NTSAD

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

You can rely on NTSAD to bring you updates on the research we've funded and/or currently involved in supporting. Below are progress reports from three Research Initiative grant recipients and updates. Also, in today's e-news, we've included some photos and news about our visit to Axovant as well as announcing the participants in the Family Conference Research Session.

New method for the determination of a GM1-Gangliosidosis-specific biomarker (final report)

Dr. Stéphane Demotz, DORPHAN
Dr. Tim Wood, Greenwood Genetic Center

Beta-galactosidase, the enzyme which is deficient in GM1-gangliosidosis, is involved in the degradation of several cell constituents, such as GM1-gangliosides, keratan sulfate and oligosaccharides attached to glycoproteins. In the absence of beta-galactosidase, these cell constituents accumulate in cells, organs and body fluids, such as plasma and urine and, ultimately, lead to the somatic features associated with the condition.
A sensitive method was developed by the Greenwood Genetic Center for the determination of an oligosaccharide (*i.e.* a structure made of 5 sugar units) which is elevated only in cells and urine of GM1-gangliosidosis patients. As this component is highly soluble in water, it is readily found in urine of patients, constituting thereby a convenient biomarker.

As this promising GM1-gangliosidosis-specific biomarker is found in cells and in urine of patients, it could be exploited for:

- The unambiguous identification of GM1-gangliosidosis patients and those responding to drug candidates. The test consists in the culture of white cells isolated from a small blood sample in the presence of the drug candidate, followed by the determination of the oligosaccharide in cell lysates. A decrease in the oligosaccharide level indicates that the patient carries beta-galactosidase mutations responding to the drug candidate.

- Monitoring the efficacy of novel therapeutic interventions for GM1-gangliosidosis patients. Determination of the biomarker in urine would allow the clinicians to rapidly adjust the dosage of the drug candidate.

- The further development of the small molecule currently conducted by DORPHAN, and which may provide therapeutic relief for a subset of GM1-gangliosidosis patients.

The characterization of this new GM1-gangliosidosis biomarker therefore constitutes an important element in the preparation of a first in man evaluation of the drug candidate DORPHAN is currently developing.

The financial support of the NTSAD has provided has helped to further our drug candidate as the first therapy for GM1-gangliosidosis.

Read the report summary **here**.

Rapid Identification of New Biomarkers for the Classification of GM1 and GM2 Gangliosidoses: A Coupled H NMR and LC/MS-Linked Metabolomics Strategy (final report)

Martin Grootveld, De Montfort University

This pilot study used a highly specialized technique using nuclear magnetic resonance (NMR) to detect hundreds of molecules, simultaneously, to find reliable biomarkers that would indicate disease activity and how it is progressing in a GM1 and GM2 (late onset) patients. Using advanced methodologies, they were able to recognize biomarkers present comparing those present in GM1 and GM2 to those in healthy and age-matched controls. The results from this study will be helpful in how patients are monitored and how they may respond to potential drug treatments.

In the near future, this information will be used to enhance our understanding of these diseases, and will also help us to design new treatments (including combination therapies) for these devastating conditions. Further experiments are currently underway, and our novel results will be submitted for publication in reputable scientific/clinical journals soon.

Read the full report **here**.

Accelerated program for CSF delivery of AAV gene therapy for Tay-Sachs and Sandhoff patients

Miguel Sena-Esteves, PhD, UMass Medical School

Studies in young adult GM2 mice treated via lumbar intrathecal infusion with a 3rd generation AAV9 vector encoding both HEXA and HEXB genes have shown substantial improvement in motor performance and extended survival. These encouraging results lend support to the translation of this AAV gene therapy for adult onset Tay-Sachs disease patients using a minimally invasive approach to access the cerebral spinal fluid.

What are biomarkers?

The term “biomarker” refers objective indications observed from outside the patient that can be measured accurately and reproducibly. Examples of biomarkers include everything from pulse and blood pressure through basic chemistries to more complex laboratory tests of blood and other tissues. Clinical endpoints, on the other hand, reflect or characterize how a subject in a study or clinical trial “feels, functions,

or survives". They are, in other words, variables that represent a study subject's health and wellbeing from the subject's perspective.*

* https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3078627/

Attention Canavan Families!

We are looking for families to share some of their time, knowledge, experience and expertise to round out the natural history studies with Dr. Heather Lau at NYU.

