Full Report from the 3rd International Symposium

Deater Foundation Helps Sponsor a Third International Symposium: "Molecular Pathogenesis and Therapy of HSAN1"

The Deater Foundation recently had the privilege of helping to sponsor a third international HSAN1 symposium, which was held November 14-16, 2013 in Boston. These conferences are a valuable use of DFI's resources in that they bring together top scientists from around the world who are currently working on research related to further understanding the causes, mechanisms, and potential treatments for HSAN1.

During the course of this 3-day meeting, researchers presented their work on various aspects of HSAN1, including updates on current research in mice and humans, structural biology and subunits of the SPT enzyme, deoxysphingoid bases, as well as new insights into programmed axonal cell death.

Some of the current research and updates included:

- Dr. Florian Eichler (Massachusetts General Hospital): Presented his findings in HSAN1 mice suggesting that there may be additional modifiers, perhaps diet, that may be helping to accelerate disease progression. Research into whether lipid (fat) substrate availability might be affecting the peripheral nerve seems to point to an earlier onset of the disease (as evidenced by myelin thinning, loss of mechanical activity, and loss of small unmyelinated fibers) in mice that were fed a high fat diet. These findings suggest

that there may also be a dietary component to the disease, and amino acid selection as well as lipid availability may be influencing the neurodegeneration seen in patients with HSAN1. It is possible that these findings could also be the start of a better understanding into the variance of disease onset, progression and symptoms sometimes seen even across members of the same family.

- Dr. Thorsten Hornemann (University of Zurich, Switzerland): Presented his research showing that deoxysphingolipids (dSBs: formed when the mutated SPT enzyme in patients with HSAN1 selects the amino acids, alanine or glycine, as its substrate instead of serine) cannot be degraded and have been shown to be neurotoxic, most likely by affecting neurite formation and branching, both of which are important processes in nerve development and communication. Also, there may be a correlation between dSB plasma levels and disease severity to an extent, but these levels most likely hit a ceiling at some point and stop advancing (even though the disease may still be progressing). These dSBs have also been found in the plasma of patients with diabetes, and giving serine to diabetic mice was shown to improve their neuropathy significantly by the end of the study. Also, dSBs were not found to be elevated in the nerves of these diabetic mice, just in the plasma (unlike HSAN1 mice showing accumulation of dSBs in both plasma and nerves) which might be a helpful indicator of what actually drives the neuropathy and whether or not focusing on just lowering dSBs in the plasma would be sufficient to treat the disease.

- Dr. Dominic Campopiano (School of Chemistry, Edinburgh, Scotland): Presented updates on the structural biology of SPT (the enzyme mutated in patients with HSAN1) and whether or not drug therapies targeting components of the SPT enzyme itself or the sphingolipid synthesis pathway as a whole might be viable options to consider for treatment development.

- Dr. Teresa Dunn (Uniformed Services University of the Health Sciences): Presented her research into the small subunits of the SPT enzyme (ssSPTs) and also provided more insight into how the SPT enzyme works as a whole. Her research suggests that the activity of SPT increases in the presence of ssSPTs. She also explained that the minimum requirement for the SPT enzyme to be active includes LCB1 (the first protein subunit of the enzyme), one isoform of LCB2 (the second protein subunit, the other form can also be LCB3), and ssSPT (subunit a or b). When all these components are combined, an active SPT enzyme is formed. She also suggested that some of the more severe phenotypes (what symptoms you see in a person as a result of the disease), for instance those HSAN1 patients with the S331F mutation, are brought about because that particular mutation in the first subunit, LCB1, results in poor activation by ssSPTs. Her research indicated that many HSAN1 mutations elevate activity of the SPT enzyme, making it harder for the enzyme to be so selective, which in turn leads to alanine and glycine binding (resulting in the neurotoxic dSBs) instead of just serine. She suggested that one avenue for potential therapy might include finding a method to lower the activity of SPT in HSAN1 patients, and therefore help maintain the enzyme's selectivity for L-serine.

