national tay-sachs & allied diseases association

RESEARCH REVIEW | December 15, 2017

NTSAD Partners with Cure Tay-Sachs Foundation (CTSF) for 2018 Request for Proposals

NTSAD is considered to be the nation's oldest genetic disease nonprofit organization. A major element of NTSAD's mission is to lead the fight to treat and cure Tay-Sachs, Canavan and related genetic diseases; therefore, NTSAD is committed to funding research projects that advance this mission. NTSAD launched its Research Initiative in 2002 to fund promising research.

This year, NTSAD will be joined by the Cure Tay-Sachs Foundation (CTSF) in this RFP. CTSF is a grassroots organization focused on funding Tay-Sachs research since its inception by parents just over ten years ago.

For researchers interested in submitting proposals, the deadline for submission of one-page pre-applications is January 12, 2018.

Read more about the 2017-2018 RFP **here**.

Paper Published by NTSAD 2017 Grant Recipient, Dr. Alessandra Biffi

A new study published December 6th led by Dr. Alessandra Biffi, the director of the gene therapy program at Dana-Farber/Boston Children's Cancer and Blood Disorders Center, details a new promising approach to lentiviral gene therapy. Dr. Biffi is currently evaluating this same approach as a therapy for Tay-Sachs and Sandhoff diseases in a NTSAD-funded study entitled "Proof of concept study of HSC gene therapy for Tay-Sachs disease".

Intracerebroventricular delivery of hematopoietic progenitors results in rapid and robust engraftment of microglia-like cells

Alessia Capotondo, Rita Milazzo, Jose M. Garcia-Manteiga, Eleonora Cavalca, Annita Montepeloso, Brian S. Garrison, Marco Peviani, Derrick J. Rossi, Alessandra Biffi

A gene therapy technique called ex vivo lentiviral gene therapy isolates hematopoietic (blood) stem cells (HSCs) from a patient and then outside the body (ex vivo), the patient's own stem cells are genetically engineered with a lentiviral vector encoding a healthy copy of the missing gene. The cells are then reintroduced intravenously (by IV) into the patient with the goal of these engineered stem cells developing in to permanent cells that now supply the deficient protein. This technique has been extensively studied and is currently in clinical trials for two types of leukodystrophy, Metachromatic leukodystrophy (MLD): **NCT01560182** and Phase 2/3 trial for adrenoleukodystrophy (ALD): **NCT01896102**.

However, in a new study published December 6th led by Dr. Alessandra Biffi, HSCs genetically engineered with a lentiviral vector were delivered directly into the lateral ventricles (cerebrospinal fluid (CSF) space) in the brain with the hopes of providing faster and more direct treatment of the central nervous system. In this study, mice first received a chemotherapy drug to wipe out their own white blood cells and make room for the transplanted cells. Then mouse HSCs were genetically engineered with a lentiviral vector expressing a marker protein green fluorescent protein (GFP) and injected into the lateral ventricles (intracerebroventricular injection). As a control, other mice where treated by the same GFP+ HSCs delivered intravenously, the traditional route. Mice treated with HSCs delivered into the ventricles showed faster and greater extent of GFP+ cells in the brain. When the transplanted cells were analyzed, they displayed functional features similar to microglia, the resident macrophage-type cell of the brain. The therapy was then evaluated in a mouse model of MLD that was also made to be immunodeficient.
Intracerebroventricular cell delivery either alone or, even more consistently, in combination with intravenous delivery resulted in a greater cell engraftment in the brain as compared to intravenous delivery alone. This study identifies a new strategy to improve engraftment of genetically engineered HSCs into the central nervous system. The hope is that the improved engraftment of genetically engineered cells will allow for the treatment to take effect more quickly, before the disease has progressed further.

In the NTSAD-funded study, Dr. Biffi is now genetically enhancing HSCs with lentiviral vectors expressing the hexosamindase enzyme. Virally transduced HSCs are then being delivered to Sandhoff mice by combination intracerebroventricular and intravenous delivery. This is an exciting new development by a leader in the field of ex vivo gene therapy which is already being evaluated in GM2 gangliosidosis.

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What is “Expanded Access?"

In response to reading about clinical trials in the news, we have been receiving a number of questions about what “expanded access” or “compassionate use” means. “Expanded access," sometimes called "compassionate use," is the use outside of a clinical trial of an investigational medical product (i.e., one that has not been approved by FDA).

