national tay-sachs & allied diseases association
RESEARCH REVIEW | October 20, 2017

NTSAD-funded Research Updates

OrPhi Therapeutics SBIR Award!

OrPhi Therapeutics, an NTSAD Research Initiative grantee, was recently awarded a Phase 2 SBIR grant of over $1 million to fully characterize a mouse model of Sandhoff disease. The mouse model was developed with a grant from the Katie & Allie Buryk research fund of NTSAD and the NIH with a focus on using the model for pharmacological chaperone (PC) therapy proof of concept studies for GM2 gangliosidoses. The mouse model will be used in intervention and prevention proof of concept studies to analyze the ability of PCs to rescue disease causing mutations for inclusion in an IND*. Additionally, an assay will be developed to analyze disease-causing mutations for both Sandhoff and Tay Sachs disease that are amenable to PC therapy.

*An Investigational New Drug Application (*IND*) is a request for authorization from the Food and Drug Administration (FDA) to administer an investigational drug or biological product to humans.

Grant funded for research project "Accelerated program for CSF delivery of AAV gene therapy for Tay-Sachs and Sandhoff patients"

Principal Investigator: Miguel Sena-Esteves, PhD
Institution: University of Massachusetts Medical School

While intracranial injection of AAV vectors is the most advanced gene therapy for Tay-Sachs and Sandhoff diseases, the current approach involves two vectors encoding separately the hexosaminidase A (HexA) alpha- and beta-subunits, which are injected bilaterally in the thalamus and one cerebral lateral ventricle. There are drawbacks to this approach, such as the invasiveness of direct injections into the brain that require a neurosurgical procedure, and its use of two AAV vectors which double the costs of manufacturing and an eventual treatment. After much initial work, there are now single AAV vectors carrying both subunits that show promising results in GM2 mice. These new vectors can enter the brain effectively after injection into the bloodstream, or injection into the cerebral spinal fluid (CSF). Presently it is unknown which approach will be the most effective and therefore it is important to test both.

To date, ongoing studies testing bloodstream delivery of these new AAV vectors in GM2 mice have shown very promising results. This project will focus on the delivery of AAV vectors to the central nervous system through CSF administration (e.g. intrathecal space) which has several advantages to treat Late Onset patients. The funding will primarily support a research associate to conduct mouse studies related to CSF delivery of AAV9 vector in GM2 mice including generating mice, injections, behavioral studies, histological and biochemical analyses of tissues post-mortem.

Funding is being made available by the Katie & Allie Buryk Research Fund of NTSAD, the Vera Pesotchinsky Research Fund of NTSAD, The Late Onset Tay-Sachs Research and Education Foundation, Lisa Robaut, and the NTSAD Research Initiative Fund.

The Mayo Clinic hosted the **Individualized Medicine Conference and Lysosomal Disease Symposium** October 9th to October 10th. It was made possible in part by the generous support of NTSAD's supporters, The Buryk family and their good friend Peggy Furth. Click here to learn more about the conference.

Watch an interview with Dr. Ferber and Katie and Allie Buryk about their perspective and experience with Late Onset Tay-Sachs **here** .

A big thank you to our incredible community of families and their friends for raising nearly $90,000 for research!!!

We have now raised $300,000 in the last seven years for research, and, at the same time, touched countless numbers of people with our stories while raising awareness. Together we have made a difference this year, and look forward to all we can accomplish for our **8th Annual Day of Hope** on September 15, 2018!

What is Tanganil?

Clinical trials for acetyl-DL-leucine (IB-1000) on the horizon

Many have heard about this compound, IB-1000 (also known as acetyl-DL-leucine or Tanganil), which has been approved for the treatment of cerebellar ataxia in France. A clinical trial is planned for children with Niemann Pick C (and possible other lysosomal diseases) in Europe soon. NTSAD recognizes this exciting development and supports our families in making the decisions that are best for their loved ones. NTSAD cannot, however, advocate for the use of unproven or unapproved potential therapies and hopes families will consult with their physicians when considering experimental therapies. We do want to share the currently published data for the use of acetyl-DL-leucine in cerebellar ataxia and in lysosomal storage diseases.

- Ataxia is an abnormality of movement that includes balance problems, difficulty walking or wobbling with sitting, slurring of speech, and additional concerns with coordination. Cerebellar ataxia refers to ataxia due to abnormalities of the cerebellum. Most published studies of acetyl-DL-leucine thus far have been in individuals with cerebellar ataxia, rather than with lysosomal storage diseases.

- A 2013 study in *the Journal of Neurology* studied acetyl-DL-leucine in 13 individuals, aged 13 to 68 years, with inherited cerebellar ataxia. Patient also received physical and occupational therapy during this time, matched to their symptoms. After 7 days, they saw improvements in 12 of 13 patients in walking, speech, and other tests of coordination. They saw no side effects. [Strupp M et al. JNeuro 2013 260:2556-2561].

- A 2015 study in the same journal evaluated 10 individuals, ages 19 to 69 years, with degenerative cerebellar ataxia. Seven of these patients reported subjective improvement of their symptoms (they felt their symptoms were better), but validated assessments of ataxia evaluated in a blinded manner (the observers did not know if the patients were receiving drug) did not show any improvement. Again, they saw no side effects. [Pelz JO et al. JNeuro 2015 262:1373-1375].

- A 2016 study in the journal *Cerebellum & Ataxias* by the same authors at the first study looked at acetyl-DL-leucine in 18 individuals, ages 23 to 73 years, treated for at least 4 weeks, 12 with sporadic ataxia and 6 with inherited ataxias (8 of these were the same patients in the 2013 study above). They saw improvements in gait in 14 of 18 patients. [Schniepp R et al. Cereb&Ataxias 2016 3:8].

