2012 PERIPHERAL NEUROPATHY SCIENTIFIC SYMPOSIUM

Challenges in developing novel therapies for peripheral neuropathies: a summary of The Foundation for Peripheral Neuropathy Scientific Symposium 2012

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Abstract On March 14–16, 2012, The Foundation for Peripheral Neuropathy organized a scientific meeting that brought together basic and clinical scientists studying peripheral neuropathies and mechanisms of axonal degeneration and representatives from the drug industry, National Institutes of Health, and Federal Drug Administration. This meeting summary covers the main discussion points laid out by the participants that hamper development of novel therapies for peripheral neuropathies and neuropathic pain. In each section of the meeting, the discussion was led by a keynote talk and was followed by a panel of discussants that were asked to bring two key questions in their areas of research. With audience participation, this format led to a lively discussion that pointed out the deficiencies in both animal modeling of human diseases and issues in clinical trial design unique to the peripheral neuropathies and neuropathic pain.

Key words: animal models, axonal degeneration, axonal regeneration, biomarkers, clinical trial design, peripheral neuropathy

Introduction

Apart from the immune peripheral neuropathies, such as chronic inflammatory demyelinating polyneuropathy and multifocal motor neuropathy, the literature is filled with failed clinical trials of disease-modifying therapies for peripheral neuropathies where the primary pathogenesis is distal axonal degeneration. There are likely many causes of this failure, but primary sources can be summarized into three categories: incomplete understanding of molecular mechanisms of distal axonal degeneration and regeneration; failure of animal models to replicate human disease; and challenges in clinical trial design for disease-modifying therapies. On March 14–16, 2012, The Foundation for Peripheral Neuropathy organized a scientific symposium to bring these issues to the forefront of scientific discussion and invited scientists and clinicians from diverse backgrounds including representatives of patient advocacy groups, pharmaceutical companies, National Institutes of Health (NIH), and Food and Drug Administration (FDA). The symposium was divided into six topics: each was introduced by a brief lecture followed by a panel discussion with extensive audience participation. In this overview, the key discussion points and roadblocks in the field that need to be overcome in order to translate basic scientific discoveries into successful therapies for patients with peripheral neuropathies are highlighted.

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Mechanisms of Axonal Degeneration and Regeneration

In his lecture on molecular mechanisms of axonal degeneration, Dr. M. Freeman highlighted the power of

fly genetics to identify novel molecular pathways that can block Wallerian-like axonal degeneration. When a spontaneous mutation called *wlds* (slow Wallerian degeneration) arose in a mouse colony *(Lyon et al., 1993)*, it taught us that Wallerian degeneration is not a passive disintegration of axon when the axon is severed from the cell body but an active process mediated by Nmnat protein *(Mack et al., 2001)*. Soon afterward, it was shown that *wlds* protected against distal axonal degeneration in some *(Wang et al., 2002; Mi et al., 2005)* but not all models of peripheral neuropathies. More recently, using a powerful forward genetics screen, Dr. Freeman's group identified a new pathway that involves Sarm protein that prevents axonal degeneration after traumatic injury *(Osterloh et al., 2012)*. It is not clear whether this pathway is related to Nmnat protein or plays a role in distal axonal degeneration as seen in human peripheral neuropathies.

In the discussion that followed Dr. Freeman's lecture, Dr. R. Baloh first focused on the role of mitochondria and calcium buffering to explain why disturbances in mitochondrial motility can explain length dependency of many peripheral neuropathies based on stoichiometric distribution of impaired mitochondria along the axon *(Misko et al., 2012)*. Dr. M. Coleman discussed the role of each isoform of Nmnat protein and showed that axonally transported Nmnat2 is the key isoform that slows Wallerian-like degeneration. He also pointed out that based on the *wlds* experience, there are likely to be multiple and parallel mechanisms by which axons degenerate in different peripheral neuropathies and traumatic injuries. While the first two discussants focused on the role of axonal degeneration pathways, Dr. J. Milbrandt discussed the importance of Schwann cells in maintenance and degeneration of axons in both acquired and inherited neuropathies. He pointed out that mitochondrial function in Schwann cells is equally important in maintenance of axons, and disruption of mitochondria in Schwann cells also leads to axonal degeneration *(Viader et al., 2011)*. Surprisingly, unmyelinated axons of Remak Schwann cells are more vulnerable to disruption of mitochondria in Schwann cells. This observation could be one of the potential explanations of why unmyelinated axons tend to degenerate first in many types of peripheral neuropathies. Dr. J. Twiss brought the topic back to intrinsic axonal mechanisms that play a role in axonal maintenance and degeneration. His work on mitochondrial permeability transition pore and cyclophilin D showed that disruption of calcium-sensing mechanism in axons can trigger a molecular cascade that leads to axonal degeneration and that this is downstream of both Sarm and Nmnat *(Barrientos et al., 2011)*.

