GM1 and GM2 Infantile and Juvenile Research Day Breakout Session
NTSAD's 46th Annual Family Conference in Chicago
April 12, 2024

The GM1 and GM2 Infantile and Juvenile Breakout Session featured updates from 12 groups of researchers, and it was moderated by Allison Bradbury, PhD.

Alyssandra Rha, PhD, Children's Hospital of Orange County (CA)

Dr. Rha presented her work on genome editing in GM1 gangliosidosis (GM1). The advantages of genome editing are that it permanently corrects the genomic variant, has limited immunogenicity, and its efficacy correlates with editing efficiency. Gene editing has shown promise as a successful therapeutic approach in multiple other disorders like hereditary angioedema and acute myeloid leukemia. It is an individualized approach, but Dr. Rha thinks that greater than 90% of the 200+ genetic variants in the *GLB1* gene encoding beta galactosidase can be addressed using genomic editing. Her current work has shown that the correction of *GLB1* genetic variants leads to restoration of beta galactosidase activity, detection of lysosomal beta galactosidase, and a reduction in GM1 ganglioside.

Barbara Triggs-Raine, PhD, University of Manitoba (Canada)

Dr. Triggs-Raine talked about her work on the development of a therapy for GM2 in collaboration with M6P Therapeutics and their licensed technologies. This is a gene therapy approach that is applicable for all types of GM2 gangliosidoses and is focused on the creation and further modification of a HexM enzyme. HexM enzyme is designed based on HexA and HexB yet it seems to be twice as active as HexA and able to degrade GM2 efficiently. Further modifications of HexM allow for an even greater increase in activity and better cell entry. Pre-clinical studies in mice are underway currently, and they show that this enzyme is able to degrade GM2 in mice brain, and they are working to optimize the dose and delivery.

Ruth Jacobs, PhD, MPH, MSