

Commentary

NCI Clinical Trials Planning Meeting for prevention and treatment of chemotherapy-induced peripheral neuropathy

Susan G. Dorsey^{1*}, Ian R. Kleckner², Debra Barton³, Karen Mustian², Ann O'Mara⁴, Diane St. Germain⁴, Guido Cavaletti⁵, Suzanne C. Danhauer⁶, Dawn Hershman⁷, Andrea G. Hohmann⁸, Ahmet Hoke⁹, Judith O. Hopkins¹⁰, Katherine P. Kelly¹¹, Charles L. Loprinzi¹², Howard L. McLeod¹³, Supriya Mohile², Judith Paice¹⁴, Julia H. Rowland¹⁵, Daniela Salvemini¹⁶, Rosalind A. Segal¹⁷, Ellen Lavoie Smith³, Wortia McCaskill Stevens⁴, Michelle C. Janelins^{2*}

¹University of Maryland School of Nursing, Department of Pain and Translational Symptom Science, and Center to Advance Chronic Pain Research, Baltimore, MD, USA

²University of Rochester Medical Center, Cancer Control Program, Department of Surgery, Wilmot Cancer Institute, Rochester, NY, USA

³University of Michigan School of Nursing, 400 North Ingalls, Ann Arbor, MI 48169

⁴National Cancer Institute, Division of Cancer Prevention, Bethesda, MD, USA

⁵Experimental Neurology Unit, School of Medicine and Surgery, University Milano-Bicocca, Monza, Italy

⁶Department of Social Sciences & Health Policy, Division of Public Health Sciences, Wake Forest School of Medicine, Winston Salem, NC, USA

⁷Columbia University Medical Center, Department of Medicine, NY, USA

⁸Department of Psychological and Brain Sciences, Program in Neuroscience and Gill Center for Biomolecular Science, Indiana University, Bloomington, IN 47401

⁹Johns Hopkins University, School of Medicine, Department of Neurology, Baltimore, MD, USA

¹⁰Novant Health-GWSM. SCOR NCORP

¹¹Children's National Health System, Department of Nursing Science, Professional Practice, and Quality; George Washington School of Medicine and Health Sciences, Washington, DC, USA

¹²Mayo Clinic; Rochester, MN 55905

¹³Moffitt Cancer Center, Tampa, FL, USA

¹⁴Hematology-Oncology Division, Northwestern University, Chicago IL, USA

¹⁵Smith Center for Healing and the Arts, Washington, DC 20009

¹⁶Department of Pharmacology and Physiology, Saint Louis University School of Medicine, 1402 South Grand Blvd, St. Louis, MO 63104, USA

¹⁷Department of Cancer Biology, Dana-Farber Cancer Institute, Boston, MA 02115 USA

*Corresponding authors were the co-organizers of the CTPM: Susan G. Dorsey PhD, RN, FAAN, University of Maryland School of Nursing, Department of Pain and Translational Symptom Science and Greenebaum Cancer Center, 655 West Lombard Street, Room 727,

Baltimore, MD 21201; email: sdorsey@umaryland.edu; telephone: 1-410-706-7250; Michelle C. Janelins PhD, MPH, University of Rochester Medical Center, Wilmot Cancer Institute, Department of Surgery, Rochester, NY, 14625. Michelle_janelins@urmc.rochester.edu; 585-276-4656.

ABSTRACT

Although recent scientific advances have improved our understanding of basic biological mechanisms underlying chemotherapy-induced peripheral neuropathy (CIPN), few interventions are available to prevent or treat CIPN. While some biological targets from preclinical studies show promise in non-human animal models, few targets have been translated to successful clinical trials. To address this problem, the National Cancer Institute's (NCI's) Symptom Management and Health-Related Quality of Life Steering Committee convened a meeting of experts in the CIPN and oncology symptom management fields to participate in a Clinical Trials Planning Meeting (CTPM). Investigators presented data from preclinical and translational studies for possible CIPN interventions; these were evaluated for readiness of randomized clinical trial testing by experts, and recommendations were provided. Breakout sessions were convened to discuss and develop future studies. The CTPM experts concluded that there is compelling evidence to move forward with selected pharmacological and non-pharmacological clinical trials for the prevention and treatment of CIPN. Several key feasibility issues need to be addressed, however. These include: identification of optimal outcome measures to define the CIPN phenotype, establishment of parameters that guide the evaluation of clinically meaningful effects, and adoption of approaches for inclusion of translational and biomarker/genetic measures. The results of the CTPM provide support for conducting clinical trials that include both pharmacological and non-pharmacological approaches, alone or in combination, with biomarkers, genetics or other measures designed to inform underlying CIPN mechanisms. Several working groups were formed to design rigorous CIPN clinical trials, the results of which are ongoing.

Chemotherapy-induced peripheral neuropathy (CIPN) is a devastating consequence of cancer treatment regimens that include neurotoxic chemotherapeutic agents (e.g., taxanes, platinum compounds, vinca alkaloids, proteasome inhibitors)¹. Symptoms of CIPN include some combination of tingling, numbness, stabbing pain, shooting pain, burning, and increased sensitivity to hot or cold temperatures. These symptoms can contribute to functional comorbidities in day-to-day tasks. The prevalence of CIPN varies from 20%-80% during treatment, depending on the chemotherapy regimen and the measures used to define CIPN^{3,4}. According to a recent systematic review and meta-analysis, the prevalence of CIPN is at its highest in the first month after completion of chemotherapy (68.1%), however as many as 30% of patients still report CIPN symptoms at 6 months or later following completion of chemotherapy³, although for platinum agents it may worsen up to 3 months after the last dose⁴. While the exact pathophysiology of CIPN, unfortunately, is not known, in the past decade, advances regarding the molecular genetics⁵ and pathobiological mechanisms⁶ associated with CIPN have been made, and the most promising of these mechanisms were discussed at a recently convened National Cancer Institute's (NCI's) Symptom Management and Health-Related Quality of Life Steering Committee Clinical Trials Planning Meeting (CTPM) and in this commentary. Despite the exciting promise of these discoveries, few if any efficacious pharmacological and non-pharmacological interventions are available to prevent or treat CIPN. More specifically, the American Society of Clinical Oncology Guidelines for CIPN indicate sufficient evidence to recommend duloxetine for the treatment of existing CIPN pain, but there is no evidence to recommend any treatments for the prevention of CIPN⁷. The lack of treatment options is likely due to an incomplete understanding of the mechanisms underlying the development and persistence of CIPN. In addition, the lack of available treatment options could

also relate to the differentiation of CIPN into subtypes or subclasses; recognizing that CIPN is not a single disorder but can be differentiated by the causative agent, clinical and demographic features of the individual (e.g., pre-existing, underlying neuropathy, age, race/ethnicity, others) and genetics. This work could move forward more rapidly if more robust, precise tools for CIPN studies, in which different phenotypes are examined separately, could be developed.

The clinical trials planning meeting

The National Cancer Institute (NCI) convened a CTPM in 2017 to examine the methodologic issues related to designing trials for prevention and/or treatment of CIPN. Basic, translational and clinical science experts from around the world in the field of CIPN were invited to join the CTPM to present basic science research that could lead to the development of clinical trials to advance the science of CIPN. CTPM participants included representatives from academia, community oncology, neurology, pharmacology, nursing, patient advocates and the federal government. The objectives of the CIPN CTPM were to obtain the latest in the state-of-the-science in biomarkers/mechanisms and intervention research and identify possible interventions to move forward in future clinical trials, synthesize the “lessons learned” in conducting CIPN research from the NCI Community Oncology Research Program (NCORP) and academic sites to inform future trials, and discuss the feasibility and next steps to successfully implement the scientific ideas presented at the CTPM into future clinical trials. The summary presented below is not meant to be an exhaustive literature review, but rather, a description of the science presented at the CIPN CTPM.

