

6th Annual WORLD* Symposium 2010

*We're Organizing Research for Lysosomal Diseases
February 10-12, 2010 -- Miami, FL

Presented by the Lysosomal Disease Network (LDN) and the National Institute of Neurological Disorders and Stroke (NINDS)

I had an opportunity to attend the 2010 WORLD Symposium as a representative of the NNPfD in February. Many of the over 425 pre-registered participants in the WORLD conference braved the winter weather at home (yes, East coasters, it was THAT weekend!) and made it to Miami for the conference. For those who did, the meeting involved 3 days of targeted presentations about basic research (Day 1), translational research (Day 2) and newborn screening and LDN NIH-funded projects reports (Day 3).

By way of background, the LDN consists of researchers and clinicians from 14 primary participating centers and at minimum, 14 associated centers across the US and Canada. The LDN received a \$6.3 million award to develop this consortium of researchers as part of the National Institutes of Health (NIH) Rare Disease Clinical Research Network (RDCRN). The NNPfD participates in two such consortia, the LDN and the Sterol and Isoprenoid-Related Disorders (STAIR) grant, and there are 19 funded consortia in the network. Within the LDN, over 18 patient advocacy groups make up the Council of Patient Advocates (COPA), and all are invited to actively participate in development and support of the funded studies. The LDN has 11 studies that are funded for the full 5 years of the grant and 7 pilot studies that will each be funded for 2 years. The WORLD meeting is the annual gathering of participating clinicians and researchers for discussion of ongoing studies and new ideas.

Studies directly relevant to Niemann-Pick disease:

During the conference, a number of presentations focused on Niemann-Pick disease. Dr. Steve Walkley's PhD student, Cristin Davidson, presented studies looking at whether storage of cholesterol and gangliosides can be reversed in addition to being prevented by use of 2-hydroxypropyl-beta-cyclodextrin. They treated mice with the severe form of NPC, daily from 4 to 7 weeks, starting when the damaging fats would already have been stored to some extent. The studies showed reduced storage of cholesterol and gangliosides (GM1 and GM2) in nerve cells, but did not explain how this happens. Dr. Walkley and colleagues now plan to study delivery of cyclodextrin directly to the brain, effectiveness of using varying dosing strategies, and testing of various forms of cyclodextrin. At the end of the presentation, Roscoe Brady asked about potential side effects of cyclodextrin including lung obstruction and hearing loss.

Dr. Marc Patterson substituted for weather-detained Dr. Denny Porter and presented the oxysterol biomarker studies. One process associated with NPC is called oxidative stress, where too many free radicals are produced. Dr. Porter and colleagues studied whether these free radicals are interacting with the excess stored

cholesterol to produce compounds that might be a good marker of early NPC1 disease. They identified cholesterol oxidation products that were elevated in mice that have NPC1 disease; these compounds appeared to be associated with disease progression. They then studied blood samples from 25 NPC1 patients, 25 age-matched controls and 17 NPC carriers. The oxidation products (triol and 7-ketocholesterol) were elevated in all 25 NPC1 patients in a pattern that appears to be specific to NPC1 disease. The oxysterol profile also correlated with age at disease onset and disease severity that might be useful for early diagnosis of NPC.

The last talk specific to Niemann-Pick disease was Dr. Patterson's presentation of his new long-term study on cognition in NPC patients. He hypothesizes that there is a specific pattern of neurocognitive difficulties that start to occur even before neurological problems are noticed, and that they correlate with disease progression. Using a standardized set of neurocognitive tests, patients will have the following measured annually at either Mayo or the NIH: intelligence, visuo-spatial abilities, memory, visuo-spatial construction, language, motor skills, attention and executive function. These measurements will be correlated with the NIH-expanded disability scale and potentially could become another marker of disease progression and the effectiveness of possible therapies.

Lysosomal Disease Research and Related Topics:

The remaining many talks were not specifically about Niemann-Pick disease, but many of the approaches to disease study may be useful as researchers continue to study and better understand ASMD Niemann-Pick disease and NPC. In particular, many of the therapeutic approaches that were presented may be useful in looking at treatment of NPA and NPB, with their focus on delivery of circulating enzymes in the body and across the blood-brain barrier (BBB).

Key topics of discussion on Day 1 included:

1. Delivery of enzymes across the BBB, for example targeted delivery and intrathecal) delivery (into the fluid around the spinal cord and brain)
2. Viral vectors for gene therapy to the brain
3. Stem cell repair and enzyme delivery to the CNS
4. Secondary genetic effects
5. Chaperone therapies (or enzyme-enhancement therapies – EET)
6. Autophagy (self-digestion) suppression
7. Biomarker identification
8. Substrate Reduction Therapy (SRT) – like Zavesca
9. Protein replacement therapy
10. Disease identification

Key topics of discussion on Day 2 included:

1. Small Clinical Trials
2. New Approaches to treatment development in LSDs

3. Lysosomal disease registries and applications of registry data
4. Enzyme Replacement Therapy for Gaucher, Fabry, and Hurler
5. Medication Management for Lysosomal Disorders

Key topics of discussion on Day 3 included:

1. Newborn screening for LSDs:
2. Overview of 19 RDCRN-funded LDN projects – each investigator was given 15 minutes to introduce his or her project, and to ask colleagues to refer patients for study
 - a. Long term studies of brain structure and function in MPS disorders
 - b. A study of intrathecal enzyme replacement for cognitive decline in mucopolysaccharidosis I
 - c. Update on the long term study of bone disease and the impact of growth hormone treatment in MPS I, II and VI
 - d. Assessment of social/emotional function in children with MPS III
 - e. The natural history of mucopolysaccharidosis type IV
 - f. The UBDRS predicts rate of JCNL (CLN3) disease progression –a disease rating scale for Batten
 - g. The Rare Disease Clinical Research Network Data Management and Coordination Center – an overview of computer resources for the 5 year longitudinal studies and the 2 year clinical /interventional trials
See <http://rarediseasesnetwork.epi.usf.edu/> .
 - h. Statistical issues in clinical trials
 - i. Long term studies of glycoproteinoses - natural history protocols
 - j. Assessment of neurological deterioration in subjects with LINCL
 - k. Immunological aspects of treatment of Pompe disease
 - l. Longitudinal study of cognition in subjects with Niemann-Pick disease, type C (see above for Dr. Patterson’s study details)
 - m. Epidemiology and natural history of Wolman and cholesteryl ester storage disease due to deficiency of lysosomal acid lipase
 - n. Fabry disease identification – looking in defined populations for Fabry patients
 - o. Natural history and structural-functional relationships in Fabry renal disease – looking for predictors of renal disease progression.
 - p. Developmental and functional surveillance in preschool children with lysosomal storage diseases
 - q. Pulmonary disease and exercise tolerance in boys with Fabry disease
 - r. Open-label phase I/II clinical trial of pyrimethamine for the treatment of chronic GM2 gangliosidosis –chaperone therapy in late onset Tay-Sachs disease
 - s. A natural history study of hexosaminidase deficiency

Lastly, Dr. Steve Walkley announced a new Gordon Research Conference dedicated exclusively to Lysosomal disease. The first conference will be January 23-28, 2011, in Galveston Texas. More information can be found at:

http://www/grc.org/programs.aspx?year_2011&program=lysosomal or contact

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I would be happy to discuss details of any of the presentations with NNPDF members who might be interested.

Respectfully submitted,

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