



National Tay-Sachs & Allied  
Diseases Association, Inc.

Saturday, MAY 14, 2016

## NTSAD Monthly Research Review

### PART II: RESEARCH SUMMARY from NTSAD's 38th Annual Family Conference

compiled and written by Allison Bradbury, PhD, Heather  
Edwards, DVM, PhD, and Staci Kallish, DO

The following are summaries from the GM-1 Research  
Meeting that was held on Saturday, April 9, 2016. The full  
meeting can be watched [here](#). Thank you to the Cure GM-1  
Foundation and Lysogene!

### OVERVIEW OF GM-1, GENETICS 101 and NATURAL HISTORY STUDIES

Cynthia Tiftt, MD, PhD, National Institutes of Health (NIH)

- Why perform a natural history trial? So we can tell if the potential therapy is helping.
- It is important because if you choose the wrong measure you can fail a clinical trial even if positive results are noted in other areas.
- In this study it was determined that there are two distinct populations in what was once considered juvenile GM1, late-infantile and juvenile
  - ○ MRI and clinical examination are both able to differentiate late-infantile and juvenile onset.
  - ○ 4 subtypes now: infantile, late-infantile, juvenile and late onset
- Testing falls into two domains:
  - ○ Talking and eating
  - ○ Ambulation
- MRI and MR spectroscopy reliably track disease and will likely become outcome measures in future clinical trials.
- Patients will likely be their own controls in any future clinical trials.

### A BIG THANKS...

Team NTSAD Rides a 3rd Year!



(Left to right: Team NTSAD Captain,  
Allison Bradbury, Staci Kallish, Chris  
Beer, David Bradbury and Heather  
Edwards)

Congratulations and a big thank  
you to **Team NTSAD** for  
representing HOPE in the  
**Third Annual Million Dollar  
Bike Ride!** There is still time to  
double your impact. EVERY  
dollar raised will be matched and  
given as RESEARCH grant to  
Tay-Sachs, GM-1, Sandhoff or  
Canavan.

**It's not too  
late!** If we  
collectively  
raise \$25,000



that will **DOUBLE** into a \$50,000  
grant all for research that could  
lead to something big!

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## CHAPERONES

Stéphane Demotz (Dorphan SA)

- Chaperones help proteins work by binding to the mutated protein helping it do its job.
- Chaperones only work on certain mutations; patients must have a certain amount of functional protein for chaperones to have a positive effect.
- They tested a chaperone called DO-1, and they estimate it will work in approximately one-third of patients with GM1.
- Dose response effect in 50 patient fibroblasts (skin cell culture): worked in 50% of the 50 tested.
- Saw reduction in keratin sulphate storage (a compound stored in GM1) of cells.
- Pilot study, tested IV dosing in 3 animals. At highest concentration in the bone, followed by the brain then in the plasma.
- Tested in fibroblasts of adult onset GM1 patients, and determined that the DO-1 increased  $\beta$ -galactosidase activity.
- Need to do before Pre-IND (before applying for clinical trial):
  - Pharmacokinetic studies in animals
  - Determine biodistribution in animals
  - Determine efficacy in animal models.
  - Determine best route.
  - Toxicity studies

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## GENE THERAPY

Miguel Sena-Esteves, PhD (Univ. of Mass. Medical Center)

- Began developing this therapy 10 years ago. GM1 cats and mice treated by adeno-associated viral (AAV) gene therapy survived years longer than untreated (>4-5fold increase in lifespan).
- Biodistribution of cat and mouse brain is similar, with only 4 injection sites.
- Started working with Lysogene to complete last preclinical animal testing and begin trials.
- Clinical trials estimated to start in 2017-2018
- Who will be eligible?

Share and pass along [this link here](#). We have until May 31st to make an impact!

### 2016 ANNUAL CONFERENCE [RESEARCH SURVEY](#)

Your input is important and will help define how we plan 2017's NTSAD Conference Research Sessions today!

## IN THE NEWS

### Canavan Research Fund of NTSAD: Full of Hope

If you missed it, NTSAD parent and former board member, Sherri Epstein was recently featured in a [Newsweek](#) article about Canavan gene therapy. This article kick-started a new NTSAD fund specifically for Canavan research.

Visit the [Canavan Research Fund](#) page [here](#).

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### Hope for Sanfilippo Disease

What could be successful for one lysosomal storage disease could very well pave the way for other LSDs in the future.

Read the recent news about a clinical trial soon to be started to treat Sanfilippo disease [here](#).

Stay tuned for the  
2016 NTSAD Research

- Least affected children will be treated first to give the therapy the best chance of passing phase I/II (safety/efficacy), followed by others. Also started working on intravascular (IV) gene therapy to prevent the risk of intracranial injection.
  - IV gene therapy of AAV9 increased lifespan of GM1 mice with partial storage clearance and reduced neuro-inflammation.
    - Survived to 1.5 years as compared to 8 months in mice
    - Female GM1 mice live longer.
  - Developed a new vector, called AS, which is better than the current gold standard in industry (AAV9), and enters neurons efficiently, which is a challenge for IV AAV gene therapy.
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## ANIMAL MODELS

*Doug Martin, PhD (Auburn University)*

- GM1 cats treated by AAV gene therapy survived > 5 fold over untreated cats (4-6 years compared to the 8 month lifespan of untreated GM1 cats) with about half of cats still alive and being studied.
  - Through a partnership with Lysogene we are currently completing the last animal studies before onset of clinical trials.
  - We started testing intravascular (IV) gene therapy in GM1 cats, because it took 10 years to get to the point where we are about to start human clinical trials for intracranial injections and we want to be ready to take a less invasive approach to GM1 in humans as soon as possible.
  - IV AAV treated GM1 cats are currently 2 years of age and indistinguishable from normal cats.
  - MRI, CSF and blood based biomarkers suggest that intracranial disease is largely ameliorated.
  - Urine GAG analysis suggest that peripheral disease is greatly corrected.
  - Abdominal ultrasound has shown now abnormalities in peripheral organs.
  - Due to this success they plan to expand testing of IV gene therapy to include safety and toxicity studies.
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# ENZYME REPLACEMENT THERAPY

Carole Cramer, PhD, and David Radin, PhD (BioStrategies)

- RTB is a plant derived compound (lectin peptide) that binds to sugars, thus helping the enzyme cross the BBB. This technology has been applied to enzyme replacement by creating a fusion protein containing the plant RTB and an enzyme for therapy.
- In another lysosomal storage disease mucopolysaccharidosis (MPS), MPS-1 mice treated with the RTB-alpha-l-iduronidase (IUDA) show improved spatial learning and memory in the barnes maze.
- Next plan to test this technology in GM1 mice using RTB- $\beta$ -galactosidase enzyme.

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