The section on mechanisms of axonal regeneration was led by a lecture by Dr. Z. He on the role of mTOR and STAT3 pathways in modulating the intrinsic capacity of neurons to regenerate. Successful axonal regeneration is controlled by both intrinsic factors (i.e., endogenous capacity of adult neurons to extend axons when injured) and extrinsic factors such as support or inhibition of regeneration by glial cells, scar formation, vascular supply, among others. Focusing on the intrinsic mechanisms, Dr. He's previous work showed that deletion of PTEN gene in retinal ganglion neurons leads to activation of the mTOR pathway and enhanced regeneration after optic nerve crush *(Park et al., 2008)*. More recently, he showed that another molecular pathway controlled by STAT3 provides a parallel mechanism to further enhance regeneration of retinal ganglion neuron axons after optic nerve crush *(Smith et al., 2009)*. Notably, manipulation of both pathways leads to a synergistic increase in axonal regeneration in the optic nerve crush model *(Sun et al., 2011)*. It must be determined whether manipulation of these pathways in peripheral neurons leads to similar increases in intrinsic capacity of neurons to regenerate.

Dr. G.-L. Ming's discussion focused on the role of epigenetic control of regeneration. Her research shows that Gadd45 alpha, one of the key regulators of epigenetic modification of gene expression, is highly upregulated after axonal injury. In parallel, many genes involved in axonal elongation and synaptic activity are demethylated upon axonal injury. It must be shown whether it is possible to use epigenetic manipulation to bring the adult neurons to a more ''immature'' state to promote better regeneration.

Dr. A. Hoke discussed the comparison between axonal growth during development vs. axonal regeneration in the adult animal as a major issue in regeneration. The prime challenge in the adult animal is the long distance of axonal elongation that is needed during regeneration. Most of the growth that occurs in the developing animal is after the axon makes contact with the target tissue, and molecular mechanisms that underlie this type of growth are different than those that control axonal elongation at the growth cone. In the adult animal, regeneration has to occur over very long distances. As the rate of axonal elongation is determined by the rate of ''slow'' axonal transport, this is a very slow process leading to chronic denervation changes in the Schwann cells in the distal nerve and target tissues such as muscle. To obtain improved clinical outcomes, scientists need either to ''speed up'' the rate of axonal regeneration or to keep the denervated Schwann cells and target muscle tissues in a ''reactive'' state so they can be reinnervated

(Hoke, 2006). A corollary of this observation is that scientists need better measures to evaluate the success of interventions in regeneration studies: these can be better imaging studies *(Lehmann et al., 2010)* or human experimental models of peripheral nerve regeneration *(Rajan et al., 2003; Polydefkis et al., 2004)*. Dr. C. Woolf discussed the critical period in which neuromuscular junction formation after regeneration may no longer be achievable if regeneration does not take place in a timely manner. A potential approach to overcome this challenge is to ''speed up'' the rate of regeneration by overexpressing a heat shock protein (hsp27) that plays a key role in axon outgrowth in injured neurons *(Ma et al., 2011)*. Although drugs may be developed to augment hsp27 expression level, this observation awaits further confirmation in large animal models of nerve injury.

Strengths and Weaknesses of Current Animal Models

This session was devoted to understanding the strengths and weaknesses of animal models of peripheral neuropathies and neuropathic pain in translating basic discoveries to successful clinical trials. Dr. D. Zochodne's lead talk centered on the fact that many of the outcome measures used in animal models of type 1 and type 2 diabetes are not reflective of the symptoms experienced by patients. He emphasized the need for longer duration models to better mimic human disease. He advocated the use of intraepidermal nerve fiber density as an outcome measure because it is an objective measure of neuropathy that can be used in clinical trials. He noted that an important aspect of experimental design in animal models is that when testing new drugs, the studies need to be designed as a therapeutic paradigm rather than as a prevention paradigm because it would mimic the human condition. Furthermore, he argued that mouse models of diabetic neuropathy are more appropriate, as genetic manipulations allow experimental evaluation of specific molecular pathways.

Dr. V. Bril reemphasized the discrepancy between evaluation tools used in animal models and symptoms in patients and brought attention to the fact that in experimental models the number of animals is often too few and the effect size is small. Extrapolation from such animal studies to humans may underlie the fact that clinical trials involving disease-modifying drugs have uniformly failed in diabetic polyneuropathy and many other diseases.

