national tay-sachs & allied diseases association
RESEARCH REVIEW | Friday, October 26, 2018

NTSAD Research Grant Progress Reports

The following progress reports are from two of the 2016 NTSAD Research Initiative grants. (Visit NTSAD's website here for other past grants.)

The NTSAD Request for Proposals (RFP) is a competitive process where applications are fully vetted and reviewed by an unbiased team of professionals familiar with our group of diseases. Each proposal is reviewed, discussed and scored based on several criteria. There are instances when specific projects come to our attention and we always look to collaborate with other groups or family funds to ensure that research keeps moving forward.

Identifying Novel Therapeutics for Treating GM2 Gangliosidoses

Investigators:
Beverly Davidson, PhD, Children's Hospital of Philadelphia
Fran Platt, PhD, Oxford University (UK)

The goal of this grant proposal by Drs. Beverly Davidson and Fran Platt was to use RNA sequencing (also called whole transcriptome sequencing) to identify if clinically available substrate reduction therapies for lysosomal storage disorders (miglustat, lucerastat, and eliglustat) elicit changes in gene expression/gene pathways. Blood samples from 7 normal donors were treated with miglustat, lucerastat, and eliglustat at two different doses for a duration of 6 hours. The cells were then analyzed by RNA sequencing to determine if the drugs altered gene expression/gene pathways. Limited gene expression changes were seen and it was deduced that this could have been a result of too short of an exposure to the treatment (6 hours); therefore, the cells from 1 donor were treated with the same 3 drugs and were analyzed after duration of treatments of 6, 12, and 24 hours. There was no increase in gene expression changes with longer treatments.

Conclusion: The investigators did not observe a marked increase in changes in gene expression with miglustat, lucerastat, and eligulustat treatments up to 24

hours. However, they were able to use the data to screen the NIH Library of Integrated Network-Based Cellular Signatures (LINCs) database and identify drugs associated with comparable changes in gene expression, validating the approach. The investigators are now using the same approach on a different cell type to see if alterations in gene expression can be found.

Ongoing and Future Studies
The ongoing and future studies will be continued and financed through a European Union RISE funded network that includes the Platt and Davidson laboratories. This will provide the resources to enable the investigations to be taken to completion.

Novel Combined Gene/Cell Therapy Strategies to Provide Full Rescue of the Sandhoff Pathological Phenotype

Investigator: Angela Gritti, PhD
San Raffaele Scientific Institute
San Raffaele Telethon Institute for Gene Therapy (Italy)

The goal of the project is to assess whether a combinatorial strategy based on neural stem cell transplant (NSCT) or intracerebral gene therapy (IC GT) in combination with total bone marrow transplant (TBMT) performed early in life might supply timely and therapeutically relevant levels of functional hex enzyme in the central nervous system (CNS) and periphery of Sandhoff (SD) mice (hexb-/-), thus preventing/delaying disease onset and progression, prolonging lifespan and correcting pathological hallmarks.

The investigators have defined the optimal conditioning regimen for SD mice in order to obtain reproducible and elevated levels of hematopoietic cell (stem cell) engraftment, both in the bone marrow and in the brain by using myeloablation with a chemotherapeutic drug, busulfan. The higher number of donor cells in the CNS, after busulfan conditioning, resulted in an increase of hex enzymatic activity, especially in cerebellum and spinal cord. However, correction of other brain regions remains suboptimal and further supports the necessity of the combinatorial approach with IC GT.

The investigators have developed a new vector which will have technical advantages in targeting cells. The new vector construct has been tested in neural stem cell cultures, and the investigators will next perform multiple intracerebral injections in a new cohort of animals and assess distribution of the viral vector and the hex enzyme. Subsequently, the investigators will treat a cohort of animals with an optimized combined approach and these mice will be then monitored for survival and to assess the extent of disease rescue.

Collaboration: Essential in Moving Forward

Late Onset Think Tank

Alexis Buryk, mom of two adult daughters affected by Late Onset Tay-Sachs, is hosting a one day brainstorming session attended by 20 thought leaders in the Late Onset Tay-Sachs and Sandhoff, who will focus their attention on therapy issues for this condition.

The goal is to identify the best avenues for therapy for LOTS and what can be done to pursue these therapeutic approaches. Drs. Cynthia Tifft and Steve Walkley are leading the meeting and have invited scientists and clinicians from the NIH, industry, and academic institutions.

Second GM1 Research Symposium, Irvine, CA

Cure GM1 Foundation, with the support of sponsors and a grant from NTSAD for scholarships, hosted a research meeting on October 5th in Irvine, CA. Families, researchers, and advocates, including NTSAD's Director of Family Services, Diana Pangonis, attended and listened to informative presentations covering the latest news in GM1 research including conversation about natural history studies and delivery techniques for therapies to the brain. The takeaway is that there is definitely hope around the corner and each person working on GM1 is passionate and committed to helping families.

Visit Cure GM1 Foundation's website for updates and summaries of the meeting including recordings of the presentations.

Rare Diseases on Capitol Hill

NTSAD, Cure Tay-Sachs Foundation and several members of our community showed their support of making rare diseases and the need for faster treatments better understood before the Subcommittee of Health, Education, Labor and Pensions (HELP) chaired by Senator Rand Paul on October 3, 2018.

Susan Kahn, Executive Director
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Staci Kallish, DO, Vice President, NTSAD Board
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