



NTSAD Annual Family Conference: Research Session

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. The main discussion and the breakouts will be recorded and made available on the NTSAD website following the conference. Below is a description of what we will be covering this year and the professionals who will be joining us.

We extend our thanks to the Mathew Forbes Romer Foundation for generously underwriting the Research Session.

Research Update Session Friday, April 13, 2018 | 9:00am to 12:15pm

The session will open with a brief update from NTSAD's Research Initiative by NTSAD's Vice President, Staci Kallish, DO. We are excited to have Steve Walkley, PhD, DVM from Albert Einstein Medical College in New York and an NTSAD Scientific Advisory Committee (SAC) member, join us to talk about recent advances, potential new therapies, and the importance of research collaboration between researchers and patient advocacy groups.



Following the opening talk, there will be four break-out groups focusing on GM2 (Tay-Sachs and Sandhoff), GM1, Canavan and GM2 Late Onset. Topics covered will include latest research updates and next steps, the continued importance of natural history studies, participating in the Patient Insights Network (PIN) for GM2, GM1 and Canavan and a new program called the TREND Health Initiative. Speakers will include Miguel Sena-Esteves, PhD*, Heather Gray-Edwards, PhD*, Cynthia Tiffet, MD*, PhD, Camilo Toro, MD, Doug Martin, PhD*, Samantha Parker, Alessandra d'Azzo*, and Dominic Gessler*. It is a wonderful opportunity to engage with the researchers, ask questions and learn more about their work. (*= researchers who have received NTSAD grant funding)

NTSAD Research Initiative Updates

Chris Stephens, MBChB
Massachusetts General Hospital
Team NTSAD 2017 Million Dollar Bike
Ride Grant Recipient

Identifying specific and sensitive aspects of disease (biomarkers) is important to measuring the success of a clinical trial. In Dr. Chris Stephen's work, he looked at correlation between eye movements and the progression of Late Onset Tay-Sachs and Late Onset Sandhoff diseases. This research was carried out with adults who traveled to MGH for the NTSAD-funded LOTS natural history study with Florian Eichler, MD.

He discovered abnormalities in eye movement increased with further progression of the diseases. This suggests that detailed assessment of eye movements may be able to detect early signs of disease and could potentially be used as an additional measure to look at effectiveness of treatment in future clinical trials. In addition, they found evidence of subtle cognitive difficulties even in asymptomatic patients suggesting the Cerebellar Cognitive Affective Syndrome, which is seen in other diseases involving the cerebellum and has a distinct pattern. There were also high levels of psychiatric symptoms, similar to other cerebellar disorders. In addition, they found evidence of widespread poor sleep quality, which will be important for doctors to appreciate and may warrant further study.

2018 Research Initiative Request for Proposals: Grant Process Update

We received 16 pre-applications in response to our Request for Proposal announced by NTSAD and CTSF. The pre-applications were reviewed by members of NTSAD's Scientific Advisory Committee, Corporate Advisory Council, and Board of Directors. Of these 16 pre-applications, seven were chosen for the next steps, which involves a detailed research plan and budget. These seven applications cover all our diseases; GM2, GM1 and Canavan. The investigators are a global group and the projects range from basic research to repurposing existing drugs.

The applications selected in the final round will be announced in May and the projects will start on July 1.



Advocacy Alert: Right to Try legislation

The [Right to Try](#) legislation has been in the news and has received attention within the rare disease community. The House passed this legislation and the next step is the Senate. This legislation will allow physicians to offer experimental therapies to terminally-ill patients that have not yet been approved by the FDA.

Read a summary of the concerns of those in support of the legislation and those who are opposed in this Politico article written by Sarah Karlin-Smith [here](#).

Sandhoff Disease and proof of principle for gene therapy | American Society for Biochemistry and Molecular Biology

Staci Kallish, DO and NTSAD Board Vice President wrote the following lay summary of an article published and shared online. Read the full article [here](#).

- A study recently published demonstrates the development of the first human model of Sandhoff disease (SD).
- This work was completed by a number of scientists well-known to NTSAD, including Cynthia Tifft, MD, PhD, Richard Proia, PhD, and Miguel Sena-Estevés, PhD and their colleagues and was published March 1st in the *Journal of Lipid Research*.
- This study used fibroblasts (skin cells) from an infant with SD to create iPS cells (induced pluripotent stem cells; cells which can then be transformed into other cell types).
- The researchers also used gene-editing technology called CRISPR/Cas9 to correct one of the Sandhoff mutations in some of these cells to create healthy cells.
- They then induced both groups of cells into groups of brain cells called organoids. This allowed them to study early brain development in the SD model compared to an unaffected model.
- As they expected, the researchers saw early ganglioside storage in the cells in the SD organoids, but not in the healthy control organoids. However, they were surprised that they saw cells overgrowing rather than degenerating. The SD organoids became larger than the controls, mimicking the enlarged brain size seen in patients with SD. They also saw changes in expression of other genes in the SD organoids, in genes which control cell maturation, which suggests that having a gangliosidosis may affect brain development in other ways in addition to the build up of storage material.
- Finally, the researchers used gene therapy (similar to the SD gene therapy being studied in SD animal models) to treat the organoids. They saw improvements in SD organoid size and reductions in ganglioside storage after gene therapy treatment. This demonstrates that organoids can be useful models of disease for the study of potential therapies. This also serves as a "proof of principle", the first evidence that gene therapy can correct abnormalities seen in SD in human cells.

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