national tay-sachs & allied diseases association
RESEARCH REVIEW | February 16, 2018

NTSAD Research Initiative Grants: Updates

NTSAD's grant policies require progress reports every six months from our investigators who have received grant awards. These reports are reviewed and approved by the Scientific Advisory Committee (SAC) chair, who currently is Fran Platt, PhD. We recently received the following two reports.

Novel combined gene/cell therapy strategies to provide full rescue of the Sandhoff pathological phenotype

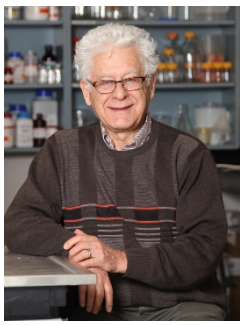
Principal Investigator: Angela Gritti, PhD
Institution: San Raffaele Telethon Institute for Gene Therapy
Progress Report after Year 1

The goal of this study is to evaluate gene and cell therapy approaches in the mouse model of Sandhoff disease (SD). In particular, the investigators are comparing three methods of therapy: 1) injection of a gene therapy using a lentivirus vector directly into the brain (intracerebral), 2) transplant of neural stem cell (NSC) (with or without added gene therapy correction of these cells), 3) and bone marrow transplantation (BMT). The therapies will initially be tested individually and then in combination, in affected mice a few days after birth. The combinatorial approach has already demonstrated a synergistic effect in a mouse model of a similar disease, thus providing the rationale to assess these therapies in the Sandhoff model. Progress have been made for each of the following milestones:

1. Optimize neonatal BMT in SD mice
2. Generate lentiviral vectors expressing the hexosaminidase (hex) a and b enzyme subunits
3. Optimize protocols to achieve hex overexpression in NSC cultures
4. Test transduction efficiency and enzymatic rescue upon neonatal intracerebral gene delivery of lentiviral vector expressing hex b (LV.hexb) and hex a (LV.hexa)
5. Start the first set of experimental groups with combined therapies

Results:
Bone marrow transplantation significantly increases the average lifespan of SD mice and decreases inflammation in the brain. However, this therapy results in only limited GM2 clearance from central nervous system (CNS) tissues. Intracerebral gene therapy injection results in local clearance of GM2 storage. Gene therapy using vectors with a combination of hex a and hex b is more effective than vector using hexb alone. We are now testing a combined setting in which mice are injected with both hex a and hex b letiviral vectors in in multiple sites (to obtain a more sustained distribution of the enzyme throughout the CNS) and then treated with BMT (under optimized conditions), in order to assess a synergic effect of the treatments. **Finally, besides assessing the therapeutic potential of the proposed strategies, this study will clarify the mechanisms of disease correction in the CNS and throughout the body, an important aim for the development of new therapeutic strategies for patients.**

Development and validation of a rapid, MS/MS-based method to detect Hexosaminidase deficiency in Tay-Sachs disease



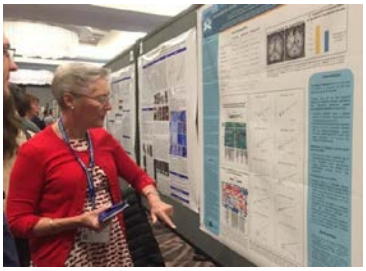
Principal investigator: Denis C. Lehotay, PhD
Institution: Queens University

Once treatment for Tay-Sachs disease (TSD) becomes available, detecting TSD by early screening and initiating early treatment will become essential to preventing the devastating consequences of this currently incurable condition. **Developing, validating, and testing a rapid MS/MS based assay for measuring hexosaminidase activity in populations with a high incidence of the disease are part of the essential steps that will eventually lead to a cure.** The investigators aimed to develop this assay for use in dried blood spots (DBS) collected for newborn screening. The project involved validating the method using DBS from known patients with TSD and unaffected individuals. They will then conduct a pilot study using DBS from an area of Quebec with a high carrier frequency among French Canadians (~1 in 25 individuals).The investigators have recently begun to analyze these samples and are establishing reference ranges. The plan is to identify normal and carrier samples from affected children by measuring hexosaminidase activity in each DBS by their newly developed assay. Those that are identified as affected or carriers) will then be tested by mutation analysis to determine the mutations they carry, and to correlate hexosaminidase activities with the specific mutations. This project will be completed in 2018.