The data from these studies will inform future clinical trials in order to ensure success. It is vitally important. Stay tuned for an upcoming opportunity to have a virtual chat with Dr. Lau to learn more and hear about the landscape of Canavan research. Email Diana **here** if that is something you'd like to join.

If you're interested in the study, please contact Patrinia, Project Manager at NYU, by email **here**.

Patient Insights Network (PIN) for GM2, GM1, Canavan

If you haven't already done so, be sure to register with one of the PINs to share your experience.

The better understanding of the community, the more it helps advance research to clinical trials.

Learn how **here**.

Meeting Axovant: An Opportunity to Share

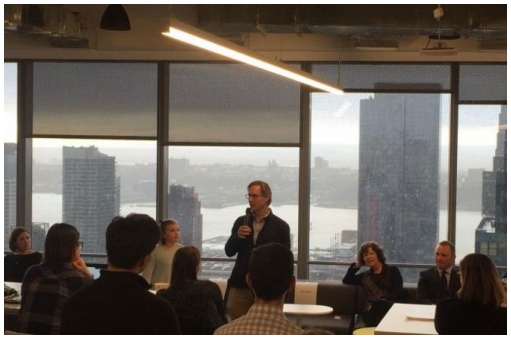
Prior to NTSAD's board meeting in New York City on January 25th, Axovant, who licensed the GM1 and GM2 gene therapy programs from UMass Medical Center, invited us to meet them and give talks to their employees. Axovant's CEO, Pavan Cheruvu, MD, opened up the session by expressing his patient-focused company philosophy. Sue Kahn gave an overview of NTSAD, but the real stars of the show were the family stories shared by Tim Lord and by Brianne Anderson (above left). Tim was joined by other family members, Blyth (NTSAD President), Charlie, and Taylor Lord, and Alex

Wright (NTSAD treasurer). The NTSAD staff was also represented by Patrick Woods, Director of Development. Brianne was joined by her family, Adam, and her beautiful children, Drew (who has infantile Tay-Sachs), Julie and Kayleigh. The kids made friends with everyone!

The Axovant team was invited to ask any question, and they did, including asking about the siblings' experience, what their hopes and expectations are of possible treatments, and what a typical day is like with Drew. Mutual appreciation was expressed from both the Axovant team and Sue, Tim and Brianne for the employees' hard work and commitment, and hopefully, a sense of urgency having heard from Brianne that "time equals brian".

Gavin Corcoran, MD, Axovant's Executive VP of R&D, shared on Twitter, "This was one of the most moving experiences of my life. Thank you to the families for sharing your stories. I am so proud to be part of the Axovant team that has joined the effort to find a treatment for [GM1 and GM2] to help these children and their families".

Sue Kahn, NTSAD's Executive Director



Tim Lord, Hayden's dad and Cameron's uncle

2019 NTSAD Annual Family Conference: Research Session

Friday, April 12, 2019
Raleigh Marriott Crabtree Valley

9:00am to 12:30pm

We are gathering 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. (The first half will be filmed and shared with the community after the Conference.)

For the general session, we have invited Marc Patterson, MD, professor of neurology, pediatrics and medical genetics at the Mayo Clinic, as our keynote speaker. We have also invited Florian Eichler, MD, a neurologist specializing in neurodegenerative disorders, to join Dr. Patterson. They have participated in clinical trials for new therapies for diseases similar to our group of diseases, i.e., Niemann-Pick C and adrenoleukodystrophy. 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.

Keynote speaker:
Marc Patterson, MD, *Mayo Clinic*

Canavan breakout
Dominic Gessler
UMass Medical School

Heather Lau, MD
New York University Medical School

Florian Eichler, MD
Massachusetts General Hospital

Kathleen Kirby and David Rintell
Aspa Therapeutics

GM1 (infantile, juvenile) breakout
Cassie Bebout
Doug Martin, PhD
Auburn University

Samantha Parker
Lysogene

Cynthia Tifft, MD, PhD
NIH

Axovant

GM2 (infantile, juvenile) breakout
Fran Platt, PhD
Oxford University

Miguel Sena-Esteves, PhD
UMass Medical School

Axovant (specific speakers TBD)

Late Onset breakout
Heather Gray-Edwards, PhD
UMass Medical School

Chris Stephen, MD
Massachusetts General Hospital

Camillo Toro, MD
NIH

Sanofi Genzyme

Taylor Fields
IntraBio

Learn more about the Conference

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