RCHSPP/DCR staff with practical knowledge of statistical design and analysis, information relevant to their tasks associated with creating, drafting, revising, and reviewing clinical research protocols. A senior mathematical statistician for the Center for Clinical Trials Network presented the workshop. All three one-hour sessions were hosted at the Fisher's Lane location and broadcast to a location in Frederick by webinar, with 70 participants in attendance. Each session offered continuing education units (CEUs).

The competency-based seminar on core concepts of clinical immunology was offered to RCHSPP/OCRPRO staff and was designed for clinical research staff members who may not have medical training or medical backgrounds, yet they review study protocols and/or monitor clinical trials. This training provided important information to assist with review of immunologically related therapies. The seminar was presented by a Leidos Biomedical Research senior medical scientist supporting the NIAID DCR Clinical Collaborative Research Branch. Hosted at the Fisher's Lane location and broadcast to a conference room in Frederick, the session offered CEUs to the 16 participants in attendance.

The competency-based seminar on dealing with difficult people was offered to our Clinical Trials Management team. It consisted of characterizing the professional environment and the professional's position in it, evaluating critical interactions and identifying strategies to optimize those interactions, specifically those involving difficult people. The CMRP clinical training manager developed and provided this seminar.

During FY2015, the following computer-based training (CBT) resources were deployed in support of RCHSPP: SOP RA-07015 RCHSPP On-site Compliance Inspections, TrackWise Protocol Record for Clinical Trials Management (CTM) team, TrackWise IND/MF Record for Managers, and TrackWise Site Record for CTM.

Provide training and professional development subject matter expertise

The clinical training manager attends all monthly Progress Meetings and provides L&PD expertise on a monthly basis. During the reporting period, she participated in a thorough review/update of the RCHSPP FDA Inspection Readiness Program.

The L&PD group is active in the TrackWise Working Group, collaborating with the IT group to optimize the configuration of TrackWise Training Manager (TWTM) for RCHSPP training records management.

Provide administrative support for activities with training implications

During FY2015, the L&PD group facilitated 13 audioconferences on the following eight technical topics: signal detecting and data mining; fundamental concepts of medical device regulations; preparing for an FDA inspection; monitoring reports; Good Clinical Practice (GCP) essential documents; risk-based monitoring; using an electronic informed consent in clinical investigations; and validation and use of spreadsheets in FDA-regulated environments.

The CMRP training coordinator assisted the compliance inspection coordinator with ensuring all new RCHSPP staff members are trained in a timely fashion on issues and standard operating procedures (SOPs) related to inspections. The L&PD group continued to maintain a spreadsheet identifying FDA Warning Letters citing GCP issues; this spreadsheet is utilized extensively by clinical research professionals to ensure compliance.

Ensure compliance and continuous improvement of training processes and initiatives

The L&PD group collaborated with the IT group to develop a systematic procedure for adding curricula to TWTM.

The L&PD group collaborated with Document Control to develop a streamlined procedure for alerting managers and supervisors when a new/revised SOP goes into effect to ensure training is performed in a timely fashion.

The L&PD group improved their training documentation process by creating an inter-departmental process for submitting and receiving approval for webinar and training requests. The L&PD group also created/revised two Standard Procedures (SP) and six forms during FY2015.

Participate in professional development to ensure that L&PD staff members maintain their subject matter expertise

The clinical training manager attended the Society of Clinical Research Associates (SoCRA) conference and gave a presentation on influencing without authority. Members of L&PD also participated in numerous training programs on topics including creating a positive work environment through personal interaction, risk management, and e-learning instructional design.

Project Management

The RCHSPP's Project Management Team (PMT) continues to provide strategic and operational planning, project management, reporting, and logistical support services to enhance the capacity of the NIAID Office of Clinical Research Policy and Regulatory Operations (OCRPRO) in conducting its mission and maintaining the infrastructure needed for RCHSPP to fulfill program management and contractual requirements. PMT considers each one of these services as core capabilities that are critical to the efficient and effective response to, and execution of, the needs of the RCHSPP's internal and external stakeholders. In collaboration with all RCHSPP program support team members and functional groups, PMT works to align organizational strategy and operational insight into project and program initiatives with the tactical goals and objectives required to achieve overall success within RCHSPP.

The main operational and strategic focus is to provide insight for managing projects/program success at the appropriate level of the RCHSPP/OCRPRO to cover a myriad of reporting requirements as specified by the customer.

At the end of FY2014, the updated program baseline was used to measure how overall program resource utilization and portfolio status aligned with the original baseline plan. The comparison aimed to provide key managerial and operational insights for senior managers in terms of overall resource utilization and requirements by all functions, labs, and protocols. The exercise allowed senior management to respond proactively in making necessary adjustments to overall budgetary and resource requirements.

The PMT is currently providing project management support to the Ebola research initiative in West African countries. As directed by the CMRP director, PMT is assisting the Ebola Project Management Team (EPMT) in implementing FNLCR's pilot project management (PM) policy that provides a framework to manage collaborative work between FNLCR and NCI. Using this PM framework and guidance, PMT is supporting the Partnership for Research on Ebola Virus in Liberia (PREVAIL). The initial study, known as PREVAIL I, is a Phase II/III vaccine study sponsored by DCR within NIAID and managed by Leidos Biomedical Research. PREVAIL I has been targeted as the pilot project to implement the FNLCR PM framework. PMT is supporting EPMT with the development of the Project Management Plan, which describes the approach and identifies specific methods and procedures, both managerial and technical, to be used to execute and monitor the PREVAIL I study. The team is also leading the development of essential PM tools such as a project plan, communication plan, risk register, issue register, change control register, and project schedule. The plan will ensure that the study is executed in accordance with customer requirements, and as a living document, it will be kept current throughout the course of the PREVAIL I study.

As part of the PM pilot project requirements, PMT also supports the EPMT with preparing Interim Progress Review (IPR) presentations that provide a snapshot of the PREVAIL I study status. The presentations provide a summary of the project status, changes since the last month or quarter, and a performance status overview

dashboard completed independently by the program director in consultation with technical project managers. PMT is also developing/customizing project management tools and templates that EPMT can leverage in managing various international projects. PMT facilitates the implementation of the project management policy that is designed to create a project management culture within FNLCR that is flexible but disciplined, and is more closely aligned with industry "best practice." Using FNLCR's project management guidelines, PMT expects improved project management systems to track and monitor PREVAIL program progress (cost, schedule, and scope), highlight issues with program execution, and facilitate rapid resolution of those issues.

PMT has added features and capabilities for improving existing reporting requirements of program initiatives. For example, one capability has allowed senior managers and customers to review a list of protocols or ancillary activities that required the largest amount of hours and dollars utilized by the RCHSPP team during a particular fiscal year. Likewise, the team has enhanced the ability for senior management to review and compare resource utilization by various protocol parameters (characteristics), including single-versus-multiple sites; countries (domestic versus international); research group; regulatory category (FDA regulated versus non-IND); and functional support (navigated versus non-navigated studies). To meet other project/program requirements as requested by the RCHSPP/OCRPRO leadership, PMT continues to enhance the integrated project management framework that allows the project team to access, customize, and utilize various project management practices, reporting tools, and templates. The reporting mechanism established using this framework will also serve as an effective project management tool to track, monitor, and report high-level Ebola-specific project expenditure related to Ebola initiatives in West Africa, and help senior management to assess additional budget, research subcontracts, and staffing requirements.

PMT is currently analyzing, reviewing, selecting, and customizing project management best practices and program reports to present to senior management and customers. The team supports indirect cost savings using project management practices such as project expense tracking and monitoring, timely expense reconciliation, data-driven decision making, and resource utilization measuring. These reports have demonstrated that RCHSPP resources were fully optimized to support ongoing and increasing project/protocol portfolios with limited budgets for the last few fiscal years.

Value-added indirect benefits noted in practice within RCHSPP include the streamlined PM processes and the strategic portfolio alignment through customer engagement, collaboration, and interaction at the program level for tracking and monitoring resource utilization within and across clinical protocol portfolios. These improved practices have enabled senior management to optimize efficiency, productivity, and funding through proper monitoring, tracking, and reporting financial data for making informed decisions. Senior management's easy access to relevant and complete information related to all protocol portfolios results in better business decisions, more efficient overall FTE resource utilization across all protocols/projects, and ultimately, improved business performance. PMT believes that these practices lead to a gradual cost savings and better program/project outcomes.

The implementation of a new ERP system has posed both opportunities and challenges. The lack of timely access and a lag time in reporting actual financial expenses from international travelers, research subcontractors, and other venders/suppliers related to clinical trials continue to present challenges such as delays in accessing complete financial data covering entire fiscal year, delays in capturing actual protocol-specific expenditures, and discrepancies that require further investigation for clarification. PMT has taken a proactive role in addressing these challenges by collaboratively working with financial, technical, and program support/functional/administrative teams to streamline processes, address data entry errors, reconcile inconsistencies, and add/refine/realign protocols as per the sources of funding within RCHSPP/OCRPRO fiscal budget. During this fiscal cycle, PMT significantly improved the quality of data sources needed to generate resource utilization reports and analyze overall program performance. PMT continues to collaborate with RCHSPP senior management, the financial team, and functional group leaders to implement flexible, customizable, repeatable, and expandable protocol models to fit OCRPRO's strategic/program reporting needs.

PMT provides customer support and meets reporting needs that include the Project Management Dashboard, a high-level snapshot of three key strategic focus areas (dollars, hours, and protocol portfolio) that compares the current fiscal year to the prior fiscal year. Senior management uses the PM Dashboard to quickly identify program resource requirements, address existing resource demands, and manage program/project risks and issues by assessing and comparing its progress from current to prior fiscal year at the program, protocol, and customer level. The RCHSPP's historical data repository, covering data as of the end of FY2014, integrates key protocol parameters using the lifecycle/milestones, financial cost status related to all protocol portfolios on an annual basis, and FTE hours charged to each protocol using the time card system. This data repository serves as the key program management reporting capability within the RCHSPP that enables PMT to conduct portfolio-level analysis and analytics while providing a solid platform for generating and customizing reports as needed using any of the parameters (protocol types, categories, and domestic versus international) presented and requested by internal and external customers.

Protocol Navigation/Protocol Development Program

Now in its sixth year, the Protocol Navigation/ Protocol Development Program (PN/PDP) is a high-priority initiative that has been successfully integrated into the research development process at the National Institute of Allergy and Infectious Diseases (NIAID). There are two aspects of this program: (1) Protocol Navigation (PN), which facilitates the research logistics that are critical to study start-up activities for protocols being conducted at the NIH Clinical Center, collaborative clinical sites, and international investigative sites; and (2) Protocol Development (PD), which involves drafting and editing protocol documents in preparation for submission to the various approving committees associated with each protocol. This involves collaboration with the functional groups within CMRP's Office of Clinical Research Policy and Regulatory Operations (OCRPRO) and the Regulatory Compliance and Human Subjects Protection Program (RCHSPP), as well as with other entities within NIAID and the larger NIH departments.

PN/PDP represents an exceptional administrative initiative that has served as a model to other NIH institutes/centers, and has improved NIH program operations and benefitted the NIH research environment. PN/PDP provides investigators with comprehensive support services to meet the increasing demands on clinical research related to the regulatory compliance process and efficient navigation through the myriad of clinical processes, from study concept to publication.

Current staff members include a PN/PDP project manager, two protocol navigators, and three medical writers. PN/PDP continues to add significant value to the protocol development process by providing services related to protocol and consent drafting and logistics management, and assisting new and experienced clinical investigators.

The program's purpose is to provide early interventions in protocol development through navigation processes, administrative and regulatory requirements management, and technical writing support. The protocol navigators guide principal investigators (PIs) through the regulatory and administrative requirements to facilitate the submission process, aiming to avoid unnecessary delays. The medical writers assist PIs in editing clinical protocols in any stage of document development, including study concepts, informed consent documents, amendments, SOPs, and publications. During protocol development, the team collaborates with PIs to ensure compliance with regulatory requirements, NIH policies, and project timelines, as well as to enhance the overall accuracy and quality of content. Logistics management includes support to NIAID intramural investigators and research study teams with developing, writing, and tracking clinical protocols through the protocol life cycle (concept stage through protocol development, review, approval, and initiation). PN/PDP involvement is very helpful in keeping investigators and collaborators engaged in the often lengthy study start-up process. Investigators continue to express their support for the services that the protocol navigation team provides, citing the team's effectiveness in keeping them on track with the protocol logistics and ensuring that protocols include consistent and applicable language for IRB submission.

During the reporting period, the PN/PDP team was involved with the development of 35 initial review protocols; 32 were new requests, and 11 of these were first-time users of the PN/PDP services. During this time, 17 protocols were IRB approved.

The working titles of the 32 new protocol requests are as follows:

- A Randomized, Double-Blind, Controlled, Phase II/III Study of the Safety and Efficacy of Ebola Virus Vaccines ChAd3-EBO Z and VSVΔG-ZEBOV in Adults in Liberia
- A Multicenter Pilot Study of the Safety and Immunogenicity of Recombinant Vesicular Stomatitis Virus Expressing the Envelope Glycoprotein of Ebola virus Zaire (VSVΔG-ZEBOV) Vaccine for Post-Exposure Prophylaxis following High-Risk Ebola virus Exposure
- A Phase Ia, Open-Label Study to Assess the Safety and Pharmacokinetics of a single ZMapp Administration in Healthy Adult Volunteers
- Study of the Seroprevalence and the Incidence of Lassa Fever in the Rural Commune of Sibirila, District of Bougouni, Mali
- A Multicenter Observational Study to Compare IRIDICA BAC BSI Assay Results of Whole Blood Specimens on the IRIDICA System to Blood Culture
- A Multicenter Observational Study to Compare IRIDICA BAC LRT Assay Results of Bronchoalveolar Lavage or Tracheal Aspirate Specimens on the IRIDICA System to Culture
- Effect of Dietary Magnesium Supplementation on the Immune System of Healthy Adult Subjects
- Natural History and Genetics of Food Allergy and Related Conditions
- A Randomized Cross-over Comparison of Vorapaxar versus Placebo for the Treatment of HIV-associated Inflammation and Coagulopathy in Patients with Well-Controlled HIV Replication
- Protocol for Collecting Umbilical Cord Blood for Malaria Studies
- Safety and Efficacy of Tenofovir Alafenamide as Part of a Salvage Regimen in Patients with Multiple-Drug-Class-Resistance HIV Infection
- A Phase I Double-Blind, Randomized, Dose-Escalation Study of a Live, Attenuated Chlamydia Trachomatis Serovar A Vaccine in Healthy Adults to Evaluate Safety, Reactogenicity, and Immunogenicity

- An Open-Label, Non-randomized, Within-Patient Dose-Finding Study Followed by a Randomized, Double-Blind Placebo-Controlled Study with Extension to Assess the Safety and Efficacy of CDZ173 in Patients with APDS/PASLI (Activated Phosphoinositide 3-kinase Delta Syndrome/ p110δ-Activating Mutation-Causing Senescent T Cells, Lymphadenopathy, and Immunodeficiency)
- A Study of Magnesium Supplementation in the Treatment of Patients with XMEN Syndrome
- NIAID Clinical Center Genomics Opportunity Protocol
- A Phase IIa Efficacy, Safety, Tolerability, and Pharmacokinetic Study of Encochleated Amphotericin B (Camb) in Patients with Mucocutaneous (Esophogeal, Oropharyngeal, Vaginal, Onychomycosis) Candidiasis Who Are Refractory to Standard or Tolerated Non-intravenous Therapies
- Tesamorelin Effects on Liver Fat and Histology in HIV
- A Phase I Pilot Study of Respiratory Syncytial Virus Human Challenge in Healthy Adult Volunteers
- A Multicenter Observational Study to Compare IRIDICA Fungal Assay Results of Bronchoalveolar Lavage Specimens on the IRIDICA System to Culture
- Systems Analyses of the Baseline and Vaccination Response in Patients with Monogenic, Immune-Mediated Defects
- Cardiometabolic Effects of Eplerenone in HIV Infection
- Long-Term Observation of Hemagglutinin and Neuraminidase Inhibition Antibody Titers after Influenza Challenge
- Evaluation of MiSeq Assay for Microbial Identification in Specimens
- Effect of Concomitant Mansonella Perstans Microfilaremia on Immune Responses Following Single-Dose Praziquantel in Subjects with Schistosomiasis: A Pilot Study
- A Multi-arm, Phase III, Randomized, Placebo-Controlled, Double-Blind Clinical Trial to Investigate the Efficacy and Safety of BMS-663068 in Heavily Treatment-Experienced Subjects Infected with Multi-drug-Resistant HIV-1
- Influenza A H3N2 Human Challenge Study in Healthy Adult Volunteers
- Iron Overload in Invasive Fungal Infections
- A Study for the Natural History of PI3K Defects with Optional Treatment Using Ralalogs
- Dose-Finding Study to Examine the Efficacy and Microfilaricidal Kinetics of Imatinib for the Treatment of Mansonella Perstans
- Partnership for Research on Ebola Vaccines in Liberia (PREVAIL) in Guinea
- PREVAIL III (Ebola Natural History Study)
- Quality Control, Test Development & Validation: A Study by the Liberia Institute for Biomedical Research

PN/PDP assisted with 16 amendments, which included assignments related to emergency IND; addressing stipulations from the Maryland state IRB; assisting with responses to the Ugandan IRB; and assisting with reliance agreements and OHSRP determinations.

Protocols have varied in phase, type, and sponsorship, and have also spanned several intramural labs, including: the Laboratory of Clinical Infectious Diseases; the Laboratory of Immunoregulation; the Laboratory of Parasitic Diseases; the Laboratory of Allergic Diseases; the Laboratory of Immunogenetics; the Laboratory of Infectious Diseases; the Laboratory of Molecular Immunology; the Laboratory of Host Defenses; the Laboratory of Malaria Immunology and Vaccinology; Laboratory of Immunology; the Laboratory of Human Bacterial Pathogenesis; the Laboratory of Zoonotic Pathogens and the Laboratory of Virology at Rocky Mountain Labs (RML); and the Collaborative Clinical Research Branch. Additional laboratories that have requested PN/PDP services this year include the Laboratory of Systems Biology and the RML Laboratory of Intracellular Parasites.

In addition to the normal work requests, PN/PDP focused on the NIAID Division of Clinical Research (DCR) high-priority Ebola research initiatives. Services included protocol editing and consent development for both domestic and international research studies. Due to the nature of the Ebola outbreak and urgency of dealing with it both in the United States and West Africa, PN/PDP has been involved in very quick turnaround requests. PN/PDP's role in the DCR efforts in Liberia focused on new ways to convey and communicate the research in a manner understood by the people in a country with scarce resources and scant health infrastructure, not to mention relatively limited experience with research studies in general and no experience with conducting studies of the magnitude and scope of this DCR study. In addition to protocol editing and consent development, PN/PDP created FAQs and video scripts. One of the most challenging projects was creating a flip-book to convey the vaccine research in pictorial as well as simply stated sentences. This required collaboration with the Centers for Disease Control and Prevention (CDC), the Liberian representatives, and the NIAID study team. The Leidos Biomed Scientific Publications, Graphics & Media department assisted with illustrations. The PN/PDP also provided support for submissions to the IRB and the Institutional Biosafety Committee (IBC). As the PREVAIL initiative expands both in Liberia and potentially into other neighboring countries, the PN/PDP was tasked with developing flip books and consents for the Ebola natural history study as

well as the potential vaccine study in Guinea. Other projects were reprioritized and reassigned to enable the team to meet the study timelines and get the requests completed in an expeditious manner for the NIAID clinical director.

Over the past year, referrals to PN/PDP from the NIAID IRB office and IRB chair have increased. This increase in referrals indicates satisfaction with the products that have been reviewed and is a good measure of the confidence in the PN/PDP's ability to produce quality documents.

In addition, the team had one-on-one sessions with new PIs to familiarize them with PN/PDP services and provide advice on protocol development issues. To ensure the provision of current information, staff members engage in webinars, videocasts, conferences, and training sessions on scientific, research, and human subject protection issues offered by internal NIH and Leidos Biomedical Research resources, as well as by outside professional organizations. PN/PDP staff members review IRB stipulations from navigation and non-navigation protocols, and maintain a document containing frequently encountered issues as a reference for all team members. This contains hot-button topics and the current thinking on human subject protection issues as they apply to protocol submissions. Specific information per logistical topic (e.g., radiation safety, ethics) is maintained for convenient reference and to decrease any duplication of efforts, should a similar situation arise in the future.

The PN/PDP convenes meetings with the NIAID clinical director, the OCRPRO branch chief, and various oversight managers to keep each party up-to-date on the workload and upcoming projects, to troubleshoot issues, and to promote the future growth of this program. A monthly status call is held between OCRPRO and RCHSPP staff members (who are involved in protocol development), so all are aware of timelines, areas of concern, and action items. This call assists the teams with planning and evaluating future workload.

The program continues to collect metric data, which include tracking milestone dates and categorizing stipulations from IRB reviews to identify areas needing quality improvement. Compared to studies that do not use the program, PN/PDP appears most beneficial in expediting the time between scientific review to IRB submission, possibly because when PN/PDP is involved prior to scientific review, team members ensure that the protocol contains the required sections and necessary verbiage for the IRB review. PN/PDP implemented a work flow in the TrackWise system to facilitate project management and capture details on milestones. New or modified reports and tracking information are added as needed to improve the functionality of the reports and usefulness to the program management.

PN/PDP also provides NIAID senior leadership with slides and information for other purposes, such as branch chief meetings, town hall meetings, and retreats, as well as for performance, operational, and strategic planning. The navigation manager provides data to management on the status of the goals identified by DCR/OCRPRO.

In addition to the support for the Liberian Ebola initiative, PN/PDP actively supported protocols domestically and at NIH related to Ebola prevention and treatment. These requests were high-priority, time-sensitive, and dealt with multiple collaborators with varying input; they required immediate turnaround to meet submission deadlines as well as patients' needs. PN/PDP successfully shifted workloads and prioritized the Ebola assignments to meet the urgent demands while maintaining customer support on the other PN/PDP research projects.

The program receives daily requests for assistance in developing new protocols or helping with amendments to existing studies. The program provides not only writing support but also navigational support, which entails fielding regulatory and human subject protection questions and guiding investigators and/or research support staff through the intricacies of the protocol implementation and approval processes both within NIAID, for multi-site studies, and international collaborations.

The program provides metrics and information for the OCRPRO Operational Plan on a quarterly basis, and information for workforce alignment efforts for the Clinical Director (CD), the OCRPRO director, and the OPOS director.

Overall, the PN/PDP outcomes have exceeded expectations. Since its inception, PN/PDP has continued to receive universally positive feedback regarding its value in reducing regulatory and administrative burdens; optimizing the use of existing clinical tools within NIAID and NIH; maintaining knowledge and implementing best practices of protocol management; assessing the impact of the various steps of protocol development on clinical trial efficiency; developing metrics to identify, measure, and target processes that create opportunities and efficiencies throughout the clinical research review and approval process; and, most importantly, reducing investigator burden while facilitating communications between the multiple organizations involved in the review of clinical research. The program has been enthusiastically received by investigators, as demonstrated by the increased utilization of services, referrals, and repeat customers. The program consistently receives positive feedback and appreciation from both investigators and management.

PN/PDP continues to be involved with the development of a protocol in collaboration with the Kirby Institute in Australia. The significant time difference between the United States and Australia requires frequent after-hours teleconferences. Support provided by PN/PDP also includes offering input on study feasibility, understanding logistics specific to the NIAID site, and guiding the new NIAID investigator through the process.

Early discussions between PN/PDP and the NIAID scientific director and scientists on future clinical protocols are under way related to Lassa fever, and rabies and Ebola vaccine development. PN/PDP has been tasked with the protocol development of a collaborative Division

of Microbiology and Infectious Diseases (DMID) proposal for a vaccine to prevent trachoma eye infection, the leading cause of infectious blindness in the world.

The PN/PDP manager was asked by the OCRPRO director to contact the *IRB Advisor* to discuss the navigation program that was created at NIAID and provide input for a publication. The *IRB Advisor* editor conducted an interview with the manager and senior navigator to discuss the program and its potential applicability to the publication's audience. The resulting article was published in the October 2014 issue. Additionally, PN/PDP presented a poster, titled Regulatory Fatigue Syndrome: A Novel Approach to a Weary Condition, at the Society for Clinical Research Associates annual conference as well as at the NIH Research Festival. The senior protocol navigator gave an oral presentation for the NIH Intramural Research Program's Protocol Navigation Training Program with the same title.

As a result of the networking between PN/PDP staff members and representatives from other research institutions at meetings where program information is discussed, centers outside NIH continue to show a great deal of interest in this program and its operations, citing its helpfulness and efficiency in getting protocols through the pipeline. New business has been generated for CMRP based on discussions with PN/PDP staff, and other institutes within NIH have started to use the PN/PDP model for protocol development. The PN/PDP project manager provided input to the international clinical regulatory website developers on the utility of the site and made suggestions for improvements.

For the fourth year in a row, the PN/PDP team was invited to participate at the PhD student summer course in clinical and translational research at the NIH Clinical Center. The course involved didactic interactive sessions given by the medical writers and protocol navigators and was an introductory program for PhD students (selected by NIH) with no prior experience in clinical research or human subjects protocols. This session provided an opportunity for PN/PDP to demonstrate resources available within NIAID to future PIs.

Regulatory Affairs

The RCHSPP Regulatory Affairs (RA) group prepares, submits, and maintains IND applications, IDEs, and DMFs to ensure that these documents comply with federal regulations and the International Conference on Harmonization/Good Clinical Practices (ICH/GCPs) guidelines. The RA group consists of one regulatory affairs director, one IND manager, six regulatory associates, and one regulatory submissions coordinator.

In collaboration with the OCRPRO IND clinical research oversight manager, the RA group fulfills IND, IDE, and DMF sponsorship responsibilities. Staff members provide overall regulatory support and guidance to the intramural investigators, serve as liaisons with various FDA divisions, and interact with various industry collaborators and other outside subcontractors to obtain information required to support OCRPRO-sponsored projects. The RA group supports investigators in the NIAID Intramural Research Program, which includes multiple laboratories within DIR, investigators within DCR, and external investigators under contract to NIH.

Additional responsibilities of the RA group include preparing, compiling, and submitting various documents (e.g., protocol amendments, information amendments, annual reports, safety reports, and responses to FDA comments/requests for additional information) to maintain and ensure regulatory compliance of OCRPRO-sponsored INDs, IDEs, and DMFs. Staff also ensures compliance with the mandated reporting requirements for the https://clinicaltrials.gov website.

Currently, the RA group provides support for 75 IND applications, 3 Clinical Trial Applications (CTAs), 3 IDEs, 5 DMFs, and 4 single-patient emergency INDs (eINDs), several of which include protocols conducted at multiple sites and international locations. During FY2015, the group prepared and submitted 15 new IND applications; at the time of this report preparation, approximately 17 INDs/ IDEs were in various stages of development. As part of the ongoing maintenance for these new and existing applications, staff developed and submitted approximately 300 IND, IDE, and DMF serial submissions, and two pre-IND meeting requests and information packages to the FDA. Staff also participated in many teleconferences with the FDA to discuss IND issues.

Other support provided by the RA group during FY2015 includes: (1) participating in numerous teleconferences and face-to-face meetings with NIAID scientific investigators, FDA representatives, PIs, collaborating industry representatives, and other stakeholders to discuss ongoing scientific issues and IND management strategies (e.g., anti-H1N1 plasma, combination antivirals for influenza, RSV vaccine studies, MedImmune pandemic influenza CRADA projects, and several important Ebola studies); and (2) providing Current Good Manufacturing Practices (cGMP) guidance to OCRPRO and investigators regarding product storage, shipment, labeling, and manufacturing issues.

The RA group continued to evaluate and improve the eCTD program with the refinement of work guidelines and process modifications where appropriate. Staff expanded and refined the eCTD product dictionary and eCTD process overview. Staff also revamped and modified the RA group Manual of Procedures (MOP) to streamline its usability and the work processes described therein.

Among the 15 new INDs submitted was the Pfs25/Pfs230 IND for the Laboratory of Malaria Immunology and Vaccinology (LMIV). This IND included a complicated chemistry, manufacturing, and controls section which RA staff was instrumental in drafting and revising to meet FDA requirements. It also required revisions to LMIV's previous IND for a similar vaccine product, which was equally complicated.

The RA group continued to provide regulatory support for ongoing and new influenza studies under the IRC, La Red, and INSIGHT networks, which make up a large and important part of the DCR portfolio. Of note, staff submitted 27 amendments, including protocol amendments, new protocols, and drug manufacturing updates. In addition, staff participated in numerous teleconferences with DCR, NIH PIs, and other IRC, INSIGHT, and La Red study stakeholders in support of these studies.

In early FY2015, OCRPRO began its response to the Ebola outbreak in West Africa with the preparation and submission of single-patient or midsize population eINDs, followed by a DMF and INDs for a vaccine study, a treatment study, and a plasma collection study. The vaccine and treatment studies were implemented in Liberia and Sierra Leone, which required CTA submissions to the regulatory authorities in those countries.

The RA group dedicated significant support to the Ebola efforts in West Africa this fiscal year. Approximately half of the RA team was involved, and contributed by writing and submitting eINDs, one within 48 hours of notice, preparing two eCTD INDs for vaccines and therapeutics, and developing three CTAs to conduct investigational new drug studies in Liberia and Sierra Leone, the first-ever such applications prepared by CMRP. The Ebola work took precedence over all other projects and greatly increased the workload volume of the group, as it came at a time when the per-person workload was already high due to the recent departure of the senior IND manager. The team worked nights and weekends when necessary to complete these required applications and documents in record time, often in less than 24 hours, which helped ensure the quickest possible start to the Ebola vaccine and therapeutics trials. In addition, the RA director traveled twice to Liberia to help with logistics, site assessment, inventory, and other tasks to support the Liberian–US partnership for Ebola studies (PREVAIL), including implementation of the 7,000-subject survivor study, PREVAIL III.

Another highlight of this remarkable effort was work conducted with NIH and FDA to define a strategy that would allow the quickest possible approval route for the vaccine study (PREVAIL I). This resulted in the RA group developing and submitting an IND for the Ebola vaccines that was subsequently converted to a Master File. Because of the limited nonclinical data available at the time, as well as the urgency of the Ebola crisis and lack of approved treatments for the disease, this strategy allowed the FDA to avoid placing the IND on clinical hold and permitted NIH to submit data to an active application as it was received.

Staff also researched and interpreted general, and often limited, country guidelines to prepare CTA applications that were sufficiently complete to garner quick approval from Liberia and Sierra Leone regulatory authorities. Staff subsequently worked with the study teams and stakeholders (e.g., University of Minnesota) to develop appropriate quarterly reports that met country requirements for reporting study safety and enrollment data. These reports were completed, reviewed, and submitted to the applicable West African countries within the required time frames.

Staff changes in the RA group involved a newly hired regulatory associate and two promotions (one regulatory associate moved up a level and one regulatory associate was promoted to IND manager).

The RA director assessed the current processes for distribution and archival of regulatory submissions and other materials. In doing so, she spoke with staff and outside recipients of distribution copies (i.e., PIs, pharmaceutical partners) and determined that a cost savings could be recognized by switching to a less expensive binder. In April 2015, the regulatory submissions coordinator began using these less expensive binders—at a savings of more than 75percent over the binders used previously—for storing regulatory files in CMRP Document Control and sharing documents with stakeholders.

The RA group's work on the aforementioned Ebola INDs and their related CTAs was a challenging operational issue. While this was within the range of standard support provided to OCRPRO, the scope of these projects was greater than expected. They required research on the format and submission processes for Liberia and Sierra Leone CTAs, as OCRPRO and the RA group had never submitted to the regulatory agencies in these countries before. The templates and subsequent submissions that the RA group put together have been successfully received and approved by the required regulatory agencies and ethics boards.

The RA director participated in a focus group with members of the NIAID ClinRegs website team so they could better understand the value of their regulatory research tool to different segments of the clinical research community. She shared her experience with the website, and subsequent to the meeting, shared information learned while researching requirements for obtaining clinical trial approval in Guinea, including English-translated forms for the Guinea Ebola Research Commission Application and the Request for CNERS Review. The ClinRegs team was very grateful to receive these forms and information.

Clinical Safety Office

The Clinical Safety Office (CSO) provides primary professional support to OCRPRO in three distinct functional areas: (1) scientific and clinical support; (2) data and safety oversight committee support; and (3) medical writing support. The CSO also provides surveillance, monitoring, and regulatory reporting of significant adverse events (SAEs) occurring on NIAID intramural clinical trials, including all trials where OCRPRO is the IND sponsor. The CSO ensures compliance with the Code of Federal Regulations, NIH policies, ICH/GCP guidelines for protocols, informed consent documents, and CRFs.

The CSO experienced significant staff loss in FY2015 due to departures and a death, and actively recruited to replace positions. An operations manager position was created within the CSO this year, and it was filled with an internal candidate from CMRP. The position was created to aid the safety office in administrative and managerial activities to allow the director/lead medical monitor to focus on medical and scientific functions. The operations manager will provide broad support across several functions, and, in particular, will add a level of coordination, tracking, and management to CSO activities. The director/medical monitor position was filled by an internal CSO candidate, leaving a medical monitoring position open; active recruitment is underway.

As of June 2015, 42 SAEs were processed and completed, along with 33 updates of information on processed events. One SAE, received by the CSO on September 29, 2014, was determined to be a Suspected Unexpected Serious Adverse Reaction (SUSAR) and resulted in a 15-day IND Safety Report submitted to FDA. Six reports of pregnancy were processed and followed. SAE reconciliation efforts were completed for 51 events related to 14 separate protocols.

As of June 2015, the medical monitors and clinical safety associates reviewed 79 clinical research protocols, which consisted of 20 PI reviews, 46 amendment reviews, two site-specific informed consent form reviews, and 11 protocol navigator reviews. Comments and edits were suggested to the PI regarding safety and regulatory compliance prior to submission to the NIAID IRB. For the initial pre-IRB reviews, medical monitors performed a final review of the entire protocol for subject safety concerns, data integrity, and clinical trial design. The review process often involves numerous conference calls with investigators to discuss and resolve regulatory or safety concerns with the protocol and thereby improve chances for approval by the NIAID IRB or FDA.

The medical monitors and clinical safety associates also reviewed 33 IND annual reports, 5 investigator brochures, and 14 investigator brochure amendments by the time this report was written (June 2015).

The CSO provides administrative and logistical support to the NIAID intramural DSMB. A clinical safety associate serves as the DSMB executive secretary and is responsible for arranging all teleconferences and face-to-face meetings; distributing review materials to the DSMB; recording and moderating the review sessions; preparing the DSMB summaries for the reviews; communicating with the members of DSMB; and maintaining records associated with DSMB membership. As a cost-saving measure, CSO electronically distributes DSMB materials to several members. The CSO will continue to assess ways in which documents can be made available electronically to the DSMB as appropriate.

During FY2015, the DSMB executive secretary arranged and facilitated 36 teleconferences for 39 protocols, with 5 of the teleconferences scheduled because of safety issues. The DSMB executive secretary additionally conducted two face-to-face meetings where 21 protocols were scheduled to be presented by 13 PIs. Preparation for the face-to-face meetings included binder creation for four of the seven DSMB members (three members receive the information electronically). Binders are created with information submitted to the RCHSPP for each study. Following each meeting and teleconference, the DSMB executive secretary, assisted by the CSO operations manager, the CSO secretary, and medical monitors, distributed review materials to the DSMB members, prepared summaries of the reviewed protocol discussions and recommendations, and distributed them to the PIs, DSMB members, OCRPRO, and select RCHSPP management. CSO also facilitated recruitment of a new DSMB member. It is anticipated the DSMB executive secretary will complete an additional 10 teleconferences.

The CSO is responsible for oversight, support, and facilitation of meetings for nine protocol-specific Safety Monitoring Committees (SMCs) and two independent safety monitors. A clinical safety associate serves as the SMC executive secretary and is responsible for arranging all teleconferences, distributing review materials to the SMC members, moderating the review sessions, preparing the SMC summaries, and maintaining records associated with SMC membership.

The CSO collaborates with the RA group and the Clinical Trials Management (CTM) group, providing guidance and expertise to staff, as needed. The CSO reviewed 60 Monitoring Visit Reports (MVRs) and collaborated with the clinical research associates to resolve any safety discrepancies found during these reviews.

The CSO medical writer reviewed grammar, formatting, and content for review protocols and associated informed consent forms. As a whole, the CSO also develops and maintains up-to-date documents for both internal and external use. Examples of key documents that were updated during FY2015 include the Safety Review and Communications Plan/Transfer of Regulatory Obligations (SRCP/TORO) template, the Protocol Safety template, the CSO SOPs, and the CSO Procedure Manual, which currently contains a total of 12 CSO procedures.

A database of more than 3,500 IRB stipulations (from protocols reviewed January 2010–January 2015) was maintained by the medical writer. The stipulations from 29 new protocols were added during this reporting period. A separate line listing of 210 stipulations related to safety has been identified and compiled from the stipulation database. During this reporting period, 18 new safety stipulations were identified. A subset of safety stipulations for select topics (e.g., withdrawal, halting, pausing, and stopping) has also been used in refining safety language in the IND template. During FY2015, the medical writer completed and implemented a new section on pausing and halting rules as part of the protocol safety section template.

To facilitate continuous monitoring and review, the CSO maintains draft revision copies of key documents, including the protocol safety template and the SRCP/TORO template to capture comments by CSO staff during their day-to-day work experience with the documents. As a consequence of comments received during the continuous reviews, the SRCP/TORO template has been updated to a new version (V 3.1 13Apr2015). Another working draft has also been created for continuous reviewer input. The SRCP/TORO work practice procedures are being revised to correspond with the updates made to the document. The CSO director/ medical monitor is also drafting an SOP to document this process. One of the goals of the CSO for FY2015 has been to identify and implement potential improvements to optimize the effectiveness and efficiency of the process. The CSO focused on streamlining and simplifying the components of the process to help achieve this goal. In addition, the CSO conducts an annual review of the protocol safety template. Comments and suggestions have been placed in the draft version of the document, and a subsequent review process will follow, similar to previous years. The current version, located on the OCRPRO portal, was revised in February 2015 to streamline and update various sections of the template.

The SRCP is an internal communications document between the PI and the IND sponsor CSO, which delineates the safety oversight responsibilities of the PI, the CSO, and other stakeholders. In some instances, the PI is responsible for conducting the periodic safety assessments under a TORO agreement drafted by the CSO and signed by the OCRPRO branch chief and PI. The PI conducts the reviews and then provides documentation to the CSO, which disseminates this information to CTM and the RA group.

One of the significant challenges presented to the CSO is managing research operations through a time of limited staffing resources. During this reporting period, the CSO director stepped down, the medical writer passed away unexpectedly, and the two clinical safety associates resigned, leaving a staff of four (two medical monitors, one administrative assistant, and the operations manager) in the CSO, which is usually an staffed with eight positions. The newly appointed CSO director (one of the medical monitors for the CSO) and the operations manager strategized quickly to overcome the challenges and implement plans to continue the same level of performance for the client. Medical writer support was obtained through the contracts office, the operations manager quickly assumed the duties of the clinical safety associates, as appropriate, and the CSO director and medical monitor effectively managed the workload to complete tasks and projects on time. Also of note, due to the increase in investigational studies and the complexity of them, the volume of work increased over the level of work in previous years. While this staffing transition has put a strain on the regular responsibilities of the CSO staff, it should be noted that client deliverables were not compromised, and the group, as a whole, made every attempt to work cohesively to support the OCRPRO mission and fulfill regulatory requirements.

With the implementation of the new Safety Expedited Reporting Form (SERF) in FY2014, CSO ensured form functionality, effectiveness, and efficient use by the sites. The CSO CROM and the CSO operations manager gave a presentation at a NIAID monthly QA meeting in April to discuss the new form with NIH clinical staff and continued to work with all IND study sites on the time-sensitive, complex process for submitting SAEs and on unanticipated problems.

Reporting pertinent obstetrical information for pregnancy, including pregnancy outcome data, to the CSO within three business days of site notification is a requirement in many IND trials. To aid the thorough and timely reporting of this information from clinical sites, the CSO clinical safety associate designed a Clinical Safety Office Pregnancy Notification Form and a Clinical Safety Office Pregnancy Outcome Form. These forms were posted on the OCRPRO web page in 2014 to facilitate consistent reporting of the required information from multiple diverse sites. In January 2015, CSO launched a Pregnancy Prevention Initiative, which will incorporate several new projects for FY2015 into FY2016, including template protocol and informed consent language for investigators and sites that were distributed to some teams in FY2015. A comprehensive review and didactic session presentation is planned for the ACRP 2016 Annual Conference and elsewhere.

A review of SAE data reported to FDA in annual reports revealed an opportunity to improve processes to help ensure more accurate safety data reporting. Beginning in 2014, CSO initiated an SAE reconciliation process that has continued with adjustments. The process includes direct contact with protocol coordinators no less than annually, depending on the number of reported SAEs to CSO. Once reconciliation of data is completed, a report indicating SAEs that occurred after exposure to the study product is sent to the RA group for inclusion in the FDA annual report. To facilitate this process, the clinical safety associate provided industry standards/best practices information, identified reconcilable data, included fields in the current CSO tracking database to capture the process, modified CRIMSON report titles to improve understanding of the content of the reports for the study teams, and created SAE Reconciliation Reports for communicating with the study teams.

As CSO innovations are initiated, refined, and finalized, the CSO solicits feedback and provides training and support to its internal and external customers.

The Safety Essentials computer-based training (CBT) module was launched during December 2014; it included valuable safety-based information relating to the documenting, reporting, and understanding clinical trial safety information. The CBT underwent several rounds of testing to ensure the content, timing, and navigation were appropriate for the audience. At this

time, based on the feedback from a few study site staff members, the CBT has been well received.

The CSO operations manager has been working with the CROM to develop a checklist of potential safety-related topics in order to standardize the MOP development process. A draft has been developed and is expected to be finalized in the third quarter of 2015.

During FY2015, CSO staff collaborated in the preparation and presentation of a poster entitled Stopping NIAID Clinical Trials for Safety. The CSO director presented this poster at the 2015 ACRP Annual Conference.

In December 2014, an annual DSMB core member satisfaction survey to evaluate program services and identify potential process change needs and solutions was launched. The survey results were evaluated in the first quarter of 2015, and a formal response to the DSMB outlining the results and actions was completed in March 2015. The CSO DSMB executive secretary and the CROM conducted and evaluated the survey and the results.

During FY2015, the CSO director presented during two sessions at the 2014 Clinical and Translational Research Course for PhD students: Informed Consent—A Document-Oriented Approach; and Protocol Development—Keys for the New Investigator. A CSO medical monitor attended the Drug Information Association (DIA) Advanced Signal Detection training in April 2015 and the World Congress on Virology in October 2014. DIA modules on pharmacovigilance were purchased and reviewed by the team from January to February 2015 and were well received by the CSO team members. CSO staff members have participated in NIAID/NIH programs, projects, and committees that expand the scope and visibility of their respective positions beyond the confines of their usual position requirements. For example, the CSO operations manager actively serves the Frederick County, MD, educational system by presenting at the FutureLink Conference, held at Frederick Community College, and by acting as a speaker for the Maryland Business Roundtable for Education for the Maryland Scholars Program.

Division of Intramural Research

Support Provided by the Cancer Research Technology Program

The Protein Expression Laboratory (PEL) supports investigators in the Malaria Genetics Section with protein expression from HEK293 cells. As of August 1, the PEL produced 81 liters of mammalian cell culture in support of this project, using DNA reagents generated by the NIAID investigators.

Support Provided by the Clinical Monitoring Research Program

India/Mali Initiative International Centers for Excellence Research

The India/Mali International Centers for Excellence in Research (ICER) initiative is an ongoing project sponsored by NIAID's DIR to establish an infrastructure that facilitates research relevant to the pathogenesis and control of lymphatic filariasis in both Indian and West African populations. Because Africa and India disproportionately bear the burden of lymphatic filariasis, the infections must be studied in these international locations. With few resources, the countries require outside assistance to develop sustainable research capabilities and program strategies relevant to their local conditions.

Since 2004, CMRP staff has assisted NIAID researchers with establishing research infrastructure and training investigators for both the Indian and Malian lymphatic filariasis research initiatives, and has conducted well-defined pilot projects. NIAID facilitates multiple clinical trials conducted by both intramural and extramural investigators.

The India/Mali effort provides dedicated off-site personnel in Frederick, MD, and through an on-site research subcontract in India. The personnel coordinate activities for state-of-the-art laboratories, manage administrative concerns, track and monitor dedicated budgets, assist with logistics, provide project procurement support, coordinate administrative program-level functions, and scientifically manage research initiatives.

The research subcontract provides a scientific director, located in Chennai, India, who oversees the research projects conducted at LPD, NIH, Bethesda, MD, and the National Institute for Research in Tuberculosis, International Center for Excellence in Research, formerly known as the Tuberculosis Research Center, in Chennai, India.

During FY2015, the collaborative program accomplished the following activities:

- Elucidated the roles ofTh1, Th2, Th9, and Th17 cells in Strongyloides infection
- Elucidated the roles of Th1 and Th17 cells in latent TB individuals with coincident diabetes mellitus
- Elucidated the roles of type 1, type 2, type 17, and other pro-inflammatory cytokines in active or latent TB with or without coincidental pre-diabetes
- Elucidated the role of type 1, type 2, and type 17 cytokines in latent TB individuals with coincidental malnutrition
- Estimated the prevalence of filarial and Strongyloides infection in latent and active pulmonary TB as well as in the community, using serological assays
- Demonstrated the impact of helminth infection on T-cell responses in active pulmonary and latent tuberculosis.

CMRP's overall goal for ICER is to facilitate communication and continuity for the clinical researchers in India and Mali. During the reporting period, CMRP provided logistical and administrative support for daily international operations; prepared and monitored budgets; prepared travel arrangements for five nonemployees; procured miscellaneous biological and laboratory supplies; continued support of service agreements for equipment located in India and Mali; and coordinated and tracked 14 perishable, 16 bulk, and 6 dangerous goods, as well as 5 direct shipments, to both India and Mali.

Laboratory of Immunoregulation

Support Provided by the Clinical Monitoring Research Program

Rakai Project

The Rakai Health Sciences Program (RHSP) is an ongoing initiative to establish the provision of antiretroviral drugs to rural villages in the Rakai District, Uganda, Africa. Since 2004, CMRP has supported RHSP by providing timely assistance with research subcontracting, purchasing, and shipping instrumentation and supplies. The Rakai Project is a NIAID International Center for Excellence in Research (ICER) initiative. An ICER is a laboratory-oriented grant that funds many of the laboratory studies conducted on biospecimens. The primary purpose of the ICER initiative has been to build infrastructure in Rakai, Uganda, for the collaborative conduct of biomedical research with Ugandan scientists.

CMRP provides dedicated personnel to the Rakai Project, both on-site in Africa and off-site in Frederick, MD, to coordinate regulatory activities; support data analysis and manuscript writing for clinical research; provide operational support in the development and implementation of clinical research protocols; manage administrative concerns; provide technical and budgetary oversight of subcontracts; track and monitor budgets; assist with personnel logistics; provide project procurement support; and provide overall coordination of administrative program-level functions.

During the first half of FY2015, a clinical project manager located in Noordhoek, South Africa, provided regulatory and data analysis support to the scientific director. The clinical project manager left the project in March, and a biostatistician based in Botswana was hired. The biostatistician supports the development and analysis of novel, clinical, virological, and immune assay data collected through various NIAID ICER studies conducted within the clinical laboratories and at the Rakai Health Sciences Program research station; performs programming and statistical analysis on a broad range of clinical and laboratory studies; creates databases to produce analysis data sets for assigned projects; maintains expertise in state-of-the-art data manipulation and statistical analyses; performs statistical analyses on data related to research, experimentation, diagnosis, treatment, prevention, and cure of human diseases; consults with investigators on the design and analysis of clinical and observational studies; identifies programming requirements and assists investigators in the development of specialized programs to resolve statistical analysis problems; provides database management support; interacts with clinical and laboratory investigators in processing data, conducting statistical analyses, and writing reports for the Data and Safety Monitoring Board (DSMB) and Institutional Review Board (IRB) requirements; assists the NIAID principal investigators (PIs) in protocol writing, study design, and Case Report Form (CRF) development; actively contributes to manuscript writing; assists the NIAID PIs on protocol implementation; and ensures that the system and program documentation for assigned projects is complete and accurate.

CMRP has provided subcontract management and operational support for two recent protocols for the Laboratory of Immunoregulation: (1) 14-I-N123: Quantitative Measurement and Correlates of the Latent HIV Reservoir in Virally Suppressed Ugandans; and (2) 14-I-N073: Impact of TMP-SMX Prophylaxis on Malaria Infection and Immunity in Children in Uganda. The studies were initiated during FY2014 and continued through FY2015.

The clinical protocol HIV-Accelerated Liver Disease in Uganda (Protocol # 12-I-N037), which began during FY2013 through a Basic Ordering Agreement, completed recruitment in December 2014. This biopsy-based study's purpose is to define the etiology of liver disease and describe the mechanisms of HIV-accelerated liver fibrosis in this rural Ugandan setting. The study recruited volunteers according to plan, and the initial safety and efficacy reviews were successfully completed; follow-up and data cleaning were completed by December 31, 2014. In total, 786 individuals were screened for the study; of the 188 participants who were eligible to complete the liver biopsy procedure, 144 successfully completed the liver biopsy and safety follow-up. Of the 44 eligible subjects who failed to complete the liver biopsy, 23 declined to follow through with the procedure, and 21 were deemed no longer medically eligible by the supervising hepatologist by the time of the biopsy; they were discontinued from the study for safety reasons.

Task Order 4, Protocol 14-I-N123, Quantitative Measurement and Correlates of the Latent HIV Reservoir in Virally Suppressed Ugandans, began recruitment during FY2014. In the spring of 2015, LBRI's Task Order picked up enrollment for this study, which continued through FY2015. This is a cross-sectional, descriptive blood-draw study to measure the size of the latent HIV reservoir in virally suppressed, HIV-infected individuals residing in Uganda and to examine the immunological and virological correlates of the latent reservoir. The investigators aim to compare data on the HIV latent reservoir in this Ugandan population to data collected from U.S. cohorts to better understand the potential for an HIV cure in the African setting.

The study will examine two groups:

- Group 1: 70 HIV-infected patients on ART with suppressed viral loads, defined as fewer than 40 copies per ml, over a period of 10 to 18 months
- Group 2: 10 HIV-infected patients with suppressed viral loads, defined as fewer than 40 copies per ml, over a period of 10 to 18 months, and not on ART (elite suppressors).

During the reporting period, support was provided for logistical and administrative tasks related to daily international operations; budget preparation and monitoring; travel preparation for new hire orientation/training and nonemployee collaboration site visits; and procurement of equipment and miscellaneous laboratory items, requiring coordination and tracking of multiple orders and two ambient shipments to Rakai, Uganda. Procurement of biologicals and lab supplies was also provided for Dr. Thomas Quinn's lab in support of the Rakai project at the Johns Hopkins School of Public Health, resulting in approximately 65 direct shipments.

Laboratory of Parasitic Diseases

Support Provided by the Clinical Monitoring Research Program

The Laboratory of Parasitic Diseases (LPD) conducts basic and applied research in the areas of prevention, control, and treatment of a variety of parasitic and tropical medical diseases of global health importance, including patient-centered research conducted at the NIH Clinical Center. The research efforts of this group are mainly focused on the identification of immunological and molecular targets for disease intervention. LPD also conducts research on eosinophil function, activation, and recruitment, and the role of eosinophil granulocytes in disease pathogenesis. Ongoing studies are exploring therapeutic options for hypereosinophilic syndromes (HES).

CMRP provides nurse case management support, study coordination services, and a physician assistant (PA) to LPD. The nurse case managers order protocol-mandated tests, labs, and procedures, coordinate patient visits, and perform initial assessments. Study coordinators are essential in developing new protocols, completing regulatory requirements to maintain active protocols, and interfacing with the IRB. The PA screens subjects for study enrollment, performs medical histories and physical examinations, obtains various data points needed to support protocol objectives, and provides continuing medical care and follow-up for patients enrolled on protocols. Together, CMRP staff members support 18 active protocols. During the reporting period, 22 site visits occurred, 110 patients were enrolled, 19 continuing reviews, and 9 amendments were completed. CMRP staff oversees weekly clinical eosinophilia and parasitology rounds. This weekly activity provides a thorough review of patients seen by the group in the Clinical Center and involves in-depth discussions of the disease process; supports analysis of new research theories and treatment options, if any; and explores specific diagnostic and therapeutic management approaches to enable formulation of appropriate medical treatment plans, as well as provides fellows with the opportunity to learn more about eosinophilic diseases and parasitic infections.

Earlier this year, LPD experienced a shortage of mid-level clinic providers and nurse case managers, which limited the volume of patients who could be accommodated and delayed nonurgent and nonprotocol-driven visits. Additionally, nurse protocol coordinators and the nurse practitioner were tasked with additional responsibilities previously delegated to other clinic staff. A PA was hired in late September 2014, and two nurse case managers were hired in January and April 2015. The CMRP nurse protocol coordinators created a timeline for training the new nurse case managers. Their approach to acclimating the new staff has eased the transition and improved clinic operations within LPD, so that the customer's needs are better satisfied. The addition of new staff has unburdened the nurse protocol coordinators and nurse practitioner, and has allowed staff members to refocus on their primary roles. Clinic flow has improved, and the backlog of patients is expected to diminish over time. Additionally, enrollment on several IND studies, which had stalled due to staffing issues, has resumed.

These new staff members, in addition to the protocol nurse coordinators, serve as associate investigators on the 18 active protocols within LPD. During the reporting period, enrollment for protocol 14-I-0191, A Multicenter Prospective Natural History Study of Patients Presenting with Neurocysticercosis in North America, was initiated. Screening and enrollment continued for the ongoing IND studies, as well as for the following protocols: 14-I-0063, An Open-Label Proof-of-Concept Study to Evaluate the Safety and Efficacy of Dexpramipexole (KNS-760704) in Subjects with Hypereosinophilic Syndrome; 14-I-0115, A Double-Blind, Randomized Placebo-Controlled Study to Investigate the Efficacy and Safety of Mepolizumab in the Treatment of Eosinophilic Granulomatosis with Polyangiitis in Subjects Receiving Standard of Care Therapy; and 14-I-0081, A Phase II Randomized Double-Blind Placebo-Controlled Study to Evaluate the Safety and Efficacy of Subcutaneous Benralizumab (MEDI-563) in Reducing Eosinophilia in Subjects with Hypereosinophilic Syndrome (HES).

One of the protocol nurse coordinators was involved in the publication of one manuscript and the acceptance of an abstract. Two CMRP staff members earned degrees in FY2015: Tamika Magee obtained a master's degree in healthcare administration, and Sheryce Lassiter earned a bachelor of science in nursing.

Based on discussions regarding cost-savings initiatives in relation to patient travel expenses, the group expects to create a set of guidelines to more appropriately allocate funds for eligible patients for expenses such as taxis.

Laboratory of Malaria Immunology and Vaccinology

Support Provided by the Clinical Monitoring Research Program

In FY2013, NIAID asked CMRP to provide clinical and operational program support, including administration and management of a subcontract, to the Laboratory of Malaria Immunology and Vaccinology (LMIV) for the conduct of a longitudinal clinical study on pregnant women and malaria in Rakai, Uganda. The study is titled Collection of Biological Material from Pregnant Women in a Highly Endemic Region for *Plasmodium falciparum*. Leidos Biomedical Research awarded Task Order No. 01 to Rakai Health Sciences Program in 2014 to conduct this study, which was initiated the same year.

Malaria during pregnancy is associated with low birth weight, maternal anemia, and gestational hypertension; both inflammation and the fetal response to infection may contribute to these poor outcomes.

The study was designed to identify pregnancy malaria vaccine candidates that will elicit antibodies with functional activity similar to that of naturally acquired antibodies. Pregnant women were recruited into a cross-sectional study conducted in Rakai, Uganda. Their biological specimens were collected and stored to perform parasitology studies, immunology studies, and assays on maternal blood, cord blood, urine, and placental tissue. The study ended in January 2015 with an enrollment totaling 933 subjects. Of the 933 subjects, 929 completed the study. CMRP provided ongoing administration and management support, and performed study close-out activities.

Aside from this study, CMRP also provided administration and management support of a subcontract for another LMIV longitudinal clinical study (14-I-N073), Impact of TMP-SMX Prophylaxis on Malaria Infection and Immunity in Children in Uganda, designed to research the effects of drugs that have been shown experimentally to kill the liver stages of the parasite on infection and immunity of malaria in children in Uganda. Leidos Biomedical Research awarded Task Order No. 02 to Rakai Health Science Program to conduct the TMPX-SMX study. Malaria remains one of the most significant causes of morbidity and mortality globally, and recent studies indicate that drugs used in HIV management (e.g., TMPX-SMX) can have antimalarial properties.

The exploratory objectives of the study are to examine the effects of TMP-SMX prophylaxis on measures of malaria infection and immunity, comparing children who are taking prophylaxis to those who are not taking prophylaxis. The study plans to enroll up to 70 HIV-uninfected, HIV-exposed (HUE) children and up to 100 HIV-uninfected, HIV-unexposed (HUU) children. As of May 31, 2015, 136 subjects had been re-enrolled, with 43 subjects in the HUE category and 93 in the HUU category.

In response to LMIV's request, CMRP provided support for all clinical, operational, and administrative aspects of this study, including: (1) the establishment of the scope of the project(s) required for the implementation of the study; and (2) the development of an implementation plan with defined milestones, deliverables, and performance evaluation criteria.

Challenges arose during the pre-award stage of the acquisition process to subcontract with Rakai Health Sciences Program (RHSP) for the TMP-SMX protocol. While the process began during the previous reporting period with a technical and price proposal received from RHSP, LMIV notified CMRP in mid-September 2014 that the effort was being put on hold for an indefinite period to allow protocol review and possible amendment; CMRP informed RHSP about the hold. At the end of November 2014, LMIV decided to proceed with the study under an amended protocol, which stated that the study would start in January 2015, giving CMRP just over a month to initiate and finalize the acquisition process. Staff accommodated the tight timeline, collaborating with the NIAID PI and other NIAID representatives to revise the statement of work (SOW) and pricing requirements and working with Research Contracts (RC) to manage the multiple steps needed to finalize the acquisition. RC issued an amendment to the RFP with the revised SOW and pricing requirements, along with the revised protocol; RHSP had to review and respond to the RFP by submitting a revised technical and price proposal.

CMRP evaluated and approved the revised proposal, and submitted an evaluation report to recommend award to RC. Obtaining a contracting officer approval (COA) from the NCI contracting officer was also required, given that the award would be issued to RHSP, a foreign vendor. This process typically takes about a month; the COA to award a research subcontract to RHSP took more than three weeks. The Task Order award was finalized by the end of January 2015. During the same time period, local IRB review was under way; IRB approval was received at the end of January 2015, coinciding with the Task Order award. The study was activated in February 2015. CMRP's efficient processes to manage the acquisition process and support administration efforts allowed the study to begin and end in the same year.

Laboratory of Virology

Support Provided by the Clinical Monitoring Research Program

The Laboratory of Virology (LV) initiated a collaborative research program with the National Institute for Communicable Diseases (NICD) in Johannesburg, South Africa, to study hemorrhagic fever viruses and other emerging infectious disease viruses. The research initiative involves ecological field studies of hemorrhagic fever viruses, pathogen discovery, and sequencing of viral isolates collected in the field, as well as studies on potential animal intermediate hosts and vectors. The studies include

establishing field research sites in the Democratic Republic of the Congo, Kruger National Park in South Africa, and other sites yet to be determined. LV investigators work closely with their counterparts at NICD in the training and execution of the research objectives.

In support of this collaborative research initiative, CMRP has provided logistical and administrative support that has included budget preparation and monitoring as well as procurement and shipping. During FY2015, quarterly discussions were held with the NIAID customer to review current project activities related to budget and procurement.

Laboratory of Host Defenses

Support Provided by the Clinical Monitoring Research Program

The DIR of NIAID conducts basic and clinical research in a wide range of disciplines related to immunology, allergy, and infectious diseases. The main focus of the Laboratory of Host Defenses (LHD) is to study immune functions essential for host defense against infection, as well as the genetics and pathophysiology of inherited primary immune deficiencies. These abnormalities may be associated with recurrent infections and/or dysfunction of immune homeostasis, which the laboratory investigates in clinical protocols. LHD clinical investigations aim to develop new diagnostic and therapeutic approaches to the management or correction of immune dysfunction.

CMRP specifically provides research subcontract oversight and management as well as program/project management by collaborating with the LHD project lead to develop plans and negotiate subcontracts with various vendors for master cell bank development, safety testing, and, ultimately, vector production.

It is imperative to the study of the immune function and genetic and pathophysiology of inherited primary immune deficiencies to have Good Manufacturing Practice (GMP)-grade, disease-specific vectors produced for use in clinical trials. These vectors must be validated and undergo safety testing to ensure the safety of the subjects. CMRP established several research subcontracts and purchase orders to support LHD and assist with the development of collaborative relationships with various vendors to address scientific immunological questions in a wide range of diseases/dysfunctions, including X-linked severe combined immune deficiency (XSCID) and chronic granulomatous disease (CGD). CMRP previously supported several similar vector productions for other immunological clinical trials (e.g., a GMP-grade clinical lot of lentivirus vector for a clinical trial of gene therapy for XSCID, a GMP-grade clinical lot of lentivirus and/or gamma retrovirus vector for a clinical trial of gene therapy for X-linked CGD). Through a shared services mechanism using the Core Services Accession System, CMRP also supports additional work within Leidos Biomedical Research's Laboratory of Molecular Technology.

CMRP managed a purchase order with the Indiana University Vector Production Facility to perform biosafety testing on a new lot of lentivector CL20-4i-EF1α-hyc-OPT for the ongoing clinical trial titled Lentiviral Gene Transfer for Treatment of Children Older than 2 Years of Age with X-linked Severe Combined Immunotherpay (XSCID). Two purchase orders were managed with BioReliance. The first, established in FY2014, was to perform biosafety testing on the same lot of lentivector mentioned above; the testing was completed in FY2015. A second purchase order was established in FY2015 to perform in vivo and in vitro testing for virus screening of a producer cell line to generate a master cell bank that will produce lentivector under GMP conditions for the clinical treatment of patients with CGD. This involved establishing a subcontract with Clongen to generate the master cell bank for two cell lines (GPRTGp47 and GPRTGgp91) associated with the clinical treatment of CGD patients.

Laboratory of Clinical Infectious Diseases

Support Provided by the Clinical Monitoring Research Program

The Laboratory of Clinical Infectious Diseases (LCID) conducts clinical and basic studies of important human infectious and immunologic diseases. LCID and others have identified adults of Asian ethnicity without HIV infection yet with autoantibodies to interferon gamma (IFNγ); all of these individuals presented with nontuberculous mycobacterial disease and other opportunistic infections. The syndrome was first recognized in 2004. An observational study was launched in 2009 to follow patients with this syndrome, investigate the origins of their autoantibodies, and examine potential immunogenetic factors influencing the development of this disease and other intracellular opportunistic infections. The results of this study could contribute further to the knowledge and understanding of the immunology of mycobacterial and other opportunistic infections in HIV-negative adult hosts.

Through a subcontract with Khon Kaen University, CMRP provided clinical and operational support for the conduct of the study, titled Mycobacterial and Opportunistic Infections in HIV-Negative Thai Patients Associated with Autoantibodies to Interferon-γ." CMRP provided programmatic support for the administration and management of the research subcontract. In addition, the clinical monitoring activities for the study were performed under a separate agreement with a clinical research organization (PPD Task Order 9) and noted under the Clinical Consulting and Support section of this report. The multi-year study was conducted at three sites in Thailand: (1) Ramathibodi Hospital, Mahidol University, Bangkok; (2) Srinagarind Hospital, Khon Kaen University, Khon Kaen; and (3) Siriraj Hospital, Mahidol University, Bangkok. The study closed at

Ramathibodi Hospital and Siriraj Hospital yet remains open at Srinagarind Hospital, Khon Kaen University.

CMRP issued a new agreement to Khon Kaen University to continue follow-up visits for enrolled study subjects through September 25, 2015. The Khon Kaen University agreement was also modified during the reporting period to expand the types of laboratory testing being performed.

CMRP also has a task order–type agreement with PPD to provide clinical trial monitoring activities in support of the study. During the reporting period, the PPD Task Order was extended to cover monitoring activities through September 25, 2015, and modified to include an additional (i.e., second) site-monitoring visit.

Vaccine Research Center

Support Provided by the Clinical Monitoring Research Program

Clinical Trials Program

CMRP and the Vaccine Clinical Materials Program (VCMP) have partnered to address the Vaccine Research Center's (VRC's) business needs that span the technical expertise of two Leidos Biomedical Research directorates. By collaborating within directorates, VRC is able to take its vaccine candidates from manufacturing into clinical trials while maintaining seamless support from Leidos Biomedical Research.

The CMRP–VCMP partnership allowed CMRP to respond to the challenge of initiating two Phase I Ebola vaccine trials in Mali during the height of the disease outbreak by quickly putting a team in place and securing subcontractors. This included hiring a clinical project manager to oversee the project and issuing letters of agreement with subcontractors to begin the work. Several months later, when NIAID director, Dr. Anthony Fauci, tasked VRC with expediting a Phase II chikungunya vaccine candidate, CMRP rapidly managed the study startup, which included site identification, site management, data management, and statistical analysis. The study is on track to meet its aggressive initiation timeline.

Given that this is the first year for both the Mali studies and the chikungunya vaccine trial, CMRP has made significant progress with the scope of activities required to initiate and manage the protocols. Work efforts are described below.

Mali I and Mali II Studies CVD01 and CVD02

CMRP partnered with VCMP to provide full clinical trial support to CVD01, a Phase I trial of a novel monovalent Ebola Zaire candidate vaccine, cAd3-EBO Z, in Malian adults. This study was amended to include the administration of a heterologous live-vector booster product. CMRP and VCMP then partnered to support CVD02, a Phase I trial of the novel bivalent Ebola Zaire and Ebola Sudan candidate vaccine, cAd3-EBO, in Malian adults. The protocol was subsequently amended to include a heterologous live-vector booster product. CMRP established two new research subcontracts to support CVD01 and CVD02 trial activities. The rapid study startup required that the subcontracts be sole sourced and that the work begin under a letter of agreement. CMRP quickly hired a new full-time clinical project manager to support this project.

CMRP entered into an additional round of negotiations with a CVD01 and CVD02 subcontractor in order to ensure VRC gained the maximum scientific value for its research dollar. Because of these collaborative efforts with the VRC, the vendor was able to keep the budget flat while adding 20 study subjects and also adding a boosting regimen to the CVD02 protocol.

Chikungunya Vaccine Trial VRC704

Building upon the successes of the CVD01 and CVD02 trials, the VRC requested the coordinated services of CMRP and VCMP that are related to clinical evaluation of VRC's chikungunya vaccine candidate, VRC-CHKVLP059-00-VP. Services include activities related to the conduct of a Phase II clinical study in the Caribbean. Approximately 400 volunteers are expected to participate. The VRC requested that enrollment be completed during the rainy season, which means Leidos Biomedical Research had to be creative in its rapid approach to conducting the work.

Leidos Biomedical Research's strategic plan to support this work included establishing three new research subcontracts as well as hiring three CMRP staff members. To meet the aggressive study timeline, two of the subcontracts were sole sourced, and one was the result of a limited competition. A limited competition of this complexity typically takes 140 days; this project's limited competition timeline was compressed to 90 days due to the project's urgency.

While putting vendors into place for the VRC 704 study, CMRP worked with Research Contracts to strategically position the limited competition for data management, statistical analysis, and clinical trial monitoring in a way that would maximize cost savings while still meeting the aggressive study initiation timeline. The strategy involved issuing one limited competition that parsed the work into distinct sections, allowing the offerors to bid on one or all sections. The ability to bid on all sections allowed the offerors to demonstrate additional cost savings; this option was made available in part because the team was able to quickly finalize a statement of work and issue the request for proposals without delaying the study initiation milestone schedule.

CMRP's role includes immediate support with clinical site selection efforts and clinical site acquisition (i.e., establishing subcontracts with qualified clinical sites). It also includes management and oversight of clinical sites, ensuring the sites' compliance with all U.S. federally-mandated regulatory requirements and

DHHS/NIH/NIAID policies, as well as subject recruitment, retention, and follow-up. The support also includes providing clinical data management system software for the electronic data capture of all clinical trial data collected for the study. This will be provided in conjunction with supplying statisticians and statistical programming support needed for activities such as preparing the statistics section of the protocol, preparing a statistical analysis plan, and analyzing data for reporting study outcomes and regulatory documents.

CMRP's role also includes support to study specimen collection, processing, management and shipment; pharmacy services; overall project management; and communications management.

Support Provided by the Vaccine Clinical Materials Program

The Vaccine Clinical Materials Program (VCMP) bulk manufacturing group was dedicated to alphavirus hemagglutinin ferritin (HA-F)flu nanoparticles, HIV bnMAb, and plasmid DNA (pDNA) raw material and master cell bank (MCB) production during the first six months of the year. In October 2014, 15 grams of A/New Caledonia raw material pDNA were produced to support bulk substance manufacturing. December 2014 was an active production month with the generation of two MCBs. One *Escherichia coli* bank (112 vials) was manufactured to support A/Singapore pDNA drug substance production. The other MCB (507 vials) was a Chinese hamster ovary (CHO) cell line for production of VRC01LS HIV bnMAb. In addition, one bulk drug substance lot of VRC07-523LS HIV bnMAb was manufactured, producing 3,492 grams. The associated end-of-production cell (EPC) bank (100 vials) also was manufactured during December.

In November and December, three cGMP lots totaling 5,479 vials of cAd3 Ebola Zaire vaccine were produced for GlaxoSmithKline (GSK). These lots were produced in rapid response to support the World Health Organization request to start international clinical trials. In addition, toxicology materials for VRC07-523LS were produced in February.

The last six months in bulk drug substance manufacturing were focused on HIV bnMAb and HA-F nanoparticle production. During this time period, one lot of VRC01LS and three lots of VRC01 HIV bnMAb were produced. In addition, one lot of HA-F A/New Caledonia nanoparticle was manufactured. Drug product manufacturing was dedicated to generating multiple products to support clinical trials. One lot of HA-F A/Singapore was produced. Also, three different HIV bnMAb drug products were vialed: VRC01, VRC01LS, and VRC07-523LS. One lot of 1 percent Alhydrogel® adjuvant was filled to support the trivalent Western, Eastern, and Venezuelan equine encephalitis (WEVEE) virus-like-particle (VLP) clinical trial. Adjuvant filling is a new capability at the VCMP, potentially adding significant value to the success of planned WEVEE clinical trials. The Fill/Finish Group also completed two aseptic media fills.

Quality Control completed method transfer activities to support HIV vaccine manufacture of three monoclonal antibody products: VRC01, VRC01LS, and VRC07523-LS. This included the qualification of Western blot analysis, reducing and nonreducing gel electrophoresis by lab chip technology, potency and identity by biolayer interferometer, imaging capillary electrophoresis, concentration by absorbance at 280 nm, size exclusion chromatography, and residual profile for each clone. Reference standard qualifications and characterization were completed. Additional method transfer and qualification activities were managed, including residual RNA by Ribogreen™ for pDNA, and size exclusion chromatography for WEVEE products. Method qualifications were completed to support New Caledonia as a new HA-F nanoparticle influenza strain. This included size exclusion chromatography, Western blot analysis, potency by biolayer interferometer, reducing gel electrophoresis, and dynamic light scattering. Methods were developed and qualified for aluminum concentration of Alhydrogel, and microorganism identification by genetic sequencing. Seventy-four stability studies were active for drug substance and drug product lots for VLP, HA-F, pDNA, mAb, and cAd3 product types, and buffers.

The following list summarizes the quality control statistics for the year:

- 2,319 raw material, in-process, release, or validation samples were tested
- 29,940 environmental monitoring and utility samples were collected/tested
- 8 analytical methods were developed by or transferred into Quality Control
- 38 analytical methods were qualified
- 2 new analytical instruments were implemented
- 61 stability interim and final reports were approved

During this review period, Quality Assurance (QA) Compliance met with representatives from the Children's Hospital of Philadelphia in support of the rAAV-VRC07 Vector Development Project to review the project status and to meet with their new leadership team. In September, an audit of the Fill/Finish operations was performed and was very complimentary on the VCMP's dedication to quality through its staff, facilities, equipment, operations, and processes.

QA Lot Release reviewed and released 27 lots, including WEVEEV VLPs and HA-F nanoparticle drug substance lots, cAd3 Ebola fills for a subcontractor, and the modified vaccinia Ankara (MVA)-Ebola Zaire master/working viral bank, drug substance, and drug product lots manufactured at another subcontractor site. QA on-the-floor support was completed to provide a real-time production review of the documentation associated with the HA-F, VRC07-523LS, and VRC01LS vaccine campaigns. QA performed GMP audits of critical materials and testing vendors, and

initiated an internal quality management meeting to review quality-based issues at the facility.

QA/Regulatory Affairs (RA) drafted the VRC293 Master File annual report and assisted with the creation of an amendment to the cAd3 Ebola Zaire Investigational New Drug (IND) in support of the Uganda study. Additionally, QA/RA drafted the Chemistry Manufacturing and Controls (CMC) sections for the alphavirus WEVEEV VLP pre-IND and the MVA-Ebola Zaire IND, and compiled the process flow diagrams for the VRC01LS and VRC07-523LS pre-INDs in order to successfully meet the client's timeline for submission to the U.S. Food and Drug Administration (FDA). RA also drafted/compiled responses to FDA's CMC comments for cAd3 Ebola Zaire/Sudan, cAd3 Ebola Zaire, Influenza H7 pDNA vaccines, and provided support for the VRC01 particulate investigation. QA/RA drafted and compiled the CMC section for the HA-F (A/Singapore) pre-IND and the second drug product (DP) lot 14-287 for VRC01. QA/RA is currently drafting and compiling the CMC section for the VRC01LS and VRC07-523LS INDs in the electronic common technical document (eCTD) format. RA also drafted/compiled responses to FDA's CMC comments for Influenza H7 pDNA, VRC01, cAd3-Ebola, and MVA-Ebola vaccines.

Equipment validation completed the qualification of 34 pieces of equipment, including the scientific alarm system (SAS) upgrade and the O_2 and CO_2 bulk gas systems; completed the qualification of an autoclave cycle for 1 percent Alhydrogel; completed the GMP warehouse summer mapping study; executed the qualification of the building alarm system (BAS) upgrade and the requalification of seven isolators; drafted the annual Phase 3 report for the water-for-injection system; and, in coordination with Quality Control and Manufacturing, completed the execution of the cryomed qualification, biological safety cabinet performance qualification (PQ), and the media qualification studies for the cell banking automatic cryo-vial filling unit in Inoculum Prep.

NIAID Extramural

Division of Acquired Immunodeficiency Syndrome

Chinese Clinical Trials Network

Support Provided by the Clinical Monitoring Research Program

NIAID, the lead NIH institute for tuberculosis (TB) research, has developed collaborations with the Chinese Ministries of Health (MOH) and other funding agencies in various countries to conduct high-quality clinical research on TB. With the second-largest TB epidemic in the world and the largest number of patients with multidrug-resistant TB (MDR-TB), China is a major priority. NIAID established a partnership with the investigators currently funded by the Chinese MOH to build a sustainable Chinese research network/consortium for the conduct of multicenter clinical TB studies. It is anticipated that several benefits will be realized from this network, such as: (1) the positioning of China to be a global leader in TB research, with the necessary infrastructure and capacity to conduct high-quality, collaborative clinical research; (2) the establishment of a mechanism by which pharmaceutical companies and other collaborators can more efficiently and effectively launch TB clinical trials in high-prevalence regions; and (3) the potential for the network to serve as a platform to empower and engage the Chinese investigators to develop a scientific agenda that identifies and prioritizes TB research of global health importance.

To foster this collaboration with the Chinese, an integrated approach has been applied that focuses on the following key disciplines: regulatory processes and standards, clinical management, laboratory and specimen management, research pharmacy management, and data management. A framework for assessing capabilities, training to enhance capabilities and address capability gaps, for establishing a clinical research management infrastructure, and for periodically evaluating performance through quality assurance review encompasses all key disciplines. The first phase of the project involved a focus on capacity building and the overall development of the network/consortium infrastructure to support network-wide operations; the second phase involves conducting TB clinical research studies and more fully establishing the network/consortium to advance the network and its sites to a level of operational independence.

The Division of Acquired Immunodeficiency Syndrome (DAIDS) is leveraging Leidos Biomedical Research/CMRP, as an experienced program in establishing international networks, to assist the DAIDS staff in this collaboration with Chinese investigators to build a clinical trials network encompassing multiple sites in China that will conduct studies on MDR-TB.

CMRP supports the mission-critical initiative of creating the Chinese Tuberculosis Clinical Trials Consortium (CTCTC) by providing technical expertise and programmatic oversight. A clinical project manager (CPM) oversees all aspects of program planning and performance; these efforts include project management and reporting, procurement and budget oversight, communications, travel, and logistical support.

From October 28 to November 1, 2014, the CMRP CPM, NIAID DAIDS staff, members of the Chinese leadership/CTCTC, and the subcontractor (Family Health International 360; FHI 360) attended the 45th Annual World Conference on Lung Health in Barcelona, Spain. In conjunction with the conference, CMRP and FHI 360 organized a project team meeting as well as an open-meeting session to allow external partners involved in international TB efforts to meet with the Chinese leadership/CTCTC members to gain knowledge on the development of the newly formed CTCTC and foster potential collaborations.

In collaboration with NIAID DAIDS, FHI 360 sought opportunities to discuss future support to CTCTC with potential partners (e.g., Bill and Melinda Gates Foundation, Janssen).

In February 2015, the FHI 360 China-based team network advisor participated in a scientific review committee meeting for the first clinical protocol using the CTCTC platform; this protocol is a randomized clinical trial comparing the safety and efficacy of a 9-month Clofazimine-containing treatment regimen with that of a standard 18-month regimen in MDR-TB subjects. The principal investigator (PI) of the protocol is a member the CTCTC. The advisor served as the conduit to provide to the committee with protocol-related comments/suggestions from the FHI 360 PI and the NIAID DAIDS branch chief.

In March 2015, CMRP's research subcontract with FHI 360 was updated to add new activities to the statement of work, extend the period of performance, and increase costs. CMRP also worked with FHI 360 on solutions to improve the invoice and report submission process. FHI 360 continued to work with the Chinese leadership on the development of SOPs for the consortium. The SOPs were reviewed and finalized in December 2014.

In July 2015, presentations were given at the 2015 National Conference of the China Medical Association TB Society in Wuhan, China.

New clinical sites were included by the Chinese leadership as members of the CTCTC. In January–February 2015, CMRP staff oversaw FHI 360 as they organized and conducted assessments of four additional sites, in addition to the six sites previously assessed. Following the site assessments, FHI 360 coordinated with Dr. Kathy Eisenach (through a subcontract with Westat/NIAID DAIDS) to conduct lab assessments in August 2015 for these four sites to determine capacity and readiness to conduct new drug trials.

Per guidance from Leidos Biomedical Research and NIAID DAIDS, FHI 360 identified and prioritized a list of critical activities needed to launch the Clofazimine (CFZ) study, and looked into tools that should be created or shared with the protocol PI in preparation of study-start. To support the upcoming trial, FHI 360 provided biostatistical support by reviewing the protocol and offering suggestions. FHI 360 coordinated the review and provided suggestions to the PI for the study case report forms and shared a sample data management plan with the PI. In April 2015, the China-based FHI 360 team participated in the Investigator's Meeting for the study protocol; the team provided training on standard operating procedures (SOPs) and quality management topics. FHI 360 also developed, in collaboration with Leidos Biomed and NIAID DAIDS, a Minimum Standards List (including lab, data, and clinical checklists) for the network and a Clinical Quality Management Plan (CQMP).

During this reporting period, FHI 360 conducted, coordinated, or facilitated training sessions to address the following topics:

- Scientific Webinar (January 2015)
- Good Clinical Practice and Data Management Webinar (May 2015)
- Site Visit in Cape Town and Johannesburg, South Africa (September 2015). The goal of this meeting was for Dr. Li Liang (part of the Chinese leadership) and other key CTCTC members to gather information on project planning and collaborative research in a network setting.
- Study Design and Biostatistics Training (September 2015)

OTHER INSTITUTES WITHIN THE NIH

Clinical Center

Support Provided by the Clinical Monitoring Research Program

District of Columbia Partnership for HIV/AIDS Progress

In 2008, the District of Columbia Partnership for HIV-AIDS Progress (DC-PFAP) was launched with the Washington, D.C., Department of Health to make Washington, D.C., a leader in the response to the HIV/AIDS epidemic. This partnership brings together the nation's leading health research institution, the district's universities, and community-based health care providers to provide D.C. residents with new ideas, services, and access to clinical research. The partnership draws upon a diverse portfolio of academic institutions, community-based organizations, and stakeholder groups for the design and implementation of specific projects and activities. CMRP has played a major role in implementing this partnership, from initial and subsequent staffing to daily program implementation.

During 2014, a Yellow Task (YT) was submitted to de-scope the work being conducted by Leidos Biomedical Research in support of the DC-PFAP initiative. The project was closed out in two phases during FY2015. During Phase 1, the support provided by the clinical staff was phased out by November/December 2014. This support included managing clinical studies, and providing health care professional and administrative personnel to enable the operationalization of protocols from concept to publication. Phase 2 included phasing out all research subcontracts in accordance with the available budget. The clinician investigator/physician supported several protocols, as outlined below.

During FY2015, three protocols were ongoing:

The first, the SYNERGY study (protocol 13-I-0066), is an eight-arm study designed to examine the efficacy and safety of combination DAA oral agents for the treatment of hepatitis for 4, 6, 8, or 12 weeks. During the reporting period, enrollment for the two ongoing arms was completed, and the patients were followed by DC-

PFAP staff. The ongoing study arms were (1) Arm F, comprising 25 treatment-experienced, cirrhotic patients receiving six weeks of combination DAA therapy; and (2) Arm D, which studies the efficacy of 12 weeks of DAA therapy in patients previously unsuccessfully treated with DAA therapy. Eighty percent of the SYNERGY subjects were recruited from, and have their study visits in, the DC clinics. A DC-PFAP physician presented preliminary data from this study at the European Association for the Study of the Liver in November 2014. Four patients were enrolled to Arm F and 34 enrolled to Arm D of this study during this reporting period, bringing the total number of patients enrolled in Arm F to 25 and the total number enrolled to Arm D to 34.

The second study, The Natural History Hepatitis Prospective Cohort Study (protocol 11-CC-0152), continues to be a robust protocol conducted in the D.C. clinics, and recruited heavily during the reporting period. Currently there are 503 subjects enrolled on this protocol, the majority of whom were referred from the DC clinics. During this reporting period, 223 patients were enrolled in this study.

The Safety, Tolerability, and Efficacy of Asunaprevir and Daclatasvir in Subjects Coinfected With HIV-HCV, also known as the CONQUER study (protocol 14-CC-0065), led by the clinical investigator, the ICMOB/NIAID physician who works closely with the DC-PFAP, continues recruitment, with 25 patients currently enrolled out of projected sample size of 30 participants. Approximately one-third of the participants were recruited from the DC-PFAP clinics. It is anticipated that the study will be fully enrolled by June 2015, and the majority of these patients will have completed the investigational drug and be followed through the end of the reporting period. During this reporting period, 15 patients were enrolled in this study, bringing the total number of patients enrolled to 25.

Also during this reporting period, seven agreements, including research subcontracts, blanket orders, and purchase orders, were fully invoiced, paid out, and closed. Leidos Biomedical Research staff successfully managed the close-out of support to the DC-PFAP, balancing available funding with specific subcontract requirements and deliverables. In addition, the Leidos Biomed team worked successfully with the government customer to ensure efficient communication regarding study timelines and feasibility of subcontractors completing study-related tasks within scope and budget. Future support to the DC PFAP initiative will be undertaken through the support of the physician/clinician investigator supported through the ICMOB/NIAID.

During this reporting period, there were several changes to key staff working with the DC-PFAP program, both within this contract and from the customer side, with the majority of the program moving to University of Maryland on November 17, 2014. The remaining support staff, including the physician and protocol nurse coordinator, concluded their Leidos Biomedical Research employment on January 2, 2015. The clinician investigator/physician (ongoing employee serving on behalf of NIAID DCR's ICMOB) oversaw the support provided by MMG, Unity, and Family Medical programs in conjunction with the clinical project manager and senior special projects administrator. Planned changes in staffing were accomplished with no disruption of clinical studies. The DC-PFAP experienced some funding challenges, resulting in the need to reduce the period of performance for the MMG subcontract and the Howard University research subcontract. The Leidos Biomedical Research administrative team, including the clinical project manager and the senior special projects administrator, continued to monitor the budget against the funding to ensure funding was spent down as the Leidos Biomedical Research support to this initiative wound down.

During this reporting period, CMRP presented information regarding the above-mentioned ongoing DC-PFAP studies to audiences at the American Association for the Study of Liver Diseases in November 2014 and at the European Association for the Study of the Liver in April 2015.

District of Columbia Partnership for HIV/AIDS Progress, Neurocognitive Initiative

DC-PFAP established a Neurocognitive Initiative in FY2013, charged with evaluating how HIV affects thinking, memory, and concentration. These neuro-cognitive disorders range in severity and are a feature of HIV/AIDS despite antiretroviral therapy. The DC-PFAP Neurocognitive Initiative is a multi-institute collaboration involving investigators from the Critical Care Medicine Department, NIAID, National Institute of Neurological Disorders and Stroke (NINDS), National Institute of Mental Health (NIMH), National Eye Institute (NEI), and National Institute on Aging (NIA).

The program comprehensively performs both short-term and long-term assessments of neurocognitive function in cohorts of HIV/AIDS patients by combining perspectives of the various partnering institutes. The ultimate goal of the program is to develop interventions to improve neurocognitive function and/or slow neurocognitive decline in HIV-infected individuals.

A protocol nurse coordinator manages the regulatory operations of the two protocols supported by the Neurocognitive Initiative. During FY2015, the NIH IRB approved two amendments and two continuing reviews. The HIV-Associated Neurological Disorders protocol was terminated at the MedStar Washington Hospital Center due to low recruitment from this site. The study site termination was submitted on January 8, 2015, and processed by the MedStar Washington Hospital Center IRB.

The Neurocognitive Initiative team pre-screened 348 potential participants and enrolled 103. The protocol nurse coordinator coordinates the participants' multidisciplinary study visits, and manages the collection and organization of data from patient evaluations. The protocol nurse coordinator also communicates results to

study participants and arranges clinical follow-up needs with the primary care or infectious disease physicians. The Neurocognitive Initiative team continues to develop new protocols.

One research subcontract with Matthews Media Group is managed by the clinical project manager and senior special projects administrator in collaboration with the protocol nurse coordinator to support patient recruitment to the various clinical studies and patient transportation to NIH. In addition, the clinical project manager and senior special projects administrator manage the DC-PFAP Neurocognitive Initiative budget and work closely with the government project lead and Administrative Office to ensure the money is spent effectively.

The National Eye Institute (NEI) joined the Neurocogitive Initiative in May 2015 as a new intramural collaborator on protocol 13-N-0149, titled Screening and Recruitment for HIV-Associated Neurocognitive Disorders (HAND) Studies and An Evaluation of HIV-Associated Neurocognitive Disorders in Virologically Controlled Patients. Participants in this protocol are now offered an optional yearly eye exam with the NEI clinic. During this visit, patients are assessed for age-related macular degeneration, which could potentially be accelerated in the HIV-positive population.

A new protocol, titled Anakinra, a recombinant human IL-1 Receptor Antagonist for Neuroinflammation in HIV-1 Infection, was developed, written, and submitted to the IRB. This is the Neurocognitive Initiative's first intervention protocol. It is a Phase I study determining the safety of using anakinra over eight weeks in patients living with HIV as well as its potential to reduce neuroinflammation.

The Neurocognitive Initiative team remains cost-conscious and consistently looks for ways to reduce redundancy and unnecessary costs. For example, if an HIV-positive participant already has a documented positive HIV test on record at NIH, the test will not be reordered. The same applies for HLA-typing, as this is a very expensive genetic test, and the results will not change over time. In addition, if a patient participates in multiple protocols, the study team makes every effort to work with the other protocol teams to combine resources, including travel costs and overlapping blood work.

One challenge that has persisted during FY2014 and FY2015 is the execution of carotid artery MRI scans for protocol 12-CC-0200, Neurovascular Magnetic Resonance Imaging in the Assessment of HIV-Associated Neurocognitive Disorders. The primary objective of this protocol is to compare carotid artery wall thickness in HIV-positive with that of HIV-negative individuals; therefore, this carotid MRI is critical to the protocol. The MRI technique for this specialized exam is difficult to execute, and these difficulties have halted the protocol's progress in the past. The Neurocognitive Initiative team collaborated to provide resources necessary to facilitate technology development and logistical scheduling. The first carotid MRI was performed on November 25, 2013; however, due to personnel changes, this imaging was placed on hold. The Neurocognitive Initiative team, championed by the PI, identified other radiology collaborators and now these scans are being performed smoothly.

During FY2015, the CMRP financial program manager worked diligently with the Leidos Biomedical Research Finance Office, the government project lead, and the government Administrative Officer to provide accurate and timely estimates at completion for the FY2015 and FY2016 budgets years.

A particularly significant accomplishment is the progression of collaboration with investigators from the DoD, who are executing a parallel, "sister" protocol to the Neurocognitive Initiative's study 13-N-0149, Screening and Recruitment for HIV-Associated Neurocognitive Disorders (HAND) Studies and An Evaluation of HIV-Associated Neurocognitive Disorders in Virologically Controlled Patients. Enrollment in the DoD parallel protocol began in the summer of 2014; however, logistics to complete the research-indicated brain MRI imaging at the NIH Clinical Center (and interpretation by Clinical Center radiologists) for Walter Reed National Military Medical Center patients were not yet in place. The first brain MRI on a DoD participant was completed at the Clinical Center on January 6, 2015, and the process is now running smoothly. The protocol nurse coordinator facilitates the logistics, allowing DoD participants to be registered as NIH patients and scheduled for MRIs, and communicates results to the necessary parties.

National Eye Institute

Support Provided by the Applied and Developmental Research Directorate

ADRD's Clinical Support Laboratory (CSL) provided ELISA-based cytokine testing of vitreous fluid and eye-wash specimens in support of Dr. Chi Chao Chan, chief, Immunopathology Section, Laboratory of Immunology, and head, Histology Core. Approximately 34 ELISAs were performed, with most requests involving the testing of IL-6 and/or IL-10. Many samples were submitted individually, with requests for rapid turnaround of test results. Additional testing requested included a single request to test 114 samples for IL-17A.

National Institute of Neurological Disorders and Stroke

Support Provided by the Applied and Developmental Research Directorate

ADRD's CSL provided sample processing support for Protocol 12-N-0137 under YT13-110. A total of 17 samples were received from eight patients, resulting in the storage of 37 vials of PBMCs. Sample collection is for future ELISPOT testing in the Laboratory of Cell-Mediated Immunity.

BioProcessing Laboratory: The BioProcessing Laboratory provided support to two National Institute of Neurological Disorders and Stroke ancillary Phase II clinical trials:

- Biomarkers in Multiple Sclerosis study. The BioProcessing Laboratory presented pilot study to describe the quality and usability of DNA and RNA in long-term storage at the NCI at Frederick Central Repository at the NICBR Spring Research Festival.
- Biomarkers in Myasthenia Gravis study. The BioProcessing Laboratory continues to provide kits and receive blood specimens for this Phase II clinical trial. The laboratory has also assisted in reconciling clinical and specimen data from 2006 to 2015. This study will conclude specimen collection in fiscal year 2016.

Support Provided by the Clinical Monitoring Research Program

The National Institute of Neurological Disorders and Stroke (NINDS) conducts and supports research on brain and nervous system disorders and has occupied a central position in the world of neuroscience for more than 50 years. The mission of NINDS is to reduce the burden of neurological disease by supporting and conducting basic, translational, and clinical research on the normal and diseased nervous system. The institute also fosters the training of investigators in the basic and clinical neurosciences, and seeks better understanding, diagnosis, treatment, and prevention of neurological disorders.

NINDS clinical research applies directly to mechanisms of the diseases of the nervous system, which can then be translated into disease detection, prevention, and treatment, including studies of brain imaging techniques, trials to test new drugs, and development of novel therapies, such as stem cell implants and gene transfer. Some key areas of NINDS clinical research include: neurological consequences of AIDS; Alzheimer's disease; brain tumors; developmental disorders; epilepsy; motor neuron diseases; muscular dystrophies; multiple sclerosis; neurogenetic disorders; pain; Parkinson's disease and other neurodegenerative disorders; sleep disorders; spinal cord injury; stroke; and traumatic brain injury.

CMRP provides regulatory, programmatic, logistical, and administrative support for clinical trial operations at NINDS. This support allows for streamlined protocol development and review, and provides NINDS with flexibility for emerging/fluctuating needs, eliminates costly time delays, and ensures the success of the program's mission. In a phased approach for supporting various NINDS activities, CMRP writes clinical protocols, informed consent forms (ICFs), and other clinical documents, including formatting and adding administrative language; liaises on regulatory issues with sponsors, the FDA, the Office for Human Research Protections (OHRP), and other regulatory bodies; and develops, assembles, submits, and maintains IND applications with the FDA.

The CMRP team supporting NINDS comprises a CMRP senior manager; a CSO director with expertise in protocol document development, clinical research methodology, and IRB requirements; as well as the regulatory affairs director and an experienced regulatory associate, both thoroughly versed in the process of IND development and submission, and FDA review.

The Regulatory Affairs group continues to provide support for the NINDS giant axonal neuropathy (GAN) gene therapy team by consolidating and submitting responses to FDA's request for information in March 2015. This submission also contained the IRB-approved protocol and the following CMC section revisions: Container and Closure; Description of Manufacturing Process and Process Controls; and Analytical Procedures. These sections were revised in response to comments received from the FDA.

Regulatory Affairs prepared the initial annual report for the GAN gene therapy IND and, following input, review and approval by NINDS, submitted the report to the FDA in July 2015. The intent of the annual report is to inform the FDA of any adverse experiences with the investigational product, any significant manufacturing or microbiological changes, the status of the study in progress, including the total number of study subjects enrolled, and the number of study subjects who completed or have discontinued the study.

The first study subject was enrolled and received treatment in May 2015. The FDA requested that a single study subject be administered the therapeutic agent to ensure safety and effectiveness of the test article prior to enrolling additional subjects. After treatment for this initial patient is evaluated and a rigorous assessment of the safety data is performed, the study team plans to enroll 3–5 additional patients five years of age or older.

The Regulatory Affairs group will also be preparing an IND Information Amendment when data are available for submission to the FDA. Additional biocompatibility testing was required due to a change in the source and manufacturer of tubing used for intrathecal infusion. The results of the biocompatibility testing indicated that the therapeutic agent does not bind to the new tubing; these study results will be submitted to the FDA once NINDS has finalized the SOP for the vector preparation and administration of the therapeutic agent using this new tubing.

National Institute of Environment Health Sciences

Support Provided by the Applied and Developmental Research Directorate

ADRD's CSL provided ongoing support to four studies. Support included preparing and shipping specimen collection kits to trial participants; receiving and processing clinical specimens; extracting DNA; and preparing invoices for National Institute of Environment

Health Sciences (NIEHS)–authorized payment of participants and physicians. Multiple specimens were received from approximately 100 patients or family members. In response to YT15-071, the laboratory worked with the Data Management Group to define changes to the patient database necessary to allow NIEHS to enter specimens into the Biological Specimen Inventory system. The database changes were implemented at the end of FY2015.

National Institute of Dental and Craniofacial Research

Support Provided by the Applied and Developmental Research Directorate

In response to CSAS-17612, the Laboratory of Cell-Mediated Immunity performed one set of three- and six-day proliferation assays to evaluate the proliferative response of cells from normal donors against mitogen phytohemagglutinin and a pool of allo-stimulator cells in a mixed lymphocyte culture, in the presence and absence of bone marrow stromal cells at multiple concentrations. A total of 66 tests were performed.

National Institute of Arthritis and Musculoskeletal and Skin Diseases

Support Provided by the Clinical Monitoring Research Program

The mission of the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS) is to support research that will lead to the promotion of knowledge and understanding of the causes, treatment, and prevention of arthritis and musculoskeletal and skin diseases. Toward this effort, the NIAMS Intramural Research Program conducts studies in natural history and treatment, as well as basic investigations of the etiology and/or pathophysiology of rheumatoid arthritis, systemic lupus erythematosus, ankylosing spondylitis, vasculitis, scleroderma, myositis, osteoarthritis, and other inflammatory/rheumatic diseases. Currently, NIAMS has 27 active studies that vary from screening and training to natural history and Phase I and II clinical trials. At this time, two of these protocols are being conducted under IND applications.

CMRP provides protocol review services and regulatory and clinical trials management support to allow NIAMS to streamline protocol development time, provide flexibility for emerging/fluctuating needs, eliminate costly time delays, and ensure the success of the their clinical mission. CMRP staff supports clinical research operations for NIAMS IND Phase I and Phase II clinical trials, including protocol and informed consent form writing, regulatory guidance and compliance, training, and clinical trials management, including case report form review and monitoring activities. Staff members also assist with document creation, data collection, and compilation for regulatory submissions (pre-IND, IND) to the FDA and other regulatory authorities, and technical review and report preparation.

In addition to regulatory and monitoring support, CMRP also provides clinical nursing and administrative support. CMRP patient care coordinator staff provides clinical support that includes assistance with scheduling appointments for the patients' routine clinical visits and serving as liaison between physicians, nursing staff, and other departments. CMRP staff maintains identification and demographic data for each patient, as well as other pertinent patient information required prior to an appointment or admission.

Clinical Trials Management (CTM) staff continued to provide NIAMS staff with information on how to best document data in the clinic charts and provided guidance on investigators' responsibilities in overseeing an FDA-regulated IND clinical trial. CTM is currently tasked with monitoring six active NIAMS studies, including two IND studies, and began monitoring eight additional studies at the end of FY2015 as a result of the audit of the natural history NOMID study (03-AR-0173), which CTM completed in September 2014. Following this audit, a meeting was held with the PI to discuss findings, and the NIAMS clinical director and clinical operations manager requested that CTM monitor additional natural history studies. Additionally, CTM has been requested to monitor the NOMID natural history study at least three times per year. To fulfill this request, CTM developed a monitoring plan, and the first monitoring visit was conducted in March 2015.

During FY2015, CTM and the Regulatory Affairs group began to provide support for the following studies: (1) Natural History, Pathogenesis and Outcome of Idiopathic Systemic Vasculitis; (2) A Pilot Use of Antiretrovirals in Aicardi Goutieres Syndrome; and (3) Safety of Tofacitinib, an Oral Janus Kinase Inhibitor, in Systemic Lupus Erythematosus: A Phase Ib Clinical Trial and Associated Mechanistic Studies (SAFE-JAK-IN-LUPUS).

In April 2015, the Regulatory Affairs group prepared and submitted an IND annual report to the FDA, to provide cumulative demographics, safety, and other information from the study of anakinra in Behcet's disease (protocol 11-AR-0241). In June 2015, an IND annual report covering two IND studies evaluating rilonacept—one in subjects with autoinflammatory disease (IL-1 TRAP study; protocol 05-AR-0014) and the other in subjects with deficiency of the interleukin-1 receptor antagonist (DIRA; protocol 13-AR-0086)—was prepared by the Regulatory Affairs group and submitted to the FDA.

Support Provided by the Applied and Developmental Research Directorate

ADRD's CSL performed EBV transformation of B cells from four subjects in response to CSAS-16902 and -16967.

National Institute of Mental Health

Support Provided by the Clinical Monitoring Research Program

CMRP provides protocol development/navigation, regulatory guidance/support, clinical trials management support, and data and safety monitoring for intramural clinical research protocols being conducted by the National Institute of Mental Health (NIMH). The protocol navigation manager works with the NIMH PIs and clinical study staff to ensure protocols and ICFs are consistent with policies that govern human subject research.

This protocol navigation manager is also responsible for managing, tracking, and coordinating associated regulatory activities and protocol writing support, and for providing expert-level regulatory guidance to PIs, key medical staff, and clinical study staff during conception/development, as well as in all actions of a protocol life cycle, including continuing review applications, bioethics reviews, protocol amendments, and applicable Data Safety Monitoring Board (DSMB) reviews.

The protocol navigation manager assists and liaises with PIs on regulatory issues with the sponsor, the FDA, OHRP, and other regulatory bodies as applicable. The protocol navigation manager acts as a liaison between clinical monitors, clinical research sites/laboratories, regulatory agencies, vendors, and other applicable internal departments. The protocol navigation manager also provides oversight and support to the PIs for IRB initial reviews, continuing reviews, ICFs, and responses to stipulations, as well as for regulatory documentation, including clinical report writing, FDA Investigational Device Exemption/Investigational New Drug (IDE/IND) serial submissions, safety reporting, and annual FDA reporting.

The protocol navigation manager continues to add significant value to the protocol development process by providing protocol services related to protocol and consent drafting and logistics management, and assisting new and experienced clinical investigators. The protocol navigation manager assists PIs in editing clinical protocols in any stage of document development, including study concepts, initial review, informed consent documents, amendments, SOPs, and continuing reviews. During protocol development, the team collaborates with PIs to ensure compliance with regulatory requirements, NIH policies, and project timelines, as well as to enhance the overall accuracy and quality of content.

The CMRP Protocol Navigation Management Program was initiated on March 10, 2014, and is made up of 115 protocols, of which 92 are active and 23 are in data analysis only. In addition, another nine protocols are in the review process and could go active in the coming months.

The program activities include managing, tracking, and coordinating associated regulatory activities for each of the 115 protocols. Each protocol requires yearly regulatory oversight in the form of a continuing review (CR), which requires a coordinated effort between the protocol navigation manager, medical writer, research staff, and the IRB. The CRs are deadline driven and require quick and accurate responses to any IRB-generated tasks prior to and after the CR review.

The protocol navigation manager also provides protocol writing support and expert-level regulatory guidance to PIs, key medical staff, and clinical study staff during conception/development and ongoing protocol maintenance as protocol templates are updated or new regulatory guidance is warranted.

The protocol navigation manager also provides assistance with protocol-related activities, including scientific committee reviews, when appropriate, protocol amendments, and applicable DSMB reviews. The protocol navigation manager serves as the executive secretary to DSMB and provides technical and operational management for all DSMB activities, including preparing the DSMB meeting documents, coordinating conference calls, and taking meeting minutes.

The protocol navigation manager attends the weekly IRB meetings to gain insight into new and ongoing regulatory issues and to build relationships with the IRB members in an effort to better support the NIMH project. The protocol navigation manager attends bimonthly meetings with the NIMH team members as applicable, providing updated status reports on clinical/regulatory activities, data quality, and FDA/IRB and DSMB submission timelines.

Additionally, the protocol navigation manager supervises the medical writer, which includes overseeing the writer's workload and schedule, as well as reviewing the work deliverables for quality, accuracy, and timeliness. The protocol navigation manager performs the medical writer's yearly performance review and assists the medical writer III with any training or development needs. The protocol navigation manager provides feedback on employee performance on an ongoing basis and also guides and mentors them.

The protocol navigation manager has reviewed the existing and pending protocols, with assistance from the associate deputy to the clinical director, and has prioritized the workload based on the protocols that are the most time sensitive, and have the greatest need for protocol navigation assistance. The most time-sensitive work for the NIMH project is making sure the continuing reviews are submitted on time. During the reporting period, 108 continuing reviews have been completed or initiated by the Protocol Navigation team (PNT), and by September, 129 continuing reviews will have been

initiated or completed. A process for preparing and submitting CRs has been established and will be modified as needed. The PNT also assisted with seven study closures during this reporting period. In addition, the share drive that was set up at the protocol navigation manager's request continues to be maintained. This share drive has allowed the protocol navigation manager, the medical writer, the associate deputy to the clinical director, and the clinical director to view and share NIMH-related documents. The share drive provides a stable platform for all NIMH-related documents, such as protocols, amendment, ICFs, CR information, templates, and training folders that are network based and are backed up regularly. In addition, the NIMH training database established by the protocol navigation manager continues to be updated and maintained by the PNT. This database provides a convenient location where all of the NIMH PIs' and AIs' training information can be located. This has helped, and will continue to help, the PI/AIs remain compliant with training requirements needed to conduct clinical research studies. This training database also streamlines the CR process, which limits the time the protocol navigation manager has to spend looking up training information. In addition, a site on the NIMH SharePoint website has been approved for use by the protocol navigation manager. This SharePoint site is in the early stages of development and will serve as a repository for all of the current versions of the NIMH protocols and ICFs. Having one location to access the protocols and consents will stabilize the version control challenges that have been an issue with this project. In addition to protocols and ICFs, templates and other relevant information will be stored on the SharePoint site. This will also benefit the group by providing a more appropriate storage location for protocols and ICFs that are currently stored on the PI's computer or on the PTMS website. Lastly, a PNT user's guide has been developed to provide all the details that are needed for navigation support to NIMH. This guide is being used as a reference for QA/QC practices and will be used as a training manual for future PNT members.

To date, CMRP staff has improved the continuing review process by helping the investigators navigate a new submission process with new submission forms. This new process has reduced the number of pre-review stipulations and IRB meeting stipulations. As a result, many more continuing reviews have no stipulations. For example, four continuing reviews were approved at the last IRB meeting without any stipulations.

During this reporting period, CMRP also improved the amendment and initial review processes. Currently, amendments are approved with multiple stipulations, which extends the time to approval. The goal is to decrease the number of stipulations issued by the IRB. During the reporting period, CMRP staff supporting the NIMH has helped the study team initiate, complete, and review their protocol amendments and initial reviews. During the last reporting period, the turnaround time for initial reviews was approximately 12 months; in this reporting period, it has been reduced to approximately 240 days, or 8 months. The ultimate goal is to reduce the turnaround time to less than 200 days. These improvements in turnaround time will improve efficiency and lead to cost savings.

National Heart, Lung, and Blood Institute

Support Provided by the Clinical Monitoring Research Program

CMRP services provided to the National Heart, Lung, and Blood Institute (NHLBI) have resulted in the rapid deployment of clinical services for time-sensitive, critical clinical research. Acquiring these services through CMRP has helped streamline protocol development time, provide flexibility for emerging/ fluctuating needs, eliminate costly time delays, and ensure the success of the NHLBI clinical mission. These services complement those that CMRP already provides to other NIH clinical research programs. The CMRP staff support to the NHLBI protocol navigation team (PNT) located at the NIH currently consists of a clinical project manager and five protocol navigators, who, along with the clinical project manager, manage 220 clinical protocols. In addition, the clinical project manager oversees the proper submission of all 220 NHLBI clinical protocols to the IRB and FDA, as applicable.

For this reporting period, the CMRP services for the NHLBI have centered on regulatory compliance and protocol navigation; NHLBI support included data/document collection and compilation for regulatory filing (pre-IND, IND, IDE) with FDA and other regulatory authorities as needed; technical review and report preparation; protocol navigation support, administrative coordination, and general logistical support for regulatory activities; training; and other services as required.

During FY2015, the clinical trials director continued to have regularly scheduled calls with the government customer and provided monthly metrics and financial data updates. The clinical trials director met with the protocol navigation manager regularly to discuss updates, NHLBI strategies, and issues that were being encountered, as well as work distribution.

CMRP staff frequently met with the PIs assigned to them to discuss their clinical research needs. Numerous PIs, including four new senior investigators, one of whom being the new branch chief for the newly created Sickle Cell Disease Branch, have taken advantage of talking with the PNT to discuss their unique research and regulatory requirements and to enlist the team's assistance with the development of their new clinical research program.

To continue to meet the requirements for this initiative during this review cycle, CMRP hired one new protocol navigator in May 2015. The protocol navigator spent the last four months of this reporting period assisting the PNT with ongoing and new protocol management activities,

while assuming the navigation responsibilities for several ongoing clinical protocols primarily supporting investigators in the Cardiovascular Branch.

To date, the PNT has been instrumental in providing comments to the staff of the NHLBI Office of the Clinical Director (OCD) on the following: DIR Clinical Research QA and QC audit review SOPs; DIR policies; NIH policy changes; NHLBI protocol navigation SOPs; and updates on the status of clinical research development plans for multiple research teams.

This last reporting period has seen a larger-than-usual growth of studies associated with the NHLBI IRB. This is because, along with the approximately 20 studies that are submitted every year by various investigators, nine studies already under way were transferred from the NIDDK IRB to the NHLBI and were assigned to a protocol navigator, who also assisted in the transfer of the studies and the files to ensure a smooth transfer.

Overall services provided by the protocol navigators in support of the NHLBI PN Office include: (1) preparing or assisting in the preparation of draft study protocols, in collaboration with PIs and the research team; (2) writing/ editing, as appropriate, sections of IND/IDE submissions, as well as providing information and guidance on the process; (3) reviewing and editing protocol documents to ensure that regulatory requirements are met; (4) working with clinical research teams and data managers to compile data for reports; (5) processing and managing final documents, including uploading documents into different systems, routing documents for signatures, and sending reminders for continuing review documents, protocol/ ICF amendment documents, and protocol deviations, assisting PIs with responses to IRB stipulations, and addressing unanticipated problems; (6) working with the clinical research teams to submit requests for informed consent short forms and informed consent translations; and (7) working with the Deputy Ethics Clearance Office (DEC) and NIH Ethics Office (NEO) to ensure "covered" protocols undergo proper clearance.

Overall support to the NHLBI OCD and PIs from the clinical project manager includes: (1) managing the quality of the FDA regulatory submissions generated in the PN Office; (2) serving as a liaison between the PN Office, and the Office of Clinical Affairs (OCA) and/or OCD; (3) serving as the liaison between the PN Office and the data management and monitoring contractors; (4) providing first-line assistance with clinical protocol design for less-experienced clinical investigators; (5) implementing processes within the PN Office to ensure the quality and uniformity of the documents generated by the protocol navigators; (6) serving as the regulatory manager for a high-profile multicenter IDE study sponsored by the NHLBI and comprising 20 clinical sites; and (7) serving as the NHLBI expert on data entry into the newly implemented IRB submission database, iRIS, assisting both NHLBI and non-NHLBI investigators who submit their studies to the NHLBI IRB with their submissions.

During this reporting period, the NHLBI PN Office continued to successfully implement improvements in the office dynamic and its interaction with members of the OCA and of the OCD, as well as with the intramural NHLBI investigators. In March 2015, a protocol navigator who was the only government FTE in this position, left the team, and the clinical project manager reassigned five of the navigator's 32 clinical protocols among the remaining team members and temporarily kept the remaining 27 studies under her oversight, enlisting the assistance of the PNT as needed. With this approach, the PIs of those protocols were more willing to be once again reassigned to a new protocol navigator as they knew that the manager was only temporarily covering for the position. In addition, working closely with these investigators provided the PNT valuable insight into how the teams worked, allowing for more comprehensive training of the new CMRP protocol navigator, who was hired in May 2015.

Thirteen SOPs have been developed for the NHLBI PN Office. The five CMRP protocol navigators and the clinical project manager have played a role in either drafting, providing input, or performing QC review of all 13 SOPs, which have been approved and implemented by the NHLBI DIR OCD. For this reporting period, the clinical project manager participated in the training of the protocol navigation group on the three most recently finalized NHLBI NP SOPs.

There are currently 17 INDs and 5 IDEs, and 34 FDA-regulated protocols within these IND/IDEs, which are managed by the NHLBI PN Office. The other 186 NHLBI protocols managed by Leidos Biomedical Research protocol navigators are non-FDA-regulated protocols and range from treatment protocols investigating off-label use of approved agents to natural history studies and training protocols.

During the reporting period, the following regulatory (FDA) submissions were handled by CMRP NHLBI protocol navigators on behalf of, or in collaboration with, NHLBI investigators: 1 IDE submission; 4 IND submissions (one was deemed exempt by the FDA); 2 emergency IND requests; and 28 amendment submissions for active INDs/IDEs. In addition, one IND study was transferred to the NHLBI, and this IND is now managed by a protocol navigator II. One IND was terminated during this reporting period, and one IND was transferred to an investigator now at Montefiore Hospital, New York.

During the reporting period, protocol navigators have been involved in and/or have submitted the following: (1) IRB submissions that include 19 initial/new protocols, 165 IRB-drafted continuing reviews, 253 protocol amendments, 227 NIH problem report forms (includes deviations and SAEs); (2) 30 DMSB reports; and (3) 8 Office of Human Subject Recruitment and Protection (OHSRP) exemptions. In addition, the PN team performed a QC review of 25 new protocols; 179 IRB continuing reviews; 264 protocol amendments; 36 NIH problem report forms; 20 DSMB reports; and 8 OHSRP exemptions. There has been a significant increase in the

number of protocol amendments and NIH problem report forms compared with the previous year, and two events are responsible for this increase. First, there has been a large increase in the number of protocols being monitored by the new monitoring contract within NHLBI, and as a result, they have requested many protocol amendments to address their queries. Second, as part of the AAHRPP accreditation of the NIH IRBs, the NHLBI IRB has stipulated the inclusion of additional information in most protocols to ensure compliance with new HRPP SOPs. This is an ongoing process which will maintain the number of protocol amendments at high numbers, at least for the next reporting period.

The NHLBI Cardiovascular and Pulmonary Branch (CPB), which conducts research on diseases that affect the heart, blood vessels, and lungs, requested that Leidos Biomedical Research provide the support of a pulmonary function technologist to perform pulmonary function tests on subjects. In addition to performing this test for clinical trials, CPB performs these tests as a service to other institutes at NIH to check the status of lung diseases, diagnose conditions, check the extent of damage caused by conditions, or check the effectiveness of treatments for pulmonary diseases.

Notably, Ms. Adriana Byrnes, a clinical project manager supporting NHLBI, earned an Orloff Science Award for her contributions to the work on ADA2 mutations and recurrent strokes in children. Mr. Vince Williams, protocol navigator, also earned an Orloff Science Award for contributions to the work on laboratory and clinical research resulting in FDA approval of the thrombopoietin agonist eltrombopag as the first new treatment for aplastic anemia.

National Human Genome Research Institute

Support Provided by the Applied and Developmental Research Directorate

ADRD's CSL received 34 whole-blood samples from patients enrolled in clinical trials 00-HG-0209 or 14-HG-0038 for density gradient separation to isolate mononuclear cells. Each day that samples were received, a normal donor research sample was also received for processing. Freshly isolated cells were submitted to the Laboratory of Cell-Mediated Immunity to perform real-time proliferation assays on clinical samples from patients with a variety of immunodeficiency disorders, for a total of 1,736 data points. This ongoing support was initiated through YT07-026 from Dr. Fabio Candotti, and continued through CSAS-16726 after Dr. Candotti's departure from NIH.

Three blood samples were received for EBV transformation in response to two CSAS requests from Dr. Daniel Kastner.

National Center for Advancing Translational Sciences

Therapeutics for Rare and Neglected Diseases

Support Provided by the Clinical Research Directorate

The Therapeutics for Rare and Neglected Diseases (TRND) program was created to accelerate new treatments for rare diseases found in limited patient populations and effective treatments for neglected diseases found in larger patient populations. Through collaborations with research partners, TRND aids in moving small-molecule and biologic drug candidates through milestones of preclinical, clinical, and Investigational New Drug (IND) application with the U.S. Food and Drug Administration (FDA).

Leidos Biomedical Research has supported TRND since 2009 through a broad range of activities and management of candidate projects. Specifically, the Leidos Biomedical Research team has provided the following services that support drug candidate development: lead optimization; in vitro pharmacology (absorption, distribution, metabolism, and excretion [ADME]); toxicology testing; biomarker assay development; in vivo drug metabolism and pharmacokinetics (DMPK), toxicology, and disease animal model development; chemistry, manufacturing, and controls of active pharmaceutical ingredients (APIs) and formulated drug products; and regulatory and clinical trial support. In addition, we have provided project and program management support, financial analysis, and subcontract administration for services noted herein.

Leidos Biomedical Research has initiated support for five new development projects based on TRND's established agreements with academic or commercial partners for treatment of the following conditions: retinitis pigmentosa, LEOPARD syndrome, hypoparathyroidism, Friedreich's ataxia, and rhAC deficiency. In addition to the new development projects, ongoing efforts exist to advance approximately 20 existing projects in various stages of the project lifecycle by maintaining subcontracts and procuring additional support services through the development cycle, or completing and closing the projects.

Within the Clinical Research Directorate (CRD) support to the National Center for Advancing Translational Sciences (NCATS), a senior special projects administrator was hired to enhance support to the TRND program, and provide improved service to the program through financial reporting, project planning and tracking, accelerated subcontracting efforts, and process improvements. Furthermore, the team has developed Basic Ordering Agreement relationships that were competitively solicited to clinical research organizations

in order to improve the efficiency for critical service needs and to accelerate the procurement process.

Support Provided by the Clinical Monitoring Research Program

The U.S. Congress mandated that NIH establish the Therapeutics for Rare and Neglected Diseases (TRND) program in 2009. This unique program creates a drug development pipeline within NIH, and is specifically intended to stimulate research collaborations with academic scientists, nonprofit organizations, and pharmaceutical/biotechnology companies working on rare and neglected illnesses. Along with developing new candidate drugs for rare and neglected diseases, TRND seeks to advance the entire field of drug discovery and development by encouraging scientific and technological innovations aimed at improving success rates in the crucial early stages of drug development.

In addition to performing extensive preclinical research, TRND conducts studies in natural history, healthy subjects, and the treatment of patients with rare and neglected diseases.

TRND has approximately 13 active projects including nondrug, natural history studies (NHS) and Phase I and II patient trials. Currently, two of these protocols are being conducted under IND applications, and two additional studies will require IND applications prior to approval and initiation.

CMRP provides a variety of services to support three TRND IND studies, including assembly, review, and submission of IND applications; general maintenance of IND and regulatory documents; direction of communications between TRND, IND sponsors, FDA, and the IRB; development of materials for, and participation in meetings with, the FDA and TRND study teams; clinical trials operational support, with quality assurance and quality control oversight; protocol and ICF development; GCP monitoring of clinical trials; audit support for regulatory inspections; and GCP and records management guidelines training for investigators and site personnel.

The Regulatory Affairs group continued to work closely with TRND's Niemann–Pick disease type C (NPC) team to support their IND Phase I clinical trial evaluating 2-hydroxypropyl-β-cyclodextrin (HP-β-CD) in NPC. During FY2015, the Regulatory Affairs group prepared six submissions to the NPC IND while it was held by TRND, including a protocol amendment, a request for a Type C meeting, and a request to transfer the IND to a new sponsor, Vtesse, Inc. Following the transfer, the Regulatory Affairs group continued to assist TRND in this transition, by preparing the acceptance submission for Vtesse and providing an in-depth regulatory review of their Type C meeting information package. The Regulatory Affairs group continues to provide administrative support to this Phase I trial by submitting 11 FDA submissions for Vtesse and TRND. Future plans include the total transition of this project from TRND to Vtesse following the completion of the Phase I study. This will include a transfer of all regulatory files and tasks.

Regulatory Affairs and CTM staff also continued to work with the Hereditary Inclusion Body Myopathy (HIBM) project team, which included discussions of the completed Phase I trial, review and submission of the Phase II protocol, which was activated by CMRP in January 2015, and development of the IND annual report. The Regulatory Affairs staff drafted the IND annual report and worked with the HIBM study team to compile the data and complete the document. The Regulatory Affairs staff also coordinated the review of this document by the HIBM team, as the TRND staff member who had done so previously left the group in late FY2013. Regulatory Affairs staff completed a draft Clinical Study Report (CSR) for the closed Phase I study in late FY2014, and worked with the HIBM team to finalize the report. This report was included as an attachment to the aforementioned IND annual report, which was submitted to the FDA in October 2014. Work on the 2014–2015 IND annual report commenced in late August 2015. The Regulatory Affairs group also converted this IND from its original paper format to eCTD in November 2014. This conversion was performed in conjunction with submission of the new Phase II protocol. The Regulatory Affairs group prepared a complicated Chemistry, Manufacturing, and Controls (CMC) amendment, in which the section was reconstructed to add new information from the manufacturer and to match the FDA-required eCTD format. The Regulatory Affairs group also prepared and submitted a request for a Type B, face-to-face meeting with the FDA and its subsequent information package. Regulatory Affairs group members also attended this meeting at the FDA in support of the TRND team. A total of 13 amendments have been submitted to the FDA during FY2015.

CTM worked with the HIBM site team to activate the new Phase II study. The CTM team performed a study initiation visit in December 2014 and activated the study on January 20, 2015. The first monitoring visit (MV) occurred in March 2015, after which CTM worked with the study team to address some source document discrepancies and other minor items noted during the visit. The CTM team conducted the second MV in July/August 2015 to ensure the study was monitored according to the plan. Based on the study timeline, a close-out visit was scheduled for late September 2015.

Regulatory Affairs staff began work with the TRND Hypoparathyroidism team in October 2014, with work focused on project development and plans to request a pre-IND meeting with the FDA, to be held in early FY2016. Regulatory Affairs staff provided regulatory guidance for team members who were unfamiliar with this process, and provided templates and draft questions for their use.

Bridging Interventional Development Gaps

Support Provided by the Clinical Research Directorate

The Bridging Interventional Development Gaps (BrIDGs) program was created to provide critical resources for developing therapeutics for common and rare diseases. Through collaborations with research partners, BrIDGs provides crucial services relating to synthesis, formulation, pharmacokinetics, and toxicology that will support the partner's IND applications with the FDA.

Leidos Biomedical Research has supported BrIDGs since 2009 through the services noted here and management of candidate projects. The team has provided the following services that support drug candidate development: chemistry, manufacturing, and controls of API and formulated drug products, pharmacokinetic and ADME studies, and toxicology studies.

Leidos Biomedical Research has initiated support for five new development projects, based on BrIDGs' partnerships, for the treatment of the following conditions: beta thalassemia, hypothermia, hematopoietic-acute radiation syndrome, diabetic keratopathy, and myocardial infarction. In addition to the new development projects, ongoing efforts exist to advance approximately 30 existing projects by maintaining subcontracts and procuring additional support services through the development cycle, or completing and closing the projects.

Within the CRD support to NCATS, a senior special projects administrator was hired to enhance support to the BrIDGs program and provide improved service to the program through financial reporting, project planning and tracking, accelerated subcontracting efforts, and process improvements. The team successfully facilitated the deployment of Leidos Biomedical Research's Biopharmaceutical Development Program (BDP) through a multiple-phase project in the development and optimization of a complex recombinant human protein. This project leveraged the BDP's resources to produce the bulk drug and improve its purity to the level that is acceptable to the FDA, in order to continue with toxicology and clinical studies. Lastly, the team has developed Basic Ordering Agreement relationships that were competitively solicited to clinical research organizations in order to improve the efficiency for critical service needs and to accelerate the procurement process.

OTHER AGENCIES

U.S. Army Center for Environmental Health Research

Support Provided by the Data Science and Information Technology Program

The U.S. Army Center for Environmental Health Research (USACEHR) Systems Biology project was initiated through a request from USACEHR to provide support for the systems biology studies of the diseases of military relevance. The project is part of the U.S. Army Medical Research and Materiel Command's Systems Biology Enterprise (USAMRMC-SBE) and is made feasible through an interagency agreement between NCI and USACEHR. The goal of the project is to provide analysis support and create a systems biology data cube that will serve as a central portal for data collection, integration, analysis, mining, and knowledge sharing by army, academic, and private institution collaborators.

In FY2015, the Core Infrastructure and Systems Biology group in ABCC added a clinical explorer interface that allows filtering, querying, and easy analytics on clinical data sets from various clinical sites. The application was developed in a disease agnostic fashion to support multiple studies within the project. The group also developed algorithms to support time-series analysis and visualize functional interactions within the differentially expressed genes. In addition, extensive analysis support was provided for microarray, methylation, RNA-Seq, miRNA-Seq, and metagenomics analysis for several studies, including post-traumatic stress disorder and coagulopathy of trauma.

U.S. Army Medical Research Institute of Infectious Diseases

Viral Immunology Section

Support Provided by the Cancer Research Technology Program

The USAMRIID Ebola Yellow Task supports investigators in the Viral Immunology Section with production of specialized filovirus glycoprotein reagents generated in HEK293 cells. The Protein Expression Laboratory (PEL) has generated these proteins for the last seven years as reagents for world-wide use in ELISA assays of patient serum samples and for internal research and development work at USAMRIID. As of August 1, the PEL produced 90 liters of mammalian cell culture in support of this project and carried out 16 large-scale purifications, delivering 124 mg of Marburg glycoprotein (GP), 293 mg of Uganda GP, and 420 mg of Zaire GP.

U.S. Food and Drug Administration

Support Provided by the Applied and Developmental Research Directorate

The Laboratory of Cell-Mediated Immunity performed ELISPOT assays and obtained 1,311 data points at the request of Dr. Suzanne Epstein (YT08NS201B).

Centers for Disease Control and Prevention

Support Provided by the Data Science and Information Technology Program

The Advanced Biomedical Computing Center (ABCC) provides analysis support for the performance evaluation of a high-performance computing (HPC) clusters and software at the Centers for Disease Control and Prevention (CDC). Support includes performing benchmark tests, as well as validation and documentation of bioinformatics software and next-generation sequencing (NGS) workflows for metagenomic analysis and phylogeny. The ABCC supports the CDC through both subcontractors with specialized skills in computer architectures and software optimization and local bioinformatics experts, who assist with the analysis, optimization, documentation, and regression testing of required software packages.

In FY2015, the ABCC has worked on a set of applications that includes Cufflinks, Tophat, RNA-Seq, and BWA. Detailed run time performance analyses are ongoing for each application using three different compiler toolchains. Three compute platforms are used as target environments, namely Intel Xeon, Intel Xeon Phi, and NVidia CUDA GPUs including the K80 processors. Various initiatives started by Intel and NVidia to modernize and optimize applications using cluster file systems and big data techniques are also being reviewed for use within the NCI and CDC infrastructures.

Operational Support

Leidos Biomedical Research, Inc.

OPERATIONAL SUPPORT

ENVIRONMENT, HEALTH, AND SAFETY

Safety and Environmental Management

The Environment, Health, and Safety Directorate (EHS) continued efforts to improve numerous Occupation Safety and Health Administration (OSHA)-related safety programs and collaborate with organizations to enhance conditions that contribute to a safe and healthful workplace. Transformative changes made in the last year include the establishment of user committees to engage stakeholder involvement in safety; development of a new, web-based safety inspection and issue management system to transform the way safety deficiencies are tracked to closure and make the process transparent to all stakeholders; and streamlining of numerous processes. Assessments began to allow for collection of data to be used to proactively manage safety in laboratories. This management system allows for increased responsiveness and timeliness to meet customer needs.

To promote safety communication at NCI at Frederick, EHS hosted an open house/small vendor fair, with an emphasis on sharps safety. Working with sharps in laboratories is inherently dangerous, so EHS proactively focused on featuring equipment that would promote safer techniques. In addition to promoting health and safety for the employees of NCI at Frederick, EHS provides crime prevention services and personal protection seminars, which is why the open house also featured self-defense expert retired Captain Kirby Maybush. Capt. Maybush has been involved in Frederick County law enforcement for 45 years and has been teaching self-defense classes for 35 years. The second nomination for the NCI at Frederick Champion of Safety was revealed during the open house. The goal of this program is to raise awareness and promote a culture of safety by showing NCI at Frederick staff members at work in their respective workplaces.

EHS continues to work with the NCI at Frederick webmaster to update and improve the EHS web pages for a more cohesive appearance that will facilitate easier navigation.

EHS has developed a new annual safety refresher training class for deployment to all NCI at Frederick employees. The objectives of the training are to ensure that all employees know how to identify hazards in the workplace, protect themselves by reducing or eliminating potential hazards, protect themselves in an emergency, and properly dispose of hazardous wastes; the objectives also include ensuring that all supervisors know their responsibilities as a supervisor and communicate "what's new in Safety" to the NCI at Frederick community. EHS is working closely with Data Management Services (DMS) to host this training class online at the NCI at Frederick training portal.

Annual Facility Safety Inspections

To monitor compliance with NCI at Frederick–approved safety and environmental requirements, EHS has the authority to enter all areas/facilities to make periodic, routine, or unannounced safety inspections. One of the mechanisms employed to satisfy this contractual agreement is the performance of annual facility-wide safety inspections.

Results of initial inspections are reported to the laboratory chief/manager/program head for corrective action. An attempt is made to resolve all deficiencies in safety and environmental regulations through the appropriate lines of authority within 45 days.

In cases where deficiencies are not resolved within 45 days, the next level of authority provides assistance to EHS to aid in deficiency resolution. EHS is contractually obligated to immediately report any safety inspection deficiencies that are unable to be resolved within 45 days to NCI at Frederick.

As of July 28, 2014, 515 safety-related deficiencies were found in the 107 locations that were inspected. Of these, 438 deficiencies were resolved within 45 days. Deficiencies not resolved within 45 days were reported to NCI at Frederick.

EHS worked closely with DMS in the development of a web-based Safety Inspection and Issues Management System (SIIMS). In the past, EHS relied on an Access-based system to track to closure safety deficiencies found during facility inspections. During contract year (CY) 2015, SIIMS was used to capture, report on, track, and close safety-related deficiencies found during performance tests of all facility emergency eyewash stations. In addition, SIIMS is being used to conduct contract-driven safety inspections. Because of the web-based application, EHS inspectors are able capture attributes of safety-related deficiencies in the field, in real time, utilizing iPads. Once an inspection is completed, reports are automatically generated and e-mailed to individuals responsible for deficiency resolution. SIIMS is then used to track safety-related deficiencies to closure. In addition, an "issues" component of SIIMS is in development. This component will ultimately allow any NCI at Frederick employee to electronically report potential safety-related issues to EHS for appropriate follow-up.

Radiation Safety

During CY2015, the Radiation Safety Office provided radiation safety support to over 400 radiation workers, 51 open source programs, 5 X-ray programs, and 2 gamma-cell irradiator programs at NCI at Frederick.

In addition, during CY2015, the Radiation Safety Office provided radiation safety support to 48 individuals who are approved to manipulate radioactive materials

and/or work with electron microscopes at the Advanced Technology Research Facility (ATRF).

The Radiation Safety Office entered into an emergency services agreement with Johnson Controls for their prompt response to any emergencies or system failures associated with the NCI at Frederick irradiator intrusion detection system.

In addition, the Radiation Safety Office obtained a quote from Johnson Controls for replacing aging components of the system. The current system was installed by Johnson Controls approximately 10 years ago, and system reliability was decreasing. Approval for an out-of-cycle budget request to move forward with the project was received in December 2014, and replacement of the aging components was completed by Johnson Controls in July 2015.

Regulatory-driven interlock challenges were performed on both gamma-cell irradiators. Interlocks performed as required.

The annual requirement to update our radioactive materials in quantities of concern (RAMQC) information into the National Source Tracking System was completed.

To satisfy the new federal regulation, Title 10, Part 37 of the *Code of Federal Regulations* (10 CFR 37, Physical Protection of Category 1 and Category 2 Quantities of Radioactive Material), the U.S. Nuclear Regulatory Commission (NRC) licensees must perform and document the following on an annual basis:

- Review of written Access Authorization Program
- Review of Physical Security Program
- Completion of refresher training for authorized users
- Coordination with the licensee's local law enforcement agencies

The NCI at Frederick Radiation Safety Office initiated the performance and documentation of all of the above in February 2015.

Regulatory-driven sealed-source leak tests were performed on all facility sealed sources that require leak testing. No leaks were detected.

Six-month Radioactive Material Inventory questionnaires were forwarded to facility radiological programs. The information provided back to Radiation Safety was complete and accurate. A subsequent physical inspection showed that the storage of licensed, radioactive materials was compliant and that these materials were secure against unauthorized removal.

An NRC License Amendment Request was sent to the NRC in March 2015 to notify them of the relocation of the radiopharmacy from Building 325 to Building 459. The request stated that ventilation systems (such as total exhaust, lead-shielded chemical fume hoods, and total exhaust, lead-shielded sterile isolator hoods) are applicable to the new facility and will be used to help ensure that exposures from radioactive materials will be kept as low as reasonably achievable (ALARA). The amended license was received from the NRC in May, and the first radiopharmaceutical was produced in Building 459 in June 2015.

The Radiation Safety Office assisted in the packaging and shipment of 42 radiopharmaceutical drugs from the NCI at Frederick to the NIH for Phase 0–Phase I clinical trials from September 26, 2014, to July 27, 2015.

The NCI at Frederick Radiation Safety Office completed a license renewal application for the NCI at Frederick radioactive materials license in early May 2015. The NRC received the application on May 15 and responded with eight technical review questions on June 29.

The NCI at Frederick Radiation Safety Office provided responses to the technical review questions to the NRC on July 15.

The current license will remain in "timely renewal" status until the technical review process has been completed and a new license is issued.

The 2015 round of radiation-producing machine audits (performed by RSO, Inc.) was completed. Thirteen systems (cabinet X-ray irradiators, SPECT/PET CTs, as well as electron microscopes) located at NCI at Frederick and at the ATRF fall under the scope of these audits. No items of noncompliance were indicated.

10 CFR 29 (for NCI at Frederick) and 26.12.10.01 of the Code of Maryland Regulations (for the ATRF) mandate that opening procedures for radioactive materials be performed and documented within three hours of receipt. As of July 27, 2015, the Radiation Safety Office met this requirement 100 percent of the time, for both NCI at Frederick and the ATRF.

From September 26, 2014, thru July 27, 2015, the Radiation Safety Office processed 492 incoming radioactive material shipments received at NCI at Frederick and 9 incoming radioactive material shipments received at the ATRF, in accordance with the above-mentioned regulatory requirements.

The Radiation Safety Office performed 100 percent of regulatory-driven contamination surveys each month. Approximately 800 survey samples (with approximately 0.1 percent showing contaminated sites above the NRC action-level requirement of 500 disintegrations per minute [dpm]) were taken each month at NCI at Frederick, and approximately 30 samples (with 0 contaminated sites above the Maryland Department of the Environment [MDE] action-level requirement of 220 dpm) were taken each month at the ATRF. This low overall level of radioactive contamination demonstrates that facility radiation workers are keeping exposures to radioactive materials as low as reasonably achievable (ALARA).

All (100 percent) individuals scheduled for bioassays (urine and thyroid) obtained their scans.

The Radiation Safety Office calibrated approximately 150 radiation survey meters in accordance with established, license-driven procedures.

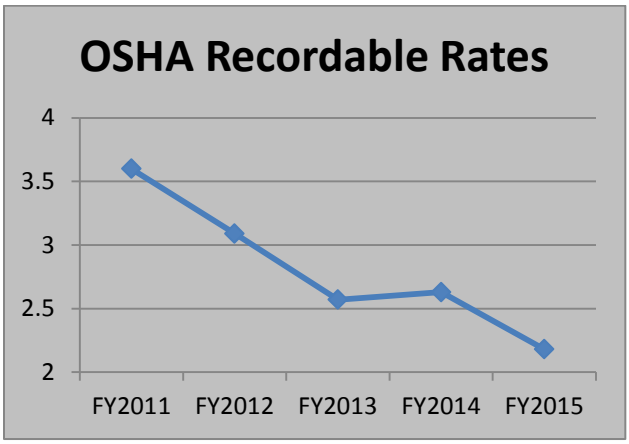
Fifty-two new radiation workers received NRC-mandated new-user radiation safety training to work with radioactive materials (RAM) at NCI at Frederick; 11 new radiation workers received MDE-mandated new-user radiation safety training to work with RAM at the ATRF.

All (100 percent) of approved radiation workers in need of radiation safety refresher training completed the required training.

The NCI at Frederick/ATRF Radiation Safety Committee continues to meet regularly to help ensure that all sources of ionizing radiation at the facility are used safely and in a manner that complies with all applicable regulatory and license requirements. The committee reports to the president, Leidos Biomedical Research, Inc., and provides policy guidance to the Radiation Safety Office.

Industrial Hygiene

Industrial Hygiene Injury and Illness Investigations: EHS substantially revised incident reporting processes. This work includes a new incident reporting system to improve compliance with OSHA and contract requirements. EHS also successfully lobbied to better define the contractual requirements pertaining to various types of incidents. Process improvements to the current work procedures and recordkeeping for incidents have improved compliance reporting. EHS investigated more than 100 reported work-related injuries and illnesses. All responses to Occupational Health Services (OHS) are recorded in the EHS response record database, and each response record, with the corresponding supervisor investigation form, is noted in the Occupational Health Manager (OHM) database. The total OSHA recordable injury rate continued to decline in this contract year.



EHS continued to work very closely with the Laboratory Animal Sciences Program (LASP) directorate to find solutions to trends in accident causes involving ergonomic injuries and animal bites. EHS initiated a goal to improve the safety of sharps use to reduce the laceration rates among laboratory staff.

Environmental/Chemical Monitoring and Risk Assessments: Approximately 1,300 EHS Medical Surveillance Enrollment Forms were reviewed and approved by the Industrial Hygiene (IH), Biological Safety, and Radiation Safety offices. Employees were enrolled in surveillance programs as needed and as indicated. EHS maintains and calibrates 20 individual pieces of monitoring equipment in order to facilitate the timely monitoring of NCI at Frederick needs.

In response to an incident in Building 560 that implicated unsafe exhaust stack design, EHS created and performed a chemical use assessment and process that will be expanded to include the entire main campus in fiscal year (FY) 2016. The resulting assessments will enable future upgrade projects to be prioritized by hazard risk and new renovations to be streamlined, and ensure the safety of existing work by documenting laboratory hazards and controls.

EHS conducted an assessment of the ventilation of bedding dump stations and created an inventory of control devices for animal facility managers. In addition, EHS evaluated current administrative controls and made recommendations on proper PPE for each device.

EHS also conducted an assessment of a power washing operation in order to evaluate controls and PPE. The station in question was not needed, and the hazard was eliminated after the review.

EHS is also in the process of conducting noise surveys to characterize ambient noise levels generated from metal carts in the process of animal care, as well as the resulting noise levels within animal rooms per Association for Assessment and Accreditation of Laboratory Animal Care (AAALAC) request.

Personal sampling for noise, formaldehyde, isoflurane, isopentane, and xylene was conducted on 12 employees to ensure compliance with OSHA, American Conference of Governmental Industrial Hygienists (ACGIH), National Institute for Occupational Safety and Health (NIOSH), or NIH policy exposure limits as appropriate.

Eight risk assessment reports for other various work processes were also completed.

Fourteen comprehensive indoor air quality investigations were completed and reported, with corrective and remedial actions included.

Asbestos and Lead Programs: Three EHS staff members are Maryland-licensed asbestos inspectors. EHS worked with Facilities Maintenance and Engineering (FME) to create a plan for managing the asbestos remediation to Building 361 in a cost-efficient and compliant manner. EHS also lobbied for and received approval to begin work to remediate asbestos in Buildings 469 and 325.

EHS conducted thirteen asbestos survey reports in support of ongoing FME renovation projects to ensure compliance and worker safety.

EHS trained 97 employees on asbestos and lead paint awareness utilizing in-house resources.

Respiratory Protection Program: There are 329 employees enrolled in the Respiratory Protection Program who require annual fit testing and training. Approximately 97 employees were newly enrolled, while 66 employees were removed from the program.

Hearing Conservation Program: IH conducted 17 noise surveys and 4 employee dosimetry tests in various areas on the NCI at Frederick campus. Classroom

training was conducted for 56 enrollees. Six employees were added to the program, and one was removed.

Forklift Program: Approximately 73 employees are enrolled as forklift drivers; 12 new enrollees were trained and evaluated by EHS, and 14 employees were removed from the program. Tri-annual forklift evaluations were completed for 54 drivers.

Ergonomics: IH conducted approximately 35 ergonomic worksite evaluations and consultations to improve employees' worksites (including office, laboratory, and animal production areas), with the intent of reducing occupational ergonomics-related injuries.

Environmental Protection

Environmental Protection and Waste Management (EPWM) manages NCI at Frederick chemical and radioactive wastes; responds to chemical spills or emergencies; tracks emissions of air pollutants; ensures storm water and sediment control compliance; oversees trash and recycling efforts; oversees compliance with city sewer discharge permits; conducts training; oversees the facility Environmental Management System; assists in emergency operations planning; conducts inspections of laboratories, mechanical shops, and warehouses; and is the lead on National Environmental Policy Act (NEPA) programs.

In January 2015, the NIH Office of Research Facilities conducted a four-day audit of the environmental programs at NCI at Frederick. Under escort by and assistance from EPWM, the audit team toured laboratories, interviewed research and shop personnel, and reviewed reports, training records, and other documents. Its report, issued in March, listed 8 corrective actions out of 121 items audited. These corrections were completed within three weeks of the audit's receipt. No major deficiencies or regulatory violations were identified.

In November 2014, the ATRF was audited by a representative of the Frederick City Department of Public Works. The auditor toured laboratories and the Biopharmaceutical Development Program (BDP) production areas as well as the wastewater sterilization and neutralization systems, and reviewed monitoring and sampling documents. No deficiencies were identified. In March, EPWM applied for a new wastewater discharge permit for the facility, which was issued by Frederick City in June.

EPWM reviewed construction designs and site safety plans, and completed NEPA documents for FME projects, including the campus Energy Savings Project, which commenced in June 2015.This project involves strong coordination between the contractor, FME, and the staff of the laboratories where work will take place.

EPWM submitted the NCI at Frederick annual toxic release inventory, a listing of chemicals used by non-laboratory programs in excess of threshold amounts.

The EPWM staff submits the annual Tier II report, which includes a listing of hazardous chemicals stored in threshold amounts at the facility. This information is sent to the Fort Detrick fire chief, the local municipal fire department, and the Local Emergency Planning Committee (LEPC), as well as the MDE, for emergency planning.

Waste Management

EPWM collects, stores, and ships radioactive and chemical wastes from laboratories and shops at NCI at Frederick, the ATRF, and the Vaccine Clinical Materials Program (VCMP). It also oversees collection of biohazardous waste by the U.S. Army Garrison (USAG), Fort Detrick, and responds to incidents involving improper waste disposal at the USAG incinerator.

EPWM offers training and investigates incidents that may negatively affect the environment or our customer's compliance record. EPWM conducts inspections of laboratories and shops that use hazardous chemicals, and ensures that practices are compliant with current policy.

EPWM assisted in multiple laboratory moves and cleanouts and delivered more than $7,516 in chemicals through its web-based Surplus Chemicals program.

EPWM performed over 94 annual laboratory inspections, including inspections of satellite hazardous waste accumulation sites and off-post facilities. EPWM also hosts training of FME and custodial personnel; provides chemical spill response and oversight of photographic chemical recovery equipment; samples and publishes data on drinking water quality; trains new employees during their orientation; and inspects and maintains Buildings 1067, 1068, and 1071, as well as all spill response equipment and protective gear.

A summary of EPWM's waste collection, recycling, and disposal efforts for NCI at Frederick from October 1, 2014, through August 30, 2015 appears in the tables below.

Our program continues to be as proactive as possible in reducing waste disposal costs without jeopardizing our many regulatory obligations or hampering the mission of the research and support personnel.

Table I. Hazardous Waste Management
October 1, 2014, to August 30, 2015

Waste Type	Waste Quantity
Scintillation vials (nonradioactive)	1,045 liters
Non-halogenated solvents	10,868 liters
Halogenated solvents	10,241 liters
Laboratory packages and miscellaneous	195 containers
Mixed radioactive/chemicals	0 liters

Table II. FNLCR Trash and Recycling Rates
October 1, 2014, to August 30, 2015

Material	Quantity
Trash	898 Tons
Recyclables	355 Tons
Recycling Rate	28%

Table III. FNLCR Waste Management Cost Savings
October 1, 2014, to August 30, 2015

Material	Quantity Diverted	Estimated Savings
Neutralization	754 Liters	$2,948
Surplus chemicals	108 Containers	$3,479
Batteries	4,297 Liters	$6,673

Biological Safety

The Biological Safety staff performs a wide range of safety- and health-related functions to ensure facilities, equipment, and procedures are appropriately evaluated and implemented to provide employee and environmental protection while working within optimum biocontainment conditions at NCI at Frederick facilities.

Institutional Biosafety Committee: The NCI at Frederick Institutional Biosafety Committee (IBC) continues to register all work with human and animal pathogens, recombinant and synthetic DNA and RNA, human cell lines, genetically modified animals, and other potentially infectious materials, including human and animal tissues as well as nonhuman primate materials.

- The IBC reviewed and approved 292 registration documents, including new, amendment, and renewal requests.
- 27 existing and out-of-date IBC registrations were inactivated.
- 38 IBC renewal submissions were approved.
- An IBC strain database continues to be maintained as a resource to provide investigators with information on animal strains maintained and research performed on the NCI at Frederick campus.
- The IBC monthly meeting minutes are made publicly available at http://web.ncifcrf.gov/ehs/ibc/Minutes.aspx.
- The IBC continues to offer training for employees who work with viral vectors. Biological Safety schedules this two-hour class on an as-needed basis;152 employees completed this Viral Vector Safety training.
- Additional training courses related to agents described in IBC registrations have been provided by Biological Safety staff for diphtheria toxin (4) and *Toxoplasma gondii* (7).
- The IBC, EHS, and DMS completed the development of an electronic IBC registration process. During this reporting period, the electronic system now accepts amendments to IBC registries initially filed through the electronic system. Phase 2 involves the development of a database and information tracking system. The electronic registration process has been well received by both principal investigators (PIs) as well as reviewers on the IBC. Requests for modifications to the registration system have been implemented as we continue to work with investigators to make the transition to the new system as smooth as possible.

Animal Safety: The biological safety officer serves as the ACUC EHS member, and the biological safety team has incurred several additional tasks and responsibilities related to ACUC Animal Study Protocol (ASP) reviews.

EHS created a new chemical risk assessment report called Chemical Safety Practices Recommendations (CSPR) in order to communicate safe work practices and hazards, such as chemicals, drugs, and toxins, associated with animal study protocols. EHS created or updated 37 detailed CSPR reports, which include recommendations for personal protective equipment (PPE), bedding and feed disposal, special precautions, and engineering controls in support of Animal Care and Use Committee (ACUC) protocols and occupational safety. Overall, approximately 200 chemicals/drugs/toxins have been researched for the purposes of performing a risk assessment with respect to animal protocols.

To enhance the ACUC ASP review process, the hazard assessment section of the ASP form was revised to capture additional relevant details in an organized manner. Over the 12-month period, 123 ACUC documents were reviewed to evaluate chemical and biological hazards associated with animal research.

An animal exposure program was developed to address potential and known employee exposures to animal allergens. The written animal exposure program was drafted, and a computer-based assessment tool was developed and implemented to identify employees eligible for enrollment based on their potential for exposure to animal allergens. As part of the initial enrollment process, 1,383 animal exposure program risk assessment tools were processed. Currently 680 employees are enrolled in the animal exposure program. A live training session on animal allergens and the animal exposure program was presented to 111 individuals, and a computer-based training module is nearing completion for launch in September to offer employees a remote training option.

As a result of the 2014 AAALAC inspection, EHS has been tasked with initiatives to clarify animal biosafety containment level requirements in research laboratories and animal housing rooms, update door signage procedures, inventory biosafety containment levels by

building, and update the Biosafety in Microbiological and Biomedical Laboratories (BMBL) matrix to include additional hazards and mitigation strategies to minimize personnel exposures.

Clean Sweep: All EHS employees participated in the NIH clean sweep initiative to evaluate facilities for the presence of biological select agents (SAs) and toxins (potentially hazardous biological materials). EHS coordinated with NIH management to provide a report documenting that all space had been searched and deemed clear of unregistered biological SAs and toxins. Additional policies are being developed to address future inventory requirements for SAs and toxins prior to long-term storage.

Laboratory Assessments: The Biological Safety Program continues to perform comprehensive evaluations for multiple laboratory programs within the NCI Division of Cancer Treatment and Diagnosis. The purpose of the audit is to evaluate infrastructure and administrative compliance with the guidelines set forth in the Centers for Disease Control and Prevention (CDC)/NIH *Biosafety in Microbiological and Biomedical Laboratories*, 5th edition, a contractual requirement. A summary report documenting current noncompliance issues is provided to the directorate head for the programs reviewed and to NCI at Frederick for review and concurrence. All deficiencies are then addressed with the laboratory program to ensure all facilities are compliant.

Select Agents: The U.S. Department of Agriculture (USDA) coordinated the relocation of all select agents (SAs) back to its possession. As of June 30, 2014, all SAs were transferred away from NCI at Frederick. The Select Agent Program registration for the USDA plant pathogens was effective through May 2015. Since the agents were all removed and there was no longer a need to renew the registration, the USDA Select Agent Program granted the NCI at Frederick's request to withdraw the registration effective November 3, 2014.

Controlled Substances: Biological Safety provides program management and oversight for the Drug Enforcement Administration (DEA) Controlled Substances Program. Biological Safety staff now has responsibility for maintaining permits and making applications for new permits. At the present time, both state and federal permits are maintained for both NCI at Frederick and the ATRF. The staff approves purchases, performs random audits, delivers drugs, and ensures compliance with all applicable DEA-controlled substance requirements. Currently, there are 32 DEA Controlled Substance logbooks.

Tax-Free Alcohol: Biological Safety provides program management for the use of tax-free alcohol within laboratories. A policy and procedure and an EHS standard operating procedure (SOP) have been drafted and are pending review and approval prior to program implementation. Biological Safety staff has responsibility for maintaining permits and making applications for new permits. At the present time, both state and federal permits are maintained for both NCI-Frederick and the ATRF. In addition, both state and federal permits are maintained for an additional off-site location. The program will include a semiannual physical inventory audit. There are currently 127 Tax-Free Alcohol logbooks.

Autoclave Monitoring Program: Biological Safety has made improvements to the Autoclave Monitoring Program to verify the effectiveness of decontamination methods. Testing ampoules are processed for autoclave validation on a semiannual basis. This program now includes 107 operational autoclaves.

Shipping Classification/Import and Export Control: Biological Safety is responsible for reviewing all shipment requests and classifying both hazardous and nonhazardous shipments for the Contracts and Acquisitions Directorate, as well as for processing Return of Goods request forms. Biological Safety averages approximately 825 online shipment classifications per month. The Biological Safety staff continues to provide support on import and export control matters, and provides assistance with U.S. Customs to obtain necessary permits for USDA/CDC/U.S. Fish and Wildlife Service, etc., on an as-needed basis.

As a result of the addition of several international laboratory sites related to activities for Ebola clinical trials, EHS reviews approximately 38 orders per month to determine hazard classifications, and packaging and labeling requirements.

Decontamination: Biological Safety staff assisted with conducting work authorization/laboratory equipment decontamination qualified training. The staff decontaminated an average of 38 biological safety cabinets every month; completed approximately five response records per month for emergency calls regarding odors, accident investigations, biological exposures, or hazardous materials; performed or assisted with more than 31 annual laboratory inspections; and participated in 21 animal facility inspections.

Publications: Biological Safety staff continues to develop BioMaterial Fact Sheets and Biological Safety Technical Bulletins. These are provided to laboratory and animal care staff to assist with providing minimum practices guidelines for particular agents and biological safety topics, respectively. The following is a list of existing fact sheets and technical bulletins:

- Disinfection and Selection of Disinfectants
- Chlorine Bleach
- *Clostridium difficile*
- Selection of Engineering Controls

Training: The Biological Safety staff offers and coordinates various training sessions for both contractor and government employees.

- **Werner H. Kirsten Student Intern Program:** EHS successfully coordinated the safety training to include hands-on demonstrations, and reviewed and approved the training plan risk assessments for 70 students hired for the 2015 cycle of the Werner H. Kirsten Student

Intern Program. EHS staff worked closely with the mentors and government program administrators in order to enable the students to perform basic science experiments in a way that ensured student safety as well as compliance with OSHA regulations and the applicable NIH policies (including NIH Policy Manual 3015 for minors). In addition, EHS presented the Student Intern Mentor training four times, telecasting three of those sessions to the ATRF. A total of 136 mentors and supervisors attended.

- **Bloodborne pathogens:** Biological Safety staff conducts bloodborne pathogen (BBP) training as part of the new employee safety orientation. Providing this course also maintains compliance with the OSHA requirement to conduct an annual BBP refresher course. Throughout the reporting period, BBP training compliance ranged from 93 to 97 percent, and as of July 2015, nearly 1,190 employees were enrolled. The Biological Safety office worked with OHS to revise the Exposure Control Plan as part of the annual requirements for the OSHA Bloodborne Pathogens standard. Also, Biological Safety staff conducted its annual BBP training session for 11 FME service workers in October 2014.

Biological Safety Officer: The biological safety officer (BSO) continues to expand responsibilities throughout the campus. The BSO:

- Functions as the contracting officer's technical representative (COTR) for the decontamination services contract.
- Represents NCI at Frederick in the National Interagency Confederation for Biological Research, participating in both the Select Agent Subcommittee and the Safety and Occupational Health Subcommittee.
- Participates in the Human Resources Working Group by contributing to revised processes for performing a job hazard assessment as part of the personnel requisition and hiring process.
- Serves as project lead representing EHS for multiple renovation and construction projects. This function includes space evaluation and risk assessment, laboratory design based on applicable regulatory requirements, attendance at project meetings, and provision of design review comments and project safety oversight during renovation and construction activities.
- Reviews contractor safety plans and safety systems for compliance with applicable regulatory requirements.

Construction and Maintenance Safety

EHS began several major initiatives to improve the safety and compliance of construction and maintenance–related activities throughout the scope of contract activities. A new safety officer was hired to assist in championing several of these new initiatives and improvements.

Confined-Space Program: EHS elicited the assistance of a subcontractor and completed a comprehensive survey to identify, classify, and assess all confined spaces throughout the facilities of the main campus, ATRF and VCMP. Approximately 1,473 spaces were documented and inspected. Approximately 1,040 previously unclassified, permit-required confined spaces were identified and will require OSHA-mandated labeling and procedure development. A comprehensive written program was developed, including six individual procedures for guidance on labelling, entering, program review, and training for confined-space work. Three forms were created to document some of the procedural requirements. During the interim, EHS has been heavily involved in supporting the work needed to meet confined-space entry requirements in a safe and compliant manner at all facilities.

Electrical Safety and Lock-Out Tag-Out: EHS acquired the services of a professional electrical safety consultant to create a written electrical safety program for EHS. The consultant identified compliance gaps and recommendations for improvement in the current procedures, delivered an editable written program, templates for creating equipment-specific procedures, and provided two courses in four days of training to selected EHS and FME personnel.

Concurrently, EHS developed 10 new procedural documents to improve the compliance and safety of control of hazardous energy lock-out/tag-out (LOTO) activities. A tentative schedule for program implementation was created, and training will be developed and provided to FME personnel during the subsequent contract year.

Cranes and Hoists: A written program for hoisting and rigging was created, along with procedures for required program administration. On-site rigging and hoisting safety training was conducted by a contractor for 55 identified individuals in EHS and FME.

Elevated Work and Fall Protection: A contractor provided EHS a written fall protection program that generated several new procedures, including portable ladder use, fixed ladder use, flat roof access, and general fall protection processes. On-site fall protection training was provided by a contractor to 70 identified EHS and FME personnel.

In addition, EHS created a risk assessment process and performed assessments, inventory, and a survey of 157 existing fixed ladders on main campus. Risk assessment revealed 6 ladders to be unsafe, and they were removed from service. Five ladders were completely compliant with OSHA standards, and the remaining ladders are being addressed by a project with FME to further prioritize and take corrective actions.

Machine Guarding: EHS developed a risk assessment process and form to evaluate existing mechanical equipment for compliance with OSHA machine guarding requirements. A pilot study was performed on the Building 550 attic and basement, which identified 21 pieces of deficient equipment that were later corrected by FME.

Subcontractor Safety: EHS updated a safety brochure for subcontractors that explains the improved safety expectations and the compliance program of the facility. EHS has carefully reviewed and provided comments for approximately 50 site-specific safety plans to help prevent subcontractor noncompliance with safety procedures. EHS has begun to develop a subcontractor safety training program to be fielded in the subsequent contract year.

EHS benchmarked numerous programmatic areas and processes including training, construction safety, electrical safety, chemical tracking, and laboratory door signage with NIH and other Federally Funded Research and Development Centers (FFRDCs).Two EHS personnel conducted a site visit to Argonne National Laboratory to initiate this review.

Life Safety and Fire Prevention Program

The Life Safety and Fire Prevention Program (LSFP) ensures that appropriate building construction, fire protection, and fire prevention features and practices are maintained in order to minimize the danger to life and property from fire and related life safety hazards. Occupancy type, function, and other characteristics of buildings are considered throughout their design, operation, inspection, testing, and maintenance. The focus of this program is the protection of life, research materials, and property from loss due to fire and related hazards.

LSFP includes subject matter expert consultation; employee training; life safety and fire prevention inspections; and fire extinguisher inspection, testing, and maintenance. To ensure regulatory compliance and to mitigate multiple hazards, LSFP coordinates directly with the NIH Fire Marshal. LSFP also coordinates and consults with Fort Detrick Fire and Emergency Services (FD F&ES), as well as with all programs within EHS, building coordinators, animal facility managers, FME management and shops, and subcontractors specializing in fire system and extinguisher inspection, testing, and maintenance.

Significant Achievements

In May, LSFP staff participated in the bomb threat management course presented by the Bureau of Alcohol, Tobacco, Firearms and Explosives at the NCI-Shady Grove campus. Based on the model program at NCI-Shady Grove, the Emergency Preparedness Awareness Series of slides on emergency preparedness was initiated at NCI at Frederick. Awareness slides are updated monthly for posting on screens in the Conference Center and Café in Building 549, and in the ATRF atrium. FNLCR and NCI Emergency Management staff participated in a Point of Dispensing exercise conducted by USAG at Fort Detrick. Effective liaison with emergency management officials provides necessary communication for situational awareness and access to resources.

A facility-wide project to label generator-powered outlets was completed during the period. The need for clear identification of outlets became apparent during an extended power outage during the previous reporting period.

The Active Shooter Plan, a hazard-specific addition to the EPP, was reinforced with training provided by the NIH Police, the Office of Research Services, and the NIH Civil Program. The training was provided to an executive group, and subsequently, a general session was provided in the auditorium for all interested employees. It is anticipated that this training in prevention and response to an active shooter event will be repeated annually.

LSFP coordinated the fall 2014 and spring 2015 schedules for safety inspections of all active animal facilities, in cooperation with the Laboratory Animal Sciences Program and the established semiannual inspection cycle of the Animal Care and Use Committee.

Prior to the fall animal facility inspection cycle and annual inspection cycle, LSFP staff provided training for EHS inspectors in the use of the Safety Inspection and Issue Management System (SIIMS). SIIMS allows EHS inspectors to use an iPad to efficiently enter inspection data in the field. The system provides efficiency by recording and organizing data into searchable segments, and automatically creates paperless inspection reports.

The completed interactive facility map of assembly areas for building evacuation was added to the EHS website. The point-and-click map was available in advance of the fall 2014 building evacuation drills.

Seventy-six building evacuation drills, involving 92 buildings and 1,372 occupants, were conducted throughout October 2014. The average evacuation time was one minute and thirty-nine seconds. Building evacuation drills are required as an educational tool to ensure the occupants are familiar with the emergency egress routes and assembly areas, and will reach them in an orderly and timely manner. It is evident that building occupants know to leave the building upon activation of the evacuation alarm and are aware of the location of the assembly area(s).

Approximately 493 NCI at Frederick employees have received training in the use of fire extinguishers since 1998. This training is provided through LSFP collaboration with FD F&ES at no cost to NCI at Frederick or to the participants.

During the period, LSFP is projected to have performed 740 consultations, an increase from 266 last year. Specialized inspections of common space, animal facilities, laboratories, and the cafeteria increased to 164 from 160 last year. In addition, 42 reports of fire, fire alarm activation, smoke, and related odors were investigated.

EHS and FME combined efforts to investigate the cause of each fire alarm activation and take steps to prevent recurrence. As a result, the number of non–fire activations of fire alarms decreased by 23 percent. The decrease in non–fire activations improves occupant confidence in the fire alarm system, reduces the number of times occupants must interrupt their work to

evacuate the building, and reduces the number of emergency responses by the fire department.

LSFP managed 108 automatic external defibrillators (AEDs) on and off-campus, and is coordinating pad replacement to ensure the continued functioning of all of the installed AED units. AED inspections, extinguisher checks, exit sign checks, and emergency light checks are performed by Protective Services officers while on patrol.

During this review period, LSFP assisted the FME Project Management and Engineering departments in matters pertaining to life safety and fire protection in numerous significant projects. This year, the NIH Division of the Fire Marshal (DFM) began providing review of construction plans, consultation, inspection prior to closing ceilings and walls, and occupancy permit authorization, which is required in NIH-owned facilities. Effective coordination with the NIH DFM allows a consistent approach within the NIH community.

An LSFP staff member received training at the Maryland Fire and Rescue Institute and continues to be certified as a fire inspector I (CFI-1). In addition, this year he attended multiple seminars to receive specialized training to meet the requirements for recertification as a certified fire protection specialist (CFPS). He represents the NCI at Frederick through membership in the National Fire Protection Association (NFPA) Industrial Section and the NFPA Healthcare Section, and he participates in NFPA section meetings and NFPA technical meetings to consider and vote on updates to the NFPA codes, which are proposed during each code cycle.

Advanced Technology Research Facility Environment, Health, and Safety

ATRF EHS is dedicated to reducing injuries, accidents, and environmental impact at the ATRF, and ensuring that activities at the ATRF are in compliance with all federal and state regulations, as well as with NIH guidelines and NCI Frederick policies and procedures. EHS accomplishes this by providing quality training, comprehensive workplace evaluations, emergency response, and hazardous materials management from acquisition to disposal, and by managing regulatory information. At the ATRF, EHS encompasses all branches of safety within one office and performs tasks associated with biological, chemical, radiological, and fire and life safety, as well as with industrial hygiene and environmental and waste management services.

Industrial Hygiene (IH) services: One hundred ninety-five eyewash stations were tested per OSHA regulations. Work orders were submitted to FME for all eyewash stations requiring repairs and follow-up was performed.

ATRF EHS researched and updated individual chemical, biological, radiological, and equipment inventory lists. As a result, new or updated signage was posted in 40 laboratories to fulfill regulatory requirements as well as alert lab users, visitors, and emergency responders to specific hazards within these laboratories. Additionally, the state of Maryland requires a list of all non-laboratory chemicals by facility. ATRF EHS reviewed and updated the list of approximately 140 non-laboratory chemical products and their accompanying safety data sheets (SDS).

During the course of the year, 5 forklift evaluations were performed, 15 safety shoe/eyewear forms were signed, 9 fall protection plans were created and approved for FME and outside contractors, 4 general safety plans were approved for outside contractors, 6 SDS were researched, reviewed, and approved for the BDP, and 1 noise survey was performed.

Also, ATRF EHS helped FME schedule all chemical fume hoods for certification.

Ten incidents were reported at the ATRF, resulting in investigations and corrective actions and completed reports. Sixty-nine ad hoc deficiencies were noted at the ATRF, and nearly all were corrected and closed out within 45 days, and annual safety inspections were performed for all areas of the facility within the calendar year (2014).

ATRF EHS also provided refresher training on waste and general safety for FME custodial workers; participated in the ATRF Clean Sweep Orientation; provided two waste disposal training sessions for ATRF laboratory personnel; and provided training to FME maintenance workers on flat roof access and safe use of portable ladder.

Environmental and Waste Management Services: ATRF EHS performed weekly hazardous waste inspections for all ATRF waste areas throughout the year, and there have been 3 hazardous chemical waste and 8 biohazardous, or medical waste, pickups.

ATRF EHS shares waste disposal tasks with the EHS Waste Department and provided numerous waste container drop-offs and autoclave waste transports throughout the year. The ATRF safety officer was trained in the wastewater permit responsibilities for the new permit cycle that started in July and will take over these duties from the Waste Department.

An inspector from the City of Frederick's Wastewater Pretreatment Office toured the ATRF to review effluent records, spill response plans, and supplies, and to ensure pH neutralization and steam sterilization equipment is maintained per the facility's Wastewater Discharge Permit requirements. No violations were noted.

Biological Safety Tasks: During the contract year, ATRF EHS received and processed 4 DEA-controlled substance shipments and performed 4 DEA-controlled substance audits. ARTF EHS helped distribute Tax-Free Alcohol logbooks to authorized laboratory programs and performed 38 tax-free alcohol audits. ATRF EHS helped the FME hood crew with biological safety cabinet (BSC) certification scheduling for all BSCs at the facility, and assisted the assistant biosafety officer in ATRF autoclave inventory.

ATRF EHS, with assistance from ATRF Security, surveyed FME and all unoccupied spaces for the NIH Clean Sweep initiative, and provided assistance with the NIH verification process.

Fire and Life Safety: ATRF evacuation maps were completed and posted in various public spaces frequented by visitors during seminars, retreats, and other public events, and maximum occupancy signage was created and posted for the ATRF auditorium. ATRF EHS had its annual fire evacuation drill in October with assistance from EHS personnel from the main campus, FME, and Security. Thirty-six hot work permits were approved by the ATRF safety officer during the contract year.

Radiation Safety Tasks: The ATRF has three radioisotope programs and one electron microscope program. ATRF EHS assisted the Radiation Safety Office in providing radiation safety support to 48 individuals who are approved to manipulate radioactive materials and/or work with electron microscopes at the ATRF.

ATRF EHS performed 100 percent of regulatory-driven contamination surveys each month. On average, 45 samples were taken each month at the ATRF (with no contaminated sites above the MDE-driven action level of 220 dpm). This low overall level of radioactive contamination demonstrates that facility radiation workers are keeping exposures to radioactive materials as low as reasonably achievable (ALARA). ATRF EHS staff also performed a six-month inventory for all ATRF radiation programs and a physical inventory for all radioisotopes present, as well as a uranium inventory for the electron microscope program. The ATRF EHS processed nine incoming radioactive materials shipments within three hours of receipt, in accordance with internal policy and the Code of Maryland Regulations.

The EHS Radiation Safety Department had an outside auditor, RSO, perform an audit of the ATRF EHS Radiation Office. The inspection included activities conducted under the ATRF limited-scope RAM license. Based on inspection findings, no violations were identified.

Facility Renovation Projects and Construction Services: ATRF EHS provided assistance to FME for 10 projects and special assists by reviewing and approving safety plans; providing room safety clearances and completion walk throughs; issuing hot work permits; creating and approving fall protection plans; assisting with facility alerts; and posting all required documents on the EHS SharePoint site.

Vaccine Clinical Materials Program Environment, Health, and Safety

Vaccine Clinical Materials Program (VCMP) EHS provides the full range of safety support functions to the Vaccine Research Center's Pilot Plant facility. This includes hazardous waste management; fire and life safety; regulatory compliance at the state and federal levels; industrial hygiene; biological safety; and environmental management. These functions are balanced within both NIH and NCI at Frederick guidelines and policies as well the U.S. Food and Drug Administration's (FDA's) Current Good Manufacturing Practices (cGMP) requirements for clinical vaccine production. EHS duties at the VCMP are carried out with one safety officer providing on-site support but utilize a coordinated effort with VCMP FME and NCI at Frederick EHS staff to ensure safe and successful operations.

Environmental and Waste Management Services: As a manufacturing facility, the VCMP at times produces both bulk chemical and biological wastes. The facility currently uses a batch steam-sterilization system for liquid biological waste processing. The VCMP also uses a pH neutralization system to process many chemical items in an effort to minimize waste disposal requirements and costs.

VCMP EHS works with EHS Waste Management in transport, packaging, consolidation, and processing of hazardous materials/waste produced in both laboratory and production activities. VCMP EHS also works with EHS Waste Management in annual Emergency Planning and Community Right-to-Know Act (EPCRA) Tier 2 inventory and reporting of large-volume hazardous materials storage and usage. For VCMP waste disposal, there have been four chemical waste shipments and weekly pick-ups of regulated medical waste.

Fire and Life Safety: The VCMP conducted an annual evacuation drill in January 2015 with assistance from EHS, FME, and Protective Services staff. Evacuation signage was updated to note the location of a new assembly point. Annual fire extinguisher training was conducted on site in March 2015. VCMP Protective Services staff also provides regularly scheduled cardiopulmonary resuscitation/automatic external defibrillator (CPR/AED) training to all VCMP staff. Thirty-four hot work permits were approved and submitted to EHS since September 2014.

Industrial Hygiene Services: An annual performance test was performed on all 29 VCMP eyewash stations, per OSHA regulations. All noted deficiencies were quickly corrected by VCMP FME staff. Two portable units were also installed in the HVAC and chiller buildings to meet OSHA requirements.

The VCMP produces vaccine materials for Phase I and Phase II clinical trials. To comply with both FDA and OSHA regulations, SDS documents are authored for all of these materials. VCMP EHS works with VCMP Quality Assurance to ensure compliance with the Globally Harmonized System for Hazard Communication on these SDS documents. VCMP EHS also manages the SDS inventory for VCMP's 511 chemical items/products.

Over the past year, the VCMP has successfully completed two confined-space entries into its 2,000-liter bioreactor for repair and maintenance. Two elevated work plans, one of which was created by EHS, have been evaluated and approved. A noise survey of the HVAC and chiller buildings was conducted. Fall protection training was conducted for all VCMP FME and EHS staff to ensure safely working at height.

Earlier this year, at the request of VCMP FME, an extensive safety audit of VCMP's HVAC and chiller buildings was conducted by EHS. Numerous deficiencies were reported and subsequently corrected in conjunction with VCMP FME. The VCMP annual safety inspection (still in progress) noted 29 deficiencies so far. FME staff corrected 26 of these within one week of reporting. The remainder are in progress or administrative in nature.

In the past year, three incidents have been reported at the VCMP, resulting in an investigation, and an additional three ad hoc deficiencies were reported. All three ad hoc deficiencies were corrected by VCMP FME within 24 hours of reporting.

Facility Renovation and Construction Projects: VCMP EHS provided assistance to FME in the review of safety plans and hazard assessments for three different projects, including an elevated work project involving crane and rigging work as well as elevated masonry repair in the VCMP warehouse area.

Biological Safety: VCMP EHS provides ongoing support to laboratory, facilities, and manufacturing staff in all areas of biosafety. An audit of the VCMP Tax-Free Alcohol Program was conducted earlier this year. New waste containers were purchased to ensure proper and compliant storage of all regulated medical waste in laboratory areas. VCMP EHS also coordinated with OHS to provide two on-site seminars to educate staff on Leidos' participation in National Institute of Allergy and Infectious Diseases' (NIAID's) and NIH's Ebola clinical research program in Liberia.

Protective Services

Protective Services Access Control performed more than 6,000 identification badge and cardkey transactions. The Protective Services Homeland Security Presidential Directive 12 (HSPD-12) Program Office fingerprinted and processed more than 1,000 FNLCR employees for their personal identity verification (PIV) badges.

EHS is part of a project team to upgrade the Pegasys P2000 cardkey system across the NCI at Frederick campus and off-site facilities. This project team includes stakeholders from FME, IT Security, and DMS, and coordinates with the NIH HSPD-12 Program Office.

Protective Services continues to provide daily inspections of NCI at Frederick fleet vehicles. Such inspections include refueling these vehicles daily and making certain vehicles are washed as needed. Passenger shuttle service to NIH was maintained throughout the year, and more than 5,500 passengers used the service. In addition, Protective Services continues to run "special shuttles" to provide guest researchers transportation between their Frederick hotels and Fort Detrick, and transportation to the NIH campus for seminars. In April 2015, Protective Services began operating an after-hours shuttle service from Building 426 to points outside the Fort Detrick gates that close early, for employees who walk to work and are affected by the new gate closing times. "Special shuttles" must be approved by the EHS director.

Protective Services closely monitors scientific equipment located on the NCI at Frederick campus, the ATRF, and the VCMP Pilot Plant. Protective Services officers performed over 200,000 foot patrols at these locations. These patrols have resulted in the discovery of more than 18,000 scientific and utility alarms, more than 2,200 security violations, and more than 150 fire safety violations (such as, for example, portable heaters or coffee pots left on).

Protective Services continues to monitor and grant access to irradiator room users, and during the past year, more than 700 FNL employees were granted access.

Protective Services dispatch officers continue to greet and register NCI at Frederick visitors. Over the past year, more than 2,200 visitor badges were issued.

Protective Services officers continue to perform monthly checks of fire extinguishers, AEDs, exit lights, emergency lights, and exterior lights. During this period, more than 700 work orders were submitted to have faulty lights repaired.

Occupational Health Services

The Occupational Health Service (OHS) program provides comprehensive occupational health services for all employees at NCI at Frederick. The mission of OHS is to maintain and enhance employee safety and productivity; comply with federal and state regulations; and decrease costs associated with absenteeism, disability, workers' compensation, and health insurance, by keeping NCI at Frederick employees aware of potential health risks. The multifaceted OHS program focuses on disease and accident prevention, treatment, management, and rehabilitation, which are accomplished through comprehensive screening and surveillance programs, health promotion, and one-on-one employee consultations.

OHS works closely with other EHS program staff and has developed collaborative relationships with experts at the CDC, NIH, (NIAID), and the local medical and scientific communities as well as the local emergency medical services (EMS) team. Through these relationships, OHS works to ensure that NCI at Frederick employees receive the benefit of every work-health-related discipline in managing occupational medical concerns and issues specific to any/all potential or sustained occupational injuries and illnesses.

An essential element to performing our role is the development and maintenance of trust by NCI at Frederick employees in the care and confidentiality of services provided by OHS.

OHS has many varied medical surveillance programs in place. The type and number of programs continue to expand to meet the needs of our biomedical research community. Through its representation on the IBC and ACUC, OHS is able to modify existing protocols to meet accepted workforce health protection requirements and recommendations. New agents are discussed at the IBC and ACUC meetings, and medical protocols for the health and safety of employees are developed and approved.

OHS works closely with EHS to monitor the safety of all NCI at Frederick employees, both on campus and at our off-site facilities. This team approach helps with accident investigation and with the evaluation of the surveillance programs. Collaborating with EHS, OHS individually screens each employee for potential hazards in the workplace and provides instructions on the emergency 1-2-3 approach to first aid. In support of EHS, OHS promotes awareness to ensure that employees know and understand all possible risks to themselves while in the workplace. As part of this tandem approach, OHS offers appropriate medical surveillance programs and necessary vaccines. When a workplace injury occurs, OHS offers immediate medical treatment and follow-up for prompt return to work.

OSHA reports, as well as accident investigations and corrective actions, are reviewed monthly by EHS and OHS to track the severity of occupational illness so that trends can be identified.

