



National Tay-Sachs & Allied
Diseases Association, Inc.

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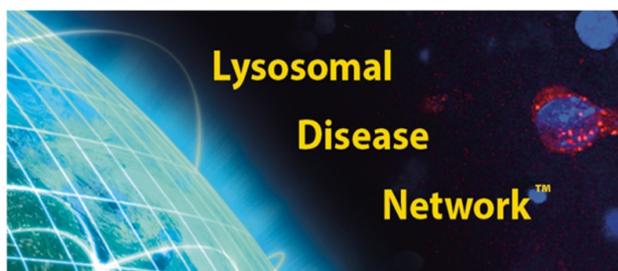
NTSAD Monthly Research Review

NTSAD @ the 12th Annual WORLD Meeting

Summaries compiled and edited by Allison Bradbury, PhD, Heather Gray-Edwards, PhD and Staci Kallish, DO

The **12th annual WORLD (We're Organizing Research for Lysosomal Diseases Symposium)** took place February 29 - March 4th in San Diego, California. There were 76 talks and hundreds of poster presentations selected from a record-breaking 370 submitted abstracts. In

addition to academic institutions across the globe, the government sector was represented by numerous presentations by the National Institutes of Health, several pharmaceutical companies offered informative satellite symposiums, and a notable number of patient advocate groups were in attendance, including NTSAD.



The meeting was solely focused on **lysosomal storage disorders (LSDs)** and progressed daily from Basic Science to Translational Research and concluded with Clinical Research.

The basic science section featured numerous talks that further explored mechanisms and pathways of disease that could serve as targets to better develop therapies. The translational research portion detailed promising pre-clinical studies in animal models of various LSDs.

While the vast majority of clinical data presented continued to be on LSDs without central nervous system (CNS, brain and spinal cord) involvement (such as Gaucher disease), there were two presentations on clinical trials for LSDs with CNS disease. First, Dr. Porter from the NIH discussed a Phase I/II evaluation of intrathecal delivery, directly in to the cerebrospinal fluid (CSF) space, of a small molecule therapy, cyclodextrin, for the treatment of Niemann-Pick disease type C1. Secondly, Dr. Dali from Denmark detailed intrathecal delivery of recombinant arylsulfatase A (enzyme replacement therapy) for children affected with late-infantile metachromatic leukodystrophy. As successful delivery of therapies to the CNS has been a major hurdle for treating the vast majority of LSDs, the advancement of 2 CNS-directed therapies in to the clinic

provides hope for other neurodegenerative LSDs including Tay-Sachs, Sandhoff, GM-1, and Canavan disease.

Abstracts from the meeting can be found in the February 2016 issue (Volume 117, issue 2) of *Molecular Genetics and Metabolism* [here](#).

Below we have highlighted presentations of the most interest to the NTSAD community, including Late Onset data collected at the 2015 NTSAD Annual Family Conference in Reston, Virginia.

BASIC SCIENCE: Highlights

Volkan Seyrantepe, PhD

Izmir Institute of Technology, Izmir, Turkey

"Deletion of sialidase NEU3 causes progressive neurodegeneration in Tay-Sachs mice"

- A mouse model of Tay-Sachs disease has previously been created by knocking out, or depleting, the β -Hexosaminidase A (HexA) gene, referred to as a HexA^{-/-} mouse. However, this model does not closely mimic Tay-Sachs disease progression seen in humans because mice have an alternative sialidase pathway (not present in humans) to degrade GM2 ganglioside.
- By knocking out a second gene, Neu3^{-/-}, believed to be involved in the alternative sialidase pathway, more severe disease features were achieved. This double knockout, or 2-gene depleted mouse, is referred to as HexA^{-/-}Neu3^{-/-}.
- In comparison to the HexA^{-/-} mice which remain asymptomatic for > 1 year, HexA^{-/-}Neu3^{-/-} mice showed signs of neurologic disease including ataxia and tremor and died between 4 - 4.5 months of age. At endpoint HexA^{-/-}Neu3^{-/-} mice had increased GM2 ganglioside storage in the brain and multiple peripheral tissues.

This data suggests that treatment of Neu3 deficiency may be another potential therapeutic target for treatment of Tay-Sachs disease.

Yvonne Latour (lab of Dr. Cynthia Tiff)

National Institutes of Health, Bethesda, MD

"Development of isogenic human cerebral organoids with beta-galactosidase deficiency"

- Dr. Tiff's lab has developed cerebral organoids ("mini-brains") with GM1 gangliosidosis.
- The cerebral organoids are made from induced pluripotent stem (iPS) cells with GM1 gangliosidosis.
- They form brain like structures including ventricles, ependymal cells, mature and immature neurons.
- They are grown in bioreactors where they can be kept for up to one year.
- They have the same missense or nonsense mutations as many human patients.

