



## national tay-sachs & allied diseases association RESEARCH REVIEW | March 24, 2017



### A Summary of the WORLD Meeting

**Allison Bradbury, PhD, Heather Gray-Edwards, DVM, PhD and Staci Kallish, DO**

The 13th annual WORLD Symposium took place February 13 – 17th in San Diego, California. This annual meeting provides an interdisciplinary forum to explore and discuss research and clinical applicability related to lysosomal diseases.

On Monday, February 13th, there was a Council of Patient Advocates Workshop. Attendees included Lorelei Sandoval, Christine Waggoner (Cure GM1 Foundation), and Rick Karl (Cure Tay-Sachs Foundation). With numerous patient advocacy groups in attendance, it was reassuring for families to see that NTSAD is excelling in many areas of focus including clinical trial readiness, organizing natural history studies, funding research, and supporting families. It is also empowering for families to participate and be involved in events like this one.



Left to right: Sue Kahn, Lorelei & Isaac Sandoval, Audrey & Janelle Marquez, Miguel Sena-Esteves, Heather Edwards, Allison Bradbury and Staci Kallish.

In the clinical trials session we also heard presentations on newborn screening for lysosomal storage diseases, enzyme replacement therapy trials (ERT), and gene therapy trials. Gene therapy trials for MPSIII included one study for MPSIIIb with direct brain injections (16 injections) of AAV taking place in France and a separate study in the United States that is evaluating systemic (intravenous) delivery of AAV for MPSIIIa. Safety and efficacy data emerging from the first ever clinical trials using gene therapy for lysosomal storage disorders will continue to inform, direct, and influence trials for other devastating lysosomal storage diseases (for which there are over 70).

## **Sphingolipidoses membrane lipids regulate and modify sphingolipid catabolism, its enzymes, lipid binding and transfer proteins**

**Dr. Konrad Sandhoff from the LIMES Institute in Bonn, Germany** gave the keynote address of the meeting “*Sphingolipidoses membrane lipids regulate and modify sphingolipid catabolism, its enzymes, lipid binding and transfer proteins*” and was the recipient of the 2017 Award for Innovation and Accomplishment. In 1968 as a biochemist studying sphingolipids and gangliosides, Sandhoff discovered the molecular defect in variant 0 GM2-Gangliosidosis, more commonly known as Sandhoff disease. Sandhoff’s lab continues to study lipid biochemistry and inherited diseases that are associated with defects in lysosomal degradation.

## **Cardiovascular manifestations of feline Sandhoff disease after intravenous gene therapy**

**Lauren Ellis of Auburn University** gave a talk entitled “*Cardiovascular manifestations of feline Sandhoff disease after intravenous gene therapy*”. Ms. Ellis, Dr. Ray Wang and Dr. Doug Martin are investigating the cardiovascular symptoms of cats with Sandhoff disease that have been treated intravenously with adeno-associated virus (AAV) gene therapy. Untreated Sandhoff cats demonstrated cardiovascular disease including abnormal heart valves and enlargement of the aorta, the largest artery in the body. Sandhoff cats had an overall decrease in elastin (a major protein component of tissues that require elasticity such as arteries) and an increase in storage material in the arteries compared to normal cats. After IV gene therapy the vessel abnormalities were improved, including significant restoration of elastin. This study suggests that the IV gene therapy may be able to ameliorate cardiovascular problems in Sandhoff disease.

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## **An FDA Perspective on Rare Disease Drug Development**

**Dr. Richard Moscicki from FDA’s Center for Drug Evaluation and Research (CDER)**, spoke about “*An FDA perspective on rare disease drug development*”. Dr. Moscicki discussed the FDA’s perspective on developing drugs for rare diseases and what the FDA is doing to improve this process. He discussed some of the challenges, many of which have been discussed within NTSAD, including poor understanding of the natural history of these diseases, small patient numbers which impact study design and complicate analysis of results, variability of clinical features among those with these rare disease, and a lack of well defined endpoints, including biomarkers. Dr. Moscicki also discussed an increased interest at the FDA in patient focused drug development. This has led to meetings and discussions with individuals with rare diseases and their families to understand

## **Long term survival of sheep with Tay-Sachs disease after intracranial delivery of a novel bicisiontronic AAV therapy vector**

