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ntsad research year-in-review friday, december 12, 2014

2014 was a busy year in the world of rare diseases research. From funding to fundraising, NTSAD proved to be a leader in its efforts to find treatments for diseases such as Tay-Sachs, Sandhoff, GM1 and Canavan diseases.

This "Research Review" gives a synopsis of the research work done this year that NTSAD funded and was featured in the "Research Reviews" throughout the year. Enjoy reviewing and looking ahead to another productive year in 2015!

NTSAD Preparing for Clinical Trial Readiness

Two New Sources of Guidance Created in 2014

The **GM2 Clinical Research Network** is a global, collaborative network of healthcare professionals and researchers that supports clinical and translational research and are working together to find a cure for a disease or group of diseases.

The network can accelerate research into our diseases by promoting inter-institutional and international collaboration, and resource and information sharing. It was clear from the meeting in July 2014 that all who participated are committed to expediting clinical trials. Read more from July 18th's Research Review here.

# # #

The **Corporate Advisory Council (CAC)** will help NTSAD as we prepare for future treatments for this family of rare genetic diseases and will complement the scientific, clinical, and lab expertise brought by our Scientific Advisory Committee (SAC). Together, the SAC and CAC will help NTSAD advance research programs, build our clinical trial readiness, and make our diseases appealing to companies to study.

Read more about the CAC in May 23rd's *Topic of the Week* here.

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NTSAD Science Symposium for Research & Healthcare Professionals
April 16, 2015
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April 17, 2015
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Announcement of 2015 Research Initiative Grant Awards
April 2015

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May 9, 2015

Tay-Sachs Gene Therapy Consortium

(Read Milestone I progress report here.)

Work continues to understand the unexpected side effects of gene therapy seen in monkeys last year.

- The selection process of new AAV vectors in mice yielded three new vectors that led to increased expression of Hex in the brain without the side effects associated with the original AAV vector. (Milestone 1)
- The three new AAV vectors were injected into the brain of normal monkeys to test safety and demonstrate increase HexA expression. As in previous experiments all animals tolerated the surgery very well with no complications.
- Brain MRI was done at 30 and 60 days after injection to determine whether there was any evidence of damage at the injection sites. The brain MRI revealed a small change in one animal near the injection site on one side of the brain. The MRI for all other animals remained unchanged compared to the MRI done before the injections.
- The brains of all animals were analyzed for HexA activity and showed increased Hex activity for all three AAV vectors at the brain injection site.
- Before making the decision to continue toward the clinical trial with this AAV vector, it is critical to demonstrate its therapeutic efficacy in a GM2 animal model. GM2 mice have been injected with the original AAV vector and the latest version to compare the reduction in GM2 ganglioside levels throughout the brain and spinal cord.

Dr. David Radin BioStrategies LLC

(from June 6th "Research Review" read here.)

In April, NTSAD awarded a Research Initiative grant to BioStrategies, LC, and David Radin, PhD, Principal Investigator for the project, **Lectin-assisted transnasal delivery of corrective enzyme for GM1 gangliosidosis.** The grant is a two-year $80,000 milestone-based grant. They believe that their new drug targeting/delivery technology has the potential to provide significant future advances in enzyme replacement therapy drug delivery challenges and also in treating symptoms affecting brain function.

The company has already accomplished the first task of producing the large fusion protein that includes both

Philadelphia, PA

Stay tuned for other updates and developments in the world of NTSAD Research News.

Special Research Fundraising Opportunities in 2014

Million Dollar Bike Ride

The UPenn's First Annual Million Dollar Bike Ride raised over $35,000 for NTSAD-focused research. We will soon learn which NTSAD grant proposal will be funded. Proposals included newborn screening and Canavan natural history studies.

Save the date for Second Annual Bike Ride on May 9, 2015!

Fourth Annual Day of Hope

Events held worldwide raised more than $35,000 this year bringing the total Day of Hope contribution, over the last four years, to research to over $122,000!

Save the date for the Fifth Annual Day of Hope on September 20, 2015.