The presentations discussed are shown in **Table 1**. Speakers and panelists were chosen by their prominence in the CIPN field. We also reviewed the current literature to identify authors that described recent state of the science discoveries that could lead to CIPN clinical trials.

State of the science in mechanisms of CIPN–preclinical

Mechanisms of axon degeneration in CIPN and therapeutic approaches in non-human animal models

There are substantial challenges associated with developing effective therapeutics to prevent or treat CIPN. These challenges include the use of therapies that are aimed at symptomatic control versus addressing the mechanisms of neuronal damage, the fact that a majority of drug screening is conducted in non-neuronal cells, the use of molecular screening versus phenotypic screening (e.g., not considered phenotypic characteristics), and the use of cellular death as an outcome versus more relevant outcome measures for human neuropathies such as axon degeneration and the limitations associated with the use of non-human animal models, particularly rodent models (Hoke, 2017 NCI CTPM). These challenges were addressed by Dr. Ahmet Hoke, who presented his work at the 2017 CTPM on his pioneering use of a relevant dorsal root ganglion (DRG) neuronal cell line, which can be used for CIPN research^{8,9}. Using this cell line to examine distal axonal degeneration as an outcome measure, a high throughput screen against antiretroviral 2'-3'-dideoxycytidine and chemotherapeutic agents (paclitaxel) resulted in more than 38 lead compounds that were identified with greater than 50% neuroprotection. Once validated in primary DRG cultures, two lead compounds showed proper dose-response curves. Of those, ethoxyquin was shown to be effective in preventing paclitaxel-induced distal axonal degeneration both *in vitro* and *in vivo* in non-human rodent models⁹. His group has gone on to

show that ethoxyquin does not block the effectiveness of chemotherapy in treating cancer in non-human animals, and ethoxyquin is effective in preventing both paclitaxel- and cisplatin-induced CIPN. Mechanistic studies demonstrated that ethoxyquin modulates the chaperone activity of heatshock protein 90 which is neuroprotective¹⁰. The next steps towards moving this compound forward for clinical trials in humans include oral validation, pharmacokinetic studies and further mechanistic studies.

Targeting sphingosine 1-phosphate receptor 1 to block and reverse CIPN – insight from preclinical models

In addition to ethoxyquin, other novel therapeutic targets presented at the 2017 CTPM have recently been identified, including work conducted by Dr. Salvemini on the sphingosine 1-phosphate receptor 1¹¹. Certain chemotherapeutic agents can activate the sphingomyelin pathway¹²⁻¹⁴, and dysregulation of sphingolipid metabolism is linked to chronic neuropathic pain^{15,16}. In preclinical CIPN studies in rodent models, the ceramide metabolic pathway is activated in the spinal cord, and blocking the formation of S1P with sphingosine kinase inhibitors reverses the phenotype of CIPN, specifically allodynia and hyperalgesia¹⁵. Daily injection of FTY720, a functional antagonist of S1P signaling, inhibits the development of mechanical allodynia and hyperalgesia induced by several chemotherapeutic agents including paclitaxel, oxaliplatin and bortezomib¹⁵. Similar effects were also noted with oral administration of S1PR1 antagonists. Moreover, extended treatment of fingolimod or other S1PR1 antagonists did not induce tolerance to their analgesic effects, suggesting that one could administer the drug for a long period of time and retain analgesic activity¹⁶. In addition to inhibiting the development of CIPN, continuous infusion of S1PR1 antagonists were effective in producing sustained

reversal of paclitaxel-induced neuropathic pain^{15,16}. In terms of translation of these findings to human patients, orally bioavailable agents that target S1PR1 have been developed and tested for non-pain conditions. For example, in 2010, FTY720 (fingolimod) was developed as functional antagonist to inactivate S1P signaling via irreversible internalization of the degradation of S1PR1 to treat multiple sclerosis. Other agents include additional functional antagonists (e.g., Ponesimod, Siponimod, CYM5442) and selective S1PR1 antagonists (e.g., W146, NIBR-14/15, TASP0251078), which are moving forward as novel drugs for the treatment of various diseases including multiple sclerosis, rheumatoid arthritis, colitis and cancer¹⁷. The S1PR1 antagonist agents developed to date are not expected to interfere with anti-cancer actions of chemotherapeutic agent^{15,16,18–20} as the agents appear to be effective for both prevention and treatment of CIPN in non-human animals. Thus, there is rationale for investigating FTY720 as an adjunct to chemotherapeutic agents to mitigate or treat CIPN.

Paclitaxel reduces axonal Bclw to initiate IP3R1-dependent axon degeneration

One of the hallmarks of CIPN is axonal degeneration of sensory fibers, which can produce paresthesias, dysesthesias, and persistent neuropathic pain. While the precise mechanisms of chemotherapy-induced axonal degeneration are poorly understood, axonal degeneration is an important contributor to neuronal pruning during normal development. In neurodegenerative disorders, axonal degeneration is a crucial component of the pathology. In the case of pathological degeneration, changes in calcium signaling, mitochondrial function and calpain activation occur. During developmental axon pruning, the pro-survival and pro-death Bcl2 family members can regulate calcium homeostasis and modulate mitochondrial function²¹. However, the potential role for these molecules in pathological axonal degeneration, or CIPN

specifically, are unknown. Since a great deal of preclinical and clinical work has shown that there is therapeutic potential in targeting Bcl2 family members for a variety of diseases and disorders²², if Bcl2 family members contribute to axonal degeneration, then potential therapeutics are available. Recent work by Dr. Segal's group at Harvard University, funded by the NCI's provocative question initiative, implicates Bclw (*bcl2l2*) in axonal degeneration caused by paclitaxel²³. Dr. Segal presented her work at the 2017 CTPM showing that paclitaxel initiates CIPN in primary DRG neuron cultures via changes in IP₃ receptor activity, altered intracellular calcium flux and activation of calpain proteases. Paclitaxel also selectively impairs axonal trafficking of RNA-granules and reduces the synthesis of axonal Bclw. The addition of Bclw, or a peptide that corresponds to the BH4 domain of Bclw, prevented paclitaxel-induced nerve degeneration via interaction with axonal IP₃R1. Mice that were engineered to lack Bclw exhibited enhanced sensitivity to paclitaxel, including statistically significantly higher thermal hyperalgesia and increased axonal loss *in vivo*. Other Bcl family members, including Bcl2 and BclXL, were not altered by paclitaxel and were not effective in preventing paclitaxel-induced nerve degeneration, suggesting that this phenomenon is specific to Bclw²³. Together, these results suggest that increasing levels and/or activity of Bclw might represent a novel therapeutic target for prevention of CIPN.

State of the science in clinical/intervention studies of CIPN

In addition to novel pharmacological targets for the prevention and/or treatment of CIPN, non-pharmacological approaches are also of interest, and may be readily translatable to the clinic. In rodent models of CIPN, volitional wheel running (i.e., or voluntary exercise) statistically significantly reduced both the development and maintenance of mechanical and cold allodynia

(unpublished, Dr. Hohmann laboratory). Dr. Kleckner presented a recent secondary analysis study in 355 patients with cancer who were scheduled to receive either a taxane, platinum or vinca alkaloid-based chemotherapeutic as a component of their treatment protocol; they were randomized to exercise during chemotherapy for 6 weeks or not. The exercise intervention was a low-moderate intensity unsupervised daily walking and resistance program developed by Dr. Mustian and used in the NCORP network. Patients in the exercise group during chemotherapy reported less severe thermal and sensory symptoms associated with CIPN compared to patients who received chemotherapy alone²⁴. This is consistent with a growing body of literature suggesting that exercise can prevent CIPN^{2,25–28}. The study of exercise for CIPN has been limited due to the lack of larger Phase II and Phase III studies of exercise for CIPN where CIPN is *a priori* declared the primary outcome.

