New NP-C Drug Trial

A clinical trial is expected to begin in the summer of 2014 using a Histone Deacetylase Inhibitors (HDACi). The goal of the Phase 1 clinical trial will be to establish the safety and tolerability of an oral HDACi as a treatment for NPC1 disease. To meet this objective, researchers at the National Institutes of Health, Mayo Clinic, Washington University and Cornell will develop a Phase 1, first-in-human, open-label, multi-center, dose escalation study of a HDACi in late adolescents and adults with NPC1 disease. Results from this study will lay the foundation for future clinical trials to assess the effectiveness of an HDACi in slowing disease progression, and may lead to the first FDA-approved drug for the treatment of this devastating disorder. The trial is dependent on an approval of an Investigational New Drug Application (IND) by the Food and Drug Administration (FDA).

The secondary objectives of the trial will be to determine biochemical efficacy of the HDACi to increase expression of the NPC1 protein and normalize lipid and protein biomarkers. A team of researchers will examine data on plasma and cerebrospinal fluid markers to use as potential clinical endpoints. These outcome measures can potentially serve as surrogate outcome measures in future Phase 2 and Phase 3 HDACi trials.

Twelve NPC1 patients (18 years and older) will be recruited for the study. Eligible patients will demonstrate at least one neurological manifestation of NPC1 (e.g., hearing loss, vertical supranuclear gaze palsy, ataxia, dementia, dystonia, seizures, dysarthria, or dysphagia). Symptoms cannot be so severe that they interfere with the patient's ability to comply with the requirements of this study. Testing will be performed on patient fibroblasts to establish in vivo responsiveness to the HDACi . The safety of HDACi in pediatric populations has not been established. Children under 18 years old are thus currently excluded due to FDA comments, in a pre-IND meeting, suggesting that safety and tolerability first be established in adults. Potential participants will be admitted to the NIH Clinical Center or Mayo Clinic for determination of eligibility and baseline clinical evaluations. Patients who have received any form of cyclodextrin or an HDACi in the past in an attempt to treat NPC1 will not qualify for the trial.

Clinical sites will be overseen by Dr. Porter at the National Institutes of Health Clinical Center and Dr. Marc Patterson at the Mayo Clinic in Rochester, MN. Dr. Ory will oversee performance biomarker analysis of clinical samples at Washington University, while Dr. Maxfield will supervise personnel in his laboratory who will perform quantification of NPC1 protein expression and histone acetylation in the clinical samples. Dr. Maxfield and his personnel will also test fibroblasts from prospective trial participants to confirm that their cells respond to HDACi treatment.

The discovery of the use of HDACi for the treatment of NP-C was first made in the labs of Paul Helquist and Olaf Wiest at the University of Notre Dame. They soon collaborated with Dr. Fred Maxfield's lab at Cornell who helped confirm their hypothesis. Recently, the Maxfield laboratory found that treatment of human NPC1 mutant cells with certain HDACi leads to clearance of excess cholesterol and other lipids from certain parts of the cells and it corrects the overall defect in cholesterol regulation. This metabolic correction was associated with increased expression of the NPC1 protein. Based on this preliminary data, the HDACi treatment could result in a benefit to NPC1 patients.

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The APMRF has been instrumental in funding the labs of Helquist, Wiest, Maxfield, Ory and Dr. Steven Sturley, at Columbia University, in the investigation of HDACi, providing the ground work for this Phase 1 trial. In addition, the APMRF has been a major supporter of the Natural History Study conducted by Dr. Porter at the NIH which has focused on gathering of clinical data and establishing biomarkers for use in clinical trials.