APMRF 2011 meeting summary for NPC families and the NPC community

The Annual Parseghian Scientific Conference for Niemann-Pick Type C Research was held at University of Notre Dame on June 9-11, 2011. Cindy Parseghian announced that Notre Dame will continue to host the annual meeting since it has been endowed. The 2012 meeting will be held June 7-9.

Niemann-Pick Disease, type C (NPC) is a fatal, complex, neurodegenerative disease. Disease is due to defects in genes *npc1* (associated with 95% of clinical cases) and *npc2* (associated with 5% of clinical cases). Natural history studies have yielded quantifiable measures of disease severity in patients. One of the highlights of the meeting was demonstrating improvement in NPC children in response to emerging therapeutics as measured by a disease severity scale (0-50) developed at the NIH by Denny Porter and co-workers.

Dr. Camilo Vieira (Federal University of Bahia) reported on the progress of two patients aged 12 and 16. They started showing symptoms at ages 7 and 5, respectively. Despite treatment with the drug miglustat, which improved eye movement and swallowing, they were withdrawn from school because of deteriorating cognition. After one year of intravenous cyclodextrin (Hydroxypropyl-beta-cyclodextrin, HPBCD; Trappsol®) treatment, both children returned to school with improved memory, fine motor skills, and MRI scans. They were free from depression and (previously frequent) gelastic cataplexy (involuntary collapse associated with strong emotion). **Dr. Ron Brown** (SOAR) summarized that for the Hempel twins, intravenous cyclodextrin administration for 9-12 months failed to prevent neurological deterioration, hypometabolism, and seizure severity. However, intra-thecal injections (directly into the brain) appeared to improve hearing, ataxia, and seizure with some reduction in cerebrospinal fluid (CSF) biomarkers. At the close of the meeting, **Dr. Denny Porter** (NIH) indicated that there would be a trial evaluating the safety of cyclodextrin for NPC1 treatment at the NIH.

Due to its therapeutic potential, researchers are also studying the effects of cyclodextrin in mouse models, cellular assays and *in vitro* studies. Studies by **Dr. Benny Liu** (University of Texas Southwestern Medical Center) using *npc1*$^{-/-}$ mice treated with cyclodextrin suggest intra-thecal injections resulted in release of cholesterol and reduction of inflammation within 24 hours. This suggests that the brain is very responsive to the administration of cyclodextrin. **Dr. Kasturi Haldar** (University of Notre Dame) demonstrated that cyclodextrin quantitatively reduces neurobehavioral disease symptoms in a mouse severity scale that mimics human disease. However, **Dr. Joyce Repa** (University of Texas Southwestern Medical Center) presented data that cyclodextrin failed to stop progression of lung disease in *npc*$^{-/-}$ mice. HPBCD in conjunction with an LXR agonist may produce an additive effect in the *npc*$^{-/-}$ mice. Both laboratories are investigating other drugs in combinations with cyclodextrin.

Dr. Paulina Ordonez (University of California, San Diego) using neuronal stem cells showed that cyclodextrin prevents fragmentation of mitochondria, probably by blocking autophagy (a natural cellular process to recycle components). **Dr. Jean Vance** (University of Alberta) investigated specialized cells within the brain to demonstrate that a low dose of cyclodextrin can mobilize cholesterol from the lysosome to the endoplasmic reticulum (mimicking the natural movement of cholesterol). **Drs. Leslie McCauliff** and **Judith Storch** (Rutgers University) showed that cyclodextrin increased the rate of sterol transfer between membranes, at a rate that mimics NPC2, one using a cellular model and the other an *in vitro* model, respectively. **Dr.**

David Thompson (Purdue University) is investigating different forms of cyclodextrin that may be longer lived in animals.