Dr. I. Obrosova pointed to overall similarities and differences between short-term vs. long-term animal models of diabetic neuropathy and emphasized the use of mouse models because of the availability of genetic manipulation. While recognizing that animal models so far had a very poor predictive value for clinical success, Dr. G. Smith used the failed clinical trials of nerve growth factor *(Apfel et al., 2000)* to point out one of the important aspects of translating from animal models to clinical trials: often the doses of drugs that show efficacy in animal models are much higher than what is safely tolerated in humans. He also pointed to the fact that many of the animal studies are not done to the same rigorous standards of a human clinical study: they often lack power analysis or justification of numbers of animals used, and there is no proper randomization or blinding.

Dr. N. Calcutt pointed out that animal models are needed that truly mimic the human disease with multiple confounding risk factors such as hypertension and dyslipidemia. Dr. R. Rappaport commented that blame does not fall only on the failings of animal models because major classes of drugs that have been shown to reduce pain in human painful diabetic neuropathy do show efficacy in animal models. Failure of phase 2 and 3 clinical trials in both disease modification and pain relief is likely to be multifactorial and improving chances of successful clinical outcomes will depend on changes in both animal models and clinical trial designs. Reproducibility of pre-clinical studies has also been a major issue not only in neuropathy research but also in basic research in general *(Prinz et al., 2011; Landis et al., 2012)*.

The following session focused on neuropathic pain models and their predictive value in translating to successes in clinical trials. Dr. J. Mogil noted that in animal models of neuropathic pain, investigators often fail to consider the epidemiology of the disease that they study. Developing an animal model using a single strain of an inbred mouse or rat (often of a young age because of convenience) is not likely to recapitulate the human condition and clinical trials that rely on such studies are doomed to fail *(Mogil, 2009)*. In addition, there are gender-specific effects of a given intervention, and this may not be recognized if all the animal studies are done in one gender. For example, there are examples of failed clinical studies that relied on pre-clinical studies done only in male animals. Lastly, many of the pre-clinical models of neuropathic pain fail to recognize that the outcome measures used are very different and not likely related to the pain experience of patients. In multiple clinical studies, the most common complaint of patients is ''spontaneous pain,'' yet very few animal studies even claim to measure it. There is a need in the field to develop non-reflexive measures of pain in animal models. A recent development is measuring spontaneous pain by facial

expression of animals through video recordings. This allows one to score spontaneous pain without the risk of unblinding, but the drawback is that it works only in a subset of animal models of pain. Discussants emphasized that painful conditions in humans are likely to have multiple pathogenic mechanisms, and animal models may help identify molecular pathways or drug candidates specific for a given painful condition but not be applicable to ''all neuropathic states.''

Dr. A. Basbaum noted that every spontaneous pain is the same and that the majority of patients complain of ''burning pain'' sensation in most peripheral neuropathies. The surrogate marker that is often used in animal models, thermal hyperalgesia, is probably not a good measure of spontaneous burning sensation that the patients experience. Dr. N. Katz commented that the outcome measures used in animal models have a very good positive predictive validity (i.e., if a drug works in humans it will have worked in animal models as well) but poor negative predictive validity. The literature is filled with studies in which animal studies gave a positive result but the clinical trials failed to show any benefit. Furthermore, many animal studies done in academic centers do not test or report reliability of their measures; reporting of reliability of outcome measures should be required for publications.

Dr. T. Ho introduced the notion of a ''connoisseur trial design'' consisting of a small number of neuropathic pain patients known to be good pain reporters and with a low placebo response. He proposed that a favorable response to an intervention should prompt moving to a formal clinical trial in a larger population. Dr. J. Levine highlighted the need for the development of measures of spontaneous pain and pain effect to better represent the human state. He noted that most basic science pain researchers continue to rely on reflexive, evoked hypersensitivity responses after nerve injury because these yield reliable dependent measures.

Clinical Trial Challenges in Peripheral Neuropathy

The final session of the meeting was devoted to understanding the challenges of designing and carrying out effective clinical trials of disease-modifying agents in peripheral neuropathies and symptom reduction agents in neuropathic pain. Dr. R. Dworkin led the initial session outlining the major unmet needs in the field. He noted that we need: (1) drugs that are effective in a larger percentage of patients; (2) drugs that even if they are only effective in a small percentage of patients, reduce those patients' pain down to mild levels, 0–2 on a 10-point scale; (3) drugs that have greater benefits on physical function, activities of daily living, mood, and sleep; (4) drugs that are safer and better tolerated with few interactions that are convenient to take and increase compliance; and (5) drugs developed ultimately based on a pathogenic mechanism of pain. There are many failed clinical trials in various peripheral neuropathies. It is not known whether those failures are due to lack of efficacy of the drug or failure due to trial design (false-negative trials) *(Taneja et al., 2012a; 2012b)*. A major contributor to false-negative trials is likely to be heterogeneity of the patient population; a careful selection of patients with enrichment for a more homogenous population will likely reduce the false-negative trials. Furthermore, selecting patients who are more consistent in their ratings of pain scales may also reduce false-negative studies. Lastly, we need to be aware of investigator bias, even in double-blind placebo-controlled studies. There is also the problem of ''professional'' patients who enroll at multiple sites in the same study. These issues are summarized in recent publications *(Dworkin, 2012; Dworkin et al., 2012)*.

