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 β-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 the brain.

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!
Intravenous delivery (by mouse tail vein) 2 times a week for 2 weeks (4 total injections) resulted in increased β-galactosidase and reduced GM-1 ganglioside storage in the spleen and liver in all 4 mice tested and increased β-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 rotorod 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 rotorod 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](#).

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**TAY-SACHS GENE THERAPY UPDATE:**

IND-enabling studies of AAVrh8-Hex gene therapy for Tay-Sachs disease

Miguel Sena-Esteves, 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

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](#).
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.

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**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 therapeutical 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.

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*Dr. 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
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.