Genetics of CIPN susceptibility and next steps regarding replication and validation studies of prior Genome-Wide Association Study (GWAS) findings

We recommend that the genetics of CIPN susceptibility be incorporated into clinical trials. There have been several recent studies examining the contribution(s) of genetics in CIPN that were leveraged with large randomized controlled trials for cancer treatment. For example, a GWAS in the CALGB (Alliance) 90401 trial²⁹ comparing docetaxel and prednisone with and without bevacizumab in men with hormone refractory prostate cancer (n=800 participants) identified one single nucleotide polymorphism (SNP), rs875858 in the *VAC14* locus, that surpassed a Bonferonni-corrected statistical significance threshold of 1.0×10^{-7} and was associated with CIPN development³⁰. *In vivo* and *in vitro* studies supported these clinical findings. While other studies have identified additional SNPs in a variety of genes, replication studies have been largely

unsuccessful. This may be due to several factors including the small sample sizes in some of the CIPN GWAS studies, the difficulty in obtaining replication datasets and the lack of consistent phenotyping of CIPN across studies¹. In addition, some of these studies have been underpowered, leading to potentially false negative results. Addressing these issues would move the field forward in identification of genes related to the development of CIPN. These findings could be used to predict CIPN susceptibility in patients prior to starting a chemotherapeutic regimen that includes neurotoxic compounds. In addition, pharmacogenomics studies could identify SNPs in genes associated with chemotherapy metabolism which could provide clinicians with important data for dosing and timing of treatment. Thus, we recommend continuing to collect DNA for pharmacogenetic studies with the strong recommendations to collect more accurate phenotype data including PRO's, dose of chemotherapeutic agents at the time CIPN develops, and whether CIPN disrupts treatment and for what period the disruption occurs.

Lessons learned in conducting CIPN research

A 2016 review paper outlined the results and lessons learned from 15 recent NCI-funded trials testing pharmacologic agents for the prevention or treatment of CIPN³¹ and a recent paper provided recommendations for CIPN trial design³² The lessons learned included: the fact that early studies were underpowered, that patient-reported symptoms of CIPN are more sensitive outcomes than clinician-based assessments of CIPN, however it is still unclear as to the best method to define the phenotype using patient reported outcomes, objective measures and clinical assessment, that certain traditional clinical practices to prevent CIPN are not effective and are thus no longer used (e.g., calcium and magnesium concurrent with chemotherapy), and that there is substantive heterogeneity in forms of neuropathy (diabetic, HIV-induced, paclitaxel-induced,

oxaliplatin-induced, etc.) and how they respond to treatment, and 5) genetic differences play a role in the development of CIPN, and warrant further study.

The 2017 CIPN CTPM corroborated these existing lessons learned and went beyond them as well. **Table 2** lists seven key lessons learned, and the following text discusses a few of these lessons in more detail. One key lesson is that we need a better understanding of CIPN mechanisms to identify treatments that have yet to be tested or optimized. Specifically, we need to understand mechanisms of axonal degeneration, perhaps via inflammation, mitochondrial damage or spingolipid metabolism. But peripheral axonal degeneration is only part of the mechanism because symptoms of CIPN—as with all mental states—emerge from the complex interplay of peripheral input to the central nervous system, intra-brain neuronal dynamics, and central output of the brain and spinal cord to the peripheral nervous system^{33,34}. Therefore, we need to understand the role of central nervous system changes (e.g., neuroplasticity, central sensitization), neuromodulators, neurotransmitters, etc. that can be leveraged via interventions to alleviate symptoms of CIPN independent of peripheral axonal degeneration.

Another key lesson is that we need to learn more about individual differences in CIPN, including CIPN etiology and phenotype: specifically, how distinct neurotoxic drugs (paclitaxel, docetaxel, oxaliplatin, etc.) interact with a patient’s genetics, epigenetics, environment, and behavior to yield his/her particular form of CIPN, as suggested in research of neuropathic pain³⁵. In addition, we need to more completely understand CIPN intolerance: the extent to which symptoms of CIPN are distressing to the patient or the extent to which they interfere with the patient’s livelihood, quality of life, and activities of daily living. We also need to critically evaluate more effective methods for CIPN prevention and treatment: for example in the future, sufficient knowledge regarding a patient’s CIPN phenotype could suggest a dysfunction of a

particular mechanistic pathway and thus a particular intervention to target that pathway, thereby improving on-target treatment of CIPN and reducing off-target side-effects by avoiding unnecessary interventions. By comparison, studies of other types of neuropathic pain have utilized phenotype-stratified randomized studies wherein each patient's pain phenotype informs their selected treatment³⁶, and overall this approach appears to be beneficial in studies of other forms of neuropathy such as diabetic neuropathic pain³⁷.

The combination of lessons learned suggests that we need a multi-faceted approach to alleviate the burden of CIPN. The challenge, however, is finding interventions that do not produce additional side effects. This could limit implementation and dissemination even if successful. Indeed, prior clinical trials investigating treatments for CIPN have been limited to single interventions (typically a single drug) that are selected because the drug of interest targets a single mechanistic pathway or was effective in treating other types of neuropathy (e.g., diabetic neuropathy). Moreover, patient samples that are available for biomarker discovery may be appropriate for the questions being asked, but may not be of sufficient quality, quantity or breadth and depth required to comprehensively evaluate the effects of the treatment on mechanistic pathway(s) of interest. We suggest that to advance clinical CIPN research we first need to test individual CIPN patient phenotype interventions that are tailored to these selected phenotypes. Once individual agents or non-pharmacological therapeutics are determined to be effective, then the use of multiple interventions (perhaps multiple drugs, or a drug in combination with exercise or other interventions) that target multiple mechanistic pathways involved in CIPN both during chemotherapy and after chemotherapy could be considered. This comprehensive approach should give the clinical team the best chance to alleviate CIPN symptoms and reduce the burden of those symptoms on the patient's daily activities and quality

of life throughout the cancer treatment continuum. Innovative trial designs are needed to support this complex approach.

Development of scientific lessons learned into future clinical trials: what is needed

One of the unique features and major strength of the CTPM was the engagement of both preclinical researchers focused on rodent and cell culture systems and clinical researchers conducting large multi-center studies to both provide input on the interventions, types of clinical trials that should move forward, and the key outcome methods that should be used. All meeting participants agreed that there is a clear need for both preclinical and clinical research trials for CIPN.

In **Table 2**, we outline current gaps, lessons learned and recommendations for moving forward CIPN clinical trials that arose from breakout sessions at the Clinical Trials Planning Meeting. For clinical research, there was consensus that well-planned Phase II intervention clinical trials and large, prospective longitudinal studies were the highest priority for designing future trials. Phase II studies should focus on promising pharmacologic agents, such as duloxetine and SIPR1-targeted agents, and non-pharmacologic interventions such as exercise could be tested in dose-comparison studies. In both cases, prevention of CIPN was thought to be the preferred intervening period. For longitudinal studies, large, prospective studies are needed that assess who is at the highest risk so that interventions can be targeted for those patients. For example, as a result of this conference, a trial is in development to assess the incidence of CIPN (SWOG 1714; <https://www.swog.org/media/2771>). Important considerations for longitudinal studies are careful assessment of CIPN domains, and the differential effects of various chemotherapy agents on CIPN phenotype, prevalence and severity. Indeed, the specification of

the CIPN phenotype should be carefully considered. We recommend the CIPN-20 as one measure of phenotype specificity.

For clinical trials, several considerations were discussed regarding how to successfully implement future CIPN studies in large nationwide studies such as through the NCORP, a research network focused on accruing patients from the community to NCI-sponsored clinical studies. NCORP has several advantages including study conduct within community oncology clinics—where 80% of patients are treated and access to diverse patient populations results in high generalizability of results³⁹. Thus, well-conducted studies in the NCORP network can have high impact and the potential to improve clinical practice. These studies could also be well-positioned to examine clinically relevant effects of the treatment on CIPN phenotype. For example, we would recommend that trials be designed within homogenous treatment regimens that take into account baseline CIPN severity scores. And in terms of study outcomes, it would be important to examine trajectories of symptoms that may or may not improve in response to the intervention. For example, the intervention might have positive effects on numbness, but no effects on tingling; thus discrete and well-defined study outcomes are important for trial design.