Work-related injuries/illnesses are treated in the Occupational Health Clinic by OHS clinicians. All workers' compensation claims are reviewed by an independent medical consultant and discussed with the provider. This in-house treatment enables OHS to help reduce employees' medical expenses and lost time, as well as workers' compensation costs. Most importantly, it enables a continuity of medical care that is the best practice for the health and welfare of NCI at Frederick employees. The OHS staff is well trained and knowledgeable in the unique risks and job requirements of working in a biomedical research facility. They work with employees, their supervisors, Human Resources, and, if required, outside medical providers to enable employees to return safely to work following injury or illness.

OHS works with NCI at Frederick staff in performing return-to-work exams for the management of complicated disability- and work-related cases, and serves as a valuable resource for other work-related issues. Episodic and acute services offered by OHS include: minor laceration repair; fracture stabilization; bumps; sore throats; ear infections; and other "just don't feel well enough to stay at work" conditions. This service encourages immediate and appropriate attention to urgent care health problems, which increase employee productivity by reducing the need for, or length of, sick leave and lost work time.

Urgent care is the treatment of a disease, illness, or injury when presented on an episodic basis. The disease, illness, or injury treated in an OHS setting is usually acute, and with treatment, is fully corrected in seven to fourteen days. The services are provided five days each week, for an average 60 minutes each day, from 10:30 a.m. to 11:30 a.m., and an appointment is not required. Nurse practitioners and nursing staff are providers in the OHS clinic. Because the focus is on only episodic problems, the OHS practitioners do not provide obstetric services, in-hospital admission, or long-term management of chronic diseases such as cancer, diabetes, heart disease, hypertension, or other conditions requiring long-term medical management.

OHS clinicians are on call 24 hours a day, 7 days a week, to respond to after-hours biological emergencies. OHS has streamlined support to the HIV production lab on campus and an ATRF lab working with frank oncogenes to establish a lock box with post-exposure medications. This lock box on site would necessitate a call to the OHS clinician on call to provide the combination and consultation for timely post-exposure medication dispensation.

Significant Achievements

American Red Cross Blood Drives: OHS hosted 4 blood drives during the year, collecting 121 units and meeting or surpassing our goal at every drive.

Hearing Conservation Program: There are 66 employees enrolled in the Hearing Conservation Program. We are in 100 percent compliance with OSHA regulations.

Reproductive Health: OHS conducted 11 pregnancy interviews; this program is voluntary but highly recommended to protect maternal health and fetal development. The supervisor, employee, and nurse practitioner meet to identify potential reproductive hazards in the employee's work environment. OHS collaborates with the NIH Lactation Program to educate the employees as well as support the Lactation Program.

Blood and Body Fluids, and Other Potentially Infectious Material (OPIM) Program: After counseling by OHS, 148 employees either started the hepatitis B series, had a hepatitis B titer drawn, or declined services.

Respiratory Protection Program: OHS performed respirator protection evaluations on 332 NCI at Frederick employees. These included all employees whose work scope requires them to wear a respirator and obtain appropriate fit testing. OHS is responsible for notifying and maintaining 100 percent compliance with this OSHA-mandated program. OHS is responsible for notification and completion of all OSHA-mandated respirator fit testing for employees at the main campus, NIH, and ATRF, including those who wear paper respirators as well as those requiring fit testing.

Animal Care Worker Program: OHS provides a medical screening program for all NCI at Frederick employees who enter into an animal facility and/or work with live animals or tissue. This screening identifies those employees who may present with allergy signs and symptoms and aims to prevent occupation-related asthma. OHS collaborates with EHS in the allergy-prone animal worker to identify PPE and to evaluate work-site practices.

Off-site, nonhuman primate workers are offered special shuttle service to OHS semiannually for medical surveillance exams, thus ensuring improved AAALAC compliance and outcomes. Additionally, OHS has a staff member on the ACUC to provide enhanced support to LASP.

Off-site Services: OHS staffs a clinic with a licensed provider at the ATRF three days a week for four-hour periods. The scope of services includes work-related visits and minor urgent care.

First Aid and Cardiopulmonary Resuscitation Program: OHS conducts first aid and CPR certification courses to employees at the NCI at Frederick campus and off-site facilities. OHS coordinated with Protective Service officers to maintain current first aid kits and planned training for off-site employees who have extended or protracted working hours (such as those working at LASP and FME). Classes are offered every month.

OHS participates in the Werner H. Kirsten Student Intern Program and is mentoring two new students for the upcoming year. In addition, OHS is sponsoring two returning students.

The manager of OHS serves as a co–contracting officer's technical representative (COTR) for the Business Health Services (BHS; Employee Assistance Program) contract. Responsibilities include reviewing quarterly utilization and examining ways to communicate to employees about BHS services.

Research Donor Program: OHS administers the NCI at Frederick Research Donor Program (RDP), which is an NIH Institutional Review Board (IRB)-approved research protocol. The RDP supplies anonymous donor blood and other human samples to researchers at NCI at Frederick. Utilization of the RDP has consistently increased, and investigators continue to express appreciation for these specialized services, as they are otherwise unavailable and are critical to the quality and continuity of their research.

These donations have helped the research for more 70 different programs.

Medical Surveillance: OHS coordinates surveillance programs with EHS for employees whose job requirements may pose potential health risks. A Medical Surveillance Enrollment Form (MSEF), developed in conjunction with the Biological Safety Program, provides a complete, systematic method of collating medical hazard information specific to the employee's work functions. EHS is responsible for the distribution and collection of the MSEF.

Staff Development and Certifications: Clinical staff members participate annually in clinical nursing skills and are tested to prove clinical competency (e.g., administration of EKG, Morgan Lens, parenteral injections). All nursing staff members are certified in spirometry and hearing conservation. OHS has a certified RN workers' compensation case manager. In addition, the manager of OHS recently achieved certification in occupational health nursing and serves on the American Association of Occupational Health Nursing Board. OHS also has a representative on the Frederick County Chamber of Commerce Wellness Committee.

Wellness Program: The Wellness Program has been clearly branded and advertised as a separate program that is voluntary and is not included in the work-related annual exam offer. The Wellness Program offers influenza vaccines, cholesterol testing, blood pressure screening, and the Take a Hike event. This past year OHS collaborated with DMS to update the Wellness Challenge website to encourage employees to participate in wellness activities.

Statistical Overview: OHS logged 5,189 encounters during the period from September 25, 2014, through July 25, 2015. The ATRF satellite clinic logged 378 encounters, and the VCMP off-site clinic logged 14. Changes in program protocols and reviews of surveillance needs, as well as efforts to limit lost work time by combining visits, have resulted in fewer visits. Some services, such as TB testing, respirator exams, and annual surveillance reviews, are combined into one visit.

FACILITIES MAINTENANCE AND ENGINEERING

During this contract year, Facilities Maintenance and Engineering (FME) achieved successful completion of a wide array of projects for NCI at Frederick. The following highlights some of these accomplishments.

Renovation of Keller, Muegge, and Hou lab, Wing 1, first floor, Building 560: The major laboratory renovation was completed on schedule, providing a complete renovation of a portion of Wing 1, Floor 1. The project also includes N+1 redundancy of heating, ventilation, and air conditioning (HVAC) equipment to serve the first and second floors of Wing 1.

Replace main head of Frederick National Laboratory for Cancer Research campus building automation system: A major upgrade to the operating system which controls the campus HVAC energy management system has been implemented with this project. The existing operating system was obsolete and needed to be replaced in order to remain compatible with the advanced computers and features being integrated into the system. The building automation equipment was supported by a building automation system (BAS) server which ran under the IBM OS2 Warp operating system. The OS2 operating system is no longer sold or supported by IBM and our computer services could not support FME with OS2 related issues. Due to the age of the operating system, it could not run on newer computers. This project provided hardware, software, licenses, and labor necessary to upgrade the existing IBM operating system to the Invensys IA (intelligent automation) system for the Frederick National Laboratory for Cancer Research (FNLCR) Campus BAS.

Renovations for installation of multiple high-end laser microscopes, room 12-47, Building 560: This project provided the renovations necessary for a high-end microscopy suite suitable for several confocal scope stations. In addition, the project consolidated much of the imaging effort for the Center for Cancer Research (CCR) and provided the upgrades necessary for the recently purchased Nikon Super Resolution N-SIM system and two existing JL microscopes.

Evaluation/repair/replacement of sidewalk, storm water drainage, and retaining wall, Building 427: This project replaced the sidewalk running from the northwest corner of Building 427, to the west entrance of Building 430. The sidewalk replacement established proper storm water drainage and eliminated ponding water. In addition, several locations had settled and shifted, presenting multiple trip hazards that have now been eliminated. This length of sidewalk provides access to four buildings, and its replacement was performed in three phases in order to maintain access to all buildings throughout construction.

Install reverse osmosis water system return line, Building 539: The purpose of this project was to improve the quality of the reverse osmosis (RO) water supply within Building 539. The main distribution piping system, composed of schedule 40 and schedule 80 polyvinyl chloride (PVC) pipe, has been replaced with state-of-the-art polypropylene piping. The piping routes have been simplified where possible, and re-circulating loops have been installed. The new RO water distribution piping system has been connected to existing laboratory RO water piping within each lab area from their takeoff points at the corridor utility chases. The existing piping within the laboratories will be replaced with polypropylene piping in future renovations. The scope of work for the project was developed to provide an RO water system that meets the requirements of the (National Institutes of Health) NIH Design Requirements Manual.

Replace air-cooled chillers, Buildings 350 and 539: This project provided chilled water to Building 350 from chilled water plant number 2, and eliminated an outdated R-22 air-cooled chiller that had been serving the building since 1997. The existing chiller number 3, in Building 539, was replaced with a more reliable, 400-ton, chlorofluorocarbons (CFC)-free machine, to provide chiller plant number 2 with greater cooling capacity for the increased load. These changes resulted in a more efficient, and environmentally friendly, system by upgrading the chiller plant loop and eliminating obsolete equipment.

Install emergency generator, Building 550: This project included the addition of two new 600 kilowatts (KW) bi-fuel (natural gas/diesel) emergency generators at Building 550. This project provides emergency power for both the animal facilities and the laboratories located on the first and second floors of Building 550. Previously, there was no backup emergency power for Building 550. The two generators run in parallel to provide a total capacity of 1,200 KW. Depending on the load required, one or both of the generators will operate in emergency situations. During power outages in the summer months, when chiller operation is essential, both generators will run. Alternatively, during outages in the winter months, when the chiller is not needed, only one generator will be required to support the reduced load. This project is part of an FNLCR initiative to connect all animal facilities to emergency power in the event of an electrical outage.

Contractual metrics: FME completed 99.89 percent of scheduled preventive maintenance activities and 99.99 percent of life safety and critical systems preventive maintenance activities.

Cost savings/containment: FME works collaboratively with NCI and program staff to provide cost-effective solutions to its customers' needs. Considerable effort has been expended in optimizing staffing levels for all departments in relation to projected workload and NCI expectations.

Customer service: FME's customer surveys represent opinions from all requesters of FME's services. For this contract year; FME received an overall performance score of 3.8 on a scale from one to four. FME continues to score high in the areas of quality of work and professionalism.

Program Initiatives

As part of the successful efforts of the Facilities Working Group, FME, in conjunction with NCI, implemented a comprehensive, revised standard work order process that streamlines the overall work order process. Reduced cycle times for approvals, simplification of the steps associated with changes during the course of design and construction were notable outcomes of this effort. This new process will be closely monitored to assess its impact and effectiveness in providing the responsive service and high-quality product expected of FME.

Information Technology Operations Group

The Information Technology Operations Group (ITOG) is responsible for computational servers, storage servers, and the NCI at Frederick network. ITOG focuses on implementing enterprise IT best practices in the areas of computational services, storage, backup, and archiving; server consolidation and virtualization; network infrastructure; unification of voice, teleconferencing, and video communication technologies; and improved infrastructure for the colocation of dedicated servers. The group is organized into three technical areas of responsibility: (1) Architecture; (2) Storage and Server Operations; and (3) Network Operations. Specific highlighted accomplishments include the following:

- Synchronized the secondary backup site for the CGhub data, with over 2.44 petabytes (PBs) of data stored at the Building 430 and Advanced Technology Research Facility (ATRF) data centers
- Virtualized more than 150 servers during the year, with more than 860 in service, and retired 100 unused servers
- Upgraded VMWare to the new version and replaced aging servers with new equipment
- Improved the MOAB batch system by adding 21 new nodes to support the Microscopy group
- Started phase two of the IPv6 project

- Continued work on the Network Access Control (NAC) implementation
- Continued work on the Voice over Internet Protocol (VoIP) implementation
- Developed a unified communications strategic plan
- Upgraded the Building 430 firewall
- Arranged for the ITOG director to take a temporary assignment at the Center for Biomedical Informatics and Information Technology (CBIIT) two to three days a week to assist with strategic and long-range planning.

Architecture

The ITOG director is working with the NCI Office of Scientific Operations (OSO), CBIIT, and Data Management Services (DMS) to develop an NCI IT research strategic plan. He has also worked with SRA International, Inc., the CBIIT IT contractor, to develop a plan to reduce the CBIIT footprint at Sterling, VA, and eventually discontinue use of the facility. This will save $1.9 million a year.

Storage and Server Operations

Secondary Backup Site for CGhub Data: The backup operations for The Cancer Genome Atlas (TCGA) data are synchronized with CGHub. Maximum download performance remains at about 15 TB/day. The data is being stored using the new Oracle/STK T10000D drives, and there are now 110,000 files occupying 2.440 PBs of data.

Server Virtualization: All of the virtual machines (VMs) support various groups and laboratories in Frederick and at other National Institutes of Health (NIH) locations. These locations include, but are not limited to, Data Management Services (DMS); the Center for Cancer Research (CCR); the Laboratory of Proteomics and Analytical Technologies (LPAT); the Imaging and Visualization Group (IVG); the Small Animal Imaging Program (SAIP, Laboratory Animal Sciences Program [LASP]); the Optical Microscopy and Analysis Laboratory (OMAL); and the CBIIT. The ITOG VMware infrastructure currently includes three vCenters hosted on Cisco UCS hardware. The primary vCenter consists of three main clusters; the first of these clusters, located at the ATRF, consists of 16 ESXi hosts that support nonscientific/business related VMs; the second cluster, also located at the ATRF, consists of 9 ESXi hosts and supports scientific and larger-resource VMs; the third cluster, located in the Building 430 data center, has eight ESXi hosts and supports mostly scientific VMs. The backup vCenter has six dedicated ESXi hosts available in the event of a disaster recovery (DR) scenario; this vCenter consists of other ESXi hosts that help support the unified communications (UC) VOIP environment and to facilitate the transfer of VMs from the Frederick to the CBIIT infrastructure. The Virtual Desktop Infrastructure (VDI) vCenter consists of six ESXi hosts that support about 100 desktop VMs. During the past year, the biggest change to the environment was that the ITOG has allowed two other groups to create and manage VMs within the infrastructure (CCR and DMS). ITOG also allows DMS to manage VDI VMs that are utilized in training rooms. Since July 2014, approximately 150 VMs have been added at the rate of 13 new VMs per month. A small number have been removed, and at least another 100 VMs are powered off and awaiting removal via the decommission process. This leaves the standing count of 861 VMs at the end of June 2015. ITOG software licensing consists of 86 [VMware vSphere Enterprise Plus] licenses used for ESXi hosts supporting virtual servers and 300 [VMware vSphere Desktop] licenses used for ESXi hosts supporting virtual desktops. ITOG has 92 [Unitrends Virtual Backup (UVB)] software backup licenses used to back up VMs and 92 [VMTurbo] software licenses used to provide automated assistance with managing, tuning, and reporting on the VM environment.

Improvements to the MOAB Batch System: The batch facility continues to see increased activity in support of sequence analysis. The facility has had additional servers placed into operation, including 21 new nodes to support the Microscopy group. These additions have been beneficial when dealing with peak user demands. A new submit facility, Nitro, which is similar to swarm on Biowolf, has been tested and is being placed into production. This is a requirement of the Microscopy group and will be useful to other users.

Lightweight Directory Access Protocol LDAP Upgrade: A new set of LDAP servers are being placed into production to support Data Science and Information Technology Program (DSITP) systems and storage units. The new servers bring in new capabilities that will reduce the amount of information being stored locally and the amount of time system administrators must spend maintaining the information. The effect of these changes will be to allow users to authenticate to DSITP systems using their Active Directory credentials.

Improved Linux Deployment: A new deployment option has been implemented to supplement the changes made in previous years. A custom boot image has been created for rapid and consistent installation of HPC nodes. In combination with existing infrastructure, a new HPC node can be brought from bare metal to a functional system within 30 minutes.

Support of the IPv6 Implementation: Procedures for enabling IPv6 on current Ubuntu and CentOS systems have been standardized, and systems are on schedule for the end-of-calendar-year deployment milestone. Owners of systems that are not IPv6 capable, such as Debian and older CentOS systems, have been contacted about upgrading the systems, and the upgrades are being scheduled.

Commodity Storage: Options for low-cost commodity storage solutions to supplement the existing Isilon storage systems have been investigated. The open-source Lustre system, with support from Intel, and the open-source Gluster system have been installed and are

being tested. A decision on which system to implement should be made in the near future.

Network and Telephone Group

Start of Phase Two of IPv6 Project: ITOG has started Phase Two of a three-year project for the mandatory migration from IPv4 to IPv6. This year, the Network and Telecommunications Group (NTG) completed Phase One of the plan, including the configuration of core and edge switches, the configuration of border routers and firewalls, an update to our Domain Name System infrastructure, and the configuration of our Infoblox appliances. Phase Two has started with the preparation of our servers, storage, and virtual machines for IPv6. Phase Three will start in CY2016 and will move workstations, printers, and other devices to IPv6.

Network Access Control Implementation: This year, NTG enabled all edge switches with an NIH-compliant Network Access Control (NAC) configuration, allowing all edge switch ports to participate in the mandated NAC project.

Voice over Internet Protocol Implementation. This year, we have completed the Voice over Internet Protocol (VoIP) hardware/software upgrades and Phase 1 of 4 of the Session Initiation Protocol SIP trunking configuration. In addition, two-thirds of VoIP end points have been deployed this year. NTG has provided customer training for each building prior to deployment.

Development of Unified Communications Strategic Plan: We developed a unified communications (UC) strategic plan to harmonize the VoIP and VTC deployments between the NCI and NCI at Frederick. The focus of the plan is on cost savings and economies of scale between the two campuses.

Building 430 Firewall Upgrade: The pair of firewalls in the Building 430 data center was replaced with a single Cisco ASA5585 firewall. The upgrade replaced hardware that had been announced by Cisco as End of Life. The new firewall is identical to the fault-tolerant unit located in Building 350.

Information Security and Compliance Office

The Information Security and Compliance Office (ISCO) within DSITP is the official NCI at Frederick office for the local information systems security officers (ISSOs), and it serves as the point of contact for NIH security compliance requirements and responses to security incidents. ISCO is responsible for security assessments, waivers, IT risk assessment, and security incident handling, and for working with NCI at Frederick IT groups to integrate best practices into IT planning and implementation. For 2014–2015, ISCO has successfully completed several initiatives within NCI at Frederick. Listed below are several accomplishments within the ISCO:

- **Security Assessments**
  ISCO conducts Federal Information Security Management Act (FISMA)–related security assessments each year. In addition to assessing new systems, ISCO conducts annual assessments each year to confirm authorized systems are up-to-date on security requirements. The following systems received new authorizations to operate, which requires a full review of all National Institute of Standards and Technology (NIST) 800-53 controls:
  - Genomic Data Commons (GDC)—provides cancer genomics data in a co-localized database to serve as a foundation for future expanded data access, computational capabilities, and bioinformatics cloud research.
  - Occupational Health Manager (OHM)—the database system used to maintain medical records for employees, visiting scientists, fellows, and others who are employed through NCI at Frederick who visit Occupational Health Services.
  - Druva Backup Solution—The Druva inSync Hybrid-Object-Based Storage system provides a backup service for Windows and Mac laptops and desktops within NCI at Frederick.
  - Sequence Read Archive repository—provides the NCI research community with secure, high-speed access to all existing sequence reads and their associated metadata from The Cancer Genome Atlas (TCGA) repository.
  - Frederick Physical Access Control System—provides perimeter security and access control for all NCI at Frederick facilities.
- **Annual Vulnerability Assessment**
  The NIH Vulnerability Assessment team performs annual testing on our network to identify any system deficiencies. The amount of vulnerabilities decreased by 65 percent during 2015's assessment, as compared with 2014's assessment. ISCO was able to work with system administrators to remediate all findings before the required NIH completion date.
- **Passive Vulnerability Scanners**
  ISCO worked with ITOG to implement passive vulnerability scanners (PVS). PVS non-intrusively monitors all traffic to identifying active systems on the network, along with detecting abnormal activity. These scans, together with our current Tenable Security Center installation, have greatly increased the visibility into the network and improved our ability to detect vulnerabilities.
- **Enhanced Visibility into Public-Facing Systems**
  NCI at Frederick has approximately 90 public-facing systems. ISCO worked the system administrator of each system to enable credentialed vulnerability scanning and categorize the data stored on the system. This information allows us to quickly

identify any vulnerabilities using scans and to ensure the system is adequately protected to reduce our risk of external compromise.

CONTRACTS AND ACQUISITIONS

The Contracts and Acquisitions (C&A) Directorate was reorganized during FY2015 as part of the organizational restructuring of Leidos Biomed's FNLCR operations. This restructuring received NCI approval in January 2015.

Responsibility for all FNLCR prime contract administrative functions was assigned to C&A in January 2015. The consolidation of all prime contract responsibilities within C&A facilitated the joint efforts of NCI and Leidos Biomed to establish a new Indefinite Delivery/Indefinite Quantity (IDIQ) Task Order Contract during FY2015 that works in tandem with the Operations and Technical Support (OTS) Contract. C&A continues to be responsible for purchasing, research and construction subcontracts, intellectual property, and logistics.

Robert Mason was appointed C&A's directorate head in April 2015. He has been with SAIC/Leidos for 20 years, during which time he has held positions of increasing responsibility in federal, commercial, and international contracting. In particular, he has extensive experience in working with IDIQ task order contracts. This experience was instrumental in the development, negotiation, and implementation of the new IDIQ Task Order Contract that was agreed to by NCI and Leidos Biomed in September 2015.

Purchasing

The Purchasing Department is responsible for the acquisition of commercial goods and services, including equipment maintenance and fleet services, as well as management and training for program areas using the blanket order and credit card programs.

The primary administrative focus of the Purchasing Department this year has been to address the changes requested by NCI to the Service Maintenance Agreement (SMA) process and SMA reporting to include additional functionality. A Purchasing and Logistics Users' subcommittee, consisting of requesters from all program areas, was formed in February 2015, to discuss the entire SMA process in its current state and determine the optimal level of functionality and reporting needed going forward. In addition, the Purchasing Department analyzed the staffing level needed to meet and sustain the current and proposed level of service. Accomplishments from periodic meetings concluding in June 2015 included the following:

- Assigned additional interim staffing to relieve the backlog of renewal and warranty expiration notices. A part-time temporary employee was hired to provide assistance and a buyer was pulled from lab supply orders and blanket purchase agreements to assist. Additional full-time employees are also being requested in support of these functions.
- Created a standardization of advance notices for both expired warranties and SMA renewals to be issued 120 days in advance of expirations with the requirement for a program response within 90 days of expiration to provide Leidos Biomedical Research sufficient time to negotiate and place the agreements.
- Updated the Service Contract Addition Form to include new information.
- Created a Service Contract Deletion Form.
- Developed a web page on FNLCR site.
- Created a 3 percent threshold on price increases to trigger communication between buyer and end-user point of contact (POC).
- Reviewed and updated all data components of the SMA Detail Report for improved functionality.
- Added preventive maintenance information to the renewal notices.
- Reached a consensus that program areas will schedule their own preventive maintenance requests or initiate with Purchasing using the request for vendor service (RVS) form. Many program areas have established routines and tracking systems that meet their individual needs.
- Purchasing conducted training on updated procedures with CCR administrative officers.
- Developed an SMA Summary Template to provide a quick reference format for the various services provided and any exclusions to the SMA; to be completed by the vendor.
- An additional software tool developed by one of the committee members was to be tested.

The Purchasing Department attended two small business outreach events this year:

- Alliance Baltimore Small Business Procurement Fair
- SMARTPROC – Strengthening the Mid-Atlantic Region for Tomorrow

The Leidos Biomed Purchasing Department is continually searching for new vendors, specifically small business vendors. This has expanded the competitive market for service maintenance agreements. Twenty-three new small business vendors registered on the Leidos Biomed Potential Vendor Database including six small disadvantaged, two service-disabled veteran-owned small businesses (SDVOSBs), one historically underutilized business zone (HUBZone), and two 8(A) businesses.

For orders placed by purchase order or blanket release, 38.8 percent were to small businesses and accounted for 33.8 percent of the total dollars spent.

The Purchasing Department continues to provide acquisition support at, or near, target performance milestones. Accordingly, some important measures of requisition actions are: 98.4 percent of material and supply requests were processed within 10 working days (target is greater than 85 percent) and 100.0 percent of radioisotope requests were processed within the established same-

working-day metric (target is greater than 90 percent; this result reflects purchase requests (PRs) that were submitted late, as well as those that were provided without the requisite Environment, Health, and Safety [EHS] signatures, both of which cause processing delays). Of the capital equipment requests processed, 91.2 percent of requests greater than $150,000 were processed within the established 25 working-day metric (target is greater than 85 percent), and 90 percent of requests between $5,000 and $250,000 were processed within the established 20 working-day metric (target is greater than 85 percent).

This activity represents total acquisition activity of 52,139 orders processed (purchase orders, credit cards, and blanket releases), totaling approximately $197.9 million through the reporting period.

Construction Subcontracts

Construction Subcontracts (CS) is responsible for all architecture and engineering, construction, and other subcontracting requirements, including the lease and utilities of off-site locations supporting NCI at Frederick operations.

During the year, CS has focused on reducing the time of the acquisition process in an effective and streamline manner. To that end, CS has modified existing agreements and secured credit cards for all staff in the efforts to increase the flexibility of placing orders for construction activities. The modifications made to existing agreements allow the issuance of task orders to single trade contractors in an expedited method, thus reducing the time between receiving a requirement, to having the work start. In addition, CS provided valued support with the development of the Lifecycle Diagram process for work orders less than $2 million. This Lifecycle Diagram process increases efficiencies in the area of reducing procurement time, reducing NCI approvals, and ascertaining commercial standards in the method of estimating and verification. Finally, CS has served, and continues to serve, as a project manager in the evaluation of lease options for Expansion of Product Development Capacity for YT15-090.

Research Subcontracts

Research Subcontracts (RS) is primarily responsible for the subcontracting of research-related work and various other services not commercially available in order to support the research activities of FNLCR, NCI, and other NCI and NIH programs. RS is currently managing approximately 450 subcontracts, totaling approximately $208 million. Many subcontracts require specialized acquisition strategy, and many are in support of major national research initiatives.

PREVAIL Clinical Trials: RS supported the establishment of a network of subcontractors necessary to start up the Partnership for Research on Ebola Vaccines in Liberia (PREVAIL) clinical trials in West Africa. This included the establishment of a number of agreements with both domestic and international institutions and consultants who provided support to the clinical trial operations and the recruitment of patients for this important vaccine clinical trial with National Institute of Allergy and Infectious Diseases (NIAID). RS has supported the effort in Liberia and will be an integral part of the expansion of the PREVAIL trial and ancillary studies related to Ebola in West Africa, and in other countries such as Sierra Leone and Guinea.

NCI–DREAM: RS provided critical support to the establishment of subcontracts with the awardees of the NCI–DREAM Challenge effort. This important NCI initiative awards important subcontracts to teams in support of precision medicine, specifically predicting the best treatment strategy based upon available genomic information. The awards under this NCI – DREAM Challenge were made in the area of drug sensitivity prediction and drug synergy.

Genomic Characterization Centers: RS worked with the Center for Cancer Genomics (CCG) to establish Genomic Characterization Centers (GCCs) with the ability to provide this high-resolution, systematic, comprehensive (genome-wide) characterization of cancer-related genomic alterations. The cancer biospecimens for these studies will be provided to the GCC through the Biospecimen Core Resource of CCG. The aim is to have all the characterizations conducted on biomolecules from the same biospecimens for optimal analytical integration for data comparability. It is anticipated that these centers will process 5,300 samples over the next two years.

Vaccine Research Center: During the year, the RS team continued to support the Vaccine Research Center (VRC) in its advancement of vaccine research, including the expansion of VRC efforts in several areas including the production of an anti-HIV monoclonal antibody (VRC01). This included the expansion of support for clinical trial production of vaccines and other immune modulators for the prevention, therapy or cure of HIV, BioD and other emerging infectious diseases, including those of high public health importance. RS supported the award of several subcontracts for chikungunya vaccine development, development of vaccines for several filoviruses and for malaria and TB.

Molecular Analysis for Therapy Choice: RS continued to support the Molecular Analysis for Therapy Choice (MATCH) Program both in the establishment of compliant clinical trials and other related support activities. During the period, testing continued on the assay with the Clinical Laboratory Improvement Amendments (CLIA) certified clinical subcontractors, and a new contract was established with ECOG-ACRIN to support providing patient samples in support of the trial. The NCI-MATCH Program will pursue a novel approach to testing therapeutic options for cancer treatment by evaluating actionable genetic abnormalities and the corresponding treatment agents against pharmaceutical agents. The study will screen for molecular features that may predict the response to a targeted agent with a specific mechanism of action, and will serve as an

umbrella for multiple, single-arm Phase II trials. Enrollment in the study is scheduled to begin in late summer or early fall of 2015.

Computational "Omics": RS provided support for the award of three novel Clinical Proteomic Tumor Analysis Consortium (CPTAC) projects related to the development of a new computational "omics" analysis pipeline and the development of new computational tools that utilize multiple large-scale "omics" datasets (examples include genomics, proteomics, transcriptomics and metabolomics), all of which will increase the knowledge available related to cancer biology and thus advance the diagnosis, treatment, and prevention of cancer. RS provided full-acquisition support, including preplanning and coordination with NVIDIA Foundation which offers a similar challenge on a smaller scale.

Therapeutics for Rare and Neglected Diseases: Therapeutics for Rare and Neglected Diseases (TRND) projects continued throughout the year, with the establishment of new basic ordering agreements and issuance of task orders to support TRND supported research. RS continued to work closely with both the National Center for Translational Sciences (NCATS) and collaborators on complex issues to ensure the protection of proprietary rights in the development process.

Contracts Department

The Contracts Department is responsible for the day-to-day administration of the OTS Contract and the newly awarded IDIQ Task Order Contract. Contract administration efforts include tracking hundreds of compliance points and deliverable requirements, managing the conflict of interest program, providing document control and maintenance, tracking contract metrics, and negotiating changes to contractual terms and conditions. As a component of overall contract administration and compliance efforts, the department has implemented five aspects of contract administration and is structured, in part, based on these aspects. The attributes of these components include, but are not limited to:

- Comprehensive Conflict of Interest Program – A conflict of interest avoidance and mitigation program, which includes a robust ethics program involving vigilant oversight, and continuous refinement and enhancement.
- Contract Communications – Involves collaboration with the NCI Management Operations Support Branch (MOSB) in the development, coordination, and execution of major administrative modifications, and numerous funding modifications to the OTS Contract.
- Contract Metrics – Includes scheduled tracking and monitoring of compliance points and deliverable requirements.
- Document Control and Maintenance – Comprises the oversight of access, location, maintenance, distribution, change identification, and modification processes.
- Contract Deliverables – Involves identifying, defining, tracking, quality control, government acceptance, and repository management.

In furthering the strategic objective of proactive contract management and consolidated communications with NCI at Frederick leadership, the department promulgates guidance and ongoing discussions throughout Leidos Biomed to effectively implement practices to realize this objective. Recently, the department has proposed to the NCI contracting office an enhanced, structured program to maintain an ongoing and collaborative program with the NCI contracting office. This collaborative program will allow for the systematic review of the language of the current OTS Contract for accuracy and currency, in order to facilitate periodic modifications to the contract, where necessary, thereby aligning current mission objectives and operational practices with contractual requirements. Furthermore, the department participated in a periodic review and assessment of the Leidos Biomed Risk Management Program.

Additionally, the department was instrumental in the development, award, and implementation of an IDIQ Contract for the purpose of awarding nonseverable task orders to enhance operational effectiveness of FNLCR. The estimated not-to-exceed value of the IDIQ Contract is $600 million.

Intellectual Property

C&A is responsible for managing all Intellectual Property (IP), technology transfer, partnership mechanisms, and oversight of IP as it relates to our subcontractors.

Invention Reporting: From September 26, 2014, through September 25, 2015, 14 inventions were reported, including an invention from a lower-tier subcontractor under the NCATS/TRND program. Of these inventions, 11 were sole inventions with only Leidos Biomed inventors.

Collaboration Agreements and Beta Test/Evaluation Agreements: Leidos Biomed collaborated with researchers at various institutions, including FedCentric, Glaxo-SmithKline, Aaron Diamond, Duke University, Thermo Fisher, and Jannsen Pharmaceuticals. Two additional agreements remain in negotiation for testing equipment including agreements with Sevident and Shimadzu.

Cooperative Research and Development Agreements/Technical Service Agreements: The IP team completed negotiation of eight contractor Collaborative Research and Development Agreements (cCRADAs) and Materials Cooperative Research and Development Agreement (MCRADAs), with four agreements currently pending. Additionally, 46 Technical Service Agreements (TSAs) were completed, anticipated to bring in approximately $395,000 in revenues. Leidos Biomed researchers participated in three active NIH Cooperative Research and Development Agreements (CRADAs).

Material Transfer Agreements/Confidentiality Agreements: The IP team negotiated approximately 39 Material Transfer Agreements, including those for RAS, during the period with approximately six pending final negotiation and execution. In addition, the IP team negotiated 53 confidentiality agreements with various entities and three are currently pending.

Licenses: During the year, the NCI granted Leidos Biomed request to assert copyright on the FLU-PRO Questionnaire, an instrument for assessing symptoms of influenza and other respiratory diseases. As such, during the year, seven license agreements were entered into for rights to utilize this copyrighted instrument. This includes organizations such as Medimmune, Gilead, and AstraZeneca.)

Procurement Compliance

The Procurement Compliance Department ensures compliance with all applicable prime contract and regulatory requirements, as well as applicable company policies across all acquisition departments.

Contract Performance Status Report: The procurement compliance program has been engaged with the NCI Office of Acquisitions (NCI OA) in a Contract Performance Status Report (CPSR) audit since May 2013. The department provided NCI OA with copies of all Leidos Biomed procurement- and subcontract-related policies and procedures. In the spirit of operational transparency, the compliance program also elected to provide NCI OA with access to the procurement compliance SharePoint site, which contains internal audit results and other guidance information. To date, the scope of the CPSR has included 31 procurement files for audit; in addition to the review of the policies, procedures, and internal audit data. During this time, the Procurement Compliance Department has responded to data calls regarding specific procurement actions and meeting certain criteria, including the following examples of procurements issued:

- As a sole/single source
- Under the Simplified Acquisition Threshold (SAT) and those over the SAT
- Competitive awards below the micro-purchase threshold and those above micro-purchase, but below SAT

The department updated audit forms based on changes from Leidos Corporate procurement, as well as specific internal criteria to be used for future reporting purposes. Specifically, these changes included those driven by the Federal Acquisition Regulation (FAR) or other regulations or policies which necessitated updates to the audit profile form, and internally, the compliance program sought to capture the general categories of findings (some examples include prime contracts, policies, and procedures). Once sufficient data is available based on these data points, the compliance program will generate trend reports on audit/compliance adherence providing data for procurement staff and management upon which to base performance assessments or process improvements.