TRANSLATIONAL SCIENCE: Highlight

Heather Gray-Edwards, PhD (lab of Dr. Douglas Martin)

Auburn University; Auburn, AL

"Long term survival after gene therapy in a feline model of Sandhoff disease"

- Untreated Sandhoff cats live to only 4.5 months of age where as cats treated with AAV gene therapy brain and cerebellar injection lived up to 3 years.
- Cerebellar injection carries increased risk in human patients, therefore alternate delivery to the cerebellum would be preferred for human clinical trials.
- Sandhoff cats treated with AAV gene therapy by intrathecal injection (into the cerebrospinal fluid that surrounds the brain and spinal cord) only survived to ~9 months of age, but were blind and deaf.
- Sandhoff cats treated by combined brain and intrathecal injection survived to ~19 months.
- Cats treated by brain + lateral ventricle injection, a fluid filled sac within the brain that regulates and produces CSF, had survival up to 30 months.

Brain combined with lateral ventricle injections is likely the safest and most efficacious therapy for use in human clinical trials.

Walter Acosta, PhD (from Dr. Radin's group)

BioStrategies

"Lectin-mediated delivery of a-L-iduronidase: a novel approach for MPS I enzyme replacement therapy"

- This approach uses RTB, the non-toxic domain of ricin, fused to a protein to help the protein enter cells. This is the same approach Dr. Radin and his group are using in studying GM1 (partially supported by NTSAD's Research Initiative). RTB is able to cross the blood brain barrier and can be fused to many proteins.
 - When fusing RTB to IDUA, the missing enzyme in mucopolusaccharidosis type I (MPS I), the fusion protein can be processed in cells and mature IDUA protein is formed. The cleaved RTB is degraded.
 - MPS I mice treated with this approach with tail vein injections show IDUA activity in liver, spleen, heart, kidney, and brain.
 - The group saw significant reduction of GAG levels (the material stored in MPS I) in organs including brain and cerebellum with weekly injections for 8 weeks.
 - These mice also showed improvements in cognitive abilities using the Barnes maze
-

Jorge Ayala

BioStrategies

"Uptake, lysosomal activation, and disease correction in GM1 gangliosidosis cells by plant-made B-galactosidase: Lectin fusions"

- Dr. Radin's group has also been studying intranasal delivery of a fusion protein to mice with GM1 in work supported by NTSAD
- This poster shared data from work supported by the NIH
- The group delivered a fusion protein of RTB with B-galactosidase by IV administration
- They saw clearance of stored GM1 in the liver, kidney, and spleen
- They also saw distribution of B-gal in the brain in the cerebellum and cortex, and in the spinal cord
- They were also able to see clearance of stored GM1 from the cerebellum

CLINICAL TRIALS: Highlights

Gerald Cox, MD, PhD

Genzyme, a Sanofi company; Cambridge, MA

"Functional performance in patients with late-onset Tay-Sachs disease"

- The team met with 10 individuals with LOTS and 2 with late-onset Sandhoff disease ranging in age from 24 to 68 years and their family members.
- Many of those interviewed had symptoms from their teen years. It took an average of 16 years to confirm a diagnosis from the onset of symptoms.
- The group evaluated individuals using a number of tools, including the Physician Global Impression scale (PGI), the Brief Ataxia Rating Scale (BARS), the Timed Get Up And Go test, a 9-peg board test, the Archimedes spiral, Trail Making test, and the Excited speech by Rainbow passage test.
- They found that overall, individuals had a high burden of disease.
- The BARS score correlated well with the other measures of function, indicating this may be a particularly useful measure to follow over time.
- The team plans to follow those with late-onset Tay-Sachs and Sandhoff using these scores to assess the sensitivity of these measures to changes over time.

It is hoped that these scores will be useful in future clinical trials for late onset disease.

Alaa Hamed, MD

Genzyme, a Sanofi company; Cambridge, MA

"Patient and caregiver experience with late-onset Tay-Sachs and Sandhoff diseases"

- During the interviews conducted at last year's conference, those with late onset Tay-Sachs and Sandhoff expressed that overall, lack of mobility and balance are the most frustrating symptoms to deal with.
- Those interviewed (12 affected individuals and 7 of their caregivers) expressed a desire for both better mobility with reduced risk of falling and for better communications. These may represent potential endpoints for future clinical trials as they are likely to have great impact on

affected individuals.

- Family caregivers were also interviewed. These caregivers expressed concern about how to best support their loved ones.

This research highlights a need for greater support for affected individuals and their caregivers.

Look for Drs. Cox and Hamed to discuss the information learned from last year's conference at the Research Update at this year's NTSAD's Annual Family Conference and look for their team to meet with those with late onset disease again to further these studies.

Chaired by *Dr. Cynthia Tift*



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GANGLIOSIDOSIS
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Saturday, April 9th, 2016
NTSAD Conference
Orlando, FL USA

A Rare Disease Collaboration

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To attend this workshop and/or the Annual Family Conference, contact **Diana** or **Becky** for more info.



**Team NTSAD Rides on May 6th
MILLION DOLLAR BIKE RIDE**

Sign up and Ride for a Cure here.

If we raise at least \$20,000, these gifts will be matched up to \$50,000 to fund a research grant focused on our group of rare genetic diseases.

If you're interested in riding

with Team NTSAD

in Philadelphia, contact Allison Bradbury [here](#).



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