With this in mind, feasibility of study conduct is vital to ensuring the success of the study. For example, obtaining a skin biopsy as a direct correlate to neuronal degeneration related to CIPN symptoms can be a vital component to determining the mechanism of an intervention and whether the intervention successfully mitigated CIPN outcomes. However, this type of endpoint is often not feasible in large-scale trials because of patient discomfort and lack of resources at sites to collect the biopsy. It was agreed that this type of measure may be more applicable for single-site Phase II studies, and that identifying other measures that may correlate with skin biopsy outcomes may be more scalable for future multi-site Phase III trials.

Another main consideration for large-scale studies in nationwide networks is that the delivery of interventions and measurement of the outcomes need to lend themselves to conduct at multiple sites and in a consistent manner. Complex assessment procedures can limit site participation because not all sites have the capacity or resources. While an assessment specialist is ideal, other health professionals, such as research nurses or study coordinators, could be trained to carry out the assessments and facilitate the conduct of the study, as is routine practice in current NCORP studies. Efforts to assess scalability of complex assessments typically done by a specialist would greatly enhance feasibility. For example, the Total Neuropathy Score, clinical may not be feasible in a multi-site study; however, if the Total Neuropathy Score, clinical could be conducted systematically by other trained professionals, this would enhance scalability of assessment. In general, however, patient reports are easier to implement across sites compared with more objective outcome measures that require specialty training to conduct. The same considerations are true for interventions. For an exercise intervention, for example, it may not be possible to have exercise physiologists at the oncology clinic. In addition, the dose, intensity and frequency required for an exercise intervention to be effective is poorly understood and additional studies in this regard would be critically important. The other issue relates to adherence with exercise interventions. In this regard, standardized manuals, videos, or other resources can help build intrinsic motivation to habitualize exercise behaviors, as has been performed in prior NCORP studies of exercise²⁴. It is also important to emphasize that tracking exercise and monitoring exercise compliance is much more convenient than in the past. Fitbits and smartphone applications offer low cost, and convenient access to collect activity measures, including time stamps of completion. Moreover, reliability and validity of gait analysis as already been reported using smartphone technology⁴⁰, suggesting that changes in gait and

balance measures that may be impacted by CIPN can also be monitored. A recent example of this is the development of a system called the PeriVib, a portable, smartphone based peripheral neuropathy test platform that can measure vibration and also report on gait and sway metrics⁴¹. More work is necessary, however, to determine whether such parameters correlate with subjective and objective measures of CIPN used in more traditional clinical assessments.

Overall conclusion

Ongoing research in CIPN is needed to advance our understanding of the etiology of, and risk assessment and intervention development for this challenging cancer treatment sequelae. In addition, genetic analysis should be considered for larger trials. For example, samples and data must be collected from large clinical trials in which there are detailed CIPN phenotype data available to discover physiological (e.g., genetic, metabolomic, transcriptomic), environmental, clinical/demographic and other biomarkers that could predict susceptibility to develop CIPN and/or CIPN severity. The most promising interventions to prevent CIPN, for which three working groups were formulated, included those focused on duloxetine, SIPR1 targets, and exercise, with the ultimate goal of conducting future trials within the NCORP network.

Notes

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PledPharma AB. CLL provides consultation to PledPharma. The other authors have no disclosures.

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TABLES

Table 1: Presentations at the chemotherapy-induced peripheral neuropathy (CIPN)

Clinical Trials Planning Meeting on March 1, 2017

Presentation Title	Speaker
Mechanisms of axon degeneration in CIPN and therapeutic approaches in animal models	Ahmet Hoke MD PhD
Targeting sphingosine 1-phosphate receptor 1 to block and reverse CIPN – insight from preclinical models	Daniela Salvemini PhD
Paclitaxel reduces axonal Bclw to initiate IP3R1-dependent axon degeneration	Rosalind Segal MD PhD
Targeting cannabinoid receptors and endogenous analgesic systems to suppress chemotherapy-induced neuropathic pain in preclinical models	Andrea Hohmann PhD
Genetics of CIPN susceptibility and next steps regarding replication and validation studies of prior genome-wide association study findings	Howard McLeod PharmD
Effects of exercise on CIPN and the role of the brain in CIPN: Evidence from human studies	Ian Kleckner PhD
Panel Discussion	Charles Loprinzi MD, Ellen Lavoie Smith RN PhD, Supriya Mohile MD, Dawn Hershman MD, Judy Paice RN PhD, Guido Cavaletti MD

Table 2. Current gaps identified during the 2017 chemotherapy-induced peripheral neuropathy Clinical Trials Planning Meeting*

Lesson Learned	Specific Examples	Action Items
Inadequate understanding of mechanisms of CIPN and its symptoms	The complementary and interacting roles of peripheral axonal degeneration and central nervous system plasticity and modulation.	Conduct more basic research (biochemical, cellular, non-human animals, humans). Clinical research should include biological endpoints (brain circuitry, genetics, inflammation, neuroinflammation, metabolites from active treatment pathways).
Inadequate understanding of the natural history of CIPN, individual differences in CIPN etiology, phenotypes, intolerance, and response to treatments	Who is at greatest risk for CIPN? For whom does each treatment work best? Can we prescribe/optimize interventions for each individual to prevent or treat CIPN?	Conduct studies with sufficient sample sizes to investigate individual differences. Conduct longitudinal cohort studies. Leverage multiple data sources to enhance power (e.g., genetic studies). Use appropriate statistical tools to characterize individual differences (e.g., mixture modeling).
Insufficient collaboration between preclinical and clinical researchers	Preclinical researchers should be grounded in clinical problems with measures and interventions that map to the human condition. Clinical researchers should study interventions and mechanistic pathways that have been mapped out in non-human animals.	Establish recurring multidisciplinary CIPN meeting or CIPN special interest group at conferences that cut across disciplines.
Lack of consensus on a consistent way to assess CIPN	Clinician-assessed (e.g., total neuropathy score clinical), patient-reported (e.g, CIPN-20, Functional Assessment of Cancer Therapy/Gynecologic Oncology Group-Neurotoxicity (FACT-Ntx) questionnaire, biomarkers (skin biopsy, imaging of Meissner corpuscles). When to assess—what day with respect to chemotherapy infusion, what time of day? See ³⁸	Future studies should consider use of the patient-reported CIPN-20 questionnaire. Future studies should measure biomarkers that may be antecedents to patient-reported CIPN symptoms.
Prevention of CIPN is	Patients would prefer to prevent	Identify interventions to prevent

more desirable than treatment of existing CIPN	the symptoms of CIPN from occurring.	peripheral neural damage and/or central sensitization. Identify mechanisms upstream of peripheral neural damage. Ensure adequate statistical power given that not all patients receiving chemotherapy develop CIPN.
Patients want non-pharmacological treatments	Patients may not want to take a drug that has side-effects to manage side-effects (CIPN) of a drug (chemotherapy).	Investigate behavioral interventions (e.g., exercise, acupuncture), psychological interventions (e.g., cognitive behavioral therapy, meditation/mindfulness) and other non-pharmacological approaches.
There are several promising and understudied interventions for preventing or treating CIPN	–	The 2017 CIPN CTPM determined three key future studies for CIPN: Exercise for CIPN prevention; Duloxetine for CIPN prevention; and Sphingosine 1 phosphate receptor blockade for CIPN prevention

* – indicates no specific examples were available to report at this time. CIPN = chemotherapy-induced peripheral neuropathy; CTPM = Clinical Trials Planning Meeting.