The procurement compliance manager created a program that includes the posting of guidance documents on the site to help procurement staff successfully navigate high-risk procurement activities and provide general information on many other procedural areas. In addition, the manager worked with subcontracts management on specific FAR or NIH regulatory requirements to ensure compliance (including salary cap, cost, and pricing data). To date, the CPSR audit has been placed on hold by NCI OA. The compliance program continues to work with procurement supervisors and managers to keep them informed of compliance risk related to file documentation and process risks.

To date, over 400 subcontracts and purchase order files have been audited by the procurement compliance manager and entered into the database.

Logistics Support

The Logistics Support Department (LSD) provides receiving, distribution, warehousing, property accountability, mail, and transportation activities for FNLCR operations and related organizations.

Property Accountability: The Contracts and Acquisitions (C&A) Government Property Section currently manages 37,624 items valued at $369,007,368.74. The C&A Government Property Section received 4,700 items of accountable property, valued in excess of $31.8 million, into the system. The Property Department is maintaining management of 1,660 accountable property items, valued at $16,036,246.03 at the various subcontract off-site locations. As part of its responsibility under the contract to effectively surplus property and equipment, the Property Section transferred 136 items of accountable property, valued in excess of $1,276,946.17 to other federal agencies and arranged for the donation of 38 items of accountable property, valued at $1,437,458.47, to nine educational institutions.

In addition, Leidos Biomed successfully re-issued 49 items, valued in excess of $31,890,766.79 from surplus to programs throughout NCI at Frederick.

Central Supply Warehouse: The C&A LSD maintains a Central Supply Warehouse to enable the quick-reaction provisioning of materials and supplies to NCI at Frederick programs. Distribution of items from the warehouse is conducted via an online ordering system.

During this period, the warehouse received 8,755 requisitions containing over 23,817 lines for materials and supplies, valued at approximately $2.3 million, for distribution to the facility.

The Consolidated Warehouse also issued 34,765 bags of animal bedding, valued at $252,741.55 and 7,317 bags of animal feed, valued at $71,706.60. During this same period, 16,857 boxes of dry ice were issued, valued at $93,848.22, along with 94,971 gallons of liquid nitrogen, valued at $36,088.98.

The annual physical inventory for the Central Supply Warehouse was conducted this year, and involved the inventory of over 372 products valued in excess of $760,000, with a net adjustment realized of only .3 percent.

Also during this period, activities for the Maintenance Supply Warehouse were as follows: the warehouse received 5,660 requisitions containing 11,686 lines for materials and supplies, valued at approximately $663,199.21 for issuance to FME craftsmen for the facility.

The annual physical inventory for the Maintenance Supply Warehouse was conducted this year, and involved the inventory of over 4,499 products, valued in excess of $978,000, with a net adjustment realized of only $64.48.

The materials stocked in the Maintenance Supply Warehouse are currently under review by FME management for items no longer needed, in order to reduce inventory levels. Numerous items have been identified for elimination through the property surplus process.

Receiving/Delivery Section: The C&A LSD is responsible for maintaining a central receiving and delivery operation for all materials, supplies, and equipment ordered and delivered to NCI at Frederick. It is through this system that accountable government property is identified and tagged before it leaves Building 1050.

During this period, the Receiving Section recorded 137,598 parcels entering the receiving area.

The Delivery Section recorded 44,474 perishable deliveries and 76,443 non-perishable deliveries during the same period. Perishable items include chemical and biological materials typically required to be maintained in a frozen state and transported in dry ice containers. Non-perishable items include all dry materials, supplies, and equipment.

The Delivery Section has also recorded 1,938 LN2 cylinder deliveries, 671 specialty gases deliveries, 32,576 bags of animal bedding, and 7,167 bags of animal feed deliveries during the same period. The delivery metrics represent both the immediate turnaround of items recorded through receiving, as well as draws from the Central Supply Warehouse.

Transportation Section: The C&A LSD maintains a Transportation Section responsible for packaging and provisioning shipments that are external to NCI at Frederick via commercial carriers. During this period, the following metrics were recorded: 292 domestic hazardous and 34 international hazardous shipments (includes chemicals/biologicals and/or blood-borne pathogens that require special handling and packaging); 2,630 domestic nonhazardous and 399 international nonhazardous shipments; 721 shipments using contracted couriers; and over 9,334 hand-carry packages. In addition, the department applied postage to over 14,550 pieces for issuance to the U.S. Postal Service for delivery.

MANAGEMENT SUPPORT DIRECTORATE

Contract Administration Support

The Contract Administration Support office provided coordination and assistance on activities that were either specific to Leidos Biomedical directorate/program needs, as well as responding to requirements from NCI programs. Management and interfacing on NCI at Frederick policies and procedures, standard processes, and standard operating policies was continued in support of NCI and contractor programs. Data call requests and management of responses were coordinated within required timelines. Operational questions from NCI and Leidos programs were managed to ensure responses, or, if required, to ensure that changes in practices were implemented in a timely and efficient manner.

Program management support for the American Recovery and Reinvestment Act of 2009 (ARRA) continued this year on the 15 scientific projects as well as the back-office/infrastructure support project. These efforts were awarded to the OTS Contract in FY2009 and FY2010, with approximately $353.6 million in funding provided, which was ultimately set to expire this FY2015. Additional emphasis of finalization of the efforts was made with closeout activities completed by July 24, 2015.

Program reviews of the efforts and their associated costs were performed throughout the year. Presentations to the Leidos Biomed key staff were accomplished in the fall of 2014, with an overall summary of the effort that had been accomplished being provided. Monthly financial summary reports were generated and submitted to NCI to provide a status of how the costs were running and the recognition of potential funds that may remain at the conclusion of the efforts. The final accounting of costs has been completed, with total costs incurred of $345.5 million, leaving a balance of funds remaining of approximately $8.1 million. A final ARRA completion report is currently under review for completion, which will be submitted to NCI as a final reporting of the efforts accomplished on the awards made to the OTS Contract.

Project Management Office

The Project Management Office (PMO) continued to support and promote the “community” of project managers across the Leidos Biomed, directorates to enhance communication and coordination between directorates, as well as between members of the senior management team and directorates, and to foster the application of sound project management principles. The PMO provides leadership for the implementation, improvement, and expansion of project management processes across Leidos Biomed by providing resources, tools, and templates to facilitate these processes. The PMO maintains and distributes recommended reading materials, and provides

facility-wide training opportunities in areas of interest, including risk management and best practices for managing projects.

The Management Support Directorate (MSD) PMO worked closely with the Project Management Operations Office (PMOO) to support the initial "pilot" phase of the implementation of the project management policy. Support included identification of a project in the "pilot" group of projects, participation in the in-progress-reviews (IPRs) for the 13 projects included in the "pilot," reviewing and providing input to documentation and systems supporting the implementation of the policy, and promoting the policy across the organization. Additionally, the MSD PMO worked with the PMOO to identify training topics in support of the policy.

Project Management Resources to Support the Needs of Programs

The PMO provided project and program management support for the following:

Physical Access Control System Project: The PMO is leading the integrated project team responding to the Division of Personnel Security and Access Control's (DPSAC) request that the Physical Access Control System (PACS) at NCI at Frederick be integrated with NIH's Quantum Secure to communicate with the NIH Enterprise Director (NED).

Enterprise Resource Planning: The program manager is responsible for coordination of the Enterprise Resource Planning (ERP) post "Go Live" activities to promote the integration of the ERP systems and processes into the daily activities across the organization. The program manager interfaces directly with the project sponsors and Steering Committee members to ensure the ERP objectives and requirements are being executed.

Accessioning System Consolidation Project: The program manager is responsible for coordinating the overall planning and management, within the context of the Accessioning system Consolidation Project requirements associated with the OTS Contract. The program manager interfaces directly with the project sponsors and Steering Committee members to ensure the Accessioning System Consolidation Project objectives and requirements are being executed.

Project Management Tools, Training, and Information

Regarding project management tools, training, and information, the PMO accomplished the following:

- Project Management Training–Continued to facilitate Project Management Training by: Providing (5) full-day seminars on project management
  - Delivering Bad News in a Good Way
  - Inspirational Leadership
  - Advanced Risk Management
  - Creating and Using a Performance Measurement Baseline
  - Project Management Essentials (2 days)
- Conducting monthly "Lunchtime Seminar" series focusing on project management techniques.
- Insite articles–Submitted articles on project management to heighten awareness of the importance of sound project management.
- NCI at Frederick project management website–Continued to maintain the NCI at Frederick project management website with the most current information regarding project management training (onsite and online), tools, templates, and project management library resources.

Quality Management Office

The Quality Management Office (QMO) integrates quality assurance activities with business process documentation, and internal business and operational communications to ensure that documented procedures are current, and that information included in these documents is communicated to the appropriate audience in a timely fashion.

Quality assurance: QMO continued to work with NCI at Frederick Office of Scientific Operations to coordinate the review and approval of operational goals and objectives for each six-month performance period of the contract year. Following the established process and associated timeline, SMART goals were approved before the start of each performance period. QMO prepares monthly status reports so that Leidos Biomed senior leadership is apprised of the status of all goals throughout each performance period. The QMO prepares a report on the final status of each goal that is provided to NCI as an attachment to the semiannual CPSR.

QMO launched a Performance Monitoring and Remediation Program at the beginning of the contract year to track the resolution of performance issues identified by both Leidos Biomed staff and their customers. In addition to monitoring how specific performance concerns are being addressed, outcomes of this effort include; lessons learned that can be shared across the organization, continuous improvement of operating procedures, and the development of metrics to evaluate performance.

In support of the NIH Risk Management Plan, the QMO coordinated the annual reassessment of FNLCR facility risks and reported the results of this assessment to NCI using the NIH Risk Inventory Report.

Business processes and documentation: QMO continues to manage the review and revision of NCI at Frederick Policies and Procedures (P&Ps) and FNLCR Standard Processes (SPs). This effort includes ensuring that new and revised P&Ps and SPs are regularly reviewed, communicating changes to Leidos Biomed managers, and making current versions available to all Leidos Biomed staff. The QMO proposed a restructuring

of the NCI at Frederick P&Ps manual that would convert P&Ps into high-level policies by moving process related information to supporting SPs, or Standard Operating Procedures (SOPs). This approach would create a policy manual, with fewer entries, which applies to both government and contractor operated components of NCI at Frederick. The process of converting Leidos Biomed and NCI at Frederick forms to the new standard format continued during the year. Revised forms are being provided in an electronically fillable format, with detailed instructions, and made available in a central location accessible through the NCI at Frederick website.

The Laserfiche Enterprise Content Management platform continued to be used to manage the creation, retrieval, and storage of records within the Operations and Financial Groups. QMO and Information Systems Program (ISP) groups provided technical and administrative support for the Laserfiche platform, including the administration of over 200 user accounts. Laserfiche is being used to store electronic versions of ARRA related documents. This centralized location facilitates information sharing and reporting, and ensures that documents are organized and can be readily retrieved as needed. This year, over 73, 000 ARRA funded subcontract documents were added to the repository bringing the total number of documents in this repository to over 108,000.

QMO continued to coordinate efforts between the vendor, NCI, and Leidos Biomed program areas to facilitate the transfer of records between NCI at Frederick and off-site storage facilities, as well as the destruction of records that no longer need to be retained. This year, QMO provided oversight for the destruction of close to 2,000 boxes of hard-copy records. In addition to hard-copy records, QMO is also coordinating the off-site storage of data stored in electronic format.

QMO coordinated the biennial review of system of record notices for those systems of records enumerated in the OTS Contract.

Business and operational communications: Weekly communications to Leidos Biomed employees continued to be managed by QMO. These communications are for the purpose of notifying all managers and supervisors of changes to NCI at Frederick P&Ps, FNLCR SPs and forms, and explaining the operational impact of these changes.

The QMO continues to manage the preparation of the Leidos Biomedical Annual Report on operations and accomplishments at the FNLCR. The QMO also participates and provides oversight for the preparation of semi-annual CPSRs in support of the OTS Contract Performance-Based Award Fee Plan.

Microsoft (MS) SharePoint tools continued to be deployed to provide NCI and Leidos Biomed directorates with a common platform to collaborate on major projects and initiatives. MS SharePoint supports team collaboration on projects and features a secure central document repository with document version control. MS SharePoint sites and sub-sites are established and maintained by QMO and ISP, which now maintain approximately 340 individual sites.

Other efforts: QMO continues to oversee the Leidos Biomedical employee recognition program. This program encourages employees at all levels to acknowledge the contributions of other employees or project teams of employees throughout Leidos Biomed.

Public Affairs Office

The Public Affairs Office (PAO) supports the mission of FNLCR through a broad program of outreach to constituents at the local, state, and national levels. The office informs key audiences about FNLCR's thoughtful stewardship of public funds, and the effective use of those assets for the prevention, diagnosis, and treatment of cancer and AIDS.

Significant Achievements

The office continued to increase visibility, both internally and externally, of the FNLCR's scientific accomplishments through interactions with the news media, by direct reporting, by encouraging coverage by Insite staff, and by working with research subcontractors and professional organizations on the public release of information.

Major topics that have benefitted from this coverage include:

- Scientists Explore Possibilities at Scientific Investigators Retreat
- Using Globus GridFTP to Transfer and Share Big Data
- PADIS Implements Investigational Device for Isolating Circulating Tumor Cells
- FDA Approves Immunotherapy for a Cancer that Affects Infants and Children
- MRI Virtual Colonography Developed to Monitor Colon Cancer in Mouse Models
- New Breed of Mice May Improve Accuracy for Preclinical Testing of Cancer Drugs
- Nanotechnology Laboratory Continues Partnership with FDA and NIST
- Doctors and Nurses Have a Challenge in Keeping up with Advances in Genetics and Genomics
- FNLCR Scientists and Collaborators Solve 3-D Structure of Key Protein in Alzheimer's Disease
- Behind the Scenes, Animal Caretakers and Technical Staff Support High-Quality Research
- Pilot Plant Makes Vaccines for Ebola and Other Diseases

News media coverage extended to the NCI Exceptional Responders Program, the Protein Science Week meeting, Genomic Data Commons, generic nanomedicine, pathogenic SHIVs, the MATCH program,

the Biopharmaceutical Development Program, Vaccine Research Center (VRC) Pilot Plant, Nanotechnology Characterization Laboratory, and AIDS and Cancer Virus Program.

The office has guided staff on the use of branding standards and elements to ensure consistency in presentation, both inside and outside of the organization. The PAO has laid the groundwork for a project to update and revise frederick.cancer.gov to give the national lab a well-articulated, public identity; reach potential collaborators, partners, and vendors; and provide for effective recruitment of FNLCR staff by way of various contractor employment opportunities. The site will aim to provide easy and efficient usage as the FNLCR evolves.

The PAO continued its contributions to the Poster and its guidance of Insite, expanding coverage of the organization's scientific accomplishments, employee achievements, institutional departments, and volunteer outreach activities. Related social media platforms further disseminated information on scientific accomplishments and employee achievements. This effort also gave additional visibility for job opportunities, active procurement and subcontracting solicitations, and community outreach activities.

The PAO played a central role in the group that resurrected the SMART PROC event in Frederick County after Roscoe Bartlett left office. The PAO worked with the SMART executive director and his consultant to gain support for the event, draw up an agenda, and engage participants in what became a successful and informative event for the government procurement community. Leidos Biomed also provided corporate sponsorship.

The PAO participated in a range of events and on-site outreach activities, including Frederick Day in Annapolis, the Frederick County Chamber of Commerce Business Expo, BIO International Convention, Spring Research Festival, FC Annual Business Reception, NCI PI retreat, FC Community Cancer Coalition, and Fort Detrick Alliance meetings and events. The office directly sponsored and collaborated with other organizations in community outreach events such as those involving Habitat for Humanity, Relay for Life, and the Children's Inn at NIH; and participated in the Fort Detrick Public Affairs Roundtable.

The PAO led the continued development of the Issues Response series of preparatory documents that address potentially sensitive issues that could arise in public forums and with the news media. The series is nearing completion.

The office maintained good working relationships with the local news media, including the Frederick News-Post. This has resulted in an increase in serious and positive coverage of the work of the FNLCR.

The PAO conducted another writing workshop for Scientific Publications, Graphics and Media (SPGM) staff and directorate representatives who contribute to Insite and the Poster. The workshop was well received and writers have benefitted from the exercise.

The public affairs director continued to represent the interests of FNLCR as communication chair of the Fort Detrick Alliance. The director served on the review committee for the Leidos Biomed–sponsored Michelle Shearer STEM Scholarship, administered by the Community Foundation of Frederick County, and led the annual employee giving campaign, which contributes to community nonprofits supporting education, workforce development, health care, and charity.

Scientific Publications, Graphics & Media

Efforts to match the Scientific Publications, Graphics & Media (SPGM) work force to the customer workload continue to be successful. Cost recovery remains positive (exceeding 50 percent), and work submissions have shown a slow but steady increase in the past year.

Manuscript editing continued to see large increases and continues to be a significant revenue source for the department. From July 2014 through May 2015, the SPGM Editorial Office edited 45 manuscripts, compared with 27 in the previous year, while continuing to write articles for numerous major scientific journals and the two online newsletters (Insite, Poster). Over the past two quarters, demand for scientific illustration has increased dramatically. Video production has slowed over the past year, but recent requests will bring video production back to the fore. Photography remains a constant. Increases in photographic requests are due in most part to the excellent work by the SPGM photographic staff. Poster production also continues to be consistently high.

SPGM hired an additional employee with a dual role of Editor and Illustrator. The new hire will help alleviate the editing departments' backlog of work and assist in the increasing demand for illustration. An intern from the Werner H. Kirsten student intern program has also been added to the SPGM team for the next 12 months.

SPGM publishes two online newsletters; the Leidos Biomed newsletter Insite and The NCI at Frederick Poster. Both newsletters have shown increases in readership and have garnered positive reactions from readers. The newsletters are focused on the ongoing research within the Frederick research community.

Video production should see a sustained increase over the next year. SPGM will be working on a public service announcement (PSA) video for the NCI Emergency Operations Program. The production of this PSA is part of a larger plan to produce safety videos for the Emergency Operations departments' safety procedures. SPGM produced an introduction video for Nazzarena Labos' paper on Kaposi's Sarcoma transmission in homosexual men. Journals are turning to video as a way to better represent scientific work in a more compelling way; this is the third video of this type SPGM has produced.

Other accomplishments included the production of materials for the AIDS and Cancer Virus Program (ACVP) site visit. The production included eight posters, five onscreen shows, lab floor plans, organization charts, and a design template for the group's overall look.

Additionally, SPGM prepared the room where the site visit was held, including setting up lights to better illuminate the posters' subject matter. The site visit received high marks from reviewers and accolades from Dr. Heimbrook.

SPGM illustrators created flip charts for the Liberian Ebola outbreak. The flipbooks visually instructed Liberian citizens on proper procedures for detection and vaccination of the Ebola virus. Additionally, SPGM created the layout and illustration for the biannual NIH publication CCR Connections, EHS Champions of Safety Posters, the Annual Achievement Awards Program (trophies, program, portraits, and event photography), the Contract Performance Status Report, the Leidos Biomed Annual Report, and RAS Program promotional materials.

Looking ahead, SPGM is working with Data Management Services (DMS) on a complete redesign of the SPGM website. A highlight of the redesign will be a new "Helpful Hints" section that will house in-depth instruction on the most frequently asked questions SPGM receives, and informative "how to" flyers on commonly used software. The flyers will also be made available through list serve announcements.

Operational Support

Travel

The purpose of the Leidos Biomed Travel Department is to coordinate travel arrangements for business travel required by scientific and administrative employees. Travel is requested by program areas to attend training sessions, participate in scientific collaborations, assist with clinical studies, or attend scientific meetings and seminars. The Travel Department obtains the appropriate approvals and coordinates arrangements for event registrations, flights, hotel, and ground transportation for employee travelers. During 2015, the Travel Department transitioned to supervision under the Management Support Directorate within Leidos Biomed. The Deltek Travel and Expense (T&E) System, a segment of the ERP system, has been operational for 15 months and has eliminated the need for manual routing of travel requests. The Travel Department is able to process many travels at one time more efficiently and effectively due to the T&E System.

The workload within the Travel Department continues to grow, particularly with the increase in overseas clinical trial support within the Clinical Monitoring Research Program (CMRP). Between September 26, 2015 and July 27, 2015, the Travel Department coordinated travel arrangements for 858 trips. The Travel Department is currently staffed with 1.5 full-time employees and continues to establish business processes for coordinating travel more efficiently.

Conference and Event Planning and Coordination

The Conference and Event Planning Department plans and coordinates U.S. Department of Health and Human Services (HHS) conferences, symposiums, workshops, and other administrative meetings for programs affiliated with the FNLCR.

The department manages a wide range of responsibilities related to the logistics of an event including finding/ obtaining appropriate meeting space, contract negotiations, database management to include establishment of websites for registration, lodging and travel arrangements for participants, and supervising selected meeting functions at the event location. The coordination and management of the travel arrangements for sponsored attendees and speakers is one of the key functions of the Conference and Event Planning Department.

During 2015, the Conference and Event Planning Department transitioned to supervision under the Management Support Directorate within Leidos Biomed. The department managed 101 conferences, symposiums, and events during CY2015. In total, these meetings were attended by over 13,700 registered participants, which included more than 1,100 sponsored attendees/speakers whose travel arrangements were supported through the department. In addition, the department was responsible for overseeing over $2.2 million worth of budgets for the various conferences and events.

Conference Facilities Management and Support

The NCI at Frederick Conference Facilities are located in Building 549 between the library and cafeteria and on the first floor at the Advanced Technology Research Facility (ATRF). The Conference Center staff is responsible for the planning, testing, setup, and execution of conferences and meetings at both sites.

Conference Center staff maintains audio-visual (A/V) equipment (such as Video Teleconference Units, Projectors, laptop computers, flat screen TV's, microphone and speaker systems) in conference rooms in Building 549 and the ATRF.

In addition to supporting the Building 549 and ATRF locations, the Conference Center staff also assists additional conference rooms with A/V or video teleconferencing (VTC) needs. This can range from assisting when technical issues arise, to helping the room owners engage with an A/V vendor to assist with assessing and recommending requirements and explaining the technology and other options available.

Conference Staff also manages major A/V technical refreshes of Conference Center–owned facilities, such as the current Building 549 refit project and planning for future refresh efforts with a strategic plan that helps lay out recurring upgrade efforts.

Advertisement of each facility's events is posted on the Infocaster digital signage system by Conference Center staff at each location in their respective lobbies on flat screen TV's.

For CY 2015, over 2,000 meetings/events were held at the Building 549 Conference Center and over 1,500 meetings/events were held at the ATRF Conference Center. For those meetings, the Conference Center staff established over 400 VTC connections at the Building 549 Conference Center and over 100 VTC connections at the ATRF Conference Center. Meetings can range from recurring one hour basic meetings, to multi-day events. Events include symposiums, workshops, town hall meetings, retreats, and other committee style meetings that may require project planning, intensive technology testing, and other resource challenges.

HUMAN RESOURCES

The Human Resources Directorate works in partnership with managers and their teams to support the mission of Leidos Biomedical Research, Inc. (Leidos Biomed) staff as they work on behalf of the Frederick National Laboratory for Cancer Research.

Human Resources provides leadership and guidance in the development, implementation, and equitable administration of policies and procedures, thus fostering a positive work environment. The core services and competencies include recruitment and staffing, employee relations and counseling, organizational and employee development, compensation and benefits, HR information management, and regulatory compliance.

Workforce Demographics

A review of Leidos Biomed demographics shows that the contract year-end employee population was 1,871. Within this total population, 53.39 percent are female and 31.32 percent are minority. Annualized voluntary turnover was 10.2 percent for this period. This turnover level continues to compare favorably with the marketplace.

Recruitment

The Human Resources Directorate (HR) continues to provide specialized recruitment strategies in response to the unique hiring needs of each program. During the past year, 457 positions have been filled; of these, 65.65 percent were exempt positions and 34.35 percent were nonexempt positions. This represents a 48 percent increase in positions filled over the previous three year average. Average recruitment time (between date of job posting and accepted offer) was 54.24 calendar days and average time for candidate to start work from date of acceptance was 19.90 calendar days.

Candidates were sourced from multiple venues, including job boards, web searches, print advertising, professional networking, job fairs, conference advertising, and employee referrals. The recruitment staff utilized multiple professional niche websites, as well as mainstream job boards, to source highly qualified candidates. Additional web and social media tools, such as LinkedIn, Bullhorn Reach, Jobs2Web, Smash Fly Recruitment Marketing Platform, http://www.HireLifeScience.com/, and Twitter were used to source and introduce Leidos Biomed to a host of passive job seekers, resulting in identifying qualified candidates for specialized positions. HR staff participated in career events, including those specifically targeting college graduates, diverse candidate pools, candidate for positions in hard-to-fill areas, such as clinical and information technology fields.

The Human Resources Manager actively represents Leidos Biomed as a member of the Frederick County Workforce Development Board, participating in various outreach initiatives to the community and job seekers. The recruitment staff partnered with the Frederick County Veteran's Representative to attract qualified military veteran candidates. To expand our recruitment diversity efforts, we engaged a diversity website to post our opportunities, and in January 2015, participated in a diversity career fair. A nurse recruitment sourcing strategy has been defined and implemented, including mass LinkedIn blasts and connections to registered nurses and nurse practitioners (NPs) and other varied targeted advertising initiatives. Utilizing an advertisement vendor, we have been able to pinpoint target markets for ad placements and sourcing passive candidates for hard-to-fill positions.

Training

Human Resources launched a training course for managers and conducted a briefing for all employees regarding career development, in March 2015, to coincide with the performance management process. This session was designed to provide employees with information to assist in understanding career development options within our organization. The course covered a summary of the promotion process, reviewed several tools available to support discussion of career development with supervisors, and the creation of Individual Development Plans.

Compensation and Benefits

Completion of the 2016 health insurance renewal process resulted in an overall premium increase of 13.1 percent with no decrements.

Leidos Biomed responded to a scheduling letter from the Office of Federal Contract Compliance Programs (OFCCP) and follow-up audit questions throughout the period. In December 2014, our name was posted on the National Pre-Award Registry, that we had been reviewed and found to be "In Compliance" with the Equal Employment Opportunity (EEO) regulations that the OFCCP is mandated to enforce.

Employee Relations and Retention

Employee relations staff supported the reduction in force and provided outplacement material to the 29 employees who received notification. Employees were provided one on one job search outplacement support.

Personnel

The Operations Group consists of 333 employees in professional, administrative, clerical, project management, customer service, and operations positions.

Operations Group	Number of Employees
Contracts and Acquisitions	100
Financial Operations Directorate	39
Human Resources Directorate	15
Management Support Directorate	23
Operations	6
Facilities Maintenance and Engineering	150
Total	**333**

FINANCIAL OPERATIONS DIRECTORATE

The Financial Operations Directorate (FOD) oversees all finance-related activities for FNLCR, including the following core accounting and finance functions: financial planning and analysis; general accounting; payroll; accounts payable; billing; accounts receivable; business information systems; and internal audit and controls. The directorate's mission is to administer an enterprise-level, fully integrated, financial management program for FNLCR and other programs at NCI at Frederick; establish fiscal policies that ensure accountability for and control of government funds; provide timely, relevant, and clear financial analysis and reporting to assist in managing fiscal resources; and deliver quality customer service to all FNLCR stakeholders.

Tim Boyle assumed leadership of the new FOD in March 2015. His appointment was part of Leidos Biomed's reorganization plan of the OTS Contract that was approved by NCI in January 2015. Mr. Boyle has been with SAIC/Leidos since 2009 and brings 30 years of experience in federal, commercial, and international financial management. His expertise in IDIQ task order contracting proved to be invaluable as NCI and Leidos Biomed worked throughout the past year to implement such a contract to work in tandem with the existing OTS Contract. Boyle successfully passed the American Institute of Certified Public Accountants examination in November 1992.

Controller's Office

The **General Accounting Department** performed a broad range of activities under each of the following categories: provided corporate interface for financial reporting and Sarbanes-Oxley (SOX) compliance issues; maintained daily activity of the Special Bank Account (SBA); processed corporate-funded accounts payable; processed billings and receivables; prepared National Cancer Institute (NCI) cost-incurred invoices; ensured compliance with accounts payable legal requirements; forecasted and monitored fringe, general, and administrative costs; and monitored Service Contract Act (SCA) Average Benefit Rate Compliance.

The **Accounts Payable/Travel Department** (the travel function transitioned to the Management Support Directorate in February 2015) performed the functions of invoice processing, and travel order establishment and processing. As invoices are received from vendors, Accounts Payable prepares them for input, verifies proper receipt and matching to a purchase order, obtains the required approval for service-related invoices, and performs a self-audit of all data input. Resolution of invoicing problems is also completed. Travel is coordinated with program areas and processed from beginning to end. Contracting officer approval (COA) is requested when required. Travel orders are closed when all transactions are completed. Interaction with purchasing, receiving, contracts, and programs is performed daily. All vendor invoices are received at a processing center, and transmitted and approved electronically, thus eliminating the need for manual entry and filing. Travel and expenses are completed electronically.

Significant Achievements

The Controller's Office certified SOX cash controls each quarter; effectively administered the SBA account; finalized the contract year (CY) 2014 fringe rate; and established a new provisional fringe rate for CY2015. The Accounting department continued participation in Enterprise Resource Planning (ERP) project meetings, cost of revenue (COR) status meetings, and program ERP working group meetings. Several enhancements were developed and made to Corcentric, including a purchase order (PO) match for P-card transactions, refined search capabilities, PO line balance corrections, and reporting capabilities. Internal department processes continue to be refined to work efficiently with the new ERP system. Accounting also provided additional training to those staff members who needed it. All procedures are being revised and documented.

Financial Planning and Analysis

The Financial Planning and Analysis (FP&A) group provides support for cost management, budgetary development, and coordination of fiscal processes to the NCI at Frederick community. For the current reporting period, the FP&A department monitored approximately

12,400 individual projects (a significant increase based on new project tracking requirements), including tracking of operating costs and associated funding levels of approximately $674 million, including $22 million of American Recovery and Reinvestment Act of 2009 (ARRA) effort.

Significant Achievements

During FY2015, FP&A has been involved in the following major activities:

- Continued to support the post-implementation phase of the ERP project, including user forums with NCI/Leidos Biomedical Research stakeholders to support evolving and new business requirements; continued design and testing of project finance reports; and enhanced data analytics utilizing the expanded data sets facilitated by the new ERP system.
- Successfully modified the annual budget development process to align with the structure and functionality of the new ERP. This project required the conversion of multiple reports and database changes to meet these deliverables.
- Continued to refine processes and procedures related to the Cooperative Research and Development Agreement (CRADA)/Technical Service Agreement (TSA) projects, which serve to expand access to the capabilities of Frederick National Laboratory for Cancer Research (FNLCR).
- Supported project close-out and funding de-obligation for expiring nonseverable projects (including the final ARRA projects).
- Expanded the role of FP&A in project tracking and control activities related to budgets and funding. The expanded activities include reviewing and approving period-of-performance and funding issues related to subcontracts, and providing analysis on division use of funds prior to expiration.
- Provided enhanced monthly/quarterly cost management/status reports for the following high-profile projects/divisions:
  - Vaccine Research Center
  - Biopharmaceutical Development Program
  - Office of Cancer Genomics
  - Division of Cancer Epidemiology and Genetics
  - NCI Center for Biomedical Informatics and Information Technology
  - Office of the Director
  - Center for Strategic Scientific Initiatives
  - Office of the Director, Immediate Office of the Director, NExT Program

  These reports are used by the customer to make financial decisions on future operations.
- Delivered all Operations and Technical Support (OTS) Contract–required financial reports on time.

Internal Audit

The Internal Audit group accomplished the following during the reporting period:

- Audited cost-reimbursable subcontracts to verify compliance with Federal Acquisition Regulation (FAR) Parts 31.201, 31.201-3, and 31.201-4.
- Audited time-and-materials subcontracts to verify compliance with FAR Part 16.601.
- Performed desk audits of 60 research subcontracts in preparation for contract closeout (including final ARRA-related subcontracts).
- Audited transactions related to 401(K) and defined benefit plans.
- Reviewed the 941 tax filings (federal, FICA, FUTA, SUTA).
- Reviewed the 940 tax filings for the 2013 tax year.

Business Information Systems

The Business Information Systems Group (BISG) mission is to enhance FNLCR business processes with available information systems. A primary focus for BISG is the ongoing support of the ERP system as specified in the OTS Contract. BISG continually works with customers to:

Automate Processes

- Provided assistance to programs that were performing current manual processes and attempted to automate through the available technology.

Enhance and Expand Business Reporting

- Supported FP&A and the specialized report requirements of the divisions and directorates at FNLCR.
- Re-engineered invoice/funding reports for the general ledger.

BISG supported the following suite of applications, which comprised the FNLCR ERP environment in FY2015:

- CostPoint; Travel and Expense; COR360; Docs for Deltek – application support, user set-up, and security
- Cognos (Reporting) – report development, model maintenance, user set-up, and security
- Time and attendance system for Leidos Biomedical Research personnel – application support, user set-up, and security
- TM1 budget – development, user set-up, and security
  - Support to the FY2016 budget development system
- Facilities Maintenance and Engineering's (FME's) computerized maintenance system, Maximo
- SharePoint site and content management to facilitate document, task, discussion, project, and process management, which promotes dynamic collaboration across FNLCR stakeholders

- Conducted an extensive site utilization review in the spring of 2015, resulting in the decommissioning of over 100 SharePoint sites that were no longer active

CENTRAL GLASSWARE SERVICES

Central Glassware Services consists of five processing kitchens and a daily van run that provides satellite services to 18 buildings.

During FY2015, Central Glassware provided glassware processing services to 220 laboratories at NCI at Frederick. Services include the daily pickup and processing of soiled glassware and the restocking of sterilized glassware. Central Glassware also provides special services on request, including washing velvets, preparing bell units, preparing pipettes, processing specialized glassware, autoclaving liquids, processing laboratory spatulas and stir bars, and transporting and delivering media. All used media bottles and caps are recycled.

Significant Achievements

During this reporting period, Central Glassware added support to one new laboratory in Building 433. Central Glassware provided services (via the van run) to Buildings 321, 376, 426 OHS, 431, 433, 469, 535, 538, 539, 550, 560, 562, 567, 1036, 1047, 1066, 1071, and the Advanced Technology Research Facility (ATRF). Centralized ordering and delivery are accomplished through the van run.

Central Glassware continues to provide media transport services to and from Building 539 (via van pickups) to 24 laboratories in Buildings 469, 535, 538, 539, 567, and 560.

