



NATIONAL TAY-SACHS & ALLIED DISEASES ASSOCIATION Research Review | March 1, 2019



Calling GM1, GM2 Tay-Sachs and Sandhoff, and Canavan families...

We will have researchers and companies developing therapies for ALL of our diseases at the **41st Annual Family Conference** from April 11-14, 2019 to meet, speak, and mingle with YOU. As a gene therapy company's chief medical officer shared on Rare Disease Day at the MassBio gathering, "Understanding diseases plays into how companies think about developing drugs. We want to understand the challenges you face in your day-to-day lives."

Helping Hand Grants are available to families to help cover the costs of hotel and registration. If traveling is a financial strain, please contact Becky Benson [here](#), our Conference Coordinator, to discuss the possibility of a travel grant.

The conference website is www.ntsadannualfamilyconference.com. The weekend supports families and all forms of GM1, Canavan, Tay-Sachs and Sandhoff. We also welcome researchers, clinicians and companies who want to learn more about our diseases.

A Robust Conference Research Session

We have gathered the experts who are scientists, physicians, and drug development experts to make this a valuable session for everyone who attends. The format is a general session for the first half of the morning followed by four smaller breakout groups by disease. See below for the line-up of speakers for each breakout. (The first half will be filmed and shared with the community after the Conference.)

Fran Platt, PhD, NTSAD's Scientific Advisory Committee chair, will kick off the general research session at 9am on Friday, April 12th. **Marc Patterson, MD**, professor of neurology, pediatrics and medical genetics at the Mayo Clinic, will be our keynote speaker. **Florian Eichler, MD**, a neurologist specializing in neurodegenerative disorders, will join Dr. Patterson in conversation. **Curt Scribner, MD**, an independent biotech regulatory consultant for several companies, including Aspa Therapeutics, will also contribute to the discussion about expanding treatment options in our rare diseases, drug development, and clinical trials. We will have time for your questions at the end of this main session. You can also ask questions at the less formal breakout sessions by disease.

GM1 Gangliosidosis

GM2 Infantile-Juvenile

Research Breakout

Axovant
(specific speakers TBD)

Cassie Bebout
Doug Martin, PhD
Auburn University

Jess Conicelli
Orphan Disease Center @ UPenn

Samantha Parker
Lysogene

Cynthia Tifft, MD, PhD
*National Human Genome Research
Institute at NIH (NHGRI)*

Research Breakout

Axovant
(specific speakers TBD)

Fran Platt, PhD
Oxford University

Miguel Sena-Esteves, PhD
UMass Medical School

Other speakers to be confirmed
and announced soon.

GM2 Late Onset Research Breakout

Taylor Fields
IntraBio

Heather Gray-Edwards, PhD
UMass Medical School

Dr. Chris Stephen (to be confirmed)
Massachusetts General Hospital

Sanofi Genzyme
(speaker to be confirmed)

Camilo Toro, MD (to be confirmed)
Sanofi/NIH Natural History

Canavan Research Breakout

Florian Eichler, MD
Massachusetts General Hospital

Dominic Gessler
UMass Medical School

Heather Lau, MD
New York University Medical School

Kathleen Kirby and David Rintell
Aspa Therapeutics

News for GM1, GM2, and Canavan

IntraBio

The company announced the Food & Drug Administration (FDA) approved their application to begin clinical trials for their compound IB1001 for **GM2 Tay-Sachs and Sandhoff**. Visit clinicaltrials.gov to learn more.

Read the full press release [here](#).

PassageBio

The launch of a new company, Passage Bio focused on diseases of the central nervous system was announced with a gene therapy program for **GM1 Gangliosidosis** as its lead program.

Read the full press release [here](#).

Aspa Therapeutics

The Canavan Foundation, Canavan Research Illinois and NTSAD met with the Aspa team in early February. Ideas were discussed that Aspa has on awareness and education about both Canavan disease and the upcoming natural history study.

Aspa has continued building operations to support this study (launch expected later this spring). We also discussed other organizations across the globe who support families with a child with Canavan disease, and a plan for reaching out to these organizations. If you are aware of an organization outside of the U.S. who supports families of patients with Canavan Disease, please reach out to us [here](#).

GLIA Meeting in May

Alison Bradbury, PhD, Sue Kahn, and Staci Kallish, DO, plan to attend the Global Leukodystrophy Initiative (GLIA) meeting in Philadelphia in early May to meet and confer with Canavan and other leukodystrophy researchers.

The **Global Leukodystrophy Initiative (GLIA)** was founded in 2013 to bring together clinicians, researchers and advocacy groups to focus and improve both clinical care and research.

*“Coming together is a beginning.
Keeping together is progress.
Working together is success.”*
~ Henry Ford

Building a Brighter Future for Rare Brain Disease Patients March 12, 2019 | Auburn University



Auburn University will be highlighting their GM1 and GM2 research being conducted the College of Veterinary Medicine. Participants can register for the free program at www.vetmed.auburn.edu, and can also join the event via live webcast live at www.vetmed.auburn.edu. The event can also be followed at #BrainAwarenessatAuburn on Twitter and Facebook. Read the full press release [here](#).

