



National Tay-Sachs & Allied  
Diseases Association, Inc.

Friday,  
OCTOBER  
14, 2016  
**NTSAD  
Monthly  
Research  
Review**

## RESEARCH PROGRESS: UPDATES

There are ten projects NTSAD currently funds that are in progress. Each one holds promise as we work toward finding treatments for Tay-Sachs, GM1, Sandhoff and Canavan diseases. Progress in one may impact progress in other neurodegenerative diseases as well! Below are updates for two projects and to the right is the list of the other research that is ongoing and funded by NTSAD.

Read more about these grants that we currently fund and those we have funded in the past [here](#).

### Interim Progress Report: "Lectin-assisted transnasal delivery of corrective enzyme for GM1 gangliosidosis"

Investigators: David N. Radin, PhD, Carole L Cramer, PhD, BioStrategies, LLC, and Alessandra d'Azzo, PhD, St. Jude's Research Hospital

- The current focus of this study is to compare intravenous and trans-nasal delivery of a RTB-fusion protein with  $\beta$ -galactosidase as a means to circumvent the blood brain barrier and deliver the enzyme to the brain.
- A key limitation in performing these experiments has been the number of GM1 affected (also known as  $\beta$ -Gal<sup>-/-</sup>) mice that are available for testing. Because GM1 is a recessive disease, carrier, also known as heterozygous, mice ( $\beta$ -Gal<sup>+/-</sup>) are used for breeding and should statistically produce 25% affected GM1 mice. However, lower yields of affected GM1 mice, often less than 10%, are limiting the number of mice to be used in studies.
- Over the last 4 months, significant efforts have been made to increase the GM1-mouse breeding colony. One way to improve breeding colonies is to treat GM1 affected males to get them healthy and old enough to use as breeders. By breeding an affected male ( $\beta$ -Gal<sup>-/-</sup>) to a carrier female ( $\beta$ -Gal<sup>+/-</sup>), the ratio of affected animals in each litter is increased. Using this strategy, the researchers have produced greater yields GM1 affected mice per litter.
- Going forward, researchers will analyze impacts on brain GM1 levels and disease phenotype in GM1 mice following longer-term  $\beta$ -gal:RTB intravenous and trans-nasal administration

## CURRENT RESEARCH funded by NTSAD

Identifying Novel Therapeutics for Treating GM2 Gangliosidosis  
*Children's Hospital, Philadelphia, PA*  
*Investigator: Beverly Davidson, PhD*

Novel combined gene/cell therapy strategies to provide full rescue of the Sandhoff pathological phenotype  
*San Raffaele Institute, Italy*  
*Investigator: Angela Gritti, PhD*

Rapid Identification of New Biomarkers for the Classification of GM1 and GM2 Gangliosidosis: A HNMR-linked Metabolomics Strategy  
*Leicester School of Pharmacy, De Montfort University, UK*  
*Investigator: Martin Grootveld, PhD*

LOTS Registry and Repository  
*Mass General Hospital, Boston, MA*  
*Investigator: Florian Eichler, MD, PhD*

Defining the Natural History of Canavan Disease through Development of an International Registry  
*New York University, New York*  
*Investigators: Heather Lau, MD, PhD and Paola Leone, PhD*

Development and Validation of an MS-MS Method for the Detection of Hexosaminidase Deficiency in Tay-Sachs  
*Queens University, Canada*  
*Investigator: Dennis Lehotay, PhD*

The Hexosaminidase A Variants of Unknown Significance (HAVUS) Project  
*Emory University, Atlanta, GA*  
*Investigator: Karen Grinzaid, MS, CGC, CCRC*

Lipid biomarkers of Tay-Sachs disease  
*Auburn University, AL*  
*Investigator: Doug Martin, PhD*

## Interim progress report: "IND-enabling studies of AAVrh8-Hex gene therapy for Tay-Sachs Disease"

Investigator: Miguel Sena-Esteves, PhD, University of Massachusetts Medical, Worcester, MA

