



national tay-sachs & allied diseases association RESEARCH REVIEW | July 14, 2017

RESEARCH INITIATIVE: PROGRESS UPDATES

NTSAD's research grantees are required to file progress reports every six months. The progress reports below are from researchers who were awarded grants in the past two years. We have briefly summarized their research for you here.



Novel combined gene/cell therapy strategies to provide full rescue of the Sandhoff pathological phenotype

*Principal Investigator: Angela Gritti, PhD
San Raffaele Scientific Institute, Italy
San Raffaele Telethon Institute*

The goal of this study is to evaluate gene and cell therapy approaches in the mouse model of Sandhoff disease (SD). Specifically, this study is comparing 3 therapeutic methods 1) direct intracranial lentiviral gene therapy, 2) neural stem cell transplantation (with or without gene correction of cells), 3) and bone marrow transplantation (BMT). These therapies will initially be tested individually and subsequently in combination. The investigators identified 3 milestones to be completed during the first 6 months of the project.

Progress has been made on each milestone:

1. To optimize BMT in neonatal SD mice.
2. To generate high titer lentiviral vectors expressing mouse hexosaminidase genes.
3. To optimize vector transduction of neural stem cells (NSCs).

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Development and Validation of an MS-MS Method for the Detection of Hexosaminidase Deficiency in Tay-Sachs Disease

*Principal Investigator: Denis Lehotay, PhD,
Queens University*

The aims of the project are to develop a mass spectrometry-based method for rapid screening of babies with Tay-Sachs or Sandhoff disease using dried blood spot (DBS) samples collected as part of the routine newborn screening, usually within the first week of life.

The investigators looked at the [enzyme assay](#) protocol used for measuring hexosaminidase. In examining the enzyme assay conditions, they realized that the conditions that were used in their earlier publication describing the assay to detect Sandhoff disease in northern Saskatchewan did not work for samples from patients with Tay-Sachs disease. So, they examined every aspect of the earlier assay, and embarked on re-developing an assay that will work in the detection of both Tay-Sachs and Sandhoff patients. This work is essentially complete.

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Identifying Novel Therapeutics for Treating GM2 Gangliosidoses

Principal Investigator: Beverly L Davidson, Ph.D., Children's Hospital of Philadelphia (CHOP)

The drug Miglustat (approved for Gaucher disease in 2002) does not cross the blood-brain barrier to an extent that could mediate benefit in a clinical trial in patients with late onset Tay-Sachs disease. In this study, they are using a powerful drug discovery approach to identify FDA approved drugs that have improved brain penetrance while simultaneously share the same efficacy as Miglustat.

They have submitted 49 samples to the University of Iowa, Genomics division for high-throughput RNA-sequencing. These samples represent 7 donors treated with the three drug treatments and controls at two different doses.

Next Steps: They will query the LINCS database with the RNA-seq data, identify drugs and validate hits over the next 4-6 months. Importance: These important preliminary studies will help identify additional, brain penetrable drugs that may find use in substrate reduction therapy for the gangliosidoses.

Rapid Identification of New Biomarkers for the Classification of GM1 and GM2 Gangliosidoses: A HNMR-linked Metabolomics Strategy

Principal Investigator: Martin Grootveld, PhD, Leicester School of Pharmacy, De Montfort University, UK (one year study)

The objective of this study is to identify biomarkers of GM1 and GM2 in plasma, CSF (cerebrospinal fluid), and/or urine that have been sampled repeatedly from affected individuals over time. This will contribute to an overall goal of a greater understanding of disease pathogenesis as well as identification of potential drug targets. The study is utilizing nuclear magnetic resonance (NMR)-linked metabolomics to screen for biomarkers in samples from GM1 and GM2 patients followed by advanced multidimensional datasets to extract detailed information. The study aims to further identify and validate potential NMR targets by liquid chromatography-mass spectrometry (LC-MS), a technique that has a higher level of sensitivity.

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PLEASE TAKE NOTE!

There has been an article from 2011 circulating on Facebook regarding a Dr. Burton Feinerman and his claims to have "successfully" treated children with Tay-Sachs with his version of stem cell therapy. His treatments did not prove to be effective and the results have never been published in a peer-reviewed journal.



There is a lot of information on the internet and many articles. If you come across an article that appears hopeful, please [contact NTSAD](#) and we will check the legitimacy of it BEFORE you share them. We have an extraordinary [Scientific Advisory Committee](#) and advisors who are experts in the field of lysosomal and leukodystrophy diseases who can confirm the legitimacy of the science in an article. We're here to help you sort through it all. Every step of the way.

**Additional NTSAD RESEARCH
Off-cycle Grant Announcements**

The following small grant awards, adding up to \$42,000, were made to supplement existing NTSAD-funded research outside of our annual Request for Proposal process.

I) Complete safety study in non-human primates. Principal Investigator: Miguel Sena-Esteves, PhD, University of Mass. Medical School. Funded by Vera Pesotchinsky Fund, Katie & Allie Buryk Fund, LOTS Education & Research Foundation

II) Purchase lambs. Heather Gray-Edwards, PhD, Auburn University, received an NIH grant for “Global AAV-gene therapy of Tay-Sachs disease in sheep” to identify biomarkers in sheep and to test a new bicistronic vector construct, but she did not receive funding to purchase the sheep. These funds will therefore supplement her NIH grant.

III) Maintain Late Onset mouse model animal colony for short-term period. Principal Investigator: Eric Sjoberg, PhD, Orphi Therapeutics. The mouse model was created through a previous Research Initiative grant. This grant will be funded by the Katie & Allie Buryk Research Fund of NTSAD.

Third Annual Million Dollar Bike Ride

Update: Team NTSAD, together with a grant from NTSAD's Research Initiative, met the minimum \$20,000 fundraising goal. NTSAD will receive a matching grant from the Penn Orphan Disease Center and then we'll announce an RFP for a new \$40,000 research grant. What a great way to get more resources for research. **Thanks, Team NTSAD!**



Team NTSAD (left to right): Miguel Sena-Esteves, PhD, Heather Gray-Edwards, PhD, David Bradbury, Don Levick, MD, Staci Kallish, DO, Meredith Margolis, PhD, Allison Bradbury, PhD and NTSAD Research Initiative Chair, Jim Margolis, PhD, and Mary Levick, MD

NTSAD Day of Hope 2017

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BONFIRE

The **Seventh Annual Day of Hope** is officially on Saturday, September 16th, but events to celebrate and raise awareness and funds for RESEARCH take place anytime from summer through October.

Visit [NTSAD's Day of Hope page here](#) for ideas and ways to support the RESEARCH.

You can also buy a [2017 Day of Hope t-shirt here](#) and support research at the same time!

Susan Kahn, Executive Director
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