Cellular studies have also suggested that inhibitors of histone deactylase (HDAC) can correct the NPC phenotype. **Dr. Olaf Wiest** (University of Notre Dame) described computational models for the structure and function of HDAC isoforms. **Dr. Fred Maxfield** (Weill Cornell Medical College) described that HDAC inhibitors are mutation-specific for NPC1. **Dr. Bill Balch's** (Weill Cornell Medical College) lab has shown that two HDAC inhibitors can synergize with each other and other compounds. His laboratory also studies the process of proteostasis, a process that controls protein stability, location, and binding partners. They have identified chemical compounds that affect proteostasis, which can help in classifying different NPC1 mutants and their variability in causing disease. **Fred Maxfield** is using mutants expressed by the **Balch** lab in cellular assays to screen for new compounds that correct the NPC phenotype. **Drs. Steven Sturley** and **Andrew Munkacsi** (Columbia University) described a yeast model of synthetic lethality that suggests HDAC inhibition is a candidate therapy for NPC1 disease. **Kasturi Haldar** and **Joyce Repa** show that HDAC inhibitors do not improve survival of $npc^{-/-}$ mice because they lack the NPC1 protein. These inhibitors need residual protein to work. HDAC inhibitors have been shown to be effective in diseases like cancer in mouse models as well as in patients, hence there is interest in learning their function and potential use in treatment of NPC as elaborated by **Dr. Norb Wiech** (Lysomics, LLC).

Investigating therapies that improve NPC disease and identifying their molecular basis, is clearly important to developing new treatments. However researchers also study the molecular processes that underlie the genetic defects to find ways to target the disease. To do this NPC researchers undertake basic studies in animal models, cellular models as well as at the molecular level.

Dr. Guosheng Liang (University of Texas Southwestern Medical Center) showed that mutations in NPC1 that abolish cholesterol transfer when expressed in mice result in cholesterol accumulation and lethal disease, definitively linking loss of the mechanism of cholesterol transfer to NPC disease. **Dr. Matthew Scott** (Stanford University) is looking at the contribution of NPC1 function in different cells in the brain and liver and is able to show that NPC1 function in cerebellar Purkinje improves balance, weight, and life span but is not enough to prevent premature death. He also showed that functional NPC1 produced in macrophages reduces foam cells (fat-rich cells) in the liver, a major disease pathology. **Dr. Frank Pfrieger** (Institute of Cellular and Integrative Neurosciences) showed that retinal degeneration occurs in $npc1^{-/-}$ mice and is a late-stage effect. One reason for the deterioration is an increase in autophagy in retinal cells.

In cellular studies, **Dr. Hongyuan (Robert) Yang** (University of New South Wales) and **Dr. Heiko Runz** (University of Heidelberg, Germany) described protein cytoplasmic regulators of cholesterol trafficking that function in conjunction with NPC1, namely Oxysterol-Related Protein 5 (ORP5) and TMEM97, respectively. Lowering TMEM97 increases NPC1, which may be a therapeutic strategy in the future. **Dr. Kevin Vaughan** (University of Notre Dame) described that the location of a new protein STARD9 which is deficient in of NPC1 mutant fibroblasts. **Dr. Suzanne Pfeffer** (Stanford University) showed that purified NPC2 protein binds to a specific region of NPC1 protein with a defined but low micromolar affinity, suggesting the mechanism by which these two proteins form a functional complex. **Dr. Nick Cianciola** (Case

Western Reserve University) described an adenovirus protein that can correct cholesterol storage because this protein (RID-alpha) transferred cholesterol to the ER. **Dr. Fabrizio Vacca** (University of Geneva) and **Dr. Yvonne Lange** (Rush University) looked at cholesterol movement in NPC1 mutant cells. **Vacca** found no difference in kinetics of cholesterol export from endosomes and **Lange** said that the cholesterol pool in NPC1 mutant cells is mobile.

Dr. Dan Ory (Washington University) closed the research talks with a description of a sensitive and specific blood test for diagnosing NPC1 disease. The work represented an integration of animal models and patient plasma samples. The diagnostic is based on the finding that levels of particular oxysterols in the blood increase with increasing NPC1 disease severity. It has the potential to decrease the time to diagnosis.

We would like to acknowledge the contributions of NPC parents and children to this meeting. **Trent Smith, Jim Greene and other families** shared their unique understanding of this disease with the NPC research community.

Thank you for coming. See you next year.

Pam Tamez and Kasturi Haldar

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