- Investigational new drug (IND) enabling studies are conducted at the highest level of rigor in order to meet strict FDA requirements to move forward to clinical trials. For gene therapy one of those high standards is preparing viral vectors at designated Good Manufacturing Practice (GMP) facilities, which comply to specific guidelines as related to environmental conditions, manufacturing procedures, and compliance.
- The AAVrh8 vectors encoding Hexosaminidase to be used in mouse and non-human primate IND-enabling studies for Tay-Sachs disease are being manufactured at the same GMP facility, Institute for Regenerative Medicine at UC Davis, where the final human vectors will be made. Due to unexpected AAV production issues, the final mouse studies, expected to start in March 2016, were not initiated until September 2016.
- To date >20 mice of the 90 total that are necessary (75 GM2 and 15 normal) have been enrolled in the latest IND-enabling studies. With expansions of the GM2 mouse colony, it is expected that enrollment will be completed in December of 2016.
- Based on the endpoints defined in the IND-enabling study, GM2 mice treated with AAV at 4 weeks of age will be kept up to 5 months of age. It is expected that the treatment phase of the study to be completed by the end of April 2017 and subsequent biochemical studies will be completed by September 2017.

### WHY DOES IT TAKE SO LONG?

It is difficult to see the headlines of gene therapy trials starting for other lysosomal storage diseases and begs the question, "What is taking so long for the gene therapies for Tay-Sachs and GM1 to get started?" "Is it a matter of money?"



Unfortunately, there can be many unforeseen challenges on the roadmap to a treatment. Two examples were reported in today's progress updates, e.g., breeding a sufficient number of affected mice and manufacturing gene therapy vectors. While frustrating, ultimately our hope is that this work will lead to an effective and safe treatment.

[Here is a link](#) to an article from the Muscular Dystrophy Association that addresses the challenges in finding treatments for neuromuscular diseases.

### MEET VERONICA

Veronica Huang, PhD, has joined NTSAD in the role of Science Communications and Outreach Intern. The NTSAD Board, over the last couple of years, has discussed the need for adding science staff to bring needed expertise as well as the ability to do work that our expert volunteers do not have time to do. After exploring various options, the decision was made to start incrementally by hiring a Science Communications and

### CLINICAL TRIAL READINESS STUDIES

In addition to pre-clinical animal studies, such as the research reported here, NTSAD has funded clinical trial readiness grants, including natural history studies.

Natural history studies are essential for understanding the range of manifestations and progression of rare diseases. According to the NIH, "Well-conducted natural history (NH) studies can yield information on biomarkers and other correlates of clinical outcome. Obtaining maximum value to support drug development programs depends on conducting these NH studies early, long before potential therapeutic agents are identified for development. Comprehensive, good quality NH studies designed with an eye toward supporting drug development programs can avoid some of the common problems that lead to stalled, slow, or inefficient drug development for rare diseases."

Both of the NTSAD-funded natural history studies awarded in 2015 for [Late Onset Tay-Sachs/Sandhoff](#) and [Canavan disease](#) are now listed on the ClinicalTrials.gov database, which is maintained by the NIH.



### 2016 Day of Hope

Thank you to all the families who supported the 2016 Day of Hope! Thanks to them we can add more than \$35,000 to research dollars raised this year!

The Artinian Family & Friends  
The Cornett/Watson Families  
The Gropp Family & Friends  
The Kenny Family & Friends  
The Manning Family & Friends  
The Ohle-Rodriguez Family

Outreach Intern in a part-time role for nine months.

Veronica has a PhD in Biochemistry from Boston College and did a Postdoc in Molecular and Cell Biology at UC Berkeley. Her primary responsibilities will involve the following areas:

1. Key resource for scientific knowledge about diseases and therapeutic approaches
2. Research Communications
3. Research Initiative Request for Proposal (RFP) process

Welcome, Veronica!

The Pounds Family & Friends  
The Ronaldson Family  
The Salazar Family  
Tackle for Tay-Sachs Group  
The Urban Family & Friends  
The Van Skoyck Family  
The Vongrej Family & Friends  
The Westerlund Family

And the many individuals who made and continue to make gifts of HOPE for research!

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