- Dr. Marc Freeman (University of Massachusetts): Presented his research on new insights into programmed axonal cell death, specifically the identification of an axon death signaling molecule and a novel fusion protein in both fly (WldS) and mouse (Sarm1) models that, when over-expressed, can actually block axonal degeneration, if the cell body of the nerve is still intact. In mice over-expressing this protein, sciatic (thigh) nerve cuts resulted in normal-looking axons with healthy neurofilaments, Schwann cells, and mitochondria after a few weeks, and it was even shown to block the typical immune response to nerve damage. Also, expression of Sarm1 in ALS mouse models resulted in a 50% protection of sciatic nerves at 130 days. Future experiments

to see how these findings could impact HSAN1 were discussed. These included plans to take a look at how Sarm1 mouse nerve cells respond to the presence of dSBs (are they protected or do they still show abnormal neurite formation and degeneration?) and also to cross Sarm1 mice with HSAN1 mice (which would result in the expression of both proteins, the axon regeneration protein plus the mutated SPT enzyme, in the same mouse) to see if this could result in sciatic nerve protection or regeneration, which could be an important finding for a potential treatment for HSAN1. Other neuropathies relative to HSAN1 were discussed, including HSAN3 (Dr. Elisabetta Morini, MGH), Hereditary Spastic Paraplegia (Dr. John Fink, University of Michigan), and spinal muscular atrophy (Dr. Kenneth Fischbeck, NIH), as well as lessons learned from these diseases and how that information could potentially be applied to HSAN1. Dr. Anne Louise Oaklander (MGH) presented her research on painful neuropathies and the role of small nerve fibers in these diseases. She suggested that nerve injuries may be a common cause of bone fracture and that losing innervation to the bone may cause the bone to be more susceptible to fractures (as sometimes seen in patients with HSAN1). She also stated that women tend to have more sensory fibers in skin biopsies initially when compared to men (which might help explain the disease variance sometimes seen among HSAN1 patients of different gender), and also that skin biopsies taken in healthy individuals without HSAN1 show that a change occurs normally in small sensory fibers around age 22 (which could also point to a possible explanation as to why a more obvious symptom onset typically occurs around this time in patients with HSAN1). She explained that small nerve fibers may deteriorate due to lack of oxygen, especially in the distal parts, and therefore she suggested improving oxygenation to the extremities (hyperbaric chamber, exercise, smoking cessation, etc.) to help stop this loss of small nerve fibers. She concluded with the recommendation that patients with HSAN1 obtain bone

scans (DEXA, x-ray) frequently, especially of the heel area, in order to help monitor any changes that may be occurring.

Dr. Mary Reilly (University College London) presented lessons learned from previous clinical trials in peripheral neuropathies as well as information about the current HSAN1 patient population in London. She brought up discussion on potentially evaluating children who might be at risk for having HSAN1 in order to better understand what is going on in the early stages. She suggested that HSAN1 neurodegeneration is probably happening around ages 6-7, but there is no clinical evidence in the patient yet. Most likely, by the time symptoms manifest around age 12 or above, there is probably already about a 30% sensory neuronal loss at this point. She also suggested there might be some value to a preventative clinical trial in children, and also that the name, HSAN1, might actually be a misnomer (due to the A for autonomic) because the disease does not seem to have a definitive autonomic component to it, although there is a definite motor component in later stages.

The meeting concluded with a discussion on HSAN1 patient populations in Boston and London, review of information obtained from the retrospective study (follow-up surveys done by Dr. Vera Fridman coupled with the original survey from the Deater Foundation in 2007), and the potential for an HSAN1 fly model (Dr. Vincent Timmerman, University of Antwerp). Potential therapies for HSAN1 including: optimizing biomarkers, improving clinical outcome measures, setting up an international registry, prospective natural history study, and possible presymptomatic study, as well as possible new research avenues to explore moving forward (many of which were mentioned above) were discussed, with a joint interest by everyone present to continue making advancements through collaboration and communication in order to further understand this disease. There was also a unanimous interest in holding more HSAN1 conferences in the future and also seeing if research pertaining to HSAN1 could be integrated into the broader-scale neuropathy symposiums held

throughout the year, like the annual International Charcot-Marie-Tooth Consortium and/or Peripheral Neuropathy Meetings.

All in all, this 3rd symposium was a productive time of research presentation, idea discussion, and potential therapy proposals by these top researchers in order to further the goal of developing a treatment and cure for patients with HSAN1. We thank you all so much for your donations to DFI, and we want you to know that your generosity helped make this important meeting possible!