



National Tay-Sachs & Allied  
Diseases Association, Inc.

Friday, MAY 13, 2016

## NTSAD Monthly Research Review

### RESEARCH SUMMARIES 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 NTSAD Research Update  
session that was held on Friday, April 8, 2016. The full session  
can be watched [here](#).

Part II will be sent tomorrow and will contain the summaries of  
the GM-1 Research Meeting that was held on Saturday, April 9,  
2016. The full meeting can be watched [here](#).

### GM-1 ENZYME REPLACEMENT THERAPY

Carole Cramer, PhD and David Radin, PhD (BioStrategies)  
2014 NTSAD Research Initiative Grant Recipient

- **RTB is a plant derived protein (lectin peptide) that binds to sugars, helping the enzyme cross the blood brain barrier (BBB).** This technology has been applied to enzyme replacement by creating a fusion protein containing the plant RTB and an enzyme for therapy.
- **RTB-fusion protein with  $\beta$ -galactosidase was created to circumvent the blood brain barrier** and allow for enzyme replacement to treat GM-1, lysosomal storage disease that affects the brain, using intranasal (through the nose) and IV delivery.
- The **RTB-fusion protein decreases GM-1 ganglioside storage** from human fibroblasts (skin cells).
- **Intranasal delivery** did not reach the olfactory bulb, the part of the brain expected, but enzyme did reach another part of

### A BIG THANKS...

#### Team NTSAD Rides Again!



(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!

the brain called the cerebellum.

- Intravenous delivery (by mouse tail vein) 2 times a week for 2 weeks (4 total injections) resulted in increased  $\beta$ -galactosidase and reduced GM-1 ganglioside storage in the spleen and liver in all 4 mice tested and increased  $\beta$ -galactosidase and reduced GM-1 ganglioside storage in the brain of 2 out of 4 mice.
- **Work is ongoing to determine if this will be an effective way** to provide needed enzymes to the brain in GM-1 and other diseases.

---

## CANAVAN GENE THERAPY UPDATE

*Dominic Gessler (Univ. of Mass. Medical Center - Dr. Gao's lab)*  
2010 NTSAD Research Initiative Grant Recipient

- **AAV gene therapy has improved over time** with each generation of therapy studied by Dr. Gao's group performing better than the previous ones.
- Mice treated by gene therapy at one day old with third generation gene therapy performed better on rotarod performance testing (a measure of motor function) than even healthy mice even 1 year after treatment.
- Pathology is **greatly improved with third generation gene therapy**, both in the living mouse MRI and in post-mortem analysis one year after treatment.
- Treatment of Canavan mice with gene therapy at a juvenile age (6 weeks) also resulted in rotarod and MRI findings indistinguishable from normal mice.
- Treatment of Canavan mice with gene therapy at an adult age (7 months) resulted in normalized gait, improved cognitive function and **normalization of myelination**.

Read the **Newsweek** article featuring their Canavan gene therapy work [here](#).

---

## TAY-SACHS GENE THERAPY UPDATE: IND-enabling studies of AAVrh8-Hex gene therapy for Tay-Sachs disease

*Miguel Sena-Estevés, PhD (Univ. of Mass. Medical Center)*  
2015 NTSAD Research Initiative Grant

- Non-human primates (monkeys) treated with original vector had abnormal MRIs and clinical signs likely related to toxicity

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

2016 FAMILY  
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: All About 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](#).

---

### 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

from over-expression of the hexosaminidase protein.

- **Three new vector designs (simpler and less potent vectors) were tested** in non-human primates and 2 of the 3 vectors resulted in normal MRI and minimal damage to the brain.
- The new vectors were then tested in GM2 mice and shown to be as good as the original vector; however, because the vector is less potent a higher dose is required.
- **FDA feedback on design of investigational new drug (IND) enabling studies** (studies suggested for application for a clinical trial) included:
  - Conduct dose escalation studies (studies at varied and much higher doses) in GM2 mice with survival until 5 months of age
  - Conduct safety and biodistribution studies in GM2 mice
  - Conduct dose escalation studies in non-human primates with some followed for one year.

## 2016 NTSAD Research Initiative Grant Awards!



*With a gift of \$1,000, you can name one of the recently born unique Jacob Sheep lambs!*

Follow the sheep on Facebook [here](#) and consider a gift to help care for these sheep and/or adopt a sheep by mailing in a donation form or [donate online here](#).

---

## INTRAVASCULAR (IV) GENE THERAPY FOR FELINE GM2 GANGLIOSIDOSIS

*Doug Martin, PhD (Auburn University)*

**2015 NTSAD Research Initiative Grant**

- IV gene therapy (rather than by brain injection) in cats with Sandhoff disease showed slight improvement in clinical disease.
- Partial normalization was detected in the brain by MRI and MR spectroscopy and cerebrospinal fluid (CSF) biomarkers.
- Little distribution of the therapeutic protein (hexosaminidase) was present in the brain of AAV treated cats, but notable levels were present in the spinal cord and peripheral tissues.
- Peripheral urinary glycosaminoglycan storage (one of the compounds stored in Sandhoff disease) was reduced with treatment.
- This is a good starting point for future studies utilizing vectors with greater ability to cross the blood brain barrier when given by IV.

*Drs. Martin and Sena Esteves were notified in March that they were awarded a \$2.9 million R01 grant from the National Institute of Neurological Disorders and Stroke (NINDS). This grant leverages the NTSAD Research Initiative grant for the IV approach as well as a vote of confidence in the current first generation intracerebral gene*

---

## Are you on Facebook and Twitter?



Like **NTSAD's Facebook page** and follow [@susanrkahn](#) for new developments in therapies, science, genetic testing, patient advocacy, and more.

---

## RESULTS OF LATE ONSET STUDIES

### 2015 ANNUAL FAMILY CONFERENCE

*Gerry Cox, MD, PhD and Alaa Hamed, MD (Sanofi Genzyme)*

- The median age of LOTS patients included in this study is 49 years with a range from 24-68 years, 58% were male, 42% were Ashkenazi Jewish, 80% have LOTS, 17% LOS (late onset Sandhoff), 58% have children.
- The time from symptom onset to diagnosis was 18 years, 42% required caregiver assistance, 92% need ambulatory assistance and 50% have difficulty with speech articulation.
- BARS score (brief ataxia rating scale) correlated with disease severity and functional performance testing suggesting that these assessments may be useful outcome measures for monitoring patients.
- Follow up testing will be useful for determining sensitivity to change over time.
- This information will be helpful in determining outcome measures and therapeutic efficacy in future human clinical trials.

#### **national tay-sachs & allied diseases association**

susan kahn, executive director ([skahn@ntsad.org](mailto:skahn@ntsad.org))

joan lawrence, development director ([joan@ntsad.org](mailto:joan@ntsad.org))

diana pangonis, family services director ([diana@ntsad.org](mailto:diana@ntsad.org))

ingrid miller, office manager ([ingrid@ntsad.org](mailto:ingrid@ntsad.org))

becky benson, conference coordinator ([becky@ntsad.org](mailto:becky@ntsad.org))

2001 beacon street

suite 204

boston, ma 02135

(617) 277-4463

[www.NTSAD.org](http://www.NTSAD.org)