Chemotherapy-induced peripheral neuropathy (CIPN) is the dose-limiting toxicity for many commonly utilized classes of anti-cancer agents. CIPN can lead to dose reductions or discontinuation of cancer therapy, which may influence survival, and can have a significant impact on patient function and Health-Related Quality of Life. At this time, there are no FDA approved interventions or prevention strategies for CIPN. Therefore, this meeting was convened to assess the critical need to develop appropriate interventions. Information about the objectives was presented and discussed:

**Identification of basic and translational mechanistic knowledge gaps**

- The management of CIPN is dependent on physiologic understanding of treatment-induced peripheral nerve damage. Animal models are relevant due to intricacies associated with non-tumor tissue peripheral nerve biopsies. Through preclinical models, hypotheses generated about CIPN pathophysiology suggest morphologic and functional insults to the peripheral nervous system, including such as dorsal root ganglion abnormalities, glial cell activation, mitochondrial dysfunction, endoneurial vascular disruption, and pro-inflammatory cytokine release. A translational approach to testing the CIPN neurobiology is lacking. Current research in pharmacogenomics, vector delivery of cytokine DNA, and neuron signaling pathways need translation to the patient condition and to target identification.

- Therefore, surrogates or biomarkers for treatment response, as well as diagnosis, are of high value for this condition. Studies correlating pharmacogenetics with symptom severity are in progress. Peripheral nerves are outside blood brain barrier and there is potential for their products, in response to injury, to circulate and be measurable.

- Patient factors that may influence the development, resolution, or persistence of CIPN need to be considered concomitantly. These factors include alterations in anti-cancer drug metabolism (such polymorphisms, drug-drug interactions, diminished clearance, etc), perhaps the interplay with other systemic adverse effects of chemotherapy (immune suppression, nausea and vomiting limiting nutritional intake, etc), and pre-existing risk factors for peripheral neuropathy (increasing age, multiple metabolic conditions, and pre-existing inherited conditions, etc).

**Evaluation of measurements employed in clinical trials to assess, characterize, and diagnose CIPN, both by clinicians and by Patient Reported Outcomes (PRO)**

- CIPN has both biologic elements and subjective experiences. Clinician assessment of symptoms does not correlate very well with patient self-assessment. Patient reported information can help focus the pathophysiologic research of CIPN, by delineating the most important sensations associated with CIPN.

- CIPN is characterized by both pain and neurosensory symptoms; some agents induce motor or autonomic dysfunction. Minimal pain can be accompanied by debilitating symptoms, such as heat alldynia or sensory numbness, which will not be recorded if patients are asked only about pain. As these symptoms can occur in differing permutations, full quantitative and PRO assessments are challenging. There is not a solitary phenotype for CIPN, necessitating more information on the natural history of CIPN.

- The physical examinations and testing for CIPN are not very specific to any peripheral neuropathy and are useful in more advanced cases. There is no precise definition of
how to diagnose CIPN. Qualitative and performance measures may be of benefit, especially in following response to therapy, knowing that patient report can be influenced by other factors. Physical findings and patient report need to be correlated in clinical trials.

- The available PRO instruments do not appear to capture all of the multiple components of CIPN and few include reports of patient function. Sometimes multiple questionnaires are utilized in clinical trials to cover all CIPN issues, increasing patient burden. New instruments developed for the particular toxicity of each anti-cancer agent may increase precision.

Analysis of completed studies, design issues for upcoming clinical trials, and assessment of potential agents against CIPN

- Earlier studies in CIPN treatments and prevention were reviewed. Many of these employed a variety of commercially available agents against CIPN, based upon patient reports of personal benefit and therapies for non-cancer associated peripheral neuropathy.
- Most of the clinical trials with these agents have been unable to define a statistically significant improvement in neurosensory symptoms or neuropathic pain. Intravenous calcium and magnesium has shown promise in preventing oxaliplatin-induced neuropathy and a trial is currently ongoing.
- These completed intervention trials have illustrated the importance patients placed on relieving CIPN, have confirmed that therapy-induced toxicity prevention trials are feasible, and revealed that therapies utilized for other neuropathies (e.g. diabetes) are not necessarily beneficial in CIPN, underscoring the need for more mechanistic data on CIPN.
- The discovery of high-risk patients, rationale therapies, and prevention strategies will inform the design of future CIPN clinical trials.

Fostering collaborations between translational and clinical investigators to provide future direction for research

- The eventual goal is to select drug-able targets for clinical testing, leading to the prevention and treatment of CIPN.
- This will involve a collaborative effort among neuroscientists, translational researchers, clinical oncologists, pain investigators, cancer symptom/toxicity management investigators, psychometricians, patient advocates, and the pharmaceutical industry.
- Clinicians need to communication with neurobiologists and pharmaceutical about CIPN, as the true scope of this problem may be unknown to the neurology community
- Given the expansion of molecular biology, genomics, and proteomics, basic and translational researchers have multiple technologies available to study CIPN.

RECCOMENDATIONS
1. More pathophysioligic data is mandatory to describe the neuronal injuries in CIPN and find key targets in the process.
2. Once identified, drugs or other interventions need to be developed to target these neurobiologic functions.
3. Clinical assessment of the CIPN natural history, including risk identification and early detection, with the collection of biospecimens can be conducted now in longitudinal studies.

4. Demarcation of PRO, qualitative, and functional assessments for diagnosis; defining clinical trial eligibility; and devising clinically meaningful intervention response parameters for CIPN are topics for current research.

5. Dissemination of information on CIPN to educate non-oncologic researchers is important to increase interest in CIPN basic science research and collaboration with the field of oncology.