



## **University of Pennsylvania Orphan Disease Center Million Dollar Bike Ride Grant Award for Team NTSAD**

Team NTSAD and the NTSAD Research Initiative raised \$20,000 that was matched by UPenn's Orphan Disease Center for a fourth year. In total, \$160,000 in grants have been awarded to researchers since 2014's First Annual Million Dollar Bike Ride. We're pleased to share below the recipient of the award and their project summary.

### **Brain MRI signatures in infants with infantile forms of GM-1 and GM-2**

Principal Investigator, Igor Nestrail, MD, PhD, University of Minnesota

#### Project summary:

The infantile forms of gangliosidoses (GM) type 1 and 2 are fatal neurodegenerative disorders with a rapid progression. The severe neurological deterioration leads to death within the first years of life. Comprehensive meaningful disease markers for children with infantile gangliosidoses are critically needed to track the brain disease very early in life. If sensitive markers that correlate to disease outcomes within the central nervous system (CNS) are identified, the monitoring of these may assist in a detailed description of the rapid CNS disease progression, and in determining the response effects of new CNS-directed therapeutic approaches that are currently being developed to be tested for GM1 and GM2 clinical trials.

Our goal is to establish sensitive MRI markers that will be utilized in future clinical trials of gangliosidoses. The primary objective is to describe the trajectory of brain abnormalities of GM1 and GM2 patients within the first two years of life. We will analyze the MRI data of normally developing infants (less than 2 years of age) and of age- and gender-matching GM1 and GM2 children whose scans were previously acquired on the hospital 3T MRI system. By comparing MRI data of GM1 and GM2 children with new MRI data to be acquired on age-matched healthy controls, we will characterize brain differences among groups at a very young age when the brain disease is not fully expressed on the MRI. This critical MRI data in very young GM patients is currently not available. We will focus on quantitative MRI markers of brain volumes, myelin content, and white matter microstructural integrity, and will evaluate their sensitivity for detection of brain abnormalities in infantile forms of GM. To determine clinical relevance of MRI markers we will examine the association of brain abnormalities with neurological outcomes in children with infantile GM utilizing neuropsychological assessments previously obtained.

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## GM2 Tay-Sachs & Sandhoff Patient Insights Network (PIN)

We're excited to announce a way families and adults can play an active role in research mirroring what has been done for the GM1 and Canavan communities. Sharing the patient experience is exceptionally important to the process of drug development and treatments.



INVITAE

Stay tuned for the official launch.



## Rare Disease Day: February 28, 2018

### Why should you show you care?

- Rare Disease Day takes place on the last day of February each year to raise awareness about rare diseases and the impact on patients' lives.
- 1 in 20 people will live with a rare disease at some point in their life.
- There is no cure for the majority of rare diseases and many go undiagnosed.

Join NTSAD and the rare disease community. Show your rare. Show you care. Learn how [here](#).

## UPDATE: NTSAD and Cure Tay-Sachs Foundation (CTSF) partner for the 2018 Request for Proposals

Fourteen pre-applications were received from investigators in nine countries. These proposals range in topics and include basic research, pre-clinical drug repurposing, biomarkers, drug screens, and natural history.

There are proposals for GM1, GM2 and Canavan. These pre-applications will be reviewed by NTSAD's Scientific Advisory Committee and Corporate Advisory Council members, and

## FDA approves novel gene therapy to treat patients with a rare form of inherited vision loss

Every success in gene therapy paves the way for other gene therapy treatments down the road.

"Luxturna is the first gene therapy approved in the U.S. to target a disease caused by mutations in a specific gene. Luxturna uses a naturally occurring adeno-associated virus, which has been modified using recombinant DNA techniques, as a vehicle to deliver the normal human RPE65 gene to the retinal cells to restore vision."

<https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm589467.htm>

then a limited number will be invited to submit a full application.

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### **Intravenous administration of scAAV9-Hexb normalizes lifespan and prevents pathology in Sandhoff disease mice**

Niemir N, Rouvière L, Besse A, Vanier MT, Dmytrus J, Marais T, Astord S, Puech JP, Panasyuk, Cooper JD, Barkats M, Caillaud C.

Adeno-associated virus (AAV) gene therapy has shown much promise for inherited diseases. Most recently, non-invasive delivery routes such as intravenous injection of AAV have been evaluated in a number of inherited diseases. In fact, clinical trials are underway utilizing intravenous AAV gene therapy for MPSIIIA and Spinal Muscular Atrophy. In January of 2018 a paper was published detailing a study evaluating intravenous AAV gene therapy in a mouse model of Sandhoff disease. The abstract is below.

- Niemir et al evaluated the long-term therapeutic efficacy of intravenous gene therapy in the mouse model of Sandhoff disease (SD) using an AAV9 vector expressing Hexosaminidase b (AAV9-Hexb), the enzyme deficient in SD.
- SD mice were treated by intravenous delivery of scAAV9-Hexb during the neonatal period (Day 1 - Day 2) with a dose of  $3.5 \times 10^{13}$  vector genomes (vg)/kg.
- Treatment with AAV9-Hexb vector led to a significant increase in the enzyme activity of Hex A and B enzymes compared to untreated SD mice. In the forebrain, the activity of Hex A reached ~ 15% of normal and in the liver Hex A activity was ~ 10% of normal.
- The enzyme activity was sufficient to almost completely prevent the accumulation of GM2 storage material in the forebrain of treated SD mice, but less pronounced reduction was seen in the cerebellum.
- Treated SD mice showed an improvement in neuropathology including less storage material in neurons, normalization of lysosomal dysfunction, and reduction in neuroinflammation.
- Compared to the average 750 day lifespan of WT mice, untreated Hexb<sup>-/-</sup> mice have a significantly shorter average lifespan of ~ 117 days. SD mice treated with AAV9-Hexb had a significantly extended lifespan that was comparable to that of WT mice (mean >750 days). AAV9-injected SD mice also demonstrated phenotypical and behavioral improvements.

The entire article can be found [here](#).

### **WORLD Symposium Meeting** February 5-9,201, San Diego, California

The Lysosomal Disease Network's (LDN) Council of Patient Advocates (COPA) will meet on **Monday, February 5, 2018 from 9:00 AM to 12:00 PM** for a morning workshop:  
<https://www.worldsymposia.org/worldsymposium-program-events-lysosomal-disease/lysosomal-disease-network/>

This year's COPA Workshop will consist of small working groups (8-10 persons/group) aimed at identifying the most important research questions for your area of interest. All representatives of lysosomal disease patient advocacy groups, patients, and other interested parties are invited to attend. There is no cost to attend this session. Click here to go to the LDN website to RSVP and for further information.

On Tuesday February 6 – Thursday February 8<sup>th</sup> researchers, physicians, industry partners, and advocacy groups will participate in a scientific program progressing from basic and bench research to translational research and clinical research.

The 2018 Preliminary Program can be found here:

<https://www.worldsymposia.org/worldsymposium-program-events-lysosomal-disease/program-lysosomal-research-care/>

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