Running head: CIPN clinical trials planning

Commentary: NCI Clinical Trials Planning Meeting for prevention and treatment of chemotherapy-induced peripheral neuropathy (CIPN)

Susan G. Dorsey^{1*}, Ian R. Kleckner², Debra Barton³, Karen Mustian², Ann O'Mara⁴, Diane St. Germain⁴, Guido Cavaletti⁵, Suzanne C. Danhauer⁶, Dawn Hershman⁷, Andrea G. Hohmann⁸, Ahmet Hoke⁹, Judith O. Hopkins¹⁰, Katherine P. Kelly¹¹, Charles L. Loprinzi¹², Howard L. McLeod¹³, Supriya Mohile², Judith Paice¹⁴, Julia H. Rowland¹⁵, Daniela Salvemini¹⁶, Rosalind A. Segal¹⁷, Ellen Lavoie Smith³, Wortia McCaskill Stevens⁴, Michelle C. Janelins^{2*}

¹University of Maryland School of Nursing, Department of Pain and Translational Symptom Science, and Center to Advance Chronic Pain Research, Baltimore, MD, USA

²University of Rochester Medical Center, Cancer Control Program, Department of Surgery, Wilmot Cancer Institute, Rochester, NY, USA

³University of Michigan School of Nursing, 400 North Ingalls, Ann Arbor, MI 48169

⁴National Cancer Institute, Division of Cancer Prevention, Bethesda, MD, USA

⁵Experimental Neurology Unit, School of Medicine and Surgery, University Milano-Bicocca, Monza, Italy

⁶Department of Social Sciences & Health Policy, Division of Public Health Sciences, Wake Forest School of Medicine, Winston Salem, NC, USA

⁷Columbia University Medical Center, Department of Medicine, NY, USA

⁸Department of Psychological and Brain Sciences, Program in Neuroscience and Gill Center for Biomolecular Science, Indiana University, Bloomington, IN 47401

⁹Johns Hopkins University, School of Medicine, Department of Neurology, Baltimore, MD, USA

¹⁰Novant Health-GWSM. SCOR NCORP

¹¹Children's National Health System, Department of Nursing Science, Professional Practice, and Quality; George Washington School of Medicine and Health Sciences, Washington, DC, USA

¹²Mayo Clinic; Rochester, MN 55905

¹³Moffitt Cancer Center, Tampa, FL, USA

¹⁴Hematology-Oncology Division, Northwestern University, Chicago IL, USA

¹⁵Smith Center for Healing and the Arts, Washington, DC 20009

¹⁶Department of Pharmacology and Physiology, Saint Louis University School of Medicine, 1402 South Grand Blvd, St. Louis, MO 63104, USA

¹⁷Department of Cancer Biology, Dana-Farber Cancer Institute, Boston, MA 02115 USA

*Corresponding authors were the co-organizers of the CTPM: Susan G. Dorsey PhD, RN, FAAN, University of Maryland School of Nursing, Department of Pain and Translational Symptom Science and Greenebaum Cancer Center, 655 West Lombard Street, Room 727, Baltimore, MD 21201; email: sdorsey@umaryland.edu; telephone: 1-410-706-7250; Michelle C. Janelins PhD, MPH, University of Rochester Medical Center, Wilmot Cancer Institute, Department of Surgery, Rochester, NY, 14625. Michelle_janelins@urmc.rochester.edu; 585-276-4656.

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ABSTRACT

Although recent scientific advances have improved our understanding of basic biological mechanisms underlying chemotherapy-induced peripheral neuropathy (CIPN), few interventions are available to prevent or treat CIPN. While some biological targets from preclinical studies show promise in non-human animal models, few targets have been translated to successful clinical trials. To address this problem, the National Cancer Institute's (NCI's) Symptom Management and Health-Related Quality of Life Steering Committee (SxQoL SC) convened a meeting of experts in the CIPN and oncology symptom management fields to participate in a Clinical Trials Planning Meeting (CTPM). Investigators presented data from preclinical and translational studies for possible CIPN interventions; these were evaluated for readiness of randomized clinical trial testing by experts, and recommendations were provided. Breakout sessions convened to discuss and develop future studies. The CTPM experts concluded that there is compelling evidence to move forward with selected pharmacological and non-pharmacological clinical trials for the prevention and treatment of CIPN. Several key feasibility issues need to be addressed, however. These include: identification of optimal outcome measures to define the CIPN phenotype, establishment of parameters that guide the evaluation of clinically meaningful effects, and adoption of approaches for inclusion of translational and biomarker/genetic measures. The results of the CTPM provide support for conducting clinical trials that include both pharmacological and non-pharmacological approaches, alone or in combination, with biomarkers, genetics or other measures designed to inform underlying CIPN mechanisms. Several working groups were formed to design rigorous CIPN clinical trials, the results of which are ongoing.

INTRODUCTION

Chemotherapy-induced peripheral neuropathy (CIPN) is a devastating consequence of cancer treatment regimens that include neurotoxic chemotherapeutic agents (e.g., taxanes, platinum compounds, vinca alkaloids, proteasome inhibitors)¹. Symptoms of CIPN include some combination of tingling, numbness, stabbing pain, shooting pain, burning, and increased sensitivity to hot or cold temperatures. These symptoms can contribute to functional comorbidities in day-to-day tasks. The prevalence of CIPN varies from 20%-80% during treatment, depending on the chemotherapy regimen and the measures used to define CIPN^{3,4}. According to a recent systematic review and meta-analysis, the prevalence of CIPN is at its highest in the first month after completion of chemotherapy (68.1%), however as many as 30% of patients still report CIPN symptoms at 6 months or later following completion of chemotherapy³, although for platinum agents it may worsen up to 3 months after the last dose⁴. While the exact pathophysiology of CIPN, unfortunately, is not known, in the past decade, advances regarding the molecular genetics⁵ and pathobiological mechanisms⁶ associated with CIPN have been made, and the most promising of these mechanisms were discussed in the Clinical Trials Planning Meeting (CTPM) and in this paper. Despite the exciting promise of these discoveries, few if any efficacious pharmacological and non-pharmacological interventions are available to prevent or treat CIPN. More specifically, the ASCO Guidelines for CIPN indicate sufficient evidence to recommend duloxetine for the treatment of existing CIPN pain, but there is no evidence to recommend any treatments for the prevention of CIPN⁷. The lack of treatment options is likely due to an incomplete understanding of the mechanisms underlying the development and persistence of CIPN. In addition, the lack of available treatment options could also relate to the differentiation of CIPN into subtypes or subclasses; recognizing that CIPN is not a single disorder but can be differentiated by the causative agent, clinical and demographic features of the individual (e.g., pre-existing, underlying neuropathy, age,

race/ethnicity, others) and genetics. This work could move forward more rapidly if more robust, precise tools for CIPN studies, in which different phenotypes are examined separately, could be developed.

THE CLINICAL TRIALS PLANNING MEETING

The National Cancer Institute (NCI) convened a CTPM in 2017 to examine the methodologic issues related to designing trials for prevention and/or treatment of CIPN. Basic, translational and clinical science experts from around the world in the field of CIPN were invited to join the CTPM to present basic science research that could lead to the development of clinical trials to advance the science of CIPN. CTPM participants included representatives from academia, community oncology, neurology, pharmacology, nursing, patient advocates and the federal government. The objectives of the CIPN CTPM were to 1) obtain the latest in the state-of-the-science in biomarkers/mechanisms and intervention research and identify possible interventions to move forward in future clinical trials, 2) synthesize the “lessons learned” in conducting CIPN research from the NCI Community Oncology Research Program (NCORP) and academic sites to inform future trials and 3) discuss the feasibility and next steps to successfully implement the scientific ideas presented at the CTPM into future clinical trials. The summary presented below is not meant to be an exhaustive literature review, but rather, a description of the science presented at the CIPN CTPM.