**Heather Gray-Edwards of Auburn University** presented on “*Long term survival of sheep with Tay-Sachs disease after intracranial delivery of a novel bicisiontronic AAV therapy vector*”. Gray-Edwards and colleagues have developed a new bicistronic AAV vector, a vector that includes both HEXA and HEXB genes in 1 construct, to ensure delivery of both Hex subunits (Hex  $\alpha$  and  $\beta$ ) to individual cells. This makes gene therapy for Tay-Sachs and Sandhoff disease more efficient. After delivery of the new bicistronic AAV vector, TSD sheep had global delivery to the cerebral cortex but reduced distribution to the spinal cord. The life of Tay-Sachs sheep is significantly extended with this therapy, with one sheep still alive at nearly 2 years of age (affected

the burden of disease and which outcomes are most important to them. They have created an avenue for patient advocacy groups to submit letters of intent to the FDA to create forums on these topics. NTSAD will be exploring this opportunity. He also discussed a number of lessons he has learned from his work in rare disease drug development, including that natural history studies are invaluable, and best if based on a protocol and prospective (looking forward) rather than retrospective.

TSD sheep normally die at 9 months). This is the most effective therapy for Tay-Sachs sheep to date and future studies will evaluate other cerebrospinal fluid (CSF) delivery routes to improve therapy to the cerebellum and spinal cord.

## MAY 20, 2017 | PHILADELPHIA MILLION DOLLAR BIKE RIDE



### JOIN TEAM NTSAD & RIDE FOR RESEARCH

If you or anyone you know likes to bike ride, consider riding for Team NTSAD on **May 20, 2017** to raise rare awareness and funds for research! **UPenn will match what is raised up, so let's make this our biggest year ever!**

There are three routes - 12 miles, 33 miles or 73 miles - for all ages and levels. Make your plans today!

Learn more and register [here!](#)

If you're too far away, consider making a gift to support those who are riding.

**Every gift will be matched!**

Make your gift [here](#) for Team NTSAD!

## NTSAD Conference Research Session on March 31, 2017

The NTSAD Research Session is a highlight of the Annual Family Conference and an opportunity for families to learn the latest news on Tay-Sachs, Sandhoff, GM1 and Canavan research developments. It is sponsored by the Mathew Forbes Romer Foundation, NTSAD's South Florida affiliate.

This year, we have put together a new format for this session based on what we heard from families and what has been in the news.

**Overview of Therapeutic Approaches to the LSDs and Leukodystrophies including gene therapy** (Fran Platt, PhD)

**Gene Therapy Panel Discussion**  
Moderator, Fran Platt, PhD

Joe Anderson, PhD  
Dominic Gessler  
Doug Martin, PhD  
Miguel Sena-Esteves, PhD

**From Research to Clinical Trial: Overview of Clinical Trial Readiness**  
Moderator, Cynthia Tifft, MD, PhD

**What is status of Clinical Trial Readiness in NTSAD's diseases?**

## **Families and Researchers Collaborate in Advancing Therapy: The Role of NTSAD, Together with Parents, in Driving Toward Treatments**

Sue Kahn, NTSAD's Executive Director, was invited to write a commentary for the February 2017 issue of **Human Gene Therapy**.

An excerpt:

NTSAD is proud to have played a role in this [gene therapy] progress. NTSAD made its first grant for gene therapy in 2002, the year that NTSAD initiated a formal research grant process. This article will discuss the role that NTSAD and related family foundations have played in advancing gene therapy for our diseases, with a focus on the formation of and collaboration with the Tay-Sachs Gene Therapy Consortium ("Consortium"), and their work in Tay-Sachs and Sandhoff diseases (collectively "GM2").

View article [here](#)

Florian Eichler, MD (GM2)  
Heather Lau, MD (Canavan)  
Samantha Parker, Lysogene (GM1)

**Regulatory and Approval Process**  
Cordula Schwarz, Sanofi Genzyme

This session will be recorded and shared on our website after the conference. A companion booklet featuring summaries of research in our rare diseases will be available to download on our website and will be in every conference packet at registration.



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Here.

**Susan Kahn, Executive Director**  
**Brian Manning, President, NTSAD Board**  
**Fran Platt, PhD, Chair, Scientific Advisory Committee**  
**Veronica Huang, Science Communications Intern**

2001 Beacon Street, Suite 204  
Boston, MA 02135  
(617) 277-4463 | [info@ntsad.org](mailto:info@ntsad.org)  
[www.NTSAD.org](http://www.NTSAD.org)