The FDA is committed to increasing awareness of and knowledge about its expanded access programs and the procedures for obtaining access to human investigational drugs (including biologics) and medical devices. Wherever possible, use of an investigational medical product by a patient as part of a clinical trial is preferable because clinical trials can generate data that may lead to the approval of products and, consequently, to wider availability. However, when patient enrollment in a clinical trial is not possible (e.g., a patient is not eligible for any ongoing clinical trials, or there are no ongoing clinical trials), patients may be able to receive the product, when appropriate, through expanded access.” "Expanded use" is now the FDA’s preferred terminology for this type of trial.

Read more about the requirements of Expanded Access **here**.

IntraBio Update

NTSAD is in close contact with IntraBio and received this statement to share:

"We are very pleased to inform you that IntraBio Inc and Pierre Fabre Laboratories have now concluded an agreement to enable IntraBio to gain full access to all documents related to N-acetyl-D, L-leucine and its enantiomer, owned by Pierre Fabre, to support the preparation of the required documents to seek regulatory approval in order for these clinical trials to be initiated in a timely manner.

Both companies are also engaged in ongoing discussions to explore the opportunity for Pierre Fabre Laboratories to provide further technical support for these clinical trials to be carried out by

IntraBio as the study sponsor.

With [NTSAD's] continued support, we very much look forward to ensuring that the clinical development will lead to new methods of treatment to benefit patients in these rare and life-threatening conditions where there is unquestionably a clear unmet medical need."

Haematopoietic Stem Cell Transplantation Arrests the Progression of Neurodegenerative Disease in Late-Onset Tay-Sachs Disease

Karolina M. Stepien, Su Han Lum, J. Edmond Wraith Christian J. Hendriksz, Heather J. Church, David Priestman, Frances M. Platt, Simon Jones, Ana Jovanovic, Robert Wyn

On December 7th a case study was published detailing results of bone marrow transplantation in a juvenile Tay-Sachs patient. The patient initially presented at age 7 with tremors and symptoms progressed to include ataxia, speech stammer, and swallowing problems. At the age of 15 he was diagnosed with juvenile TSD. In light of his deteriorating neurological function, the patient underwent preconditioning with busulfan, a chemotherapy agent, followed by a hematopoietic stem cell transplant (HSCT) from a matched sibling donor, and a post-transplant immunosuppression regimen. To date the patient is 23 years of age and 8 years post-HSCT has retained full donor chimerism (his white blood cells are those from the donor) and normal white blood cell Hexosaminidase A (the enzyme deficient in TSD) levels. The patient has demonstrated stabilization of his neurologic regression with improvement in swallowing dysfunction and no change in the severity of tremor. MRI of the brain at 12 months, 4 years, and 8 years post-HSCT showed no progression compared to pre-transplant scans.

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Going Big: How Massachusetts General Hospital (MGH)

Neurology is Using Big Data for Big Benefits

NTSAD-funded grants for Canavan and Late Onset natural history studies utilize NeuroBank, an online patient-centered platform to help researchers collate patient data for rare diseases. “NeuroBANK links data from an individual patient across multiple research projects to a variety of sources, from medical images to genetic data to tissue repositories.

Researchers designing neurological research studies can choose to use NeuroBANK and its standard libraries of disease-specific forms instead of creating their own databases, thus speeding the development of their study… After data are analyzed and the results are published, the entire study data set is de-identified and released into a central pool of disease-specific information available to anyone studying” that disease.

"For a biotech company to take on a drug development, especially for a rare disease, clear biomarkers and outcome measures must be in place. Determining and validating such biomarkers require lots of information: clinical and phenotypical data, DNA, disease natural histories, -omics, and images. Of course, just having the data is not enough. Compliance to regulations, legal requirements and laws, both national and international, and recommendations from governing bodies in data acquisition, curation and handling without compromising patient privacy is paramount."

Read the entire article **here**.

Join NTSAD, the Cure GM1 Foundation and be a part of the **GM1 Patient Network HERE** to accelerate treatment for GM1 Gangliosidosis! The health information of those impacted by GM1 Gangliosidosis is essential to advancing medical research and for drug developers working to translate research to the clinic and to treat patients.

COMING SOON: GM2 Patient Insight Network for Tay-Sachs and Sandhoff

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