



## NTSAD Annual Family Conference: Research Session Overview

The Research Update session at the NTSAD Annual Family Conference offers families and other attendees the opportunity to hear directly from the professionals the news relating to therapies in development for GM2 (Tay-Sachs, Sandhoff), GM1 and Canavan diseases.

View the general Research Session [here](#).

2018 Annual Family Conference

Research Updates

Jacksonville, FL, April 2018



NTSAD's Vice President, Staci Kallish, DO, opened the session with an overview of NTSAD's Research Initiative goals, process, and progress to date. (See her introduction slides [here](#).)

Below are the summaries of what was discussed including the breakouts that followed.

### Steve Walkley, PhD, DVM NTSAD Scientific Advisory Committee Member Albert Einstein Medical College

Steven Walkley, PhD, gave the keynote address, titled, "Neurometabolic Diseases: A New Era Is Upon Us". In this talk, he highlighted three themes:

1. Modern studies in cell biology are ushering in new insights into how cells work in both health and disease.
2. These new insights in turn are providing new clues as to why certain neurometabolic diseases cause brain dysfunction and are suggesting new avenues toward treatment.
3. There is also a growing realization, one particularly prominent in the rare disease community, that collaboration is the way forward for successful development of therapy.



## New Initiatives to Help Research

Two new initiatives were introduced to encourage participation in the name of research and future drug development. If you'd like more information or have questions about either, please contact the office.



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.

NTSAD and CTSF have asked **TREND** to conduct a Health Initiative to document and analyze GM2 and GM1 patient experiences with off-label use of Tanganil, available without a prescription from Europe and indicated for the treatment of positional vertigo (dizziness). NTSAD and the Cure Tay-Sachs Foundation will help facilitate the Health Initiative by introducing TREND Community to their respective members who either have, or are caretakers for, those suffering from GM1 and GM2.

NTSAD, CTSF and TREND are nearing completion of their agreement so we can move forward with this program.

**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 is also partnering with the Cure Tay-Sachs Foundation (CTSF) on a soon-to-be launched PIN for all forms of GM2 Tay-Sachs and Sandhoff.**

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!

# Research Session Breakouts by Disease

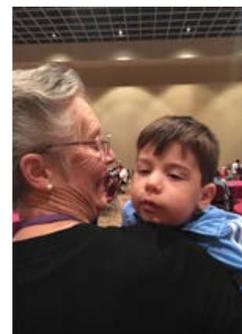
## GM2 (Tay-Sachs, Sandhoff) - Infantile and Juvenile

**Cynthia Tifft, MD, PhD** presented her work on the development and the use of Human "Brain in a Dish," which takes cells from a Sandhoff patient, generating Induced Pluripotent Stem Cells (IPS), and then give rise to neuron cells. She proposed using this as the final pre-clinical test to provide data on efficacy for the FDA. Read a recent article [here](#).

**Miguel Sena-Esteves, PhD** presented an overview of the history of the Tay-Sachs Gene Therapy Consortium work that has been done dating back to 2007. (See slides [here](#).) He reviewed the lessons learned with the toxicity findings in 2012. He concluded by saying the research is complete in compliance with the plans developed with the FDA. The next steps are to move into manufacturing of the vector and prepare the protocol and plans for clinical trials in accordance with the FDA.

The speakers explained that the disease progression happens very early in development in utero. Screening plays an important role, both in promoting the addition of our diseases to newborn screening panels (though newborn screening is most likely to be approved once a treatment exists) as well as promoting carrier screening. Even once treatment exists, the idea of administering gene therapy in utero puts both the healthy mom and affected child at risk at the same time and would be dependent on knowing a child is at risk before birth.

As the speakers discussed, as Tay-Sachs occurs in cells throughout body, there is a need deliver the treatment to the brain and peripheral system. Work continues to evaluate both intravenous (IV) and intracranial methods of delivery as well as cerebrospinal fluid (CSF) delivery. The speakers also discussed that the adeno-associated virus (AAV) vectors, with both alpha and beta versions of hexosaminidase, positions within the cells separate from the chromosomes instead of integrating into the genome. The cells cross transfer the messaging to the lysosomes of other cells to produce the missing enzymes.



## Adeno-associated Virus (AAV) Delivery Routes: What are they?

### Intraparenchymal Delivery of AAV:

Injecting directly into the brain tissue

### Intra-CSF Delivery of AAV:

Injecting directly into cerebrospinal fluid (CSF)

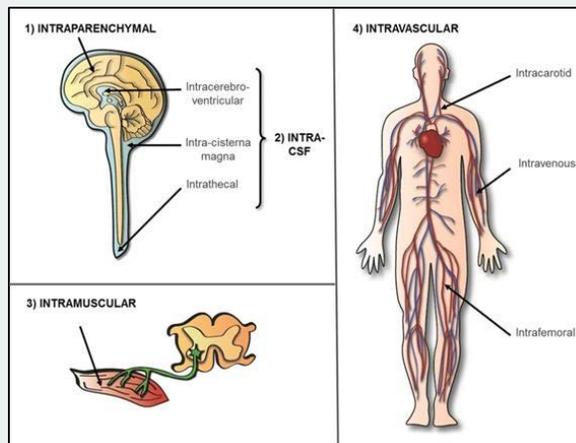
### Intramuscular Delivery of AAV:

Injecting directly into the muscles

### Systemic/Intravascular Delivery of AAV:

Delivery of AAV vectors directly into the blood stream

To read a full explanation of these delivery methods visit [NTSAD's website here](#).



## GM1 Gangliosidosis

**Doug Martin, PhD** spoke about his GM1 gene therapy program. (See slides [here](#).) They have been treating via intracranial for a long time, with good success in cats (some have lived to 8 years and are still living, compared to 8 months in untreated cats). More recently they are looking at IV delivery but see less distribution to brain and spinal cord. The IV studies are in pre-IND stage and likely to be applicable for late infantile and juvenile. They are also looking at CSF delivery, which in the pre-IND stage and could be applicable for multiple forms of the disease. They have not seen toxicity in GM1 cats via any of these routes.



**Samantha Parker** shared the background information that **Lysogene** entered into a collaboration agreement with Auburn University (AU) and University of Massachusetts Medical School (UMMS) in 2015. The goal has been to combine Lysogene's translational and clinical expertise in gene therapy for CNS disorders with the unique design and preclinical expertise of UMMS and AU to test innovative AAV-based gene therapy approaches to treat GM1 gangliosidosis. Nonclinical studies are on-going in animal models. Lysogene is planning a first-in-human clinical trial to be initiated in 2019 at EU and US sites following successful completion of the nonclinical development program and availability of clinical grade drug product.



**Alessandra d'Azzo, PhD**, discussed the enzyme replacement therapy research program as she is a co-investigator with BioStrategies. (See slides [here](#).) Given the complexity of diseases, combinatorial therapies may be necessary. In their work to date, they have seen little enzyme in brain and spinal cord, although a lot of enzyme in liver and spleen with IV injection. They see better distribution in brain with intraventricular injection. They also see enzyme peripheral in organs with intranasal therapy in mouse models but seems promising when administration is successful.





## Canavan Disease

Dominic Gessler discussed the research progress and results of additional experiments to strengthen the case for Canavan gene therapy. See slides [here](#).

Dominic showed the comparison between healthy mice and treated mice looking at the brains and their gait, treated versus untreated. The results are hopeful and promising and even more so in light of the news of BridgeBio's interest in this Canavan gene therapy program. (See block to the right.)

Many of you have met Dr. Gao and / or Dominic Gessler, who works closely with Dr. Gao, on the Canavan gene therapy research when they have attended NTSAD's Family Conferences.

It was exciting to announce the news about BridgeBio's interest in advancing gene therapy for Canavan disease. Our patient advocacy contact, David Rintell, sent us this message to share:

"BridgeBio is honored to have licensed the Canavan Gene Therapy program developed by Dr. Guangping Gao. We will be working with Dr. Gao and UMass Medical School to move this forward as fast as the science and regulators will allow us to go. We are in the process of starting a subsidiary, Aspa Therapeutics, to house the program, and we will keep the Canavan community updated on our progress. Most of all, we look forward to getting to know you and this community, and learning from all of you as we go forward together."

David Rintell, Head of Patient Advocacy for Aspa, anticipates sharing updates at this time through all the Canavan patient organizations including NTSAD, Canavan Research Illinois, and Canavan Foundation.

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## Late Onset Tay-Sachs and Late Onset Sandhoff diseases

**Drs. Camilo Toro, MD, and Sarah Ying, MD**, asked the adults affected by Late Onset disease questions about the aspects of the disease that bother them most to understand what is most important to them as treatments are developed.



To share more information about your disease experience, be sure to register with the **GM2 Tay-Sachs and Sandhoff PIN** when it launches.

**Heather Gray-Edwards, PhD**, shared her progress working on a novel vector encoding both HexA and HexB genes which is ideal for treating adults. She is working mainly with the sheep disease model, which is closest to the Late Onset form of the disease. (See her slides [here](#).)

Learn more about the Jacob Sheep [here](#) and the ways you can support them!

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### **RARE Toolkits: A Guide to Gene Therapy**

This resource from our friends at Global Genes is informative and explains the process from its definition to the steps to get gene therapy into the clinic.

Download your electronic copy [here](#).



### **Celebrating the Moms of Gene Therapy**

An article highlighting mothers in the rare disease community that have taken action to move the needle for gene therapy research.

Read more [here](#).



### **2018 Million Dollar Bike Ride: Team NTSAD**

Our thanks to Meredith and Jim Margolis, and their friends, for representing NTSAD in the **5th Annual Million Dollar Bike Ride** in Philadelphia. We hope they had a terrific ride in the name of research!

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**Blyth Lord, President, NTSAD Board**  
**Staci Kallish, DO, Vice President, NTSAD Board**  
**Fran Platt, PhD, Chair, Scientific Advisory Committee**  
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