The presentations discussed are shown in Table 1. Speakers and panelists were chosen by their prominence in the CIPN field and by a review of the current literature for recent state of the science discoveries that could lead to CIPN clinical trials.

STATE OF THE SCIENCE IN MECHANISMS OF CIPN – PRECLINICAL

Mechanisms of axon degeneration in CIPN and therapeutic approaches in non-human animal models

There are significant challenges associated with developing effective therapeutics to prevent or treat CIPN. These challenges include the current situation in which: 1) current therapies are aimed at symptomatic control versus addressing the mechanisms of neuronal damage, 2) the majority of drug screening is conducted in non-neuronal cells, 3) use of molecular screening versus phenotypic screening (e.g., not considered phenotypic characteristics), 4) use of cellular death as an outcome versus more relevant outcome measures for human neuropathies such as axon degeneration and the limitations associated with the use of non-human animal models, particularly rodent models (Hoke, 2017 NCI CTPM). These challenges were addressed by Dr. Ahmet Hoke, who presented his work at the 2017 CTPM on his pioneering use of a relevant dorsal root ganglion (DRG) neuronal cell line, which can be used for CIPN research^{8,9}. Using this cell line to examine distal axonal degeneration as an outcome measure, a high throughput screen against antiretroviral (ddC) and chemotherapeutic agents (paclitaxel) resulted in more than 38 lead compounds that were identified with greater than 50% neuroprotection. Once validated in primary DRG cultures, two lead compounds showed proper dose-response curves. Of those, ethoxyquin was shown to be effective in preventing paclitaxel-induced distal axonal degeneration both *in vitro* and *in vivo* in non-human rodent models⁹. His group has gone on to show that ethoxyquin does not block the effectiveness of chemotherapy in treating cancer in non-human animals, and ethoxyquin is effective in preventing both paclitaxel- and cisplatin-induced CIPN. Mechanistic studies demonstrated that ethoxyquin modulates the chaperone activity of heatshock protein 90 (HSP90) which is neuroprotective¹⁰. The next steps towards moving this compound forward for clinical trials in humans include oral validation, pharmacokinetic studies and further mechanistic studies.

Targeting sphingosine 1-phosphate receptor 1 to block and reverse CIPN – insight from preclinical models

In addition to ethoxyquin, other novel therapeutic targets presented at the 2017 CTPM have recently been identified, including work conducted by Dr. Salvemini on the sphingosine 1-phosphate receptor 1¹¹. Certain chemotherapeutic agents can activate the sphingomyelin pathway¹²⁻¹⁴, and dysregulation of sphingolipid metabolism is linked to chronic neuropathic pain^{15,16}. In preclinical CIPN studies in rodent models, the ceramide metabolic pathway is activated in the spinal cord, and blocking the formation of S1P with sphingosine kinase inhibitors reverses the phenotype of CIPN, specifically allodynia and hyperalgesia¹⁵. Daily injection of FTY720, a functional antagonist of S1P signaling, inhibits the development of mechanical allodynia and hyperalgesia induced by several chemotherapeutic agents including paclitaxel, oxaliplatin and bortezomib¹⁵. Similar effects were also noted with oral administration of S1PR1 antagonists. Moreover, extended treatment of fingolimod or other S1PR1 antagonists did not induce tolerance to their analgesic effects, suggesting that one could administer the drug for a long period of time and retain analgesic activity¹⁶. In addition to inhibiting the development of CIPN, continuous infusion of S1PR1 antagonists were effective in producing sustained reversal of paclitaxel-induced neuropathic pain^{15,16}. In terms of translation of these findings to human patients, orally bioavailable agents that target S1PR1 have been developed and tested for non-pain conditions. For example, in 2010, FTY720 (fingolimod) was developed as functional antagonist to inactivate S1P signaling via irreversible internalization of the degradation of S1PR1 to treat multiple sclerosis. Other agents include additional functional antagonists (e.g., Ponesimod, Siponimod, CYM5442) and selective S1PR1 antagonists (e.g., W146, NIBR-14/15, TASP0251078), which are moving forward as novel drugs for the treatment of various diseases including multiple sclerosis, rheumatoid arthritis, colitis and cancer¹⁷. The S1PR1 antagonist agents developed to date are not expected to interfere with anti-cancer

actions of chemotherapeutic agent^{15,16,18–20} as the agents appear to be effective for both prevention and treatment of CIPN in non-human animals. Thus, there is rationale for investigating FTY720 as an adjunct to chemotherapeutic agents to mitigate or treat CIPN.

Paclitaxel reduces axonal Bclw to initiate IP3R1-dependent axon degeneration

One of the hallmarks of CIPN is axonal degeneration of sensory fibers, which can produce paresthesias, dysesthesias, and persistent neuropathic pain. While the precise mechanisms of chemotherapy-induced axonal degeneration are poorly understood, axonal degeneration is an important contributor to neuronal pruning during normal development. In neurodegenerative disorders, axonal degeneration is a crucial component of the pathology. In the case of pathological degeneration, changes in calcium signaling, mitochondrial function and calpain activation occur. During developmental axon pruning, the pro-survival and pro-death Bcl2 family members can regulate calcium homeostasis and modulate mitochondrial function²¹. However, the potential role for these molecules in pathological axonal degeneration, or CIPN specifically, are unknown. Since a great deal of preclinical and clinical work has shown that there is therapeutic potential in targeting Bcl2 family members for a variety of diseases and disorders²², if Bcl2 family members contribute to axonal degeneration, then potential therapeutics are available. Recent work by Dr. Segal's group at Harvard University, funded by the NCI's provocative question initiative, implicates Bclw (*bcl2l2*) in axonal degeneration caused by paclitaxel²³. Dr. Segal presented her work at the 2017 CTPM showing that paclitaxel initiates CIPN in primary DRG neuron cultures via changes in IP₃ receptor activity, altered intracellular calcium flux and activation of calpain proteases. Paclitaxel also selectively impairs axonal trafficking of RNA-granules and reduces the synthesis of axonal Bclw. The addition of Bclw, or a peptide that corresponds to the BH4 domain of Bclw, prevented paclitaxel-induced nerve degeneration via interaction with axonal IP₃R1. Mice that were engineered to lack Bclw exhibited enhanced sensitivity to paclitaxel, including significantly higher

thermal hyperalgesia and increased axonal loss *in vivo*. Other Bcl family members, including Bcl2 and BclX_L, were not altered by paclitaxel and were not effective in preventing paclitaxel-induced nerve degeneration, suggesting that this phenomenon is specific to Bclw²³. Together, these novel results suggest that increasing levels and/or activity of Bclw might represent a novel therapeutic target for prevention of CIPN.

STATE OF THE SCIENCE IN CLINICAL/INTERVENTION STUDIES OF CIPN

In addition to novel pharmacological targets for the prevention and/or treatment of CIPN, non-pharmacological approaches are also of interest, and may be readily translatable to the clinic. In rodent models of CIPN, volitional wheel running (i.e., or voluntary exercise) significantly reduced both the development and maintenance of mechanical and cold allodynia (unpublished, Dr. Hohmann laboratory). Dr. Kleckner presented a recent secondary analysis study in 355 patients with cancer who were scheduled to receive either a taxane, platinum or vinca alkaloid-based chemotherapeutic as a component of their treatment protocol; they were randomized to exercise during chemotherapy for 6 weeks or not. The exercise intervention was a low-moderate intensity unsupervised daily walking and resistance program developed by Dr. Mustian and used in the NCORP network. Patients in the exercise group during chemotherapy reported less severe thermal and sensory symptoms associated with CIPN compared to patients who received chemotherapy alone²⁴. This is consistent with a growing body of literature suggesting that exercise can prevent CIPN^{2,25-28}. The study of exercise for CIPN has been limited due to the lack of larger Phase II and Phase III studies of exercise for CIPN where CIPN is *a priori* declared the primary outcome.