14th Annual WORLD Symposium: Highlights

The WORLD Symposium focused on the lysosomal diseases took place February 5-9 in San Diego, California. Below we're sharing abstract summaries the researchers wrote that may be of particular interest to our NTSAD families. You can learn more about the research, meet the researchers, and ask questions at the 40th Annual Family Conference from April 12-April 15, 2018 in Jacksonville, Florida.

Clinical outcomes and brain metabolites in patients with late onset Tay-Sachs and Sandhoff disease



Cynthia J. Tifft, Camille Wang, Jean Johnston, Katherine Alter, Edythe Wiggs, Beth I. Solomon, Colleen E. Wahl, MIchele Nehrebecky, Rena Godfrey, Lea Latham, Catherine Groden, Eva Baker, Tanya Lehky, Camilo Toro

We have evaluated 23 patients, 18 with Tay-Sachs disease (TSD) and 5 with Sandhoff disease (SD), with an age range of 20 to 61 years. The average age at symptom onset was 16.7 years, and average time to diagnosis 17.3 years. Clinical assessments included Brief Ataxia Rating Scale (BARS), Archimedes spiral, neuropsychological testing, speech assessment, MRI/MRS, electrodiagnostics, muscle strength and ultrasound, and quantitative gait and balance testing. All patients demonstrated a distinctive pattern of severe muscle weakness and atrophy (wasting) predominantly in quadriceps and triceps muscles. BARS scores, measuring ataxia or the loss of control of body movements, were 11.8 + 6.5 for TSD and 7.6 + 6.6 for SD. Sensory complaints and deficits were more prevalent in SD than in TSD. Electrodiagnostic evidence of sensory neuropathy (nerve damage or disease) was also more common and severe in SD than LOTS. Speech characteristics at the conversational level included mixed dysarthria (difficult or unclear articulation of speech), rapid rates of speech, and stuttering in worse in LOTS. Full scale IQ (WAIS-IV, N = 19) was in the average range with verbal comprehension a relative strength. Magnetic resonance spectroscopy (MRS) allows quantification of specific brain metabolites by MRI. MRS was performed 21 patients (40 scans) and revealed significant deficits of N-acetyl aspartate (NAA) particularly in 2 parts of the brain, the left thalamus and superior cerebellar vermis (SVERM) ($p < 0.0005$). NAA deficit in the SVERM progressed with time since diagnosis. **Careful phenotyping of late onset GM2 patients has distinguished subtle differences in TSD and SD and will inform the design and outcome measures of future clinical trials.**

Functional performance in late-onset GM2 gangliosidosis (Tay-Sachs and Sandhoff diseases), longitudinal data over 3 consecutive years

Ana C. Puga, Alaa Hamed, Julie Kissell, Pascal Minini, Anureet K. Pabla, Susan Kahn, Florian Eichler, Christopher D. Stephen, Cynthia J. Tifft, Camilo Toro, Jean Johnston, Heather A. Lau, Elizabeth Haxton, Heather Gray-Edwards, Tanya Fischer

A longitudinal study was conducted among patients with late-onset GM2 gangliosidosis (Tay-Sachs and Sandhoff diseases) who attended the National Tay-Sachs & Allied Diseases Association (NTSAD) Annual Family Conference in 2015, 2016, and 2017, to characterize disease severity, functional performance, and quality of life. Assessments included Patient Global Impression (PGI), Brief Ataxia Rating Scale (BARS), Friedreich's Ataxia Rating Scale (FARS), Timed Get Up and Go Test (TGUG), 9-hole Pegboard Test (9HPT), Archimedes Spiral (AS), Assessment of Intelligibility of Dysarthric Speech (AIDS), Trail Making Test Parts A and B (TMTA/B), Cerebellar Neuropsychiatric Rating Scale (CNRS), and Quality of Life (SF-12 and EQ-5D). Twenty-one unique patients were recruited and assessed at least one year, with eight patients seen for 2 consecutive years and five patients seen for 3 consecutive years. At

baseline mean age was 46 years (range from 24-68 years) with median duration of disease symptoms of 24 years and median time since diagnosis of 7.5 years. In 8 patients who had two consecutive assessments between 2016 and 2017, a mean increase by 3.08 points in FARS total score, a mean increase by 0.56 points in BARS total score, and a mean decrease of 2.22% in AIDS mean score were observed. Late-onset GM2 gangliosidosis patients have a high disease burden confirmed by physical performance measures. **Results suggest AIDS, FARS, and BARS may be useful outcome measures.** FARS captures more domains than BARS with good correlation between the measures. (Supported by Sanofi Genzyme)

NOTE: Another round of assessments will be taking place at the 40th Annual Family Conference in Jacksonville, Florida from April 12 to April 15, 2018.

