

SOAR – NPC

Support of Accelerated Research for Niemann-Pick Disease Type C

Progress Report – February 2009

SOAR-NPC (Support of Accelerated Research for Niemann-Pick Disease Type C) is a collaborative research project funded by The Addi & Cassi Fund, The Ara Parseghian Medical Research Foundation, Dana's Angels Research Trust, The Hadley Hope Fund and The Hide & Seek Foundation for Lysosomal Disease Research.

The goal of SOAR is to accelerate therapy development for Niemann-Pick Disease Type C, a neurodegenerative disorder in the lysosomal disease family. Conceived in early 2007, the research consortium began receiving in 2008 the critical funding necessary to support ongoing research in NPC funded by others.

During 2008 a group of four distinguished scientists conducting basic research on NPC established a collaborative agreement with the objective of creating, within a three year time frame, a combination therapy of FDA approved drugs and nutraceuticals that can be tested clinically to prevent or significantly delay the onset and progress of clinical neurological disease in NPC patients. The four investigators are:

- 1) Dr. Dan Ory, Washington University School of Medicine, St. Louis, MO
- 2) Dr. Steven Walkley, Albert Einstein College of Medicine, Bronx, NY
- 3) Dr. Yiannis Ioannou, Mt. Sinai School of Medicine, NY, NY
- 4) Dr. Fran Platt, University of Oxford, Oxford, UK

This core group of scientists conducts bi-weekly teleconferences to discuss research findings and set project objectives. Each of the scientists brings unique expertise to the SOAR-NPC, which fosters collaboration between the laboratories, and allows the collaborative to coordinate research efforts towards the common goal of developing treatments for NPC disease. CollabRx, Inc provides project management.

The research by NPC-SOAR is focused on three areas necessary to identify potential therapies suitable for clinical trials:

1. High throughput screening

A new assay, based upon up-regulation of NPC1 protein, has been developed. A key antibody necessary for the assay has been made and production is being increased. The antibody has been sent to the NIH Chemical Genomics Center for evaluation and is expected to be used in high throughput screening of over 3,000 FDA approved drugs using human cell lines derived from NPC patients.

An FDA approved drug library has been screened for up-regulation of expression of a molecule involved in intracellular movement of cholesterol. Several compounds that are active in this screen are currently being evaluated in cell-based and whole animal experiments.

2. Mouse model of NPC

Experiments to expand on the finding that a cyclic sugar, cyclodextrin, prolongs the life expectancy in a mouse model of NPC have been conducted and a recent finding by the collaborative indicates that repeated, chronic administration can double the life expectancy in this model. Further, studies show that even starting the cyclodextrin in juvenile mice can have a beneficial effect. Further studies to elucidate the mechanism of action of the cyclodextrin and to examine other cyclodextrin molecules are planned. Studies are ongoing to examine several drug combinations in this animal model. These include miglustat, allopregnanolone, curcumin, ibuprofen, and salicylates. As other lead compounds are identified they will be profiled in this model. For example, pilot studies have begun with L-cycloserine and alternative forms of cyclodextrin.

3. Biomarkers

Analysis of blood and CSF from NPC subjects and age-matched controls has recently identified several circulating lipid molecules that appear promising as biomarkers, as they are specifically elevated in NPC subjects, but not control subjects or subjects with other lysosomal storage disorders.

These findings may not only lead to a new diagnostic for NPC, but also offer the potential to examine changes in biomarker levels during therapeutic efficacy trials. Current activities around this finding include attempts to correlate biomarker levels with disease severity, and validate these findings in an animal model of NPC. It is noteworthy that this effort could not have succeeded without the direct involvement of NPC parents in allowing their children to participate in the NIH observational study and in assisting the SOAR scientists in obtaining age-matched control blood samples.

Recent studies by SOAR investigators have implicated a sphingolipid, sphingosine in the cellular defect in NPC disease. An assay has been established for measuring sphingosine levels, which may represent a potential NPC biomarker.

The near-term objectives of the SOAR Collaborative are to vigorously continue their efforts in each of these target areas.

Realizing that the two-year objective of the SOAR-NPC effort is to identify and initiate clinical testing of a combination therapy, efforts to facilitate clinical trials have been initiated. Relationships have been established with a leading NPC physician (Dr. Marc Patterson, Mayo Clinic) and with the National Institutes of Health (Dr. Denny Porter), where an ongoing observational study in NPC is being conducted.

Because established endpoints for use in clinical studies of NPC have not yet been established, a video-based assessment of NPC patients obtained by parents and analyzed by neurologists may provide a method for conducting future clinical studies in NPC. A pilot feasibility project related to this approach was initiated late in 2008 and is ongoing.