Genetics of CIPN susceptibility and next steps regarding replication and validation studies of prior GWAS findings

We recommend that the genetics of CIPN susceptibility be incorporated into clinical trials. There have been several recent studies examining the contribution(s) of genetics in CIPN that were leveraged with large randomized controlled trials for cancer treatment. For example, a genome-wide association study (GWAS) in the CALGB (Alliance) 90401 trial²⁹ comparing docetaxel and prednisone with and without bevacizumab in men with hormone refractory prostate cancer (n=800 participants) identified one single nucleotide polymorphism (SNP), rs875858 in the *VAC14* locus, that surpassed a Bonferonni-corrected significance threshold of 1.0×10^{-7} and was associated with CIPN development³⁰. *In vivo* and *in vitro* studies supported these clinical findings. While other studies have identified additional SNPs in a variety of genes, replication studies have been largely unsuccessful. This may be due to several factors including the small sample sizes in some of the CIPN GWAS studies, the difficulty in obtaining replication datasets and the lack of consistent phenotyping of CIPN across studies¹. In addition, some of these studies have been underpowered, leading to potentially false negative results. Addressing these issues would move the field forward in identification of genes related to the development of CIPN. These findings could be used to predict CIPN susceptibility in patients prior to starting a chemotherapeutic regimen that includes neurotoxic compounds. In addition, pharmacogenomics studies could identify SNPs in genes associated with chemotherapy metabolism which could provide clinicians with important data for dosing and timing of treatment. Thus, we recommend continuing to collect DNA for pharmacogenetic studies with the strong recommendations to collect more accurate phenotype data including PRO's, dose of chemotherapeutic agents at the time CIPN develops, and whether CIPN disrupts treatment and for what period the disruption occurs.

LESSONS LEARNED IN CONDUCTING CIPN RESEARCH

A 2016 review paper outlined the results and lessons learned from 15 recent NCI-funded trials testing pharmacologic agents for the prevention or treatment of CIPN³¹ and a recent paper provided recommendations for CIPN trial design³². The lessons learned included: 1) early studies were underpowered, 2) patient-reported symptoms of CIPN are more sensitive outcomes than clinician-based assessments of CIPN, however it is still unclear as to the best method to define the phenotype using patient reported outcomes, objective measures and clinical assessment, 3) certain traditional clinical practices to prevent CIPN are not effective and are thus no longer used (e.g., calcium and magnesium concurrent with chemotherapy), 4) there is significant heterogeneity in forms of neuropathy (diabetic, HIV-induced, paclitaxel-induced, oxaliplatin-induced, etc.) and how they respond to treatment, and 5) genetic differences play a role in the development of CIPN, and warrant further study.

The 2017 CIPN CTPM corroborated these existing lessons learned and went beyond them as well. Table 2 lists seven key lessons learned, and the following text discusses a few of these lessons in more detail. One key lesson is that we need a better understanding of CIPN mechanisms to identify treatments that have yet to be tested or optimized. Specifically, we need to understand mechanisms of axonal degeneration, perhaps via inflammation, mitochondrial damage or spingolipid metabolism. But peripheral axonal degeneration is only part of the mechanism because *symptoms* of CIPN—as with all mental states—emerge from the complex interplay of peripheral input to the central nervous system, intra-brain neuronal dynamics, and central output of the brain and spinal cord to the peripheral nervous system^{33,34}. Therefore, we need to understand the role of central nervous system changes (e.g., neuroplasticity, central sensitization), neuromodulators, neurotransmitters, etc. that can be leveraged via interventions to alleviate symptoms of CIPN independent of peripheral axonal degeneration.

Another key lesson is that we need to learn more about individual differences in CIPN, including 1) CIPN etiology and phenotype: specifically, how distinct neurotoxic drugs (paclitaxel, docetaxel, oxaliplatin, etc.) interact with a patient's genetics, epigenetics, environment, and behavior to yield his/her particular form of CIPN, as suggested in research of neuropathic pain³⁵; 2) CIPN intolerance: the extent to which symptoms of CIPN are distressing to the patient or the extent to which they interfere with the patient's livelihood, quality of life, and activities of daily living; and 3) CIPN prevention and treatment: in the far future, sufficient knowledge regarding a patient's CIPN phenotype could suggest a dysfunction of a particular mechanistic pathway and thus a particular intervention to target that pathway, thereby improving on-target treatment of CIPN and reducing off-target side-effects by avoiding unnecessary interventions. By comparison, studies of other types of neuropathic pain have utilized phenotype-stratified randomized studies wherein each patient's pain phenotype informs their selected treatment³⁶, and overall this approach appears to be beneficial in studies of other forms of neuropathy such as diabetic neuropathic pain³⁷.

The combination of lessons learned suggests that we need a multi-faceted approach to alleviate the burden of CIPN. The challenge, however, is finding interventions that do not produce additional side effects. This could limit implementation and dissemination even if successful. Indeed, prior clinical trials investigating treatments for CIPN have been limited to single interventions (typically a single drug) that are selected because the drug of interest targets a single mechanistic pathway or was effective in treating other types of neuropathy (e.g., diabetic neuropathy). Moreover, patient samples that are available for biomarker discovery may be appropriate for the questions being asked, but may not be of sufficient quality, quantity or breadth and depth required to comprehensively evaluate the effects of the treatment on mechanistic pathway(s) of interest. We suggest that to advance clinical CIPN research we

first need to test individual CIPN patient phenotype interventions that are tailored to these selected phenotypes. Once individual agents or non-pharmacological therapeutics are determined to be effective, then the use of *multiple* interventions (perhaps multiple drugs, or a drug in combination with exercise or other interventions) that target *multiple* mechanistic pathways involved in CIPN *both* during chemotherapy and after chemotherapy could be considered. This comprehensive approach should give the clinical team the best chance to alleviate CIPN symptoms and reduce the burden of those symptoms on the patient's daily activities and quality of life throughout the cancer treatment continuum. Innovative trial designs are needed to support this complex approach.

DEVELOPMENT OF SCIENTIFIC LESSONS LEARNED INTO FUTURE CLINICAL TRIALS: WHAT IS NEEDED

One of the unique features and major strength of the CTPM was the engagement of both preclinical researchers focused on rodent and cell culture systems and clinical researchers conducting large multi-center studies to both provide input on the interventions, types of clinical trials that should move forward, and the key outcome methods that should be used. All meeting participants agreed that there is a clear need for both preclinical and clinical research trials for CIPN.

In Table 2, we outline current gaps, lessons learned and recommendations for moving forward CIPN clinical trials. For clinical research, there was consensus that well-planned Phase II intervention clinical trials and large, prospective longitudinal studies were the highest priority for designing future trials. Phase II studies should focus on promising pharmacologic agents, such as duloxetine and SIPR1-targeted agents, and non-pharmacologic interventions such as exercise could be tested in dose-

comparison studies. In both cases, prevention of CIPN was thought to be the preferred intervening period. For longitudinal studies, large, prospective studies are needed that assess who is at the highest risk so that interventions can be targeted for those patients. **For example, as a result of this conference, a trial is in development to assess the incidence of CIPN (SWOG 1714; <https://www.swog.org/media/2771>).** Important considerations for longitudinal studies are careful assessment of CIPN domains, and the differential effects of various chemotherapy agents on CIPN phenotype, prevalence and severity. Indeed, the specification of the CIPN phenotype should be carefully considered. We recommend the CIPN-20 as one measure of phenotype specificity.