WORLD Meeting Summaries

Allison Bradbury, PhD, Sue Kahn, and Staci Kallish, DO attended the 15th Annual WORLD (We're Organizing Research on Lysosomal Diseases) Symposium in Orlando. Over 1,000 people gathered from around the world. The attendees were basic, translational and clinical researchers;

patients and patient advocacy groups; clinicians and industry. It was a great meeting with 3 days of talks on research on lysosomal storage diseases (LSDs) (and some leukodystrophy), ranging from basic science to clinical trials. Thanks to Allison and Staci for writing up the following highlights on the talks and abstracts about the gangliosidoses.





Cassie Bebout, student at Auburn University and NTSAD sibling, gave a talk titled “Analysis of the effect of intravenous gene therapy on brain and peripheral disease in a feline model of GM1-gangliosidosis”, discussing her work with Dr. Doug Martin and the latest data from IV gene therapy studies in cats with GM1 gangliosidosis.

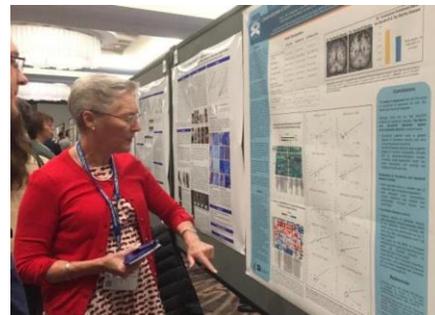
- 4 cats with GM1 were treated with gene therapy by intravenous (IV) injection, with 2 studied after a short period (16 weeks), and 2 followed longer
- The cats were treated before symptoms of GM1 appeared
- The cats in the long term study lived to 38 and 43 months, which is a 5.4-fold increase from those not treated (untreated cats reach their humane endpoint around 8 months of age)
- The treated cats also showed significantly improved quality of life and were almost neurologically normal (score 9-10 on 10-point scale) at endpoint. The cats reached humane endpoint due to weight loss as opposed to neurologic disease in untreated cats.
- They also saw that B-galactosidase (the enzyme deficient in GM1) distribution improved throughout brain with activity 0.3-1.3-fold normal levels.
- Both urine and brain GAGs (storage material) were elevated in the short-term (16 week time point) treated cats but were normalized in the long-term treated animals. Since urine and brain GAG levels mirrored each other, urine GAGs may be able to serve as a non-invasive biomarker to track disease progression and therapeutic efficacy in the brain of cats and patients.

Cassie ended her talk by stating the treatment was “effectively curing the cats of disease,” and they are “hoping to translate this work to the clinical side”

[Read this news article](#) featuring Cassie's story about how she ended up working with Doug Martin on the disease that took her brother's life much too soon. We are thrilled that Cassie will be at our 41st Annual Family Conference along with her family!

Brianna Glase from the National Institutes of Health (NIH) gave a talk titled “Robust clinical outcome measures for patients with juvenile onset GM1-gangliosidosis,” presenting work completed with Dr. Cynthia Tiffit.

- Their group evaluated 16 patients with GM1 gangliosidosis over 10 years, seeing 9 of the individuals for multiple evaluations
- They used the Vineland adaptive behavior scale to evaluate socialization, communication, motor, and daily living skills
- They also used an exploratory motor function score created to further evaluate motor function, called the Upright mobility score



- They found that individuals with GM1 lose skills (adaptive behavior, communication, socialization, and daily living skills) as they age, as expected, and found that more skills were lost earlier in the course of the disease
- Individual patient's trajectories fit well with trajectory for data as whole
- They plan to correlate these metrics with biomarker and imaging data
- They also plan to use these scores as outcomes measures in an upcoming GM1 gene therapy clinical trial

Dr. Chet Whitley from the University of Minnesota presented work completed with Jeanine Jarnes in a talk titled “**Chitotriosidase** as a Biomarker for Central Nervous System Inflammation in the Gangliosidosis Diseases”.

- Chitotriosidase is a biomarker used to monitor disease status in other LSDs
- Drs. Whitley and Jarnes measured chitotriosidase in plasma and CSF (spinal fluid) in patients with Tay Sachs, Sandhoff, and GM1
- Blood samples from children and adults with TSD, SD, and GM1 did not show any significant differences in chitotriosidase levels
- Some CSF samples, particularly from children with infantile forms of these diseases, showed elevations in chitotriosidase, suggesting this may be a biomarker for inflammatory diseases in CNS, especially in gangliosidoses and may correspond to the rate of disease progression
- Chitotriosidase has also been shown to be a marker of disease in a leukodystrophy, cerebral X-ALD, correlating with progression of disease and predicting prognosis

What is chitotriosidase? Chitotriosidase (ChT) is an enzyme that is selectively activated in tissue macrophage. Read the full definition [here](#).