We also thank the many

the protein carrier and the beta-galactosidase enzyme, which is the enzyme that's missing in GM1. The carrier delivers the enzyme into cultured GM1 cells which degrades the GM1 substrate that had accumulated in the cells because of the disease. The next step is to produce the fusion protein at levels and purity to support the planned initial mouse trials.

Dr. Alessandra d'Azzo
St. Jude's Children's Research Hospital
(from October 14th "Research Review" read here.)

Research led by **Alessandra d'Azzo, PhD** has revealed commonalities between **sialidosis**, a rare pediatric lysosomal storage disease, and Alzheimer's disease (AD), a severe neurodegenerative condition that usually develops in older adults.

The connection lies in the lysosomal enzyme Neuraminidase 1 (Neu1), which brain cells normally use to digest special proteins called glycoproteins. A deficiency of the Neu1 enzyme has been known to result in sialidosis; however, this latest research reveals that animals lacking the enzyme also develop plaques, or abnormal clumps of proteins, in the brain that are typically seen in AD.

* Results collected in year one of this 2-year study were published in *Nature Communications* in November 2013. The full article can be found at here.

Dr. Doug Martin
Auburn University
(from August 15th "Research Review" read here.)

Doug Martin, PhD and his research team at Auburn University completed a three year study on the Jacob sheep with Tay-Sachs disease. His group conducted safety and efficacy studies of AAV gene therapy in the affected sheep. Since the sheep have a mutation in the Hex A gene they are an authentic model of Tay-Sachs disease. Their large brain size allows researchers to confront certain challenges of gene therapy including brain targeting and distribution.

- GM1 cats treated by direct brain injection of AAV gene therapy are continuing to be followed long-term and are doing very well. The longest living GM1 cat in the history of the colony is now beyond 5 years of age, whereas untreated GM1 cats reach humane endpoint at approximately 8 months of age. The results of short-term and long-term studies were published this year in Science Translational Medicine (McCurdy et al. Science Translational medicine:

generous supporters of NTSAD's Research Initiative.

It truly empowers researchers as they move closer to treatments for our family of rare genetic diseases!

Research + Funding = HOPE

Make a gift to research here.

2015 Research Initiative Request for Proposals Issued

The deadline for this year's RFP one-page pre-application is due Friday, January 2nd by 5:00 pm EST. Click here for more details.

2014 NTSAD Annual Family Conference Research Speakers Brought Hope

The research small group discussions are always a highlight. This past spring we were lucky to have Doug Martin,

http://www.ncbi.nlm.nih.gov/pubmed/24718858)

- GM2 cats were treated by AAV gene therapy delivered by two different brain injection routes to determine if a route with less surgical risk was as beneficial at treating the disease as the initial route used. Short-term studies show that both injection routes have great clinical benefit. Results of one study were published very recently in Gene Therapy (McCurdy et al. Gene Therapy: http://www.ncbi.nlm.nih.gov/pubmed/25474439) and the second study will be available early in 2015.
- GM2 cats from both short-term treatment groups were studied extensively in search of biomarkers to track disease progression and measure therapeutic benefit. Numerous potential markers were found that changed with disease progression, and many of them were normalized after AAV gene therapy. These results were also published recently in Experimental Neurology (Bradbury et al. Experimental Neurology: http://www.ncbi.nlm.nih.gov/pubmed/25284324).
- Long-term studies of these two injection routes are also being conducted with promising results. Both injection routes have extended the lifespan of some GM2 cats in to the second year of life, whereas untreated GM2 cats reach humane endpoint at approximately 4 months of age.

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

PhD of Auburn there to discuss the animal models of GM-1, Tay-Sachs and Sandhoff diseases; Dr. Cynthia Tifft spoke about her GM-1 Natural History Study; Gerhard Bauer, PhD talked about his work with the lentiviral vectors and gene therapy for the gangliosides; and Dr. Dominic Gessler reviewed his and Dr. Guangping Gao's Canavan gene therapy research.

Read more in the April 25th Research Review here.

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"A great accomplishment shouldn't be the end of the road, just the starting point for the next leap forward."

- Harvey McKay

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