For clinical trials, several considerations were discussed regarding how to successfully implement future CIPN studies in large nationwide studies such as through the NCORP, a research network focused on accruing patients from the community to NCI-sponsored clinical studies. NCORP has several advantages including study conduct within community oncology clinics—where 80% of patients are treated and access to diverse patient populations results in high generalizability of results³⁹. Thus, well-conducted studies in the NCORP network can have high impact and the potential to improve clinical practice. These studies could also be well-positioned to examine clinically relevant effects of the treatment on CIPN phenotype. For example, we would recommend that trials be designed within homogenous treatment regimens that take into account baseline CIPN severity scores. And in terms of study outcomes, it would be important to examine trajectories of symptoms that may or may not improve in response to the intervention. For example, the intervention might have positive effects on numbness, but no effects on tingling; thus discrete and well-defined study outcomes are important for trial design.

With this in mind, feasibility of study conduct is vital to ensuring the success of the study. For example, obtaining a skin biopsy as a direct correlate to neuronal degeneration related to CIPN symptoms can be a vital component to determining the mechanism of an intervention and whether the intervention successfully mitigated CIPN outcomes. However, this type of endpoint is often not feasible in large-scale trials because of patient discomfort and lack of resources at sites to collect the biopsy. It was agreed that this type of measure may be more applicable for single-site Phase II studies, and that identifying other measures that may correlate with skin biopsy outcomes may be more scalable for future multi-site Phase III trials.

Another main consideration for large-scale studies in nationwide networks is that the delivery of interventions and measurement of the outcomes need to lend themselves to conduct at multiple sites and in a consistent manner. Complex assessment procedures can limit site participation because not all sites have the capacity or resources. While an assessment specialist is ideal, other health professionals, such as research nurses or study coordinators, could be trained to carry out the assessments and facilitate the conduct of the study, as is routine practice in current NCORP studies. Efforts to assess scalability of complex assessments typically done by a specialist would greatly enhance feasibility. For example, the Total Neuropathy Score, clinical (TNSc) may not be feasible in a multi-site study; however, if the TNSc could be conducted systematically by other trained professionals, this would enhance scalability of assessment. In general, however, patient reports are easier to implement across sites compared with more objective outcome measures that require specialty training to conduct. The same considerations are true for interventions. For an exercise intervention, for example, it may not be possible to have exercise physiologists at the oncology clinic. In addition, the dose, intensity and frequency required for an exercise intervention to be effective is poorly understood and additional studies in this regard would be

critically important. The other issue relates to adherence with exercise interventions. In this regard, standardized manuals, videos, or other resources can help build intrinsic motivation to habitualize exercise behaviors, as has been performed in prior NCORP studies of exercise²⁴. **It is also important to emphasize that tracking exercise and monitoring exercise compliance is much more convenient than in the past. Fitbits and smartphone applications offer low cost, and convenient access to collect activity measures, including time stamps of completion. Moreover, reliability and validity of gait analysis as already been reported using smartphone technology⁴⁰, suggesting that changes in gait and balance measures that may be impacted by CIPN can also be monitored. A recent example of this is the development of a system called the PeriVib, a portable, smartphone based peripheral neuropathy test platform that can measure vibration and also report on gait and sway metrics⁴¹. More work is necessary, however, to determine whether such parameters correlate with subjective and objective measures of CIPN used in more traditional clinical assessments.**

OVERALL CONCLUSION

Ongoing research in CIPN is needed to advance our understanding of the etiology of, and risk assessment and intervention development for this challenging cancer treatment sequelae. In addition, genetic analysis should be considered for larger trials. For example, samples and data must be collected from large clinical trials in which there are detailed CIPN phenotype data available to discover physiological (e.g., genetic, metabolomic, transcriptomic), environmental, clinical/demographic and other biomarkers that could predict susceptibility to develop CIPN and/or CIPN severity. The most promising interventions to prevent CIPN, for which three working groups were formulated, included

those focused on duloxetine, SIPR1 targets, and exercise, with the ultimate goal of conducting future trials within the NCORP network.

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peripheral neuropathy test platform. *Conf Proc IEEE Med Biol Soc.* 2018; 1-4.

TABLES

TABLE 1: Presentations at the CIPN CTPM on March 1, 2017

Presentation Title	Speaker
Mechanisms of axon degeneration in CIPN and therapeutic approaches in animal models	Ahmet Hoke MD PhD
Targeting sphingosine 1-phosphate receptor 1 to block and reverse CIPN – insight from preclinical models	Daniela Salvemini PhD
Paclitaxel reduces axonal Bclw to initiate IP3R1-dependent axon degeneration	Rosalind Segal MD PhD
Targeting cannabinoid receptors and endogenous analgesic systems to suppress chemotherapy-induced neuropathic pain in preclinical models	Andrea Hohmann PhD
Genetics of CIPN susceptibility and next steps regarding replication and validation studies of prior GWAS findings	Howard McLeod PharmD
Effects of exercise on CIPN and the role of the brain in CIPN: Evidence from human studies	Ian Kleckner PhD
Panel Discussion	Charles Loprinzi MD, Ellen Lavoie Smith RN PhD, Supriya Mohile MD, Dawn Hershman MD, Judy Paice RN PhD, Guido Cavaletti MD

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Table 2. Current gaps identified during the 2017 CIPN Clinical Trials Planning Meeting

Lesson Learned	Specific Examples	Action Items
<p>Inadequate understanding of mechanisms of CIPN and its symptoms</p>	<p>The complementary and interacting roles of peripheral axonal degeneration and central nervous system plasticity and modulation.</p>	<p>Conduct more basic research (biochemical, cellular, non-human animals, humans).</p> <p>Clinical research should include biological endpoints (brain circuitry, genetics, inflammation, neuroinflammation, metabolites from active treatment pathways).</p>
<p>Inadequate understanding of the natural history of CIPN, individual differences in CIPN etiology, phenotypes, intolerance, and response to treatments</p>	<p>Who is at greatest risk for CIPN?</p> <p>For whom does each treatment work best?</p> <p>Can we prescribe/optimize interventions for each individual to prevent or treat CIPN?</p>	<p>Conduct studies with sufficient sample sizes to investigate individual differences.</p> <p>Conduct longitudinal cohort studies.</p> <p>Leverage multiple data sources to enhance power (e.g., genetic studies).</p> <p>Use appropriate statistical tools to characterize individual differences (e.g., mixture modeling).</p>
<p>Insufficient collaboration between preclinical and clinical researchers</p>	<p>Preclinical researchers should be grounded in clinical problems with measures and interventions that map to the human condition.</p> <p>Clinical researchers should study interventions and mechanistic pathways that have been mapped out in non-human animals.</p>	<p>Establish recurring multidisciplinary CIPN meeting or CIPN special interest group at conferences that cut across disciplines.</p>
<p>Lack of consensus on a consistent way to assess CIPN</p>	<p>Clinician-assessed (e.g., total neuropathy score clinical), patient-reported (e.g, CIPN-20, FACT-Ntx), biomarkers (skin biopsy, imaging of Meissner corpuscles).</p> <p>When to assess—what day with respect to chemotherapy</p>	<p>Future studies should consider use of the patient-reported CIPN-20 questionnaire.</p> <p>Future studies should measure biomarkers that may be antecedents to patient-reported CIPN symptoms.</p>

	infusion, what time of day? See ³⁸	
Prevention of CIPN is more desirable than treatment of existing CIPN		<p>Identify interventions to prevent peripheral neural damage and/or central sensitization.</p> <p>Identify mechanisms upstream of peripheral neural damage.</p> <p>Ensure adequate statistical power given that not all patients receiving chemotherapy develop CIPN.</p>
Patients want non-pharmacological treatments	Patients may not want to take a drug that has side-effects to manage side-effects (CIPN) of a drug (chemotherapy).	Investigate behavioral interventions (e.g., exercise, acupuncture), psychological interventions (e.g., cognitive behavioral therapy, meditation/mindfulness) and other non-pharmacological approaches.
There are several promising and understudied interventions for preventing or treating CIPN		The 2017 CIPN CTPM determined three key future studies for CIPN: (1) Exercise for CIPN prevention, (2) Duloxetine for CIPN prevention, and (3) Sphingosine 1 phosphate receptor blockade for CIPN prevention