

National Cancer Institute

The Nation's Investment in Cancer Research



Connecting the Nation's
Cancer Community

AN ANNUAL PLAN AND BUDGET PROPOSAL FISCAL YEAR 2010

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
National Institutes of Health

Director's Message

In the nearly four decades since passage of the landmark National Cancer Act of 1971, America's progress against cancer has been significant and steady – although, typical of science, most often measured in small increments. In 1991, cancer death rates began to drop, by about one percent each year. Of late, many cancer incidence rates have also been decreasing on an annual basis.

This incremental progress is particularly impressive, when viewed through the prism of other, more sobering statistics. Cancer, as a disease burden, is rising across the globe. By the year 2010, cancer is expected to pass heart disease as the number-one killer. Clearly, our work – in the United States and worldwide – is far from complete.

Cancer affects each of us, whether directly, as a patient, or in the reflected struggles of a loved one or a friend. It is no surprise that, as director of the National Cancer Institute, the questions I most often hear – from cancer survivors, from patient advocates, and from legislators – begin with “What will it take...” What will it take, I am asked, to accelerate the downward curve of cancer death rates? What will it take to deliver on the promise that cancer can be made more chronic than killer? What will it take, in dollars, to rid us of this burden?

This document is an attempt to bring some realistic answers, with appropriate dimensions, to these questions. It is based on



science – on the exciting forefronts in laboratory research that are vastly expanding our knowledge of cancer’s origins, processes, and weaknesses. It is based on the need to more rapidly translate this new knowledge into safe, effective, targeted interventions for cancer patients. It is about the resources that could hasten our efforts. It is about the importance of increasing our intellectual capacity, our workforce, to take full advantage of the opportunity to make real changes.

In sum, this document is the National Cancer Institute’s professional judgment of what a financial infusion could make possible and how NCI would spend those monies.

In the pages ahead, I hope you will also recognize NCI’s deep commitment to outstanding science that benefits all Americans. Cancer is – and will continue to be – a model for the study of disease biology, for new thinking about the delivery of health-care, for the development of electronic medical records, and for a healthcare system based on the uniqueness of each individual. Those responsibilities, those commitments, drive us – in NCI’s own laboratories, through the thousands of outstanding scientists we support across America’s cancer research enterprise, and in the vital collaborations we foster around the world. This document is, after all, about progress, about opportunity, and about reducing the cancer burden for all people in every nation.

A handwritten signature in black ink, appearing to read "John E. Niederhuber". The signature is fluid and cursive, with a large initial "J" and "N".

John E. Niederhuber, M.D.

Director, National Cancer Institute



Following Important Leads

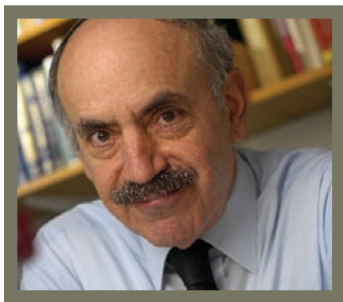
LESS THAN A DECADE INTO THE NEW CENTURY, AMERICA'S CANCER RESEARCH ENTERPRISE – LED AND FACILITATED BY THE NATIONAL CANCER INSTITUTE – IS COMING TO DEEPLY UNDERSTAND CANCER'S CAUSES, INNER WORKINGS AND COMPLEXITIES AT AN EVER ACCELERATING PACE. SPURRED BY THE 2003 COMPLETION OF THE LANDMARK HUMAN GENOME PROJECT, WE NOW UNDERSTAND, AS NEVER BEFORE, THAT CANCER IS PRIMARILY A DISEASE OF OUR GENES – BOTH IN THE GERMLINE DNA PASSED ON TO US BY OUR PARENTS AND IN THE CHANGES TO OUR GENES THAT ACCUMULATE OVER A LIFETIME. THE TUMOR, AS WE HAVE KNOWN FOR SOME YEARS NOW, IS NOT A SINGLE ENTITY. SCIENTISTS HAVE LEARNED THAT CANCERS ARE COLLECTIONS OF ABERRANT CELLS, WHICH MAY RELY ON SEEMINGLY NORMAL TISSUE IN THE MICROENVIRONMENT THAT SURROUNDS THE TUMOR, IN ORDER TO COMMUNICATE, GROW, AND METASTASIZE. AS WE CONTINUE TO MAKE MANY UNEXPECTED DISCOVERIES ABOUT CANCER'S COMMON PATHWAYS AND STUNNING INTRICACIES, EACH DISCOVERY MAY ALSO REVEAL AN OPPORTUNITY FOR SOLUTIONS TO A COMPLEX PROBLEM. THE PAGES THAT FOLLOW HIGHLIGHT SOME OF THE EXCITING CANCER RESEARCH OPPORTUNITIES BEFORE US TODAY – AND SOME OF THE VISIONARY SCIENTISTS WHO HAVE GREATLY ENHANCED OUR KNOWLEDGE OF CANCER.

Tumor Microenvironment

Much of the basic cancer research conducted over the past 30 years has been focused on the cancer cell, without particular concern for its surroundings. Researchers are finding, however, that tumor cells do not live independently. To survive and proliferate, tumors require assistance from the microenvironment of cells, molecules, and blood vessels immediately surrounding them.

“Non-cancerous cells recruited from the host are now seen as rate-limiting determinants of how well the tumor grows and how it is able to metastasize and establish itself in distant organ sites,” explained Robert A. Weinberg, Ph.D., a member of the Whitehead Institute for Biomedical Research at the Massachusetts Institute of Technology. Dr. Weinberg discovered the first human oncogene, which directs tumor growth, as well as the first tumor suppressor gene.

At the heart of the tumor microenvironment is the signaling that goes on between cells. Research in this area is yielding evidence of a greater number of cytokines, which are proteins that guide interactions



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— ROBERT A. WEINBERG, PH.D.

between cells. These cytokines facilitate talk between pre-cancerous cells and other cells that have been recruited to build a tumor’s framework. The basic characteristics of malignant cancers are developed and stimulated by signals originating in this framework.

Because standard research models and methods for analyzing cancer cell behavior cannot adequately capture the complex nature of the tumor microenvironment, more advanced models are now being developed, in order to realistically mimic the signaling pathways and interaction between the tumor and its surrounding environment. A highly sophisticated computer model, developed in conjunction with scientists from disciplines such as mathematics and bioinformatics, is providing a fuller picture of cancer as a biological system.

One eventual use for these so-called *in silico* models could be to generate a virtual model of individual patients’ tumors, then simulate how various treatments would affect the tumor and patient, pointing to the most effective and least toxic therapy. Such computer models hold great potential for studying diseases other than cancer.

Because of the fundamental importance of this area of research, NCI launched a tumor microenvironment initiative in 2006 with the funding of 10 programs, most of which are university based, and the establishment of a network to facilitate the programs. The primary objective of the initiative is to delineate mechanisms of tumor-host interactions in cancer by better understanding the role that the stroma, or supporting tissue and elements surrounding the tumor, plays in initiation, progression and metastases of a tumor.

Tumor Stem Cells

In the mid-1990s, Canadian researchers discovered the first cancer-initiating cells in patients with acute myeloid leukemia. These so-called cancer stem cells, which make up less than five percent of a tumor, may, in fact, be the cells that are the earliest precursors of cancer's spread and the cells most resistant to conventional treatments.

In the years since that initial discovery, cancer stem cells have been identified in other blood-borne cancers, along with brain, breast, ovarian, and, most recently, colon cancers. By any measure, the science of cancer stem cells is both a young avenue of investigation and an extremely promising one. Scientists believe that some tumors contain small populations of these self-renewing cells. They also note that the tumor microenvironment is crucial to a complete understanding of stem cells, as the microenvironment's noncancerous host tissue plays a major role in cancer progression, in the nourishment of the tumor, and in its ability to communicate.

NCI supports research to isolate cancer stem cells, based on markers that are

shared by normal tissue stem cells of the same type – and occasionally by other cells, as well. The hope is that scientists can develop therapies that target and control cancer stem cells before they lead to metastasis – or, via some fascinating new insights, engineer certain other tissue stem cells to create healthy organs.

Among the many investigators NCI supports across the United States is Anthony Atala, M.D., from Wake Forest University, a leader in the emerging field of tissue engineering using stem cells. Recently, Dr. Atala isolated stem cells through a procedure familiar to millions of expectant mothers: amniocentesis. This common technique, normally performed about 16 weeks into pregnancy, tests the fluid that surrounds a growing fetus for signs of genetic disorders. As Dr. Atala has noted, amniotic fluid cells are also proving useful for other areas of scientific study and may, in time, be therapeutically valuable, since they will not form tumor cells, as embryo-derived cells can. Furthermore, because they grow slowly, amniotic fluid cells can also be more readily controlled.

It is important to remember that cancer stem cells have only recently been discovered. As a cautionary example, a recent scientific publication suggests that many more tumor cells have tumor initiating potential than previously thought. To answer fundamental questions about cancer stem cells, scientists will need to develop more efficient techniques for isolating the cells and maintaining them in culture, as Dr. Atala has done. Single-cell analyses will also likely be needed to distinguish events present in cancer stem cells from the more differentiated cells that make up the majority of the tumor.

Anthony Atala on Tissue Regeneration and Stem Cells



Using a process he likens to “baking a layer cake,” Dr. Atala is creating new organs and other tissues in the laboratory. Dr. Atala, director of the Wake Forest University Institute for Regenerative Medicine, leads a team of more than 150 investigators doing this transformative work. The researchers remove postage stamp-size tissue samples from cancer patients. “We start by placing cells, one layer at a time, into three dimensional scaffolding, and then we place this new tissue into the body for baking,” said Dr. Atala. In a recent clinical trial at Thomas Jefferson University Hospital in Philadelphia, a patient had a bladder transplant – with a new organ grown from her own cells. Just eight weeks after physicians harvested the patient’s tissue, her new bladder was in the operating room ready for transplant. This technique shows promise to move forward from the experimental stage. Private industry bought the license and is now producing the bladders that Dr. Atala and his group created at Wake Forest.

The biggest challenge, Dr. Atala says, is to get cells to grow in large quantities outside the body, and that is where stem cells may play a vital role. Peering into the future, Dr. Atala says he would like to induce regeneration inside the body, by using stem cells to regenerate part of an organ at the site of injury or disease. Ultimately, “studying cancer stem cells will open the window to understanding how to best use a patient’s own cells for cancer therapy, because you want to make sure the cells you’re producing are normal cells. From this better understanding we should also be able to figure out what is the switch that could make them abnormal.”

Advances in regenerative medicine have been made possible by gathering and pooling expertise in bioengineering, cell biology, physiology, surgery, molecular biology, and other fields. “NCI plays a major role in the acceleration of these new technologies,” Dr. Atala noted. “This technology has broad-reaching implications for all types of diseases, not just for cancer.”

Signal Transduction Pathways

Signal transduction pathways are communication routes for transmitting information between cells and within cells. Simply put, these pathways are like electrical circuits made from molecules, which deliver signals that drive decisions about whether cells will proliferate or die; whether they will invade surrounding normal tissue; whether new blood vessels will grow into the tumor to bring essential oxygen and nutrients; and whether cells will travel to other sites in the body. NCI is exploring two areas of interest in this field: cross talk and termination of signaling.

Cross talk, in which a signal jumps from one pathway to another, permits more finely tuned regulation of cell activity than do individual, independent pathways. However, inappropriate cross talk can cause messages to be misinterpreted or not delivered.

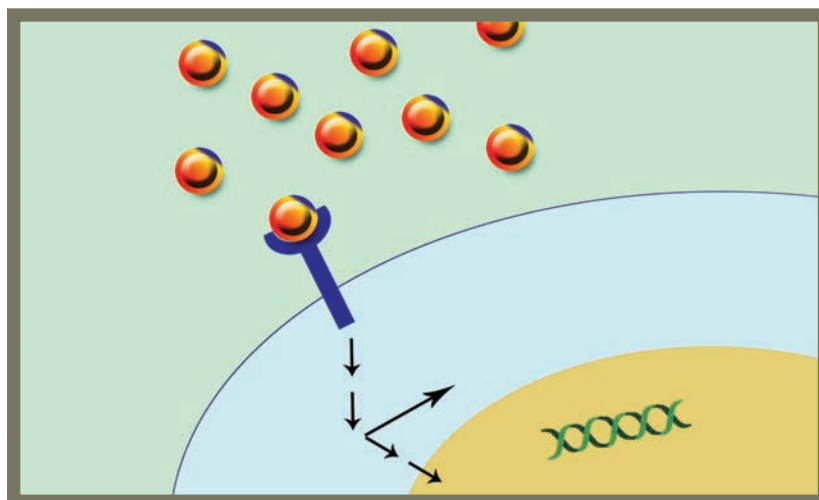
After a signaling process has been initiated and the information has been transduced, or transferred, to affect cellular processes, the specific signaling processes must be terminated. Without such termination, cells lose their responsiveness to new signals. Signaling processes that fail to properly ter-

minate can lead to uncontrolled cell growth and the possibility of cancer.

In order to better understand the importance of controlling and regulating complex signaling pathways, NCI's cancer Biomedical Informatics Grid program, better known as caBIG[®], is developing a tool called Biological Pathway Exchange as a data standard for the modeling of biological pathways. This tool should be of great value to scientists in the field of proteomics, where signaling pathways are key to understanding how proteins talk to each other.

RNA Interference

Our understanding of the role that RNA plays in cellular processes and in cancer has evolved rapidly this century. Messenger, transfer, and ribosomal RNA are still vitally important to the cell as a translation mechanism, but regulatory RNAs are now known to play a very important role as well. MicroRNA can block translation or accelerate cellular degradation and small interfering RNAs (siRNA) can act in a similar manner. And there are a number of other types of RNA that can play an important role in activating or blocking important cancer pathways.



Signal Transduction
Pathway
NCI

The regulation of gene expression by microRNAs and siRNAs is called RNA interference, or RNAi, for short. This phenomenon has recently been exploited to develop molecular tools for cancer research. By injecting short strands of RNA molecules into cells, scientists are now able to silence, or turn off, certain genes. This technique allows experiments, which used to take months or years, to be completed in weeks or even days.

Use of RNAi has also been enabled by new generations of highly-efficient, cost-effective, high-throughput genetic screening techniques that make it possible to identify genes associated with cancer. Isolating genes that control disease progression will lead to identification of potential targets and, in turn, to new targeted cancer therapeutics.

“High-throughput sequencing will change everything. It will tell us about the cell state in the tissue, and not in just cell lines,” said Nobel Laureate Phillip A. Sharp, Ph.D., of the David A. Koch Institute for Integrative Cancer Research at MIT.

“We are going to accelerate the rate at which we’re going to be able to effectively treat cancers, and I think we will find ourselves in a 10 to 15 year window where we will see that many of the cancers that develop in mid-aged and young people will be treatable for very long periods of time.”

RNAi can also be used to investigate the mechanism of action of drugs that are, for reasons unknown, effective against cancer. In addition, RNAi screening can be used to identify genes that enhance the ability of chemotherapy to fight cancer.

“We need to look, at a basic level, at particular cells and particular states, as that’s the only way to design drugs and interventions,” continued Dr. Sharp. “This wasn’t possible in the pre-genome era – we didn’t have enough granularity and now we do, so we’ve got a specific way of intervening.”

One particular area of study, the regulation of gene activity by methylation, could benefit from advances in RNAi techniques. Methylation involves the addition of



methyl groups (molecules made up of one carbon atom with three hydrogen atoms attached) to DNA or proteins. Stephen Baylin, M.D., and his team at Johns Hopkins University are very involved in the field of epigenetics, which centers around methylation, and they are looking at how gene expression may be caused by mechanisms other than changes in the underlying DNA sequence. The researchers used high-throughput screening techniques to study a large pool of genes thought to be involved in cancer. Their aim was to identify genes with potential prognostic value. They found that 36 of 189 genes they had previously identified as being associated with breast or colon tumor development were often hypermethylated. RNAi techniques may allow them to confirm or refine their findings.

RAISING THE SUCCESS RATE FOR RESEARCH PROJECT GRANTS AND RAISING THE AVERAGE AWARD PER GRANT WOULD REQUIRE \$340 MILLION.

ENHANCING BIOMEDICAL COMPUTING CAPABILITIES TO CAPITALIZE ON VIRTUAL MODELS WILL REQUIRE AN ADDITIONAL \$45 MILLION.

Genome-Wide Association Studies

One of NCI's promising avenues of research, genome-wide association studies (GWAS), has begun to reveal some of the key genetic factors that affect risk for many cancers. Genome-wide association studies involve two groups: those with a given cancer and a group of equal size that does not have the disease. Through genetic characterization, followed by finer and finer mapping and analysis, scientists are able to identify common genetic aspects for the cancers being studied. These new findings, in breast, prostate, colon, and other cancers, have raised hopes that genetic profiles based on germline genetic variation could identify individuals at high risk for cancer and also identify who might benefit from a variety of interventions.

Across all diseases, in just the last three years, genome-wide association studies have identified more than 150 common markers associated with over 40 common diseases. Yet, as Stephen J. Chanock, M.D., chief of NCI's Laboratory of Translational Genomics in the Division of Cancer Epi-

“High-throughput sequencing will change everything. It will tell us about the cell state in the tissue, and not in just cell lines.”

— PHILLIP A. SHARP, PH.D.

demology and Genetics, often reminds colleagues, we are “at the beginning of the beginning.” Genome-wide association studies will be the basis for future laboratory studies, with the goals of regulating gene expression and understanding cell biology, in order to fully comprehend alterations in cellular function and to design novel gene and drug therapies that will be effective at the earliest possible points in cancer’s development.

Importantly, the vast expansion of genome-wide association studies in U.S. and international laboratories has benefitted from a tremendous boost in technology. The Human Genome Project cost approximately \$2.7 billion to complete. According to *Science*, by 2006, a draft genome sequence of the rhesus monkey cost \$22 million. Today the race is on for the \$1,000 genome sequence that can be completed in virtually real time. So, in addition to the boon in technology, the costs saved by advancing technology may be as tremendous.

INVESTING IN GWAS AND OTHER INITIATIVES THAT MAKE UP NCI’S INTRAMURAL RESEARCH PROGRAM WOULD REQUIRE \$100 MILLION.



We are “at the beginning of the beginning.”

— STEPHEN J. CHANOCK, M.D.

The Cancer Genome Atlas

In addition to Genome Wide-Association Studies, which seek to identify common DNA variants associated with cancer, NCI is conducting crucial studies into the entire genetic composition of many cancers. The Cancer Genome Atlas (TCGA) project, begun in 2005 as a collaboration between NCI and the National Human Genome Research Institute (also part of the National Institutes of Health), has utilized and helped develop tools and technologies to generate impressive amounts of data on the genetic make-up of tumors. In September 2008, TCGA reported the first results of its large-scale, comprehensive study of glioblastoma, the most deadly form of brain cancer. The study, reported in *Nature*, identified three previously unrecognized mutations that occur with significant frequency, and the delineation of core pathways disrupted in this type of brain cancer. One of the most exciting results is an unexpected observation that points to a potential mechanism of resistance to a common chemotherapy drug used for brain cancer.

At present, TCGA, through its network of characterization, sequencing, and analysis centers, is also working on lung and ovarian cancers. Moving forward, TCGA has established a goal of rigorously, comprehensively, and reproducibly characterizing the genomes of four to six tumor types per year – with all results both ensuring patient privacy and providing ready access to the research community.

EXPANDING TCGA WOULD REQUIRE AN ADDITIONAL \$200 MILLION.

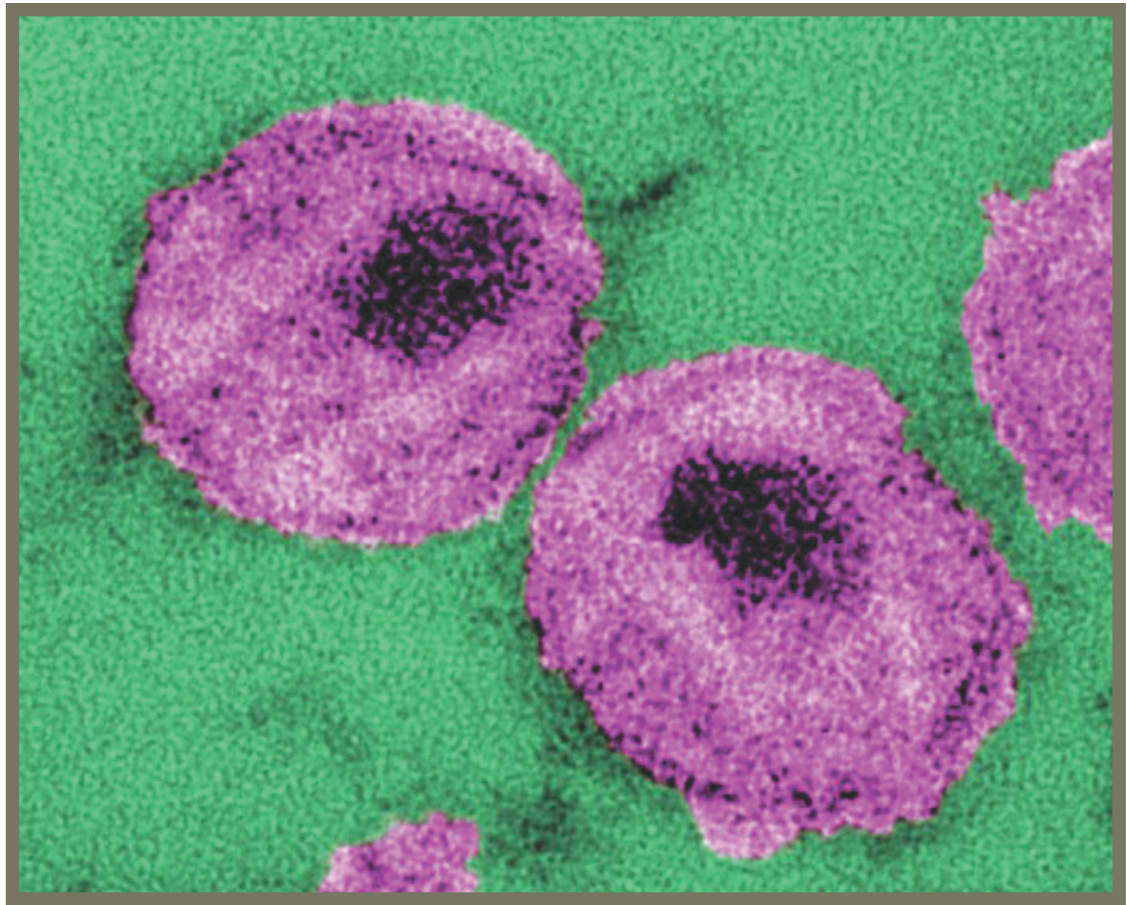
Infectious Etiology

Some cancer-associated viruses appear, in rare cases, to cause cancer. Other viruses, however, substantially increase the risk for cancer and the burden of this disease in the population. For example, HIV-1 infection is responsible for substantial increases in some cancers in young adults in the United States. Although it is not yet clear how to prevent most cancers that occur among HIV-infected people, understanding the transmission routes of the virus and finding preventive measures could lower the incidence of infection, and the subsequent risk of non-Hodgkin's lymphoma and Kaposi's sarcoma. Previously, only a small percentage of cancers were thought to be caused by infectious agents, but current analyses put that number closer to 18 percent.

Similarly, reducing the transmission of human T-lymphotropic viruses will lower the incidence of adult T-cell leukemia/lymphoma. Furthermore, knowing which cancers are associated with different viruses helps to promote targeted cancer screening, early detection, treatment, and prevention.

Scientists in the NCI's Infections and Immunoepidemiology Branch are using principles of both infectious and chronic disease epidemiology to investigate the biology and transmission of cancer-causing organisms and to clarify the relationship between infectious organisms and cancer and other diseases. In addition to studying viruses that are associated with cancer, these scientists are also investigating other microorganisms, such as *Chlamydia pneumoniae*, which have been linked to lung cancer, and sexually-transmitted viruses that may cause prostate cancer.

Thin-section transmission electron micrograph depicts the ultrastructural details of a number of HIV virus particles. Photo courtesy CDC.



NCI's Center for Cancer Research supports researchers who are making important advances in understanding the relationship between infection and cancer. These scientists are investigating tumor-causing viruses and bacteria at the molecular level. Areas of investigation include genes and gene products that regulate cell growth and pathways that contribute to the development of cancer.

The knowledge gained in studying the links between viruses and certain types of cancer has been instrumental in helping scientists develop strategies to fight cancer, such as vaccines directed against human papillomaviruses to prevent cervical cancer and hepatitis B virus, which has been associated with some forms of liver cancer. The study of viruses has also been an important tool in revealing the mechanisms that are involved in carcinogenesis.

Cancer Vaccines and Immunotherapy

Many deadly infectious diseases that were capable of killing millions of people have been tamed because of vaccines, which stimulate the immune system to recognize and attack pathogens before they cause disease. In the future, this approach may also be effective in preventing and fighting cancer.

A major step toward this goal came when the FDA approved a vaccine for the prevention of human papillomavirus (HPV) infection. NCI investigators throughout the Institute were involved in the discovery that HPV is a major cause of cervical cancer. Among these were Douglas Lowy, M.D., and John Schiller, Ph.D., of the Center for Cancer Research, who were instrumental in the discovery of the virus-like particle technology that led to the vaccine's development.

HPV vaccines represent one type of cancer vaccine, which may prevent cancer before it occurs, while others, termed therapeutic cancer vaccines, may help turn a patient's immune system against already-existing cancer cells.



“The beauty of using the immune system to fight cancer is its exquisite specificity. Radiation kills everything in its path. Chemotherapy kills many cells besides cancer cells.”

— JAY BERZOFSKY, M.D., PH.D.

Using a mouse model, Jay Berzofsky, M.D., Ph.D., of the Center for Cancer Research's Vaccine Branch, developed a vaccine containing proteins from breast cancer cells that is capable of inducing immune responses strong enough to kill large breast cancer tumors and tumors that have metastasized to the lungs. These results show the potential for a vaccine that can stimulate the production of antibodies directed against a cell surface receptor such as HER2, which is found on breast cancer tumors.

Vaccines may be most effective as adjuvant therapy following surgery to remove the bulk of the cancer. They can be administered in conjunction with other standard treatments, such as chemotherapy or radiation, and given with cytokines to enhance the immune response.

More than a dozen vaccines are in or nearing phase III trials to refine their use, including dosing, booster schedules, and the site of vaccine administration. But for now, the FDA has not approved any therapeutic cancer vaccines.

In another example, Steven A. Rosenberg, M.D., Ph.D., NCI's chief of surgery, has been successfully using altered versions of a patient's own white blood cells to recognize and attack the cells of advanced melanoma. The ability to genetically engineer human white blood cells to fight against cancer, called Adoptive Cell Therapy, has opened possibilities for many other types of cancer. Dr. Rosenberg and his colleagues are currently researching use of Adoptive Cell Therapy in metastatic melanoma and renal cell cancer, among others.

“The beauty of using the immune system to fight cancer is its exquisite specificity,” says Dr. Berzofsky. “Radiation kills everything in its path. Chemotherapy kills many cells besides cancer cells. The immune system – if you could take full advantage of it – can be so specific that it can kill one cell and not all the other cells around it. You could potentially eliminate cancer cells without having the side effects of other therapies.”

HIV/AIDS

When the first signs of the AIDS epidemic appeared, NCI scientists were at the forefront of the effort to identify HIV as the cause of AIDS, characterize how it hijacked cellular machinery, and, in turn, develop the first treatments for it. They were able to quickly apply their expertise in epidemiology, cancer, retroviruses, cell biology, the immune system, and drug development to this public health crisis.

A research team, led by Robert Gallo, M.D., then at NCI's Laboratory of Tumor Cell Biology, discovered the first two human retroviruses, HTLV-1 and -2, which laid the groundwork for the co-discovery of HIV. This team also led the development of the first diagnostic blood test for HIV infection. Soon thereafter, other NCI researchers, including Robert Yarchoan, M.D., of NCI's HIV and AIDS Malignancy Branch, began to seek effective therapy for AIDS, and discovered or co-developed the first effective drugs – AZT (zidovudine), ddC



“We have been able to generate a very large number of immune cells that appear in the blood and constitute a majority of the immune system of the patient.”

— STEVEN A. ROSENBERG, M.D., PH.D.

(zalcitabine), and ddI (didanosine). In particular, this group identified the anti-HIV activity of these drugs and, with support from other NCI components, conducted initial clinical trials with these agents.

NCI's Center for Cancer Research currently has one of the largest and most productive HIV/AIDS research programs in the world. Researchers in the Center for Cancer Research's HIV and AIDS Malignancy Branch, the HIV DRP (Drug Resistance Program) Host Virus Interaction Branch, and Vaccine Branch are continuing to make advances in HIV/AIDS research. All of this work lays an important foundation for current research into the viral aspects of cancer development.

Among these advances are the identification of genetic mutations that appear to protect against HIV infection or slow its progression, new insights into HIV viral diversity that contributes to drug resistance, and the development of new treatments for AIDS-related cancers, including

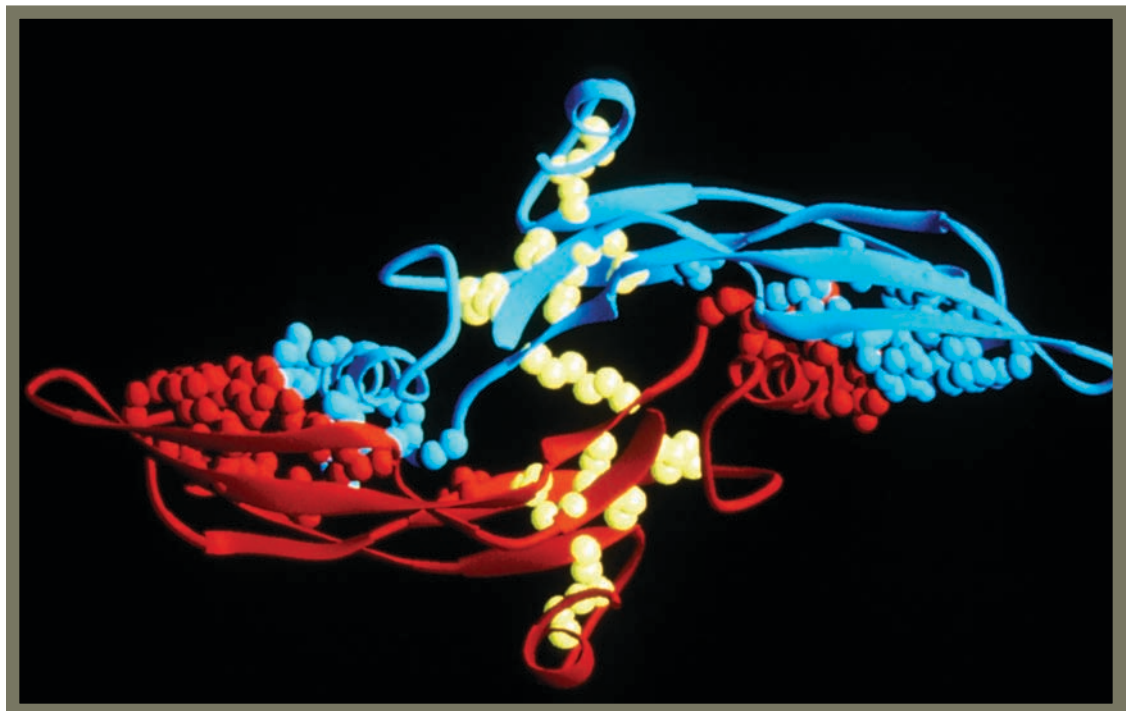
Kaposi's sarcoma and lymphoma. NCI researchers also are at the forefront of efforts to develop both preventive and therapeutic HIV vaccines and new treatments derived from natural products.