- There has been one published study on acetyl-DL-leucine in lysosomal storage diseases, specifically on Niemann Pick type C (NP-C), published in 2015 in *Neurology*. This study evaluated 12 individuals with NP-C treated, ages 13 to 26 years, with acetyl-DL-leucine for 1 month, then taken off of the drug for 1 month. They saw improvements in ataxia after treatment, with a return to baseline when the drug was stopped. One patient experienced dizziness, which improved when the dose was lowered, and did not recur when the dose was increased again. [Bremova T et al. Neuro 2015 85:1368-1375].

First gene therapy for inherited disease recommended for approval!

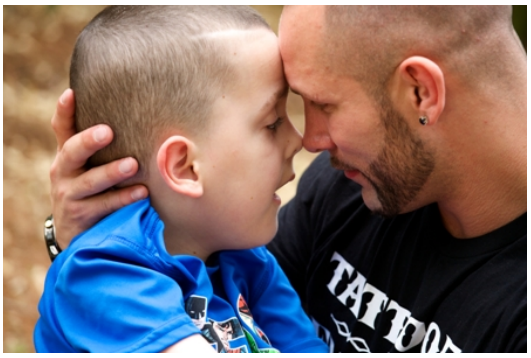
The FDA's Cellular, Tissue, and Gene Therapies Advisory Committee voted unanimously to recommend approval of Luxturna, a gene therapy for the treatment of an inherited eye disease. The FDA usually follows the recommendations of its advisory committees, and a decision is expected in January 2018. An approval would make this the first FDA-approved gene therapy for an inherited disease (the FDA has recently approved two gene therapies for the treatment of certain forms of leukemia and lymphoma). Luxturna has been studied in two Phase I trials and a Phase III trial, showing both safety and efficacy, including improvements in functional vision. These studies continue to follow patients treated with the therapy, some as early as 2007.

Stem cell gene therapy shows positive results in clinical trials for an inherited leukodystrophy

- Earlier this month, the *New England Journal of Medicine* published a study of hematopoietic stem cell gene therapy for the childhood cerebral form of X-linked adrenoleukodystrophy (X-ALD). NTSAD Scientific Advisory Committee member Dr. Florian Eichler was the first author.

- This phase 2-3 study for safety and efficacy treated 17 boys (X-ALD affects mostly boys). It used gene therapy to treat hematopoietic (blood) stem cells from affected boys, which were then returned to the patients. Two patients died after treatment, one from progression of disease and one from complications of the transplant.

- The remaining patients showed stabilization of disease, measured by a neurologic function scale specific to cerebral X-ALD, though 1 patient had a small increase in score due to a seizure. 12 of the 17 patients had stabilization of brain MRI findings,



*Wishing our friends at **Canavan Research Illinois** a successful evening gathering together to raise funds for Canavan Research on October 21st in Chicago, Illinois!*

with limited progression seen in the remainder.

- Ongoing studies with larger patient populations and longer follow up are planned to confirm these findings.

This technology is being used by Dr. Joe Anderson and his group at UC Davis in studies for GM2. Dr. Anderson discussed this approach as part of a panel discussion on gene therapy at the Research session at the 2017 Annual Family Conference in Dallas, TX. Revisit what was discussed **here .*

Prospective natural history in GM1 and GM2 gangliosidoses

Dr. Jeanine Utz and Dr. Chester Whitley with their team recently published findings from their prospective natural history study in the journal *Molecular Genetics and Metabolism*. They followed 23 children, 8 with infantile GM1, 9 with Infantile Tay Sachs, and 6 with infantile Sandhoff.

- Overall, they found that children with the diseases often show decreased muscle tone by 6 months of age and severe impairment of motor skills by 12 months. The development of seizures and swallowing difficulties often occurred by 18 months. Using well-established developmental scores, they showed that most children reach the floor of this testing between 20 to 28 months of age.

- Among these groups, a few symptoms were unique to children with GM1 gangliosidosis, including scoliosis, kyphosis, and changes to the shape of the vertebral bodies.

- The authors suggest that overall survival may be a useful clinical outcome in future clinical trials for the infantile forms of these diseases.

ENZYVANT

Enzyvant Initiates Farber Disease Natural History Study

The Farber Disease Natural History Study has officially started! The goal is to learn more about the natural course of Farber disease, and anyone diagnosed with Farber disease is eligible.

Farber disease is a rare lysosomal storage disease caused by mutations in the *ASAH1* gene, resulting in deficiency of the lysosomal enzyme acid ceramidase. This deficiency leads to the accumulation of the pro-inflammatory sphingolipid ceramide, and a macrophage-driven inflammatory process causing the development of typical clinical symptoms.

The three cardinal symptoms of Farber disease are:

- Joint contractures or arthritis
- Subcutaneous nodules
- Weak or hoarse voice

Read the full press release **here** .

Sunday, October 29, 2017
12:00 p.m.
Our Heritage and Our Health: Ashkenazi Jewish Genetic Diseases and the Founder Effect

Learning about your heritage is a beginning. All around the world distinct ethnic groups have been identified as having increased risks for particular genetic diseases. In the Ashkenazi Jewish population, several such inherited diseases are known. These include Gaucher disease, cystic fibrosis, Canavan disease, Bloom syndrome and others. To learn more about genetic diseases among persons of Ashkenazi Jewish descent, please attend this complimentary presentation. Visit the event's Facebook page here.

Location:
Temple Emanuel
7 Haggetts Pond Road
Andover MA

Guest Speaker
Gary S. Frohlich, MS, CGC
Senior Patient Education Liaison
Sanofi Genzyme

2001 Beacon Street
Suite 204
Boston, MA 02135
(617) 277-4463 | info@ntsad.org
www.NTSAD.org

www.NTSAD.org