Reclassification of common variants of unknown significance in the hexosaminidase A gene: implications for Tay-Sachs carrier screening

Elizabeth D Smith , Karen A Grinzaid, Melanie Hardy, Alana Cecchi, Laura Kiger, Dale Muzzey, Eerik Kaseniit, Krista Moyer

Hexosaminidase A (HexA) enzyme analysis has long been considered the gold standard for Tay-Sachs disease carrier screening. **Limitations of the HexA assay—including specimen requirements, medication contraindications, and the potential for false positive and inconclusive results—have led to increased utilization of HEXA molecular analysis (at the genetic level instead of protein level).** DNA-based screens using full-exon next-generation sequencing typically have higher detection rates compared to a targeted genotyping, particularly in non-Ashkenazi Jewish populations. However, full-exon sequencing raises challenges in the interpretation of variants of unknown significance (VUS) (mutations previously not associated with disease). The goals of this project were to reclassify common HEXA VUS (as disease causing or likely benign) and make this information publicly available through submission to ClinVar. Counsyl has sequenced HEXA in a diverse population of hundreds of thousands of patients. At the time of study design, 6 HEXA variants—c.253+5074C>T, c.1074-100T>C, c.8G>C, c.1435G>A, c.1397A>G, and c.1074-86G>A—accounted for almost half of VUS identified. Reclassification of these variants from VUS to likely benign/benign reflects a reduction in their risk of being clinically deleterious, thereby conferring a higher detection rate for full-exon sequencing. Eligible subjects were identified because their healthcare provider or JScreen ordered HEXA sequencing-based carrier screening through Counsyl, and carried one of the six VUS. Subjects were consented for HexA enzyme analysis to investigate genotype-phenotype correlation. Four to five unique patient samples were sent for enzyme analysis per VUS (n=29 total). Results from HexA enzyme analysis revealed negative Tay-Sachs carrier states for all subjects. ACMG/AMP sequence variant interpretation criteria were applied to all 6 VUS and all 6 variants were reclassified to likely benign/benign. Follow-up counseling was provided. These reclassifications add to the growing public repository of variant interpretations for HEXA. **Analyses are currently underway to evaluate whether reclassification of these variants leads to an increase in detection rate for a HEXA sequencing-based carrier screen.**

This research was supported by NTSAD, Cameron & Hayden Lord Foundation, Mathew Forbes Romer Foundation, Evan Lee Ungerleider Fund and the New York Area Fund of NTSAD.

Encouraging News from the CATS Foundation

The **Cure & Action for Tay-Sachs (CATS)** Foundation shared an update on the proposed clinical trial for GM2 gangliosidoses (Tay-Sachs disease and Sandhoff disease) in Europe.

The research team at the University of Cambridge led by Timothy Cox, PhD has hit important milestones that are essential in getting a clinical trial launched in Europe. The European Medicines Agency (EMA) granted European designation as an Orphan Medicinal Product. "In addition, the medicine and procedure being developed by Professor Cox and his team has been recognized as meeting the criteria as an Advanced Therapy Medicinal Product (ATMP) by the EMA." They have also received an Orphan Drug Designation by the FDA in the U.S. What does that mean? The team can begin the process of planning "how the trial will be implemented and we will start deciding on both the outcome goals we want to measure and the recruitment criteria."

Note: An update from the Tay-Sachs Gene Therapy Consortium (TSGT) is forthcoming, as will a further update at the NTSAD Annual Family Conference on April 13, 2018 in Jacksonville, Florida.

Susan Kahn, Executive Director
Blyth Lord, President, NTSAD Board
Staci Kallish, DO, Vice President, NTSAD Board
Fran Platt, PhD, Chair, Scientific Advisory Committee
Allison Bradbury, PhD, Research Initiative Committee

2001 Beacon Street
Suite 204
Boston, MA 02135
(617) 277-4463 | info@ntsad.org
www.NTSAD.org