The Research Small Group Discussions are a highlight of the Annual Family Conference. We invite leading Tay-Sachs, Sandhoff, GM-1 and Canavan researchers, many of whom have received an NTSAD Research Initiative grant, to discuss their projects in small groups. Speakers rotate from table to table, repeating their talk four times so everyone has the chance to engage directly with the experts. Families are encouraged to ask lots of questions and keep the conversation open. By the end of the session, the speakers are exhausted but the families are informed, empowered and engaged! Thank you to the Mathew Forbes Romer Foundation for sponsoring the session.

Animal Models of GM-1, Tay-Sachs and Sandhoff

Doug Martin, PhD

Dr. Martin's research facility is located at Auburn University in Auburn, AL. His gene therapy efforts utilize adeno-associated virus (AAV) vectors expressing lysosomal enzymes. Cat and sheep models of GM-1 and GM-2 gangliosidoses (Tay-Sachs and Sandhoff) are treated by targeted brain injection of the gene therapy vector and followed closely to determine if the therapy is efficacious.

- GM-1 gangliosidosis cats were treated with an AAV vector expressing β-galactosidase bilaterally into two brain targets and followed long term. The mean life span was extended >4.7-fold and continues to increase because most of the treated cats are disease-free or have only subtle symptoms at this time.
- GM-2 gangliosidosis cats (Sandhoff disease model) were treated with an AAV vector expressing Hexosaminidase bilaterally into two brain targets and followed long term. The mean life span was extended >4.2-fold and quality of life for the animals was greatly improved.
- This past year the GM-2 gangliosidosis Jacob

In this Issue

Tay-Sachs Gene Therapy Consortium News

The six non-human primates that received Tay-Sachs gene therapy using the newly developed vectors continue to display normal behavior. The Tay-Sachs Gene Therapy Consortium plus four board certified neuroradiologists reviewed the 30 day MRIs and noticed a few animals showed faint signal changes along the gene therapy injection track. It is unclear whether this is reason for concern as they continue to display normal behaviors. The primates will be monitored closely. The next round of MRIs will take place in approximately 30 days. (60 days after gene therapy injection.)

Doug Martin, PhD, was featured in the Auburn University *Veterinarian* magazine as part of a story that introduces a local Auburn, AL family whose son has GM-

sheep (Tay-Sachs model) were moved to Auburn University and breeding is currently underway. Targeted brain injections of an AAV vector expressing Hexosaminidase have proved to increase the lifespan of affected sheep by 50%.

GM-1 Natural History Study
Cynthia Tifft, MD, PhD

Dr. Cynthia Tifft is the Deputy Clinical Director at the National Human Genome Research Institute at the National Institutes of Health in Bethesda, MD. She is currently conducting a GM-1 natural history study to further characterize the disease and to identify biomarkers of disease progression.

- Dr. Tifft has created a clinical rating scale in which she tracks patient's clinical disease progression. She is also analyzing blood and cerebrospinal fluid (CSF) samples for potential biomarkers of disease.
- MRI Spectroscopy is also being conducted on GM-1 patients which allows the measurements of specific metabolites in the brain. Some metabolites, such as N-acetylaspartate (NAA), may be altered with neurodegenerative diseases such as GM-1.
- Correlations between clinical disease progression and alterations in brain metabolites as measured by MRI spectroscopy have been found in this study. These results suggest that non-invasive brain imaging may serve as an effective biomarker for the gangliosidoses.

Lentiviral Vector Expression of HexA/HexB via Blood Cells to Treat Tay-Sachs Disease,
Gerhard Bauer

Dr. Gerhard Bauer is the director of a Good Manufacturing Practice (GMP) laboratory at UC Davis in Sacramento, CA. His research efforts are focused on gene therapy for the gangliosidoses using lentiviral vectors expressing lysosomal enzymes. With this approach, a patient's own stem cells are removed from their bone marrow, transduced with the therapeutic lentiviral vector, and transplanted back into the patient.

- Initial experiments in cell culture were very successful, with over 90% of cells transduced with the viral vector. This greatly surpasses the 50% transduction rate that was anticipated.
- In the near future, the lentiviral gene therapy will be conducted on mouse models of GM-2

1. You can read the full story here. Doug received the 2014 Above & Beyond Award at the 36th Annual NTSAD Family Conference in Atlanta, GA earlier this month.

An Inspiration

Our deepest condolences to the Bihn family as they say goodbye to their daughter, Dakota, today. Her long and valiant battle with Tay-Sachs came to an end on Monday, April 21st. She has inspired many as they have raised over $3 million for research to cure Tay-Sachs through her family's foundation, the Cure Tay-Sachs Foundation. Their contributions to research will forever have an impact.

Dakota will be missed.

Thank you Allison Bradbury, a research graduate assistant at Auburn University, for writing these easy to understand summaries of the Research Small Group Discussions! Your passion and enthusiasm for helping the families of NTSAD is outstanding!

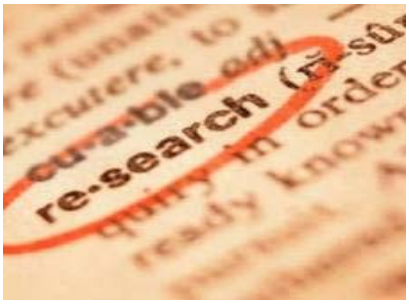
gangliosidosis.
- Because mice are being treated with the human form of the lysosomal enzyme, it may not be necessary to try this therapy in larger cat and sheep models of the gangliosidoses.

Canavan Gene Therapy

Dominic Gessler, MD postgraduate Research Fellow

The laboratory of Dr. Guangping Gao is located at the Gene Therapy Center at the University of Massachusetts Medical School in Worcester, MA. Dr. Dominic Gessler joined Dr. Gao's laboratory in 2013 as a post MD graduate research fellow. The research in Dr. Gao's lab is focused on AAV gene therapy for Canavan Disease.

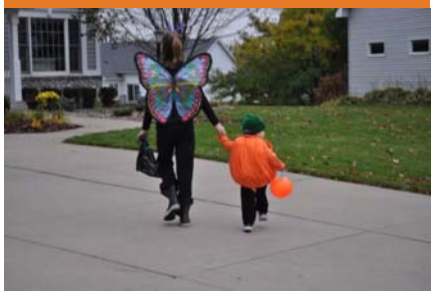
- A single intravenous (IV) injection of an AAV vector expressing aspartoacylase rescued early lethality, extended survival, and alleviated many disease symptoms in Canavan mice.
- The gene therapy results emphasize that early intervention is therapeutically more beneficial, with life span extended as long as 2 years when mice were treated at postnatal day 0. Treatment as late as postnatal day 20 was sufficient to completely rescue early lethality and partially restore growth and mobility.
- AAV vectors with different serotypes, AAVrh8, AAV9, and AAVrh10, were found to be therapeutically equivalent. This expands the options of vectors to select from for different patient populations.



Research + Funding = Hope

Support Research with a gift here.

Read more about current and past grants funded by NTSAD on our website here.



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Never, never, never give up.
Winston Churchill

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