Dr. R. Rappaport discussed the issue of primary vs. secondary outcome measures and challenges in developing a primary outcome measure that is relevant to the general patient population. Another major hurdle in the field is relative lack of ''disease-modifying'' treatment trials for peripheral neuropathies and lack of reliable surrogate markers of disease progression.

Dr. D. Cornblath focused on the use of ''enrichment design'' in clinical neuropathic pain trials to reduce the chances of false-negative results. This will reduce variability in patients' responses to treatments and help eliminate dropouts from the studies. Another major issue in clinical trial design for neuropathic pain is lack of comparator groups with existing treatment arms. This is often an issue with drug companies but the general public and treating physicians need to know if a new treatment is better than existing ones.

Dr. C. Sang brought additional attention to the issue of unblinding and the need to report blinding confounders in clinical trial publications. A Cochrane review of all trials done in 2001 showed that only 2% of publications had adequate blinding. Dr. J. Tobias pointed out that the gold standard, double-blind, placebo-controlled trials have at least one important shortcoming; the placebo is not without a biological effect. There have been numerous studies demonstrating that placebo can have biological effects and lead to improvements in outcome measures, especially in pain *(Finniss et al., 2010)*. Clinical trials that are negative may in fact be false-negatives and this needs to be taken into consideration.

The last session of the meeting was on surrogate markers for peripheral neuropathy clinical trials. Dr. J. McArthur pointed out that despite many attempts we still do not have good surrogate marker(s) or surrogate endpoint(s) for peripheral neuropathies, while pointing out the success of measuring viral load as a surrogate marker for HIV infection and development of antiretroviral therapies. One potential surrogate marker is the density of intraepidermal nerve fibers; it correlates with neuropathy severity as gauged by the total neuropathy score, sural sensory nerve action potential amplitudes, and quantitative sensory testing using toe cooling and vibration detection thresholds, and with neuropathic pain as measured by the Gracely visual analog scale *(Ebenezer et al., 2007; Herrmann, 2008)*. This needs to be further validated in multiple clinical studies, as there have been other studies in which the correlations between epidermal nerve fiber density and other measures of peripheral neuropathy or neuropathic pain do not exist.

Dr. V. Apkarian noted that brain imaging in patients with various chronic pain states can be helpful in demonstrating the state of brain connectivity in chronic pain as well as a predictor of placebo responders *(Baliki et al., 2007)*. Dr. M. Backonja focused on biochemical surrogate markers such as positive correlation between pain and cerebrospinal fluid levels of interleukin-1 and negative correlation between pain and serum interleukin-10 levels *(Backonja et al., 2008)*. A major confounding factor in such studies is the heterogeneity of the potential pathogenetic mechanisms of pain.

Dr. J. Farrar argued that for surrogate markers to be useful they need to be easier to measure. Markers that are difficult to quantitate are not useful. Adequate surrogates should also have a larger effect size, be easier to detect, and be more rapid in their response. Dr. M. Polydefkis brought up the utility of skin biopsies and epidermal nerve fiber density measurements as surrogate markers for regeneration in human experimental models of nerve injury and advocated the use of skin biopsies in evaluating potentially ''regenerative'' therapies for peripheral neuropathies *(Polydefkis et al., 2006)*.

Conclusion

The first scientific meeting of The Foundation for Peripheral Neuropathy was successful in bringing together basic and clinical scientists from academia, NIH, FDA, and industry to outline the roadblocks in developing effective therapies for peripheral neuropathies and neuropathic pain. Developing regenerative therapies will require better understanding of the mechanisms of axonal degeneration in multiple disease models. In terms of evaluating the role of animal models in pre-clinical effectiveness studies, it was clear that some of the animal models had shortcomings because of the outcome measures that are used (not relevant for human condition) and the lack of rigor with which they are conducted (unblinding is a major issue). Clinical trials face a major problem with false-negative studies and the field needs more innovative trial designs to combat this issue. Surrogate markers can probably aid in this regard but they need to be validated in multiple studies.

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