



NTSAD's Research Initiative Process

NTSAD's annual Request for Proposal process reaches out to scientists and investigators around the world to attract the best and most relevant research grant proposals for funding consideration. This year, we received 16 pre-proposal applications and invited seven of them for full applications. The grants are available for up to two years and \$80,000. Most scientists seek to use NTSAD's grant award to develop data that supports applying for more significant funding to further their research. It is a competitive process. Our goal is to advance research toward treatments for all our diseases.

NTSAD is proud to make three grant awards to the talented investigators and their institutions. Information about their grants is described below. This year's grants are for Sandhoff/Tay-Sachs and GM-1 diseases, our goal is to advance research towards treatments for all of our diseases. We always welcome the opportunity to co-fund research grants whenever our interests overlap with other foundations equally committed to finding a treatment for these diseases. The success in other diseases (such as Cystic Fibrosis and Duchenne Muscular Dystrophy) has proven that it takes collaboration wherever possible for maximum efficiency and to attract industry, to get to a treatment.

NTSAD has now funded over \$4 million in grants with over \$30 million in follow-on funding (updated from over \$20 million with new NIH grant awards in the past two years). Over the last 15 years, half of the funding has gone to investigators involved with the Tay-Sachs Gene Therapy Consortium, and the other 50% is diverse by disease (i.e., LOTS, GM1 and Canavan) as well as type of grant (e.g., newborn screening, biomarkers, basic research, drug screen, natural history, etc.) An updated list of NTSAD-funded grants from 2002-2018 can be found [here](#).

In addition to funding research grants, we work to establish contacts with biotech / pharma companies working in gene therapy, rare neurological diseases, carrier screening, and other areas of overlap with NTSAD's diseases. As a result, NTSAD is contacted by representatives of these companies as well as consultants exploring possible therapeutic programs in our diseases. In the last month alone, I have spoken with four organizations who have pre-clinical drug development programs in Canavan disease or who are exploring starting a program in Canavan disease! As always, I mention to these companies the other foundations who overlap in our disease interests so collectively we can represent the whole disease community. I look forward to soon joining the Canavan Foundation and Canavan Research Illinois for an all-day meeting in Boston with one of these companies.

I look forward to a day when we have treatments for all! ~ Sue Kahn, Executive Director

NTSAD Research Initiative 2018 Grants

Role of Plasma membrane-ER Contact Sites in GM1-mediated Neuronal Cell Death

Principal Investigator: Alessandra D'Azzo, PhD
St. Jude's Children's Research Hospital



GM1-gangliosidosis is a neurodegenerative lysosomal storage disorder that presents with a spectrum of severity. It is caused by genetic mutations in the *B-Gal* gene that affect the expression and/or function of the *B-Gal* enzyme, leading to impaired degradation of one of its major target substrates, GM1-ganglioside (GM1). GM1 is particularly abundant in the nervous system, because it is a major component of neuronal outer membranes.

Thus, the direct consequence of *B-Gal* deficiency is the relentless and progressive accumulation of GM1 in lysosomes and other subcellular membranes, which leads to the death of neurons, neuroinflammation and neurodegeneration. A deep understanding of the cellular and molecular events downstream of *B-Gal* loss of function and GM1 accumulation may give us the chance to identify alternative ways to tackle the disease therapeutically or provide us with appropriate end points to assess the extent of functional reversal of phenotypic abnormalities after treatment.

With these studies we plan to evaluate in the mouse model of GM1-gangliosidosis how GM1 accumulation affects the membrane contact sites formed between cellular components and the neuronal outer membranes. In particular, we will analyze the protein and lipid components of these membrane contact sites in order to assess whether they are altered by abnormal local concentrations of calcium ions caused by the accumulated GM1. This will help us to understand the role of calcium and calcium-binding proteins at these contact sites in causing the damage to neurons. We will perform therapeutic proof of principle studies aimed to inhibit the function of a specific calcium-binding protein, which, if successful, may set the foundation for a novel therapeutic approach for the treatment of this lysosomal disease in children.

Role of microglia in Sandhoff disease pathology

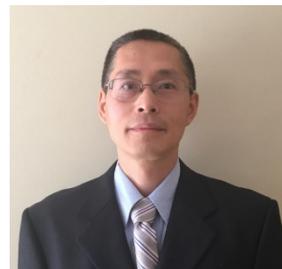
Principal Investigator: Tony Futerman, PhD
Weizmann Institute of Science (Israel)



- Microglia are inflammatory cells found in the central nervous system. They are known to play a role in the pathophysiology of Sandhoff disease but the inflammatory pathways activated are not known.
- This study aims to better understand these pathways to delineate potential targets for therapeutic intervention in Sandhoff and Tay-Sachs diseases.
- This lab has a record of success identifying pathways that might be amenable to therapeutic intervention in other lysosomal storage diseases.

Oligosaccharide Biomarkers for Disease Progression and AAV Therapeutic Efficacy in GM1 Gangliosidosis

Principal Investigator: Xuntian Jiang, PhD
Washington University School of Medicine (St. Louis, MO)



A major challenge for developing treatments for GM1 gangliosidosis (GM1) disease is difficulty in evaluation of efficacy. This is complicated by limited patient numbers, and variability in age, severity, and stage of disease progression. Biomarkers that reflect disease status could provide a valuable surrogate endpoint for assessment of treatment effect and reasonably predict clinical benefit. We have identified an oligosaccharide (carbohydrate whose molecule is composed of a relatively small number of monosaccharides) biomarker that is significantly elevated in the urine, cerebrospinal fluid (CSF) and plasma from GM1 patients and brains from GM1 cat model. This biomarker in GM1 cat brains was reduced in response to gene therapy. These results suggest that the oligosaccharide is a sensitive biomarker for disease severity and progression and for assessing treatment efficacy. In this proposal, we will identify the structure of the oligosaccharide biomarker and evaluate this marker as a surrogate outcome measure of treatment for GM1. This project will provide a much-needed tool for assessing GM1 disease severity and therapeutic efficacy.

Second GM1 Research Meeting Friday, October 5, 2018 Hotel Irvine, Irvine, California



The First GM1 Research Meeting was held at NTSAD's Annual Family Conference in 2016. The 2nd GM1 Research meeting, organized by Cure GM1 Foundation, will include talks by key opinion leaders, experts in lysosomal storage diseases, and pioneers in gene therapy.

The **Cure GM1 Foundation** is dedicated to catalyzing research and drug development for GM1 Gangliosidosis. **NTSAD's** mission also focuses on funding and fostering GM1 research.

NTSAD and Cure GM1 are offering a limited number of travel stipends to attend the GM1 Symposium on Friday, October 5, 2018. Up to \$1000 will be reimbursed per family to cover the expenses of travel/flight and one-night hotel after receipts are submitted to NTSAD and Cure GM1 and after the Symposium. Costs for food, beverage, and entertainment will not be reimbursed. The scholarships will be offered on a first come first serve basis. (If the expense of travel and one-night hotel does not exceed \$1000, only the total of the expenses will be reimbursed.)

To apply for a stipend, please email diana@ntsad.org and christine@curegm1.org including your name, address, best phone number to reach you, your loved one's name, diagnosis, diagnosis date, and their age, along with a brief description of what you hope to learn at the symposium meeting.

Please submit your requests in July and August so that awards (up to a total of \$6,000) can be made by September 1, 2018.

Read more about the meeting [here](#).



trend.community
TURNING ANECDOTES INTO EVIDENCE™

NTSAD is partnering with the Cure Tay-Sachs Foundation (CTSF) to get a better understanding of a particular aspect of the patient experience regarding off-label use of a drug that has yet to be approved or proven effective for our group of diseases.

We encourage families and individuals who are or have used Tanganil to please sign up for the TREND Community here.

Tanganil for Tay-Sachs & Sandhoff
on Facebook [here](#)

**TREND Community GM1 and GM2
Tanganil Health Initiative**

Join the **GM1 & GM2 Tanganil Health Initiative** on the TREND Community platform (participation is free). Go to www.trend.community, scroll to the bottom and request an invite.

We're excited to announce the official kick-off of the 2018 Eighth Annual Day of Hope for research!

Families come together once a year to raise funds solely for research. They host events leading up to the official date, Saturday, September 15, 2018.

Last year, families had t-shirt campaigns, garage sales, motorcycle rides, scavenger hunts, sports tournaments, community parties, hikes and lemonade stands from August through October. Thanks to their amazing commitment we raised over \$100,000 for research!!!



INVITAE

Patient Insights Network (PIN) is a platform offered by Invitae to gather information about the patient experience within the rare disease space in order to provide researchers and companies anonymous data that could help them with future drug development. It is also a way to be a part of a greater community through shared patient experiences.

NTSAD partners with the Cure GM-1 Foundation on the **GM1 PIN**, and with Canavan Research Illinois and Canavan Foundation on the **Canavan PIN**.

We encourage your participation!



One way you can support this global effort is to purchase an NTSAD t-shirt to wear proudly on Saturday, September 15, 2018. Visit this page [here](#) to place your order by July 30th.



Susan Kahn, Executive Director
Blyth Lord, President, NTSAD Board
Staci Kallish, DO, Vice President, NTSAD Board
Fran Platt, PhD, Chair, Scientific Advisory Committee
Allison Bradbury, PhD, Research Initiative Committee

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

www.NTSAD.org