Material Processed Annually

Building	Material Processed
ATRF	69,400
535	171,000
538	81,200
539	172,300
560	224,400
Van Run Pickups	
321 (from 560)	1,200
376 (from 560)	30,500
426 OHS (from 560)	70
431 (from 538)	850
433 (from 538)	1,250
469 (from 538)	8,400
550 (from 560)	850
562 (from 560)	4,200
567 (from 560)	38,500
1036 (from 560)	1,300
1047 (from 560)	1,000
1066 (from 560)	1,200
1071 (from 560)	700
Total, material processed	**808,320**

AMERICAN RECOVERY AND REINVESTMENT ACT OF 2009 INFRASTRUCTURE SUPPORT

Support Provided by the Clinical Monitoring Research Program

Financial Management

The CMRP Financial Management Group (FMG) continued to maintain and close out all budgets and staffing support for all ARRA projects during FY2015.

As a result of the expiration of ARRA funding, the FMG coordinated and completed the closure of all ARRA open purchase requests, purchase orders, and travel in order to comply with the internal Leidos Biomedical Research–proposed deadlines. The oversight of closure activities included one budget for CMRP ARRA infrastructure; one budget for ARRA The Cancer Genome Atlas (TCGA); three budgets for ARRA NCCCP; and three budgets for CADP.

During the reporting period, the FMG worked closely with technical project managers to provide weekly financial report information for budgets, anticipate estimates-at-completion (EACs), and track project costs for all budgets to ensure accuracy and accountability for all ARRA costs. By doing so, the FMG was prepared to respond quickly and accurately to requests for final EACs as they related to the close-out of all CMRP ARRA projects.

As a result of the closure of all CMRP ARRA projects, the CMRP FMG worked diligently with all Leidos Biomedical Research ARRA technical project managers and staff in Research Subcontracts, Auditing, Accounts Payable, and Property Control departments to ensure that all open commitments and encumbrances were closed; supporting document details were archived; final expenses were audited; and property inventory was reallocated to other supporting programs within Leidos Biomedical Research or determined to be surplus, in which case it was stored accordingly. This effort was accomplished by coordinating monthly ARRA budget status meetings in collaboration with various Leidos Biomedical Research departments. Those meetings resulted in effective and efficient management of the closure of all ARRA activities by the proposed Leidos Biomedical Research planned deadlines.

Appendix A:
Company Overview

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Leidos Biomedical Research, Inc.

Leidos Biomedical Research, Inc.

2014-2015 Annual Report

Appendix A

Company Overview

OFFICE OF THE PRESIDENT

David Heimbrook, Ph.D., President

Cancer Genomics Research Laboratory

Meredith Yeager, Ph.D., Senior Principal Scientist/Scientific Director

With remarkable advances in genomic technologies, the Cancer Genomics Research Laboratory (CGR) was established by the National Cancer Institute to investigate the contribution of germline genetic variation to cancer susceptibility and outcomes in support of the Division of Cancer Epidemiology and Genetics (DCEG). Working in concert with epidemiologists, biostatisticians, and basic research scientists in DCEG's intramural research program, the CGR provides the capacity to conduct genome-wide discovery studies and targeted regional approaches to identify the heritable determinants of various forms of cancer. CGR supports DCEG in all stages of cancer research, from planning to publishing, including experimental design and project management, sample handling, genotyping and sequencing assay design and execution, development and implementation of bioinformatic pipelines, and downstream research and analytical support.

Currently the CGR utilizes a variety of technology platforms to assess human genetic variation. Platforms and technologies include: (1) single-nucleotide polymorphism (SNP) detection via TaqMan™ fluorescent 5' nuclease cleavage with detection on the Applied Biosystems 7900; (2) Illumina bead-based SNP array multiplexing technologies, both for genome-wide discovery and targeted custom analysis; (3) Illumina genome-wide methylation arrays; (4) relative telomere length analysis; (5) sequencing of large genomic regions, including whole exomes, as well as targeted sequencing and analysis using five platforms (Illumina HiSeq2000/2500, Ion Torrent Personal Genome Machine (PGM), Ion Torrent Proton, Illumina MiSeq, and Illumina NextSeq 500) in conjunction with a wide range of sequence capture and targeting methods and instrumentation.

CGR also includes the DNA Extraction and Staging Laboratory (DESL). This highly automated laboratory is responsible for all DCEG specimen preparations, including nucleic acid extractions, sample staging, generation of run-ready plates for genotyping and sequencing applications within CGR, and specimen aliquotting for use by collaborators around the world.

It would not have been possible to manage the laboratory work, project planning, quality control, assay validation, sample handling, and data analysis without the support of the staff members organized across CGR's eleven functional groups: DESL, the Production Laboratory, the Scientific Research Group, the Functional Research Group, Technology Implementation, Quality Assurance/Quality Control (QA/QC), LIMS Development, Bioinformatics, IT Core Services, Project Management, and Administration.

Program Management

Kathy Terlesky, Ph.D., Director, Project Management Operations Office

The Project Management Operations Office was established in January 2015 to drive project execution excellence at FNLCR. A draft Project Management Policy was developed and released to a cohort of 24 project managers for testing in a pilot phase for nine months. The policy and pilot implementation were designed to create a project management culture within Leidos Biomedical Research that is flexible, but disciplined, and is more closely aligned with industry best practices. Similar to the way that the Yellow Task tracking system highlights issues with respect to project initiation, we expect improved project management systems to highlight issues with project execution, and facilitate rapid resolution of those issues. The purpose of the policy is to provide a framework to manage mutually agreed upon work between Leidos Biomed, NCI, and other FNLCR customers. The expected outcome of using the framework described here is successful project execution and proactive management of problems to a quicker resolution.

The pilot activities included implementation of a SharePoint Project Status Monitoring site that project managers used to update their project statuses monthly. These updates were presented in teleconferences to directorate management and executive management using the standardized format. The reviews gave executive leadership visibility into projects across the diverse customer set and the venue to provide targeted solutions to issues or risks the project managers were facing. In addition, the pilot implemented a means to survey the entire stakeholder and project team on communication effectiveness three times during the pilot. The feedback obtained from the survey was provided to the project managers in a timely manner to adjust their management for improved project status awareness.

The Project Management Operations Office also provided lunchtime training sessions on financial reporting best practices, risk management, and project status reporting. The pilot participants provided timely feedback on the tools and processes, allowing for continual improvement in the processes.

Metrics were collected throughout the pilot to assess project execution, customer perception of execution, and project communication across the team. Project manager performance and project execution were measured monthly, providing a means to rapidly assess the health of the Leidos Biomedical Research project portfolio, target troubled projects for intervention support, and improve overall customer satisfaction with project execution.

SCIENCE AND TECHNOLOGY GROUP

David Heimbrook, Ph.D., Chief Science Officer, Interim

Cancer Research Technology Program Directorate

Dwight V. Nissley, Ph.D., Director

The Cancer Research and Technology Program (CRTP) provides technical and scientific solutions to the National Cancer Institute (NCI) and National Institutes of Health (NIH) institutes to meet the challenges of, and carry out, biomedical research. Leidos Biomedical Research received a request from NCI to develop a plan for accomplishing the goals of the RAS Initiative, using the existing resources at the Frederick National Laboratory for Cancer Research (FNLCR). In conjunction with the NCI Office of the Director and Dr. Frank McCormick, a consultant recognized as an expert in the RAS field, Leidos Biomedical Research developed, implemented, and launched the NCI RAS Initiative.

CRTP is composed of the following:

Dedicated programs

- Antibody Characterization Laboratory
- Nanotechnology Characterization Laboratory
- Sequencing Facility
- Center for Cancer Research–Dedicated Core Services

RAS support

RAS research

- Validation of KRAS as a target (Project Zero)
- Structural and biophysical characterization of KRAS (Project 1)
- Identify compounds that inhibit KRAS-driven tumors (Project 2)
- Characterize and disrupt KRAS complexes and probe the nature of KRAS dimerization (Project 3)
- Cell surface mapping (Project 4)
- Synthetic lethal screens (Project 5)
- RAS reference reagents (Project 6)
- Target Biology Unit – Calmodulin (TBU-C)
- Scientific Mission Coordination – RAS Initiative Bioinformatics

Core support to RAS

- Electron Microscopy Laboratory
- Protein Characterization Laboratory
- Protein Expression Laboratory
- Optical Microscopy and Analysis Laboratory
- Genomics Laboratory

The RAS Initiative has been up and running for more than a year and has made significant progress in all major areas of research. The key Hub projects are: target ID and validation, cell-based screens, assay development (biochemical and cell-based), protein production and structural biology, KRAS cell-surface analysis, and RAS cancer data mining.

One area of significant progress is that we were able to bind fully processed KRAS4b proteins to lipid nanodiscs and lipid bilayers. We were able to investigate the biochemistry and biophysics of KRAS–membrane interactions utilizing our collaborations with scientists at the University of California, Berkeley, the University of Illinois Urbana-Champaign, and the National Institute of Standards and Technology (NIST).

Additionally, over 70 pancreatic and colorectal cell lines were used in a multi-parameter flow cytometry–based assay (siREN) to simultaneously monitor the effect of the complete ablation of 40 KRAS signaling pathway nodes on cell size, viability, proliferation, reactive oxygen species, and apoptosis. Integrating these results with genomic and gene expression data has identified novel vulnerabilities in the KRAS signaling network.

The RAS Initiative continues to move forward and will initiate the next phase of operationalizing the RAS Initiative Hub-and-Spoke Model. These efforts include collaboration between the FNLCR Hub, extramural NCI-supported labs, pharmaceutical companies, and intramural labs. These collaborations will be initiated via partnerships facilitated through NCI and contractor mechanisms, which include Material Transfer Agreements, Technical Services Agreements, Collaboration Agreements, and Cooperative Research and Development Agreements.

AIDS and Cancer Virus Program Directorate

Jeffrey D. Lifson, M.D., Director

The AIDS and Cancer Virus Program (ACVP) consists of both investigator-initiated research sections and research support core laboratories. During the review period, the research portion of the ACVP comprised the laboratories of six principal investigator (PI)-headed research sections pursuing independent, yet related, multidisciplinary research programs in basic or applied molecular virology, viral immunology, retroviral pathogenesis, and viral oncology. The scientific staff of the ACVP encompasses expertise in a broad range of scientific disciplines, and there is a strong tradition of collaboration between the PIs. The studies pursued by the laboratories have, as a unifying feature, their direct or potential relevance to the overall goal of developing an effective vaccine or other approaches for the prevention or treatment of HIV infection and AIDS, as well as relevance to the study of viruses involved in cancer. The program helps fulfill the mission of NCI by contributing to the advancement of our understanding of HIV and AIDS, a major cause of morbidity and mortality in the United States and around the world, and a predisposing factor for AIDS-associated malignancies. Through research on vaccines and other approaches for the prevention and treatment of HIV infection and AIDS, the ACVP also seeks to have a practical impact on this global problem. Finally, the ACVP seeks to add to the legacy of important contributions to AIDS research and viral oncology made by NCI scientists. The ACVP has been very productive over the last year, contributing to 64 articles in peer-reviewed journals, including multiple high-impact publications.

In addition to investigator-initiated research conducted within the program, in keeping with the mission of FNLCR, the eight research support cores of the ACVP also provide useful and unique products and services to the broader research community, including both intramural and extramural investigators.

Basic Science Program Directorate

Mary N. Carrington, Ph.D., Director
Jonathan R. Keller, Ph.D., Acting Director

The Basic Science Program (BSP) consists of both investigator-initiated research laboratories and personnel who work in support of the National Cancer Institute (NCI) Center for Cancer Research (CCR) laboratories. The research component encompasses laboratory sections of seven principal investigators (PIs), each of whom pursues independent, multidisciplinary research. The PI laboratories include: the Human Leukocyte Antigens (HLA) Immunogenetics Section, headed by Dr. Mary Carrington; the Molecular Immunology Section, headed by Dr. Stephen Anderson; the Molecular Immunotherapy Section, headed by Dr. Thomas Sayers; the Hematopoiesis and Stem Cell Biology Section, headed by Dr. Jonathan Keller; the Molecular Genetic Epidemiology Section, headed by Dr. Cheryl Winkler; the Computational Structural Biology Section, headed by Dr. Ruth Nussinov; and the Epigenetics Section, headed by Dr. Katherine Muegge. Researchers who are embedded in CCR laboratories are organized into four scientific sections: the Chemistry and Nanotechnology Section, the Cancer and Immunology Section, the Basic Research Section, and the Genetics Section.

BSP also provides services and products to support CCR's research efforts. The Cancer and Inflammation Program (CIP) Genetics and Microbiome Core carries out statistical and bioinformatics analysis in support of CIP investigators; the Fluorescence-Activated Cell Sorting (FACS) Core carries out flow cytometry and analysis for CIP and CCR scientists; the Media Laboratory produces media and reagents for more than 45 CCR laboratories; Central

Glassware Services provides glassware processing to the laboratories; and the BSP program office provides logistical and administrative support to CCR laboratories.

The scientific staff encompasses expertise in a broad range of the basic science disciplines, and a strong collaborative tradition exists between the research staff and their CCR colleagues. The unifying feature of the studies pursued by the investigators is their direct or potential relevance to the overall goal of gaining knowledge and developing cutting-edge tools that can be applied to human diseases. The progress of the PIs and their scientific efforts are monitored through CCR site visits. BSP's contributions focus on cancer and retrovirology, and its researchers seek to understand basic biology, the cellular mechanisms that contribute to carcinogenesis, and the genetic factors that influence disease susceptibility and progression.

Laboratory Animal Sciences Program Directorate

Rick Bedigian, Ph.D., Director, Interim

The Laboratory Animal Sciences Program (LASP) represents a comprehensive resource for the National Cancer Institute's (NCI's) animal research programs on both the Frederick and Bethesda campuses, with the aim of providing the highest-quality animal care and animal support services possible. This is achieved by ensuring that the investigators' needs are met through the use of healthy animals appropriate for their research requirements; ensuring that all animals are housed, handled, and cared for in a humane manner in accordance with regulatory guidelines; and providing scientific support for investigators performing animal-based research.

To support the diverse research requirements of the scientific community, LASP provides an integrated range of high-quality services, facilities, administrative infrastructure, and technologies that are functionally organized within the Animal Research Facilities Oversight, the Scientific Support Programs, and the Center for Advanced Preclinical Research (CAPR).

Animal Research Facilities Oversight includes the Laboratory Animal Medicine (LAM), the Animal Health Diagnostic Laboratory (AHDL), and Receiving and Quarantine (R&Q). Through these programs, LASP staff engages in preventive medicine by providing clinical diagnosis, therapy, and preoperative care for research colonies, and maintains high-quality animal-holding facilities and services, which include quarantine of imported animals, rederivation of pathogen-carrying strains, and comprehensive diagnostic services to monitor and maintain the health status of the animal research colonies.

The Scientific Support Program, which comprises laboratories and programs dedicated to the generation and characterization of mouse models for human disease, includes the following:

- Transgenic Mouse Model (TMM) Laboratory: Provides core capabilities and facilities for the production and characterization of genetically engineered mice (GEM) by pronuclear microinjection and gene targeting in embryonic stem cells.
- Cryopreservation Laboratory: Provides archiving of unique and valuable GEM strains by preserving their frozen germplasm to prevent loss of animal colonies due to disease outbreak or to genetic and environmental factors.
- Pathology/Histotechnology Laboratory (PHL): Provides comprehensive veterinary pathology and molecular histopathology services that are focused on the phenotypic characterization of animal disease models; PHL's capabilities include immunohistochemistry (IHC), laser-capture microdissection, blood chemistry analysis, and digital whole-slide image capture and analysis.
- Small Animal Imaging Program (SAIP): State-of-the-art multimodality animal imaging facility (magnetic resonance imaging [MRI], positron emission tomography/computed tomography [PET/CT], single-photon emission computed tomography/computed tomography [SPECT/CT], ultrasound, X-ray, and optical imaging) for real-time in vivo monitoring of tumor cells and metastases, tracking of gene expression, and assessment of effects of pharmacological interventions.
- Animal Molecular Diagnostics Laboratory (AMDL): Use molecular-based technologies for detection of animal pathogens, assessment of the genetic purity of animal-related reagents, and genotyping of complex genetically engineered mouse strains.
- High-Throughput Animal Genotyping Laboratory (HTAGL): Provides platform for large-scale genetic monitoring and management of complex genetically engineered mouse model colonies.
- Molecular Imaging Laboratory (MIL): Develops and implements new methods for preclinical and clinical in vivo imaging in support of the Molecular Imaging Program in Bethesda.
- NCI Mouse Repository: Central resource for maintenance and propagation of mouse cancer models and distribution of strains throughout the scientific community (academic, nonprofit, commercial).

- Center for Advanced Preclinical Research (CAPR): A program initiative funded by the Center for Cancer Research (CCR) that focuses on the generation of novel, and the use of established GEM models of human cancer and their application to the development of targeted effective cancer diagnostics and therapies.

Data Science and Information Technology Program

David Heimbrook, Ph.D., Director, Interim

The Data Science and Information Technology Program's primary focus is to develop an enterprise-level, consolidated information technology infrastructure that provides exceptional IT capabilities to NCI at Frederick and the Frederick National Laboratory for Cancer Research (FNLCR) in support of basic, translational, and clinical cancer and AIDS research.

ADVANCED BIOMEDICAL COMPUTING CENTER

Jack Collins, Ph.D., Director

The primary focus of the Advanced Biomedical Computing Center (ABCC) is to support scientific research at NCI at Frederick, NCI-Bethesda, NIH, and other federal agencies through the Economy Act. The ABCC provides bioinformatics, systems biology, data integration and analysis, mathematical simulation and modeling, image analysis and visualization, nanoinformatics, proteomic analysis expertise, and web-enabled application delivery to these communities.

IT OPERATIONS GROUP

Greg Warth, Director

The IT Operations Group (ITOG) is responsible for computational servers, storage servers, virtual machine infrastructure, and the FNLCR network. ITOG focuses on implementing enterprise IT best practices in the areas of computational services, storage, backup, and archiving; batch and application support; server consolidation and virtualization; network infrastructure; unification of voice, teleconferencing, and video communication technologies; and improved infrastructure for colocation of dedicated servers.

CBIIT TECHNICAL OPERATIONS SUPPORT GROUP

Braulio Cabral, Director

The Center for Biomedical Informatics and Information Technology (CBIIT) Technical Operations Support consists of several major categories of work related to the development and/or acquisition of biomedical informatics and other information technology resources. CBIIT seeks direct support from NCI at Frederick for resource acquisition and subcontracting, project management and oversight, deliverable review, intellectual property and licensing negotiation, financial management, and coordination with other CBIIT and NCI programs.

CBIIT Technical Operations Support provides these core capabilities as the base of this task order. These activities include the following:

- Support for the definition of scope, time, and budget for information technology activities
- Development of software products
- Development of other information technology products, including vocabularies/ontologies, common data elements, data standards, and data or other biomedical capabilities associated with information technology systems
- Support for open-source resource development activities not directly funded by NCI or funded via non-contract mechanisms
- Acquisition of commercial information technology products
- Review and assessment of information technology resources from all subcontract activities and from such non-contract activities as designated by the contracting officer's technical representative
- Coordination and participation in the National Cancer Informatics Program (NCIP)

HIGH-PERFORMANCE COMPUTING INITIATIVE

Eric Stahlberg, Ph.D., Director

The primary focus of this group is to work collaboratively across the NCI CBIIT and FNLCR to develop a strategy for expanded use of high-performance computing to support cancer research.

INFORMATION SECURITY AND COMPLIANCE OFFICE

Natasha Freeman, Manager

The Information Security and Compliance Office (ISCO) provides IT security auditing, engineering, and incident response support for NCI at Frederick and FNLCR. ISCO supports the life cycle of information security for the scientific mission and administrative functions of NCI at Frederick/FNLCR to ensure the availability of information systems, protect the integrity of information, and protect the confidentiality of intellectual property and patient data.

STRATEGIC PROGRAMS

Braulio Cabral, Director

The Strategic Programs group supports exploratory programs focused on the development and integration of advanced technologies, and transdisciplinary approaches, infrastructures, and standards to accelerate the creation of publicly available, broadly accessible, multidimensional data sets to benefit the cancer research community.

CLINICAL GROUP

Barry L. Gause, M.D., Director

Clinical Research Directorate

Barry L. Gause, M.D., Director

The Clinical Research Directorate (CRD) was established in November 2006 by bringing together the Clinical Monitoring Research Program (CMRP), and the Quality Assurance programs of the Pilot Plant and the Biopharmaceutical Development Program (QA-BDP). The major purpose for establishing a new directorate was to bring those programs at the clinical end of the translational spectrum under an umbrella that fosters interactions in areas of overlap and provides clinical supervision of such activities. In addition, assigning the QA programs to this directorate was necessary to provide the required autonomy and transparency required of GMP quality assurance operations.

The overall objective of the directorate is to provide clinical research support for clinical trials and quality assurance for the production of vaccines and biological agents at the National Institutes of Health (NIH). This includes support for clinical trials management, regulation, pharmacovigilance, and protocol development and navigation, as well as operational support for clinical research. The directorate accomplishes its mission by providing comprehensive, dedicated clinical research support to major clinical programs within the NIH.

In addition, the directorate establishes quality systems at Pilot Plant and BDP before the initiation of manufacturing, and follows through on all regulatory aspects of production, including providing support for Investigational New Drugs (INDs). Detailed descriptions of QA activities are presented under the sections for the Pilot Plant and BDP.

CLINICAL MONITORING RESEARCH PROGRAM

The primary mission of the Clinical Monitoring Research Program (CMRP) is to provide comprehensive, dedicated clinical research support to major programs within the NIH, including the National Cancer Institute (NCI), National Institute of Allergy and Infectious Diseases (NIAID), National Heart, Lung and Blood Institute (NHLBI), National Institute for Arthritis and Musculoskeletal and Skin Diseases (NIAMS), National Center for Advancing Translational Sciences (NCATS), National Institute of Mental Health (NIMH), National Institute of Neurological Disorders and Stroke (NINDS), and the NIH Clinical Center. To support the diverse research requirements of the clinical research community, CMRP provides an integrated range of quality services that are functionally organized

within CRD. CMRP represents a comprehensive resource for a number of the intramural clinical research programs at NIH. CMRP staff continues to support an extensive variety of high-profile NCI and NIAID initiatives, as described in this report.

As a program, CMRP has provided high-quality clinical research support services to meet the expanding and new challenges faced by NIH researchers. CMRP has recognized that there are numerous barriers to conducting clinical research, not only domestically, but particularly in an international setting. Successful completion of our mission directly benefits the mission of NCI, NIAID, and other institutes, and has contributed to improving the overall standards of public health globally. The repertoire of support services provided to clinical researchers throughout the world has expanded dramatically over the last 14 years, assisting researchers in providing the highest-quality clinical research that is compliant with applicable regulations and guidelines, and maintaining data integrity, with the overall goal of protecting human subjects. CMRP has supported the goal of increasing the capability of international locations to participate and partner in cancer research, and has assisted in the critical development of clinical trial networks across the world.

As the largest program under CRD, CMRP continues to provide regulatory, clinical trials management, pharmacovigilance, protocol development and navigation, and project/program management services to support more than 400 domestic and international studies related to cancer; avian flu/severe human influenza; HIV; HCV; TB; malaria; Ebola; heart, lung, and blood diseases and conditions; parasitic diseases; rheumatic and inflammatory diseases; arthritis; musculoskeletal and skin diseases; and neurological diseases.

Applied and Developmental Research Directorate

Michael W. Baseler, Ph.D., Director

The Applied and Developmental Research Directorate (ADRD) consists of two main program areas: the Clinical Services Program (CSP) and support to the NCI Division of Cancer Treatment and Diagnosis (DCTD). In FY2014, CSP laboratories supported over 150 NCI and National Institute of Allergy and Infectious Diseases (NIAID) clinical trials, as well as trials from additional institutes. Clinical trial support included processing and cryopreserving clinical materials; database tracking of clinical samples received; performing sequential studies of immune function in patients with cancer, AIDS, other infectious diseases, chronic granulomatous disease, and other diseases associated with immune deficiency or autoimmunity; testing viral burden; identifying viral quasi-species; and determining viral mutations associated with drug resistance. These efforts include the evaluation of new technologies and the development of new assays that can be used to monitor patients during therapy. Seven program laboratories performed high-complexity testing under the auspices of CLIA, with test results used to aid in patient diagnosis or treatment decisions.

Laboratories within CSP provide dedicated support to the clinical trials programs at NCI, including the Division of Cancer Epidemiology and Genetics, the Center for Cancer Research, the Division of Cancer Prevention, and NIAID. Support also extends to preclinical and translational research. Several program laboratories provide shared services that can be accessed by other institutes within NIH through the NCI at Frederick Core Service Accessioning System (CSAS). CSP laboratories have also provided support to other government agencies through the Economy Act. CSP also provides technical project management support to the Fisher BioServices Biorepository subcontract.

Biopharmaceutical Development Program Directorate

George Mitra, Ph.D., Technical Director/Program Director

The Biopharmaceutical Development Program (BDP), formerly the Monoclonal Antibody Recombinant Production Program, was established in 1993 to provide dedicated services to the Biological Resources Branch (BRB), Developmental Therapeutics Program (DTP), and Division of Cancer Treatment and Diagnosis (DCTD), National Cancer Institute (NCI), as well as to provide support to intramural and extramural National Institutes of Health (NIH) investigators, government agencies, and independent parties through interagency agreements or Cooperative Research and Development Agreements (CRADAs). BDP continues to take on new challenges in support of BRB, DTP, and DCTD, NCI.

BDP provides leading-edge development of monoclonal antibodies, recombinant proteins, peptide and DNA vaccines, virus vaccines and oncolytic viruses, gene therapy products, and other biological and immunomodulating agents. BDP maintains biopharmaceutical production and testing facilities that are compliant with relevant current Good Manufacturing Practices (cGMP). BDP provides complete support, from manufacturing feasibility through process development and clinical manufacturing, with all required regulatory documentation. With a staff of 32 highly trained and experienced personnel, BDP's facilities are designed to be flexible, which enables staff to work

on multiple projects for a variety of different therapies. BDP concentrates on products that are in early development, beginning with the demonstration of product feasibility on the bench through the production and biomolecular characterization of Phase I/II clinical supplies.

During this period, PVS-RIPO, ganitumab and panitumumab-IRDye were in GMP operations. Significant efforts were expended leading towards GMP lyophilized IL-15. Process development of mammalian IL-7, PTEN-Long and RLIP76 were continued.

Vaccine Clinical Materials Program Directorate

David Lindsay, Ph.D., Director

The Vaccine Clinical Materials Program (VCMP) has two major missions: (1) the operation of the Frederick, MD-located Pilot Plant, where clinical trial supplies are manufactured under current Good Manufacturing Practice regulations; and, (2) the management of multiple subcontracts providing preclinical and clinical support services to advance research initiatives of the Vaccine Research Center (VRC), in conjunction with the Research Subcontracts Department. The mission of the VRC is to conduct basic research that facilitates the development of effective vaccines for human disease. The Pilot Plant provides a unique government-owned, contractor-operated facility to produce clinical-stage vaccine candidates, in collaboration with the VRC, being evaluated for prevention/treatment/cure of infectious diseases of global significance, including HIV-AIDS, influenza -flu, emerging diseases, and possible biodefense threats.

VCMP has a total of 111 employees. Most of these employees have completed at least a bachelor's degree and have significant bio/pharmaceutical manufacturing experience.

OPERATIONS AND FINANCIAL GROUP

David F. Bufter, MBA, Chief Operating Officer, Interim

Contracts and Acquisitions Directorate

Bob Mason, Director

The Contracts and Acquisitions Directorate (C&A) provides all purchasing, subcontracting, receiving, warehousing, distribution, and transportation services for the FNLCR and NCI at Frederick operations.

During the year, the subcontracting department (construction and research subcontracting) continued to see growth in activity. This growth was the result of new program requirements. Construction subcontracts worked closely with the Facilities Maintenance and Engineering (FME) directorate as well as NCI Management Operations and Support Branch (MOSB), and Office of Scientific Operations (OSO) leadership to establish streamlined procedures for work orders less than $2 million. The acquisition group completed a significant program to make more efficient and effective the establishment and administration of service maintenance agreements, and has increased its internal staff training and awareness programs. The Contracts Department maintains accountability for the compliance with hundreds of contractual requirements, the negotiation and execution of modifications to the contract and, this year, a significant effort in partnership with the NCI contracting office to establish an IDIQ contract (a second prime contract).

The C&A office of Procurement Compliance continued its support to the NCI Purchasing System review and to further develop and promulgate compliance related guidance and processes.

Management Support Directorate

Richard A. Pendleton, MBA, Director

The Management Support Directorate (MSD) is responsible for providing solutions to administrative, operational, and program-specific activities for the Operations and Technical Support (OTS) Contract. This involves planning and implementing integrated policies and procedures, and providing direct program and surge support in response to Leidos Biomedical Research's directorate's requirements. MSD staff also work with NCI program staff

on programs and projects that support the NCI at Frederick community. A major emphasis for MSD is management of quality assurance and customer satisfaction systems to assess project status and facilitate the initiation of working project teams. MSD staff members support a wide range of activities related to OTS Contract administration and operational support as identified by senior management.

Human Resources Directorate

Jill S. Sugden, MA, SPHR, Director

The Human Resources Directorate (HR) works in partnership with managers and their teams to support the mission of Leidos Biomedical Research staff as they work on behalf of the Frederick National Laboratory for Cancer Research (FNLCR).

HR provides leadership and guidance in the development, implementation, and equitable administration of policies and procedures, thus fostering a positive work environment. The core services and competencies include recruitment and staffing, employee relations and counseling, organizational and employee development, compensation and benefits, HR information management, and regulatory compliance.

Facilities Maintenance and Engineering Directorate

Dante Tedaldi, Ph.D., P.E., Director

The Facilities Maintenance and Engineering (FME) Directorate plans, designs, develops, and executes facility improvements for NCI at Frederick. FME provides ongoing support to the scientific mission with routine daily operation and maintenance duties, as well as by providing around-the-clock emergency maintenance/repair services. The work ranges from in-house designs of small projects to outsourced contracting for large-scale project designs. The diversified in-house resources have expertise in cost estimating and project planning, construction management, and facilities maintenance. FME emphasizes interactive working relationships with scientists, administrative staff, and management staff to identify schedule-driven and cost-effective solutions that effectively respond to the changing needs of the research community.

Environment, Health, and Safety Directorate

Terri S. Bray, Director

The Environment, Health, and Safety Directorate (EHS) is dedicated to ensuring a safe, healthful, and environmentally friendly workplace for all employees of, and visitors to, NCI at Frederick.

It is the policy of NCI at Frederick to create and maintain a healthy and safe workplace, and to promote a healthy workforce as its most valuable and enduring resource. EHS provides comprehensive health services to NCI at Frederick employees, as well as emergency medical services and treatment for accidental injury or illness sustained by NCI at Frederick employees.

Our goal is to maintain and develop safety programs and regulations that establish guidelines for full compliance with all applicable federal, state, and local occupational safety and environmental laws and regulations.

Financial Operations Directorate

Tim Boyle, Director

The Financial Operations Directorate oversees all finance-related activities for the Operations and Technical Support (OTS) Contract, including the following core accounting and finance functions: financial planning and analysis; general accounting; payroll; accounts payable; billing; accounts receivable; business information systems; and internal audit and controls. The directorate's mission is to administer an enterprise-level, fully integrated, financial management program for NCI at Frederick; establish fiscal policies that ensure accountability for and control of government funds; provide timely, relevant, and clear financial analysis and reporting to assist in managing fiscal resources; and deliver quality customer service to all FNLCR stakeholders.

Appendix B: Publications

leidos

Leidos Biomedical Research, Inc.

Leidos Biomedical Research, Inc.

2014-2015 Annual Report

Appendix B

Publications

OFFICE OF THE PRESIDENT

Cancer Genomics Research Laboratory

JOURNAL ARTICLES

Al Olama AA, Kote-Jarai Z, Berndt SI, Conti DV, Schumacher F, Han Y, Benlloch S, Hazelett DJ, **Wang Z**, Saunders E, Leongamornlert D, Lindstrom S, Jugurnauth-Little S, Dadaev T, Tymrakiewicz M, Stram DO, Rand K, Wan P, Stram A, Sheng X, Pooler LC, Park K, Xia L, Tyrer J, Kolonel LN, Le Marchand L, Hoover RN, Machiela MJ, **Yeager M**, **Burdette L**, **Chung CC**, **Hutchinson A**, Yu K, Goh C, Ahmed M, Govindasami K, Guy M, Tammela TL, Auvinen A, Wahlfors T, Schleutker J, Visakorpi T, Leinonen KA, Xu J, Aly M, Donovan J, Travis RC, Key TJ, Siddiq A, Canzian F, Khaw KT, Takahashi A, Kubo M, Pharoah P, Pashayan N, Weischer M, Nordestgaard BG, Nielsen SF, Klarskov P, Røder MA, Iversen P, Thibodeau SN, McDonnell SK, Schaid DJ, Stanford JL, Kolb S, Holt S, Knudsen B, Coll AH, Gapstur SM, Diver WR, Stevens VL, Maier C, Luedeke M, Herkommer K, Rinckleb AE, Strom SS, Pettaway C, Yeboah ED, Tettey Y, Biritwum RB, Adjei AA, Tay E, Truelove A, Niwa S, Chokkalingam AP, Cannon-Albright L, Cybulski C, Wokołorczyk D, Kluźniak W, Park J, Sellers T, Lin HY, Isaacs WB, Partin AW, Brenner H, Dieffenbach AK, Stegmaier C, Chen C, Giovannucci EL, Ma J, Stampfer M, Penney KL, Mucci L, John EM, Ingles SA, Kittles RA, Murphy AB, Pandha H, Michael A, Kierzek AM, Blot W, Signorello LB, Zheng W, Albanes D, Virtamo J, Weinstein S, Nemesure B, Carpten J, Leske C, Wu SY, Hennis A, Kibel AS, Rybicki BA, Neslund-Dudas C, Hsing AW, Chu L, Goodman PJ, Klein EA, Zheng SL, Batra J, Clements J, Spurdle A, Teixeira MR, Paulo P, Maia S, Slavov C, Kaneva R, Mitev V, Witte JS, Casey G, Gillanders EM, Seminara D, Riboli E, Hamdy FC, Coetzee GA, Li Q, Freedman ML, Hunter DJ, Muir K, Gronberg H, Neal DE, Southey M, Giles GG, Severi G, Breast and Prostate Cancer Cohort Consortium (BPC3), PRACTICAL (Prostate Cancer Association Group to Investigate Cancer-Associated Alterations in the Genome) Consortium, COGS (Collaborative Oncological Gene-environment Study) Consortium, GAME-ON/ELLIPSE Consortium, Cook MB, Nakagawa H, Wiklund F, Kraft P, Chanock SJ, Henderson BE, Easton DF, Eeles RA, Haiman CA: A meta-analysis of 87,040 individuals identifies 23 new susceptibility loci for prostate cancer. Nat Genet 46(10): 1103-9, 2014. DOI: 10.1038/ng.3094. PMID: 25217961.

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