Antibodies and Cancer

Antibodies are proteins produced by the body's immune system that are directed against antigens, which are usually associated with molecular components of foreign and infectious agents, such as viruses and bacteria. Researchers can use laboratory-created antibodies, called monoclonal antibodies, in a similar manner to detect antigens in biological samples that may play a role in the development of cancer and thus may be good targets for new cancer therapies. Well-characterized antibodies may speed the identification of key proteins and peptides.

One of the most significant roadblocks of advanced molecular diagnostic techniques like proteomics is a lack of high-quality

Computer graphic of
tgf-beta, a cytokine that
regulates many cellular
functions including
cell proliferation,
differentiation, adhesion
and migration.
NCI, Dr. Michael Sporn



and well-characterized reagents. This barrier was recognized by the NCI, which led to the development of the Antibody Characterization Laboratory. The Antibody Characterization Laboratory at NCI's laboratories in Frederick, Md., part of the Clinical Proteomic Technologies for Cancer initiative, performs sophisticated testing to analyze and validate antibodies – highly critical tools used in research and diagnostic laboratories around the world.

“As industry and academia invest significant resources in the promise of proteomics and ultimately molecular-based tools, well-characterized antibodies will be vital to advancing these disciplines,” said Henry Rodriguez, Ph.D., who directs NCI's Clinical Proteomic Technologies for Cancer initiative. “This is especially true of proteomics, where an antibody can be used to recognize a unique protein in the midst of millions of other proteins that the human proteome comprises.”

ENHANCING TECHNOLOGY DEVELOPMENT
IN CLINICAL PROTEOMICS WOULD REQUIRE
\$35 MILLION.

Nanotechnology

Nanotechnology materials are so small – less than one-billionth of a meter in size – that they are measured on a molecular scale. Many are so tiny that they can penetrate a tumor cell, and are already being used in imaging to make a tumor light up during an MRI scan. Others are being employed to convert magnetic fields into heat, thus destroying cancer cells. In the near future, nanoscale devices will be available to detect the presence of cancer at its earliest stages and to deliver targeted anticancer agents to the tumor.

One of today's challenges is characterizing these materials. For example, slight changes in size or surface chemistry can dramatically influence a physiological response and make a significant difference in safety or potency. Laboratory methods used to evaluate physicochemical or immunological properties, and assays routinely used in preclinical characterization of conventional pharmaceuticals, often yield spurious results when applied to nanoparticle samples.

NCI's Nanotechnology Characterization Laboratory (NCL) is an important component of the larger Alliance for Nanotechnology in Cancer. NCI, in partnership with the National Institute of Standards and Technology and the FDA, is analyzing the growing number of nanotechnology products that have potential in the detection, diagnosis, and treatment of cancer. The NCL's primary focus is to help move these products towards clinical trials.

The NCL performs physiochemical characterization and safety and toxicity characterization, including both laboratory tests and animal studies, and provides information needed to help investigators. To date, the NCL has characterized over 130 different nanomaterial samples including liposomes, gold colloids, quantum dots, and metal oxides – submitted from laboratories in academia, industry, and government.

“At the NCL, we are evaluating nanoparticles and devices to inform the regulatory process and support environmental, health, and safety research of nanotechnologies,” said Scott McNeil, Ph.D., director of the NCL.

ENHANCING TECHNOLOGICAL EFFORTS
AROUND NANOPARTICLES AND PROTEINS
WOULD REQUIRE \$40 MILLION.

Systems Biology

The growing field of systems biology incorporates a broad view of bioinformatics and how data applications and complex mathematics apply to cancer. Current NCI-supported research in model organisms, computational biology, and signaling, just to name a few, are all moving forward at a faster pace, thanks to the higher integration and speed of today’s computer processors and some truly innovative thinking. Measuring, modeling, and manipulating how we view cancer through networks, not individual components, is possible, in part, because of highly sensitive and groundbreaking technology.

Using a concept similar to forecasting the weather, but considerably more complex, Vito Quaranta, M.D., director of

“Green Brushes”
Researchers at the
“Emory/ Georgia Tech
Center of Cancer
Nanotechnology
Excellence are
creating novel arrays
of nanowires that
are being used to
sense cancer
biomarkers,
manipulate cancer
cells, and convert
mechanical energy
into electricity
to power other
nanodevices.

Image courtesy of
Professor Z.L. Wang, PhD,
Georgia Institute of Technology.



Vanderbilt University's Integrative Cancer Biology Center, and colleagues developed a computer model that simulates tumor growth. The model predicts that a harsh microenvironment, such as that created by chemotherapy drugs, causes more aggressive, invasive cells to dominate, increasing the chance of metastasis. In the model each time a cell divides, researchers can randomly pick from a set of 100 different "phenotypes" – behaviors that result from distinct genetic characteristics, such as traits that allow it to divide more quickly. The environmental conditions, such as the level of oxygen and the characteristics of the microenvironment, are set by the researchers. "What we get is a picture of cells that are evolving and growing within a microenvironment," said Dr. Quaranta. "The nice thing about computer simulations is you can create 'what if' scenarios: what if we make the oxygen very high, what if we turn oxygen off in the middle of tumor growth, what if we change the landscape of connective tissue." The long-term goal of this research is that, with the tools of mathematical modeling and computer simulation, physicians will be able to determine the best drugs to treat each stage of a patient's cancer.

In the coming years, NCI will more fully integrate diverse scientific fields of study into our current cancer research agenda, as clearly, we're already learning a great deal from our colleagues across the scientific universe.

INVESTING MORE DEEPLY IN SYSTEMS BIOLOGY
WOULD REQUIRE \$40 MILLION.

Subcellular Imaging

Residing inside the cell's nucleus, the genome is, we have discovered, highly organized. The positions of many genes and genomic regions change during physiological processes, and those changes may provide the earliest foreshadowing of cancer development.

That remarkable knowledge comes from imaging that has moved far beyond the realm of the diagnostic. Advances in imaging devices and contrast agents used to improve image quality are revolutionizing how cancer researchers look inside cells and, consequently, think about cancer diagnosis and treatment.

"We're at a point where we now understand the fundamental concepts, the fundamental principles by which genomes are organized in the nucleus, and I would argue, even the principles by which genomes function," said Thomas Misteli, Ph.D., the head of NCI's Cell Biology of Genomes group in the Center for Cancer Research. The next step, said Dr. Misteli, "is to link some of these morphological observations to function, to physiology, and to disease."

Technological breakthroughs combined with advances in computational analysis of imaging data have driven the field dramatically forward. It has now become possible to visualize nuclear processes and movement of gene loci in single living cells, and generate spatial maps of how genomes are organized in the nucleus.

“This is an area of research that five or six years ago, literally nobody in the United States worked on because it was extremely high risk,” explained Dr. Misteli. “I came to NCI because it provided a lot of freedom to do high-risk research, which is increasingly more difficult in the outside [research] world.”

Sriram Subramaniam, Ph.D., of the Laboratory of Cell Biology in NCI’s Center for Cancer Research, recently published research using electron tomography to visualize the way HIV enters and infects cells. “We can enter structures in their native, physiological context and essentially... zoom into cells, increasing the magnification to a point where you can actually see the atoms and molecules,” said Dr. Subramaniam. “Although you cannot do this with a single microscope, the combination

of things we are doing experimentally and computationally has the end effect that we are literally walking into these viruses and cells at resolutions that are close to looking at these structures and molecules directly.”

“Previous research showing how HIV interacts with immune system cells and antibodies has been important in vaccine design,” said Dr. Subramaniam. “However, understanding the complete structure of the viral spike may reveal other vulnerable targets. This knowledge will be crucial to solving the puzzles associated with strategies at the heart of virus invasion.”

DEVELOPING NEW, ENHANCED IMAGING TOOLS WOULD REQUIRE \$150 MILLION.



“Previous research showing how HIV interacts with immune system cells and antibodies has been important in vaccine design.”

— SRIRAM, SUBRAMANIAM, PH.D.

Cancer and Aging

Cancer and aging are inextricably linked, so the study of specific aging syndromes has the potential to lead to clues about various aspects of cancer. Recent research by the laboratories of Paola Scaffidi, Ph.D., and Thomas Misteli, Ph.D., show that cells affected by Hutchinson-Gilford Progeria Syndrome (HGPS), a disease associated with premature aging, can be made healthy again. Using specially modified segments of DNA, the scientists reversed the abnormalities seen in HGPS cells by correcting defects associated with a key protein.

HGPS is a rare inherited disease affecting about one in eight million children. While appearing normal at birth, infants with HGPS age rapidly after their first 18 months, and physical symptoms include stunted growth, loss of hair and body fat, joint stiffness, osteoporosis, and heart problems.

The genetic basis for HGPS is a single mutation in the gene encoding lamin A, a critical structural protein in the cell's nucleus. Without lamin A, the nuclei of progeria cells become wrinkled, misshapen, and unable to function normally. Experiments showed that "in order to achieve a potential therapeutic effect, we needed to completely eliminate the mutant protein," said Dr. Scaffidi.

Misteli and Scaffidi designed a chemically stable DNA sequence that the cell wouldn't be able to degrade, which would bind to the mutant gene splice site in RNA transcribed from the defective gene. The resulting DNA-RNA complex prevents the splicing machinery from cutting the RNA in the wrong place. "You can think of it as a molecular Band-Aid®," said Misteli. The researchers inserted their bandage into the progeria cells and observed that after four days almost all the mutant lamin A RNA had been eliminated and replaced with the properly spliced counterpart.

"It's amazing that we could take a cell that looked about ready to die, and a few days later it was healthy and ready to divide again," said Dr. Misteli.

One of the unique features of HGPS is the absence of tumors; most other premature aging diseases are characterized by high tumor volume. Consequently, the researchers are currently exploring whether HGPS will be a useful model system for finding the molecular links between aging and tumor formation.



Tom Misteli, Ph.D.,
Head, Cell Biology of
Genomes Group, NCI

Bringing the Physical Sciences to Cancer

A problem as complex as fighting the constellation of diseases that make up what we collectively call cancer should always welcome new ideas, perspectives, and approaches.

In workshops throughout 2008, NCI assembled groups of biologists, physicists, chemists, and others to come up with new scientific approaches to age-old quandaries. Biologists, for example, are familiar with complex changes in cell biology, while physicists can apply their knowledge of how discrete entities interact to a system where millions of cells are bumping into each other in the tumor microenvironment. Chemists understand the reactive potential of carcinogens and can bring a knowledge of that reactivity to yield a better understanding of the cancer initiation process.

At an October 2008 NCI-sponsored meeting on the physical sciences in oncology, Philip LeDuc, Ph.D., associate professor of mechanical and biomedical engineering at Carnegie Mellon University, discussed cellular decision-making processes from a mechanical perspective. “Two important areas [of interest to us] are signal integration – how does a system respond to two distinct signals – and noise. Noise can be a reason a system functions well, as perturbations can help maintain system functionality as seen, for example, in dormant cancer cells.”

Princeton University biophysicist Robert Austin, Ph.D., notes that physics has evolved as a discipline and that physicists have learned to work with more and more complex systems. “We started out working with hydrogen atoms, very simple things, but we are now learning how to work with

complex multi-bodied problems,” he said. “So I think it’s sort of natural for a physicist to go over into this area here because cancer, in my mind, is a very complex multi-bodied interaction phenomenon.”

Physicists can bring to cancer their insights on the properties of matter, including the study of time, energy, heat, and even the evolution of cells. Paul Davies, Ph.D., director of BEYOND: Center for Fundamental Concepts in Science at Arizona State University, even posits there may be significance in the fact that cancer cells are “squishy.”

“This is obviously something rather basic and yet it seems to me that it is not fully understood. Wouldn’t it be nice if we could cure cancer just by making those cells a bit stiffer? It just might be a matter of giving them some glue or something and making them stiffer and stickier – maybe something that would change their mechanical properties...”

While theoretical physics is not a field normally associated with cancer research, the field of biophysics is not new to NCI. The Institute has a Structural Biophysics Laboratory that focuses on solution structural biology and biophysics aimed at understanding and regulating the mechanism of action of proteins and nucleic acids. The laboratory has a very strong interdisciplinary drug design effort, which encompasses synthetic and mechanistic chemistry, structure-based design and modeling, confocal microscopy, and biochemical and biological mechanisms.

ADDING A NETWORK OF CENTERS FOR THE STUDY OF THE PHYSICAL SCIENCES AND CANCER WOULD REQUIRE \$50 MILLION.

Dr. Robert Austin and the Physics of Cancer

Robert Austin has spent his career looking at the community aspects of physics and how that relates to biological processes. He hopes to bring some of this community perspective to the field of cancer research. “The communal aspect of the way organisms responded to stress really surprised me and so I began to think about cancer in terms of communities and their response to stress,” Dr. Austin said.

In his lab, he started building micro-habitat patches, “which are complex microenvironments. We discovered that bacteria responded in the microenvironment in a much different way than you would expect from just culturing them in a test tube. We’re realizing that the microenvironment around a cell in your body is very, very important and so I felt there was a connection between what I could do for making microenvironments and maybe trying to understand the way a cancer cell responds to its own microenvironment.”

“I think treating cancer as a disease may be the wrong approach. Take, for instance, antibiotics. What bacteria have done when you try to kill them is simply evolve their way around the antibiotic and do it very rapidly in response to the stress that the system has put on it, and cancer does the same thing. So that approach of trying to kill the cancer may be exactly the wrong thing to do; it just turns on the evolution machine, if I could use that word, and it starts to mutate evermore rapidly to get around that stress.”

“You can live with a tumor. It’s the transition from a tumor which is not invasive to one that is metastatic, which is an invasion. If we could learn to just keep this tumor intact, reasonably well fed, and not under stress so it’s under no evolutionary push to try to escape where it finds itself in trouble might be a more useful approach than trying to kill it or destroy it. Actually feed it, which sounds nuts, but that might actually be a better way to go about it.”

“I think physicists and other people are receptive to the idea that evolution is a very dynamic thing that’s turned up and down in response to stress, maybe in direct ways. That’s a pretty radical statement, but it may be true. So, physicists like that because they have no preconceptions.”

Conclusion

NCI’s cancer research portfolio is vast and complex, delving into the collection of diseases we call cancer through many different avenues of study. Importantly, cancer research benefits the study of dozens of other diseases, for research in cancer greatly informs science’s understandings of human biology, in the healthy person and the patient. Likewise, given its burden and impact, cancer affects the entire healthcare system, so NCI’s work can lead in many healthcare management areas, just one of which is the adoption of electronic medical records. The next section of this publication will delve into many of the ways NCI strives to put its science to work for patients.



NCI's Drug Development Platform

CLEARLY, WE ARE IN A NEW GENOMIC ERA OF SCIENCE. LABORATORIES ARE GENERATING AND DISCOVERING NEW KNOWLEDGE ABOUT CANCER AT A PACE NEVER BEFORE SEEN. YET, FOR A CANCER PATIENT, WE MUST PROVIDE MUCH MORE THAN NEW KNOWLEDGE. CANCER PATIENTS WANT SOLUTIONS. THEY WANT THERAPIES THAT ARE EFFECTIVE AND FREE OF DEBILITATING SIDE-EFFECTS. THEY WANT EARLIER DETECTION. THEY WANT COMPREHENSIVE ANSWERS TO A COMPLEX PROBLEM. THROUGH OUR KNOWLEDGE OF GENES, PROTEINS, AND PATHWAYS, NCI IS DEMONSTRATING TRUE AND LASTING VALUE, WHEN MEASURED IN LIVES EXTENDED, LIVES SAVED, AND LIVES SPARED THE IMMENSE BURDENS OF CANCER. THE PAGES THAT FOLLOW DISCUSS NCI'S VISION OF A UNIFIED PLATFORM OF EFFORTS TO UTILIZE ITS SECOND-TO-NONE RESOURCES IN DEVELOPING NEW, SAFE, AND EFFECTIVE DRUGS.

To advance NCI's mission of bringing novel therapies to patients – and to more fully exploit its expertise in the later stages of preclinical development – NCI is focusing efforts and resources on the identification of drug candidates and on ways to enhance the entry of early-stage drug candidates into the therapeutics pipeline.

The path from discovery to a new drug necessarily begins with establishing which opportunities to pursue. The virtual avalanche of genome-wide association studies and the genomic information about tumors that has begun to spring from The Cancer Genome Atlas project will overwhelm our capacity to study new targets. Consequently, it will be necessary to review new findings and come to agreement on which concepts should rapidly move into the process of further refinement. NCI will require great scientific minds to help us make the most important choices.

NCI has state-of-the-art resources that span candidate identification through first-in-human testing. These unique resources and programs may offer technologies and capabilities that few universities or private sector entities have at their disposal. NCI must, in fact, become a better facilitator of their work, helping to reduce barriers and to provide developmental assistance. Additionally, NCI's intramural scientists will continue to develop and test new therapies for rare cancers, which tend to draw lesser interest from industry.

High-Throughput Screening

An important tool to identify potential drug targets is high-throughput screening, which allows researchers to quickly conduct millions of biochemical, genetic,

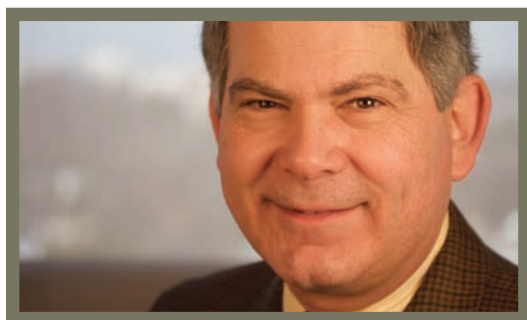
or pharmacological tests. Using this sophisticated, automated process, involving robotics, complex software, and sensitive detection methods, scientists can identify active compounds, antibodies, or genes involved in a particular biochemical pathway that may lead to cancer. This approach runs a screen of a potential target against individual or mixtures of known synthetic or natural compounds that may bind to or alter the function of the target. Identifying compounds that interact with the target provides a starting point for drug discovery and design, and for understanding the role of a particular biochemical process in cancer.

NCI's Molecular Targets Development Program (MTDP) is working to identify and evaluate molecular targets that may be candidates for drug development. As the centerpiece of the Center for Cancer Research's high-throughput efforts, the MTDP develops and evaluates high-throughput screening assays, evaluates screening results from libraries of natural products and synthetic compounds, and aids scientists in the identification of molecular targets and the development of screening tests for molecules that interact with these targets. In collaboration with NCI's Developmental Therapeutics Program, the MTDP provides collections of compounds for screening to other researchers. The MTDP has also begun depositing screening data for more than 100,000 publicly available compounds into the NIH Roadmap project, PubChem. This allows the data to be cross-correlated with data on the same compounds from other sources and should prove to be of great utility to many researchers in the near future.

Chemical Biology Consortium

When its Chemical Biology Consortium (CBC) is up and running, NCI will have the capacity to bring the skills of hundreds of synthetic and medicinal chemists to bear on a singularly challenging problem. Designed to accelerate the discovery and development of effective, first-in-class targeted therapies, the CBC will choose high-risk targets that are of low interest to the pharmaceutical industry. To take a hypothetical example, a natural product might, theoretically, show effect in targeting a gene revealed by a characterization study to be defective in esophageal cancer. The CBC could rapidly deploy resources in order to synthesize that natural product. CBC chemists might also work on ways to make new compounds water soluble, re-engineer investigators' assays into high-throughput screens, review data and design optimized analogs, select promising candidates based on established development milestones, and promote candidates with targeted activity to the clinic.

The process for accomplishing CBC goals is largely based on the drug discovery strategy used by the pharmaceutical industry, but dedicated to studies of those



“There have been some dramatic changes in the past five to seven years in the way the chemistry and the screening is done, to optimally define and develop probes and then drugs from probes when one discovers a new target.”

— JAMES H. DOROSHOW, M.D.

new targets that might otherwise not be developed.

“There have been some dramatic changes in the past five to seven years in the way the chemistry and the screening is done, to optimally define and develop probes and then drugs from probes when one discovers a new target,” said James H. Doroshow, M.D., director of NCI’s Division of Cancer Treatment and Diagnosis. “We believe there is this need for us to help facilitate the drug discovery process by providing resources to chemists and biologists who can help work with their own molecules or take molecules in from other academic investigators and help speed the development of not just probes, but eventually drugs that can move along through the pipeline,” he said.

The long-term vision of the CBC is to bridge the gap between basic scientific investigation and clinical research supported by the NCI, as a first step in reinforcing the NCI as a world leader in the area of innovative cancer therapeutics discovery.

DRUG DEVELOPMENT INFRASTRUCTURE
ENHANCEMENT WILL REQUIRE AN ADDITIONAL
INVESTMENT OF \$150 MILLION.

Rapid Access to Intervention Development Program

Among its many resources, NCI has deep experience in the pre-clinical development of drugs, biologics, and vaccines – from toxicity testing, to pharmacodynamics, histopathology, and the production of materials that meet FDA Good Manufacturing Practice standards for testing in humans. Launched in 1998, NCI's Rapid Access to Intervention Development (RAID) program makes those formidable resources available to academia, providing a bridge between discovery of a new agent and its introduction into Phase 0 or Phase I human clinical trials. Drug company scientists may have such services at their disposal, but many academic researchers do not.

In addition, RAID supports principal investigators who are working on rare diseases and pediatric malignancies, and who are attempting to validate new therapeutic targets. The RAID program is currently developing significant upgrades, including mentoring and training for principal investigators, regulatory assistance in the filing of Investigational New Drug applications with the FDA, and even conducting initial clinical trials at the NIH Clinical Center. To better enable the success of the research projects it supports, the RAID program is establishing a business model approach – complete with firm timelines, developmental milestones, and regular reviews to make important go or no-go decisions on research projects.

So far, the RAID program has approved 133 projects which resulted in 21 small molecule and 25 biologic investigational new drug approvals. The RAID program was instrumental to the efforts of Leisha

Emens, M.D., Ph.D., of Johns Hopkins University as she began a clinical trial of a breast cancer vaccine for patients with metastatic breast cancer. RAID support included formulation, packaging, and release-testing of three peptides. Five hundred vials of material were produced, quality-control tested, and shipped to Dr. Emens so that her team could begin vaccination. Early results in six patients revealed evidence of vaccine-activated immunity in at least four patients.

Clinical Research

NCI's mission includes extensive funding and conducting of clinical research. The Institute supports a vast array of clinical trials designed to test new ways to treat, prevent, detect, or diagnose cancer – as well as new methods to improve cancer patients' quality of life.

The trials NCI supports take place at the NIH Clinical Center and in many outside institutions, including hundreds of academic or private hospitals, NCI-designated Cancer Centers, NCI Community Cancer Centers, and community-based medical practices located in the United States, Puerto Rico, Canada, and worldwide. This research has helped save or extend the lives of people everywhere.

NCI enrolls thousands of people in more than 150 clinical trials at the NIH Clinical Center each year. Home to a variety of science programs and scientists at many of the 27 institutes and centers that make up NIH, about 40 percent of the Clinical Center's activity is comprised of studies conducted by the NCI intramural program. A large presence at the Clinical Center provides unique opportunities for

NCI to add to its valuable resources and commitment to patient care.

For example, NCI's Pediatric Oncology Branch led partnerships that facilitated several therapeutic advances first tested in children at the NIH Clinical Center. Among them was the first use of gene therapy, development of volume photography to measure growth of neurofibromatosis-1 tumors, and even the first multi-institute hospital unit designed specifically for children at the NIH Clinical Center.

Beyond the NIH campus in Bethesda, NCI coordinates a network of NCI-designated Cancer Centers, which are principally based at our country's major research universities. These centers play a vital role in both basic and clinical research. More than half of the extramural researchers funded by NCI work in NCI-designated Cancer Centers. At several NCI-designated Comprehensive Cancer Centers, for example, scientists are involved in research to develop novel methods that make use of genomic technologies to guide the chemotherapy choices of oncologists, by helping them determine the right drug for a particular patient, based on the patient's genomic profile. Ongoing clinical trials

are studying the use of genomic signatures to guide therapy for breast, ovarian, and other cancers at a number of Comprehensive Cancer Centers.

The 63 NCI-designated Cancer Centers are often referred to as crown jewels. Importantly, the directors of the NCI-designated Cancer Centers recognize that changes are happening across biomedicine, and they are determined to contribute. In a recent report, the directors wrote that "advances in treatment will come from understanding the molecular causes of disease and using combination treatment approaches employing multiple modalities." That report, "Accelerating Successes Against Cancer," contains recommendations on goals for NCI and the Cancer Centers to pursue, centering around prevention, early detection, treatment, survivorship, collaborations, and the dissemination of cancer control best practices. NCI is actively engaged in the implementation of those recommendations in consultation with the Centers.

Yet, we also realize that approximately 85 percent of cancer patients receive care in the communities where they live. Receiving treatment at a world-class cancer center is,



for too many, not an option. Frailty, age, language capacity, distance, and insurance limitations often keep patients close to home. NCI is deeply involved in fixing that problem, through its NCI Community Cancer Centers Program (NCCCCP) that is studying, in a three-year pilot, how best to deliver state-of-the-art care and clinical research to patients in their local communities. Importantly, the 16 NCCCCP sites are also focusing nearly half of the resources from this program on overcoming the disparities that lead to intolerable differences in cancer outcomes.

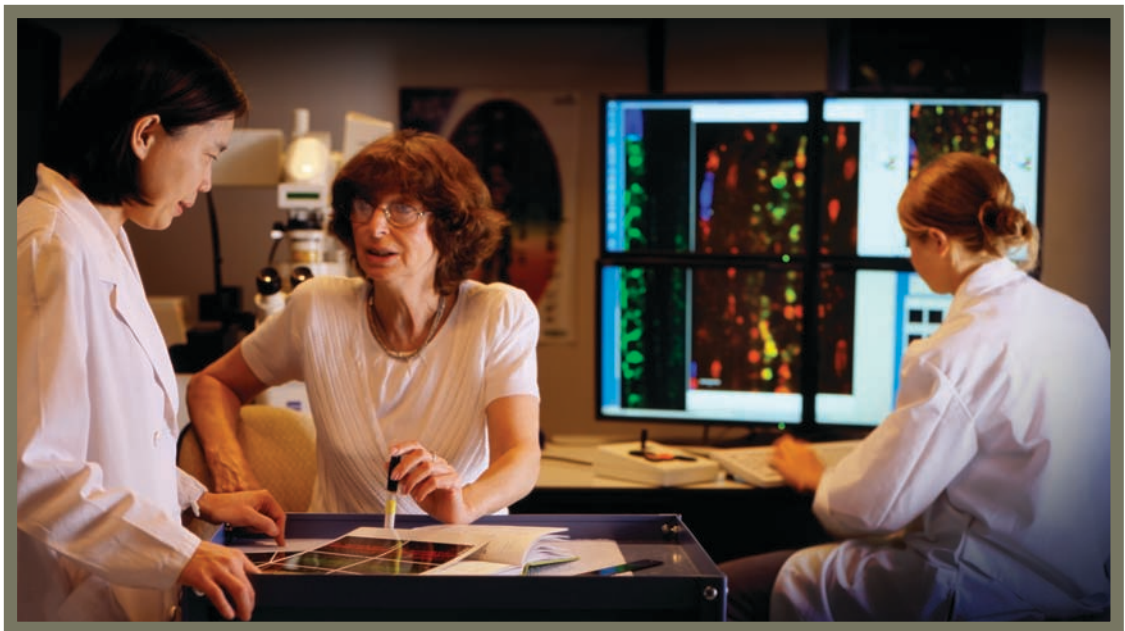
“NCI’s Community Cancer Centers Program is about bringing things closer to home. It’s having the technology and infrastructure in place so our patients in Montana can get NCI Cancer Center level of care and access to clinical trials without having to go live in Denver or Seattle,” said Dr. Tom Purcell of the Billings Clinic Cancer Center, an NCCCCP pilot site.

EXPANDING THE NCI CANCER CENTERS PROGRAM WOULD REQUIRE AN ADDITIONAL \$120 MILLION.

Reforming Clinical Trials

A linchpin of any effort to improve drug development must be improvements in the way science tests new therapies. A large part of today’s clinical trials system is an antiquated one, built around the study of one agent, one hypothesis at a time. It has become clear that a future with multi-agent therapies will demand a better testing system. In 2005, NCI received the final report from its Clinical Trials Working Group, and has been hard at work implementing many of its recommendations. This task requires the collaboration of the FDA, the Centers for Medicare and Medicaid Services, industry, and academia. Yet, despite the hurdles, NCI is the ideal leader of this effort, as a facilitator and honest broker between all parties.

In its own studies, NCI has been a pioneer in the development of so-called Phase 0 (zero) clinical trials, which help researchers and industry make smarter decisions about which experimental agents should move into more extensive human testing. “This new approach has already demon-



strated its ability to significantly shorten the drug discovery process,” said Jerry Collins, M.D., director of NCI’s Developmental Therapeutics Program.

Phase 0 clinical trials – the first of which was conducted at the NIH Clinical Center in 2007, along with Abbott laboratories – use very low doses of an investigational drug in just a few patients, to determine whether the drug is likely to be biologically effective and a good candidate to advance to later phase human clinical trials, or if development should be halted before the expenditure of hundreds of millions of dollars and years of work.

Earlier testing of promising compounds in Phase 0 trials should lead to a better understanding of their molecular mechanisms of action, provide a closer approximation of what a safe but potentially effective starting dose will be, and help decrease the failure rates in late-stage oncology drug development. NCI estimates that such studies can reduce drug development times by as much as one year.

“The data you generate in Phase 0 testing allows you to design a Phase I study that is more well-informed,” said Dr. Collins. “Now you can select doses based on data that show you can achieve levels in patients that have an impact on the molecular target and the tumor. You can more rationally design your later clinical trials based on Phase 0 results.”

REENGINEERING CLINICAL TRIALS WOULD REQUIRE \$300 MILLION.

EXPANDING PHASE 0 EARLY PHARMACODYNAMIC STUDIES WOULD REQUIRE AN ADDITIONAL INVESTMENT OF \$25 MILLION.



Clinical Trial Case Study: Marker Validation for Erlotinib in Lung Cancer

Because lung cancer has proven to be one of the more intractable cancers to treat, NCI recently launched a large national clinical trial for non-small cell lung cancer to validate whether a biomarker can predict clinical benefit in the treatment of the disease. The biomarker would identify a target known as epidermal growth factor receptor (EGFR). This receptor can be increased in some lung cancers due to the presence of extra copies of its coding gene. These extra copies can result in activation of tumor growth, so drugs that block this activation could have a significant impact on lung cancer treatment.

The study, called MARVEL (Marker Validation for Erlotinib in Lung Cancer), is also important because of its collaborative nature. “The MARVEL trial is unique and an important first because it is an outgrowth of specific NCI initiatives designed to advance lung cancer therapies and received broad input from the FDA, NCI cooperative groups, the biomarker industry, and the pharmaceutical industry,” said Alex A. Adjei, M.D., Ph.D., senior vice president of Clinical Research at Roswell Park Cancer Institute in Buffalo, N.Y., and chair of the study.

Both EGFR-positive and EGFR-negative patients will receive either erlotinib (Tarceva®) or pemetrexed (Alimta®) after they have received their initial, standard chemotherapy. Erlotinib specifically targets EGFR, whereas pemetrexed blocks tumor cell growth by another mechanism.

It is hypothesized that erlotinib will be superior in the patients with EGFR-positive lung cancer, whereas pemetrexed would be favored in patients with EGFR-negative lung cancer, based on knowledge from earlier, smaller studies. As with most newer trials that NCI currently supports, MARVEL will incorporate genetic studies that should help identify patients with different sensitivity and toxicity profiles to these therapies.

MARVEL is the outcome of a unique and innovative collaboration, formed in 2006 between NCI, the FDA, and the Centers for Medicare and Medicaid Services, called the Oncology Biomarkers Qualification Initiative. The initiative was designed to qualify biomarkers for use in clinical trials and, ultimately, to speed better agents to cancer patients.

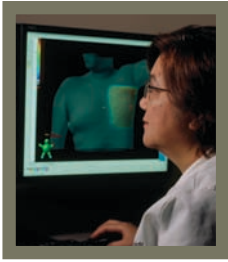
Conclusion

Everything that happens at NCI – in its laboratories and in those laboratories it supports across this great country – is ultimately about cancer patients: making new discoveries and translating new knowledge into interventions that prevent, detect, and treat cancer. As much as we are entering a new era of science and medicine, it is clear that we must orient NCI in a way to facilitate a certain future when cancer is a manageable disease. There is little doubt about where the National Cancer Institute must lead. The questions that remain to be answered in the coming years center around the resources and, therefore, the time it will take to get there.



Building the Right Kind of NCI for the Future

THE NATIONAL CANCER ACT OF 1971 GAVE NCI A NUMBER OF UNIQUE RESPONSIBILITIES AND AUTHORITIES. AS THE LEADER OF THE NATIONAL CANCER PROGRAM, NCI IS THE PRINCIPAL AGENCY FOR SUPPORT OF CANCER RESEARCH IN THE UNITED STATES. THIS MISSION MAKES NCI NOT SIMPLY A FUNDING SOURCE, BUT A CONVENER AND A FACILITATOR OF SCIENTISTS FROM GOVERNMENT, ACADEMIA, AND INDUSTRY, WHOSE MUTUAL UNDERSTANDINGS AND COLLABORATIONS WILL BE PART AND PARCEL OF MEDICINE'S FUTURE. IT IS, HOWEVER, A DIFFICULT TIME FOR SUCH AN AGENDA, AS IT IS FOR EVERY ASPECT OF OUR COUNTRY'S ECONOMY. NCI'S BUDGET REMAINS NEARLY FLAT; ONCE BIOMEDICAL INFLATION IS FACTORED IN, THAT BUDGET HAS EFFECTIVELY DIMINISHED BY A LITTLE MORE THAN THREE PERCENT FOR EACH OF THE LAST FIVE FISCAL YEARS. NOTHING WILL STOP NCI FROM ITS LIFESAVING EFFORTS, AND WE WORK EACH DAY TO MAKE SURE THE INSTITUTE WISELY SPENDS EVERY DOLLAR. HOWEVER, WERE NCI TO RECEIVE AN INFUSION OF FUNDING, NCI WOULD CAREFULLY AND THOUGHTFULLY SPEND THOSE DOLLARS, IN AN EFFORT TO, FIRST, REBUILD AMERICA'S RESEARCH INFRASTRUCTURE CAPACITY AND THEN TO ACCELERATE THE PACE OF OUR RESEARCH EFFORTS AND PROGRESS.



Building Capacity

In the years since the doubling of the NIH budget (in fact, about an 85 percent increase for NCI over five years, not considering medical inflation), we have learned that building a better, more effective research infrastructure takes time, careful planning, and ongoing support. NCI's portfolio is a complex mix of thousands of contracts and grants to outside researchers, combined with the support of the hundreds of scientists who work in our labs on the Bethesda NIH campus and in Frederick, Md. We fund individual investigators working on hypothesis-driven science and large, collaborative, technology-driven projects. In many cases, a grant NCI funds is a five-year commitment of resources, which must be fulfilled, even if budgets are flat or go down. NCI has had to make the difficult choice recently of reducing the dollar amount of our grants, often by 25 percent or more. The result has been labs that have reduced the scope of their research and labs that have reduced staff, or taken on fewer young investigators.

Consequently, NCI's first job, were it to receive more funding, would be to help increase America's research capacity in several areas:

- **Funding scientists.** In academic cancer research, obtaining tenure is most often tied closely to getting – and renewing – an NCI grant. We have an obligation to help young investigators navigate the arduous grant application process and make sure their academic homes have mentoring committees in place. We must strive to assure that new faculty members are not just ad-

equately funded for their research, but that they are primed for success from the outset.

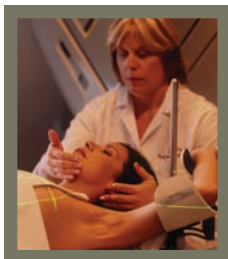
ADDING NEW INVESTIGATORS AND BUILDING CAPACITY TO ATTACK RESEARCH CHALLENGES WOULD REQUIRE \$30 MILLION.

- **Fostering the next generation.** Much has been discussed in recent years about the graying of America's scientific workforce, and the dearth of great new scientific minds entering cancer research. We must work, in every way possible, to foster scientific careers, to increase diversity among the scientific workforce, to advance scientific education and to make research a rewarding career that will keep our cancer research labs focused and thriving.

EXPANDING RESEARCH TRAINING OPPORTUNITIES WOULD REQUIRE \$30 MILLION.

- **Supporting technology.** The equipment necessary to conduct high-volume genomic sequencing has become faster, even as it has greatly fallen in price. In time, most physicians will have each patient's complete genetic profile available. Until that day comes, however, whole-genome sequencing, characterization, and analysis remain outside the capacity of most researchers. For just that reason, NCI envisions several strategically placed genomic research centers that could serve the entire research community.

ESTABLISHING CERTIFIED, CENTRALIZED TUMOR CHARACTERIZATION LABS WOULD REQUIRE \$30 MILLION.

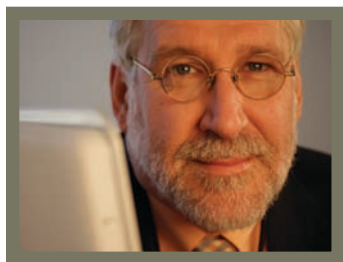


- **Supporting research infrastructure.** In the early years of this century, as research universities received large increases in their funding from NCI and NIH, the construction crane was a common site on hundreds of campuses. In the years since, as research funding has flattened, many of those structures are underused and ill-equipped. Greater NCI funding will, indeed, help universities hire more research faculty; those dollars will also help fulfill the physical capacity of research institutions.

REBUILDING SCIENTIFIC INFRASTRUCTURE AND TECHNOLOGY WOULD REQUIRE \$285 MILLION.

The cancer Biomedical Informatics Grid

The technologies of 21st century cancer research are generating virtual mountains of data. As the collection of genomic data becomes the norm in medicine, it will be necessary to confront a wide range of issues, from the protection of patient privacy to the timely sharing of large volumes of research data to the management of clinical trials across many participating institutions. NCI's cancer Biomedical Informatics Grid (caBIG®) came into existence to tackle these and other challenging issues. caBIG is, first and foremost, about connections –



“Personalized medicine is all about information. But for information to be useful, it has to be accessible.

– KENNETH BUETOW, PH.D.

between NCI researchers, cancer centers, Community Clinical Oncology Program participants involved in clinical trials, cooperative groups that conduct trials on NCI's behalf, and participants in the NCI Community Cancer Centers Program. It is, in many ways, an internet for cancer research, an organized grid, with strict protections of patient information and carefully monitored access to research data. caBIG is also a suite of software applications designed to help manage clinical trials, integrate disparate elements of cancer research, share data, and establish common vocabularies. caBIG is also serving as a public model for the development of electronic medical records, which will be a necessity in a data-driven era of medicine.

caBIG is not simply an NCI program. It is a collaboration of more than 800 individuals from more than 80 organizations working on a wide variety of projects. That spirit of collaboration is now finding a new and broader home in a bioinformatics grid for healthcare, the BIG Health Consortium™, a recently launched effort to bring together public and private healthcare and information technology leaders, to model new approaches in which clinical care, clinical research, and scientific discovery can be electronically networked.

Speaking to the urgent need for interoperability, Kenneth Buetow, Ph.D., leader of caBIG, said, “Personalized medicine is all about information. But for information to be useful, it has to be accessible. What we are doing with caBIG is facilitating accessibility through interoperability, essentially creating an environment where information can be exchanged, integrated, and acted upon. The BIG Health Consortium is a logical next step, to build upon what we have learned from caBIG and broaden our scope, by listening to the most important voices in healthcare.”

EXPANDING caBIG AND LAUNCHING THE BIG HEALTH CONSORTIUM WILL REQUIRE AN ADDITIONAL \$100 MILLION.

Advanced Technology Partnerships Initiative

NCI’s Advanced Technology Partnerships Initiative (ATPI) is about taking a proactive approach to accelerate progress against cancer, not just by funding and conducting research, but also by establishing the platforms – in this case, state-of-the-art technology and drug development platforms – to turn that research into effective interventions as quickly and efficiently as possible.

In November 2008, NCI took part in a ground-breaking ceremony in Frederick, Md., for a new research facility that will play a major role in advancing the goals of the ATPI. This groundbreaking was truly the beginning of a new era of expanded drug and technology development via public, private, and academic partnerships. The research park represents an opportunity to co-locate private sector research and development programs, biotechnol-

ogy partners, and academic collaborators on a research campus dedicated to reducing the cancer burden.

The ATPI will also take advantage of the unique capabilities of NCI’s current Frederick campus at Ft. Detrick. NCI-Frederick is one of just 38 Federally Funded Research and Development Centers, and the only FFRDC devoted solely to biomedical research. The designation allows NCI-Frederick to be operated by a private contractor, which is able to more rapidly deploy resources than a purely governmental entity. Using the FFRDC capabilities, the ATPI will expand collaborations with a variety of private companies and institutes to develop new agents, new diagnostics, and new ways of monitoring response to therapy – and then carry them forward to first-in-human studies.

The ATPI will help provide access to cutting-edge, often costly technologies that are not readily available in the research community. Partnerships, two of which are already in place, will flow from access to these technologies and the expertise required to operate them. Under the ATPI, for example, NCI could collaborate with partners to test the optimal use of new technologies in cancer research, or to aid start-up biotechnology and pharmaceutical companies that have received small business grants by providing the expertise and equipment needed to characterize their investigational agents or manufacture pharmaceutical-grade agents for use in human trials.

What the new Frederick facility, in particular, will provide is a tremendous opportunity to expand training capabilities. With the space and expertise available

in a single facility, NCI will significantly enhance its ability to teach the next generation of scientists how to use emerging technologies, a process that they can then repeat at their home institutions. “The new facility,” said Craig Reynolds, Ph.D., director of the Office of Scientific Operations at NCI-Frederick “will provide the physical infrastructure to carry out the ATPI and should help free up space on the Ft. Detrick campus to enhance other programs and core services that support both the intramural and extramural cancer research community.”

Biobanking

Groundbreaking efforts such as Genome-Wide Association Studies and TCGA depend heavily on the quality of their specimens, which must be obtained, staged, annotated, stored, and distributed according to the highest standards. Organizing those tasks, on a national level, falls to NCI’s Office of Biorepositories and Biospecimen Research (OBBR).

Considerable variability exists in the collection, processing, storage, and annotation of the majority of human specimens available for research. To solve this critical problem, NCI is leading an effort to ensure that human biospecimens available for cancer research are of the highest quality. The first step was development of the NCI Best Practices for Biospecimen Resources, a document that spelled out procedures for standardizing biobanking practices and operations. The second stage is to develop and implement state-of-the-science data-driven procedures to provide human biospecimens that have molecular integrity and clinical relevance for cancer research and treatment.

OBBR’s director, Carolyn Compton, M.D., Ph.D., and her staff are currently developing the concept for a new national biobank: a unique, non-profit public resource that will ensure the adequate and continuous supply of human biospecimens and associated measurable, high-quality data, all acquired with the highest ethical standards.

Carolyn C. Compton,
M.D., Ph.D., Director,
Office of
Biorepositories
and Biospecimen
Research, NCI



Common Language for Clinical Trial Contracts

Clearly, the future of personalized oncology will require the use of multiple, targeted therapies in order to block the many pathways that cancer cells exploit to grow and spread throughout the body. Testing combinations of such therapies in human clinical trials, however, has proven to be a daunting task. Such trials often involve collaboration between several companies, each of which has intellectual property concerns. Dealing with such issues and hammering out contract details often leads to long delays, if not complete derailment, of clinical trials.

NCI's leadership, as a broker between the public and private sectors, is helping break the logjam of lengthy and costly contract negotiations for partnerships between the pharmaceutical industry and academic research institutions, including NCI-designated Cancer Centers. This came about through NCI's participation in the CEO Roundtable on Cancer, a unique group of corporate CEOs, academic research presidents, and other leaders from 42 organizations.

"NCI's involvement with the CEO Roundtable since its inception in 2001 has been critical," commented the group's chief operating officer, Martin J. Murphy, Jr., Ph.D. "We pledged to shorten the time for industry-academic partnership negotiations from as much as 300 days down to 30 days...but it couldn't have happened until NCI got involved."

Dr. Murphy credits NCI's leadership for recommending that the CEO Roundtable establish a Life Sciences Consortium (LSC) made up of Roundtable members from the pharmaceutical, biotechnology, and academic research communities. The goal of the LSC is to "look into the pre-competitive space where there are problems common to all members of the Consortium," Dr. Murphy said.

The first major impediment the LSC addressed is the length of time it takes to negotiate a clinical research agreement between a pharmaceutical company, which has a drug to be tested, and an academic institution such as an NCI-designated Cancer Center. "It currently takes anywhere from 180 to 300 days," Dr. Murphy noted, costing companies more than \$1 million a day in delays. The CEO Roundtable identified this as a priority issue four years ago, he recalled, but progress stalled until NCI leaders stepped forward in 2007, "that was the key that opened the door."

With financial support from NCI and the CEO Roundtable, the LSC analyzed 84 clinical contracts. They created an online Master Agreement template of "harmonized" contract language "that will eliminate literally hundreds of days of back and forth negotiations," Dr. Murphy added. The Master Agreement is free for everybody to use, and is posted on Cancer.gov at <http://cancercenters.cancer.gov>.

On Sept. 17, 2008, The Department of Justice announced that it would "not oppose" the model contract language, which "is not likely to be anticompetitive and can be used to help increase efficiency in contract negotiations, potentially reducing costs and shortening the time needed to begin clinical trials."

NCI, along with the LSC, will now move on to tackle issues of intellectual property rights that often impede public-private sector collaborations. "I applaud NCI's leaders for doing what they do best – which is not only pioneering research but also in pointing the way for research to prosper in the future," Dr. Murphy said.

NCI's Commitment to Its Staff

In 2008, the National Cancer Institute qualified for the CEO Cancer Gold Standard™. Bestowed by the CEO Roundtable on Cancer, the nonprofit organization of cancer-fighting CEOs, this award recognizes the commitment of companies and non-profit organizations to fighting cancer one employee at a time. Gold Standard recognition means that NCI has, first, established and enforced tobacco-free worksite policies. In fact, the entire National Institutes of Health campus in Bethesda, Md., is now tobacco-free. In addition, the Gold Standard designation means NCI also provides no-cost coverage for evidence-based tobacco treatments for employees and their family members. Other requirements include sustaining a

culture that promotes diet and nutrition; promoting physical activity; and providing prevention, screening, and early detection – along with access to quality treatment and clinical trials.

In announcing the designation, William C. Weldon, chairman and chief executive officer of Johnson & Johnson and chair of the CEO Roundtable on Cancer, said, “It is both appropriate and inspirational that the preventive health and wellness guidelines and unparalleled cancer care for which the National Cancer Institute and its director, Dr. John Niederhuber, stand for are provided for NCI’s own employees and their family members who are on the frontlines of our nation’s battle against cancer each and every day.”



NCI's Commitment to All

Because cancer is, in reality, not a singular disease but many conditions, its causes, its progression, and its effects vary tremendously. Despite its heterogeneity, there is perhaps one common trait of all cancers that particularly stands out: fear. Virtually all of us fear cancer. We fear that, as we age, cancer may come to us. If we have survived cancer, we fear it may return. We fear that cancer may take our lives or the lives of those we care about.

The National Cancer Institute is, of course, dedicated to research. And dedicated research can help replace fear with hope. In the years to come, NCI will remain focused on its work and its missions that will, by their very nature, require great change.

- We will need to change how we think about cancer prevention. Choosing the right healthy behaviors – diet and exercise, for example – and avoiding exposure to certain environmental risk factors, none more important

than tobacco, can help prevent the development of cancer. Yet, why one person will develop cancer and another will not, given the same exposures, remains largely unknown. We need to apply our rapidly increasing knowledge of both the tumor and its microenvironment, as they relate to specific organ sites, in order to find new targets and markers of early carcinogenic events and, additionally, to study transcriptional regulation and epigenetic changes. We must then find ways to take highly characterized individuals whom we have determined are at high risk and intervene, with manipulations or prevention measures, to mitigate their risk. We need to include earliest diagnosis as a preventive strategy and more deeply incorporate biomarkers and imaging technology into our prevention portfolio.

- We will need to change how we contemplate cancer survivorship. Cancer is rarely a transitory event: something that is dispatched with and then disappears. For a significant proportion of cancer patients, second, third, and even fourth malignancies are a linger-



ing worry. NCI is committed to research that studies the genetics of survivorship in order to better reveal those individuals most at risk for new cancers – and then to design prevention and early detection protocols for each patient.

- **We must change how we fight the disparities in cancer care that lead to unequal outcomes.** Cancer does not discriminate, but its outcomes are all too frequently affected by race, ethnicity, income, age, and frailty. We must not allow those differences to alter the care we offer. As we bring cancer care closer to patients in their communities, through efforts like the NCI Community Cancer Centers Program, and work to reduce barriers to care through programs like the Community Networks Program, the Minority Institution/Cancer Center Partnership Program, and the Patient Navigation Research Program, we must ensure that all patients who need care have equal access to the latest treatments and techniques – the fruits of our latest science. We must also work to understand the genetic differences that may lead to

different disease burdens, such as the disproportionate rates of prostate cancer among African American men.

- **We must remember that research into the causes of cancer equals progress against many diseases.** Cancer research studies biological processes at their most basic, molecular level. The knowledge we gain about cancer, about its growth, nourishment, and spread, have been shown time and again to have significance against many diseases. For example, recent studies show that the leukemia drug Gleevec may help in an array of illnesses that have nothing to do with cancer. Among them: diabetes, Crohn's disease, pulmonary arterial hypertension, rheumatoid arthritis and scleroderma and maybe even seasonal allergies. Our models for cancer care also can lead the way for improved, less costly medical care – from the adoption of electronic medical records, to electronically interconnected hospitals and patients, and to greater use of evidence-based care.

Conclusion

Despite difficult economic times, the National Cancer Institute must not allow the pace of its progress to diminish. NCI must be – and must remain – visionary. Simply stated, NCI must lead. We must carefully consider every opportunity, and we must invest prudently and wisely. That guiding philosophy will never change, for it is our commitment to all Americans.

The 2010 Professional Judgment Budget Request

The National Cancer Institute's research portfolio encompasses thousands of grants it funds in universities and cancer centers across the United States and internationally—along with the studies conducted by a cadre of government scientists in the Institute's own laboratories. The numbers you see on this page represent the NCI's professional judgment on potential budget increases—additions to NCI's research portfolio in the first year of increased funding—that could hasten our research progress against cancer, bringing new therapies, earlier detection and better prevention techniques to all people.

National Cancer Institute

New Investments

(dollars in millions)

Increase biomedical computing capabilities	45
Develop imaging tools	150
Invest in intramural program	100
Expand The Cancer Genome Atlas	200
Establish certified centralized tumor characterization labs	30
Create a U.S. oncology tissue bank	30
Increase drug development infrastructure	150
Invest in resources – nanoparticles, proteins, and clinical proteomics	75
Reengineer Clinical Trials	300
Expand caBIG® and launch BIG Health Consortium™	100
Fund early-phase pharmacodynamic studies	25
Invest in systems biology	40
Raise RPG success rate and average cost per grant	340
Expand research training opportunities	30
Increase the number of new investigators	30
Rebuild scientific infrastructure	285
Expand Cancer Centers program	120
Add a network of centers for the study of the physical sciences and cancer	50
Total Annual Increased Investment	2,100



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