Dr. Alaa Hamed from Sanofi presented a poster titled “Qualitative and quantitative evidence for the use of clinical outcome assessments in GM2 gangliosidosis diseases”, reporting data from their evaluations of adults with late onset TSD and SD, much of which was collected at NTSAD Annual Family Conferences.



- They studied a number of measures in affected adults and have been following these measures over time to see how well they match disease progression
- They found a number of measures to be valid for following disease in LOTS and LOSD, including the Friederich's Ataxia Rating Scale Neurologic Examination (FARS-Neuro), the Assessment of Intelligibility of Dysarthric Speech (AIDS), and the Nine-hole pegboard test (9HPT)
- These measures appear to be sensitive to change, showing rate of progression in affected adults

- Through discussions with affected adults and their families, they have learned that these measures have meaningful impact, suggesting that these measures could be useful outcomes for potential upcoming clinical trials
- They hope to continue collecting data at this year's Annual Family Conference.

Vanessa Rangel Miller, CGC, from Invitae and CureGM1 presented a poster titled, "GM1 patient network: enabling patients to characterize and share their disease journey" highlighting the GM1 gangliosidosis PIN platform."



- PINs are Patient Insight Networks, online portals that allows patients and their families to share information about their symptoms, treatments, and other information
- PINs then make this information available to patient advocacy groups and researchers in a de-identified way
- To date, more than 80 people have completed this process through the GM1 PIN, from around the world
- The PIN also allows families to be contacted when clinical trials become available, should they be interested

NTSAD is supporting PINs for Tay-Sachs, Sandhoff, GM1, and Canavan Disease partnering with Cure Tay-Sachs, CureGM1, and Canavan foundations. There will be opportunities to sign up at the upcoming Annual Family Conference or you can sign up online. Learn more about all the PINS [here](#).

Todd Vanyo, PharmD, presented work from the University of Minnesota in a poster titled "Genotype-phenotype correlation in 54 patients gangliosidoses".

- This study evaluated both retrospective and prospective data from 54 individuals with Tay-Sachs, Sandhoff, and GM1 diseases, including those with the infantile, juvenile, and late onset forms
- They found that onset and progression of disease was fairly similar among those with infantile disease, while those with juvenile and late-onset disease had more variability in terms of symptom onset and progression

Dr. Eric Hui from Armagen presented a poster titled "Platform technology for treatment of the brain in lysosomal disorders: application to Tay Sachs disease".

- This technology is using a "Trojan horse approach" which uses an antibody to the human insulin receptor, fused to HEXA, to allow the HEXA to enter the brain
- Studies of this technology in monkeys show distribution can occur throughout brain (these studies used the enzyme missing in another LSD, MPSI)
- Studies in MPSI are also ongoing in humans
- For TSD and SD, the researchers have created the required fusion protein using HEXA and have

shown this is successful in cell studies

- Animal studies for TSD and SD are planned

Dr. Kohji Itoh from Tokushima University gave a talk entitled “In vivo gene therapy for Tay-Sachs and Sandhoff diseases by utilizing AAV9 vector encoding modified HEXB.”

- This work involves using an AAV9-modHexB vector for gene therapy injection into the cerebrospinal fluid (CSF) space via the lateral ventricle (intracerebroventricular injection) of 8 week old mice with SD (treatment before the mice develop symptoms)
- The modifications made to the HexB subunit extend the half-life of the enzyme and increase its stability.
- Using this method, they are able to see restoration of HexA activity in brain and peripheral organs (liver, spleen) and reduction in GM2 storage and inflammation
- The lifespan of the mice was increased to beyond 1 year (vs 16 weeks in affected mice without treatment) and motor coordination was improved.
- They have conducted safety studies in cynomolgus monkeys again targeting the CSF space but this time through a lumbar intrathecal injection, and see enzyme activity throughout brain and spinal cord regions
- They hope to complete their preclinical studies between now and 2021 and hope for a clinical trial in 2022

Amelia Ahern-Rindell from the University of Portland gave a talk entitled “Design and analysis of a CRISPR gene editing strategy in a sheep model variant of GM1-gangliosidosis.”

- Sheep have been identified with reduced β -galactosidase enzyme activity (the enzyme deficient in GM1 gangliosidosis) and also reduced alpha-neuraminidase activity (the enzyme deficient in sialidosis). This is unlike the cat and dog models of GM1 in which only β -galactosidase is deficient.
- Since 2 different enzymes are defective, the mutation could be resulting in improper formation of lysosomal multi-enzyme complex.
- A mutation was identified in Exon 6 of the *GLB1* gene and is currently being evaluated to determine if it is the disease causing mutation.
- To do this investigators are using CRISPR technology to create the same mutation in normal sheep cells and determine if the mutation results in decreased β -galactosidase and alpha-neuraminidase enzyme activities.
- Once the mutation is confirmed, this could serve as another animal model of GM1 gangliosidosis with a mutation that is different from what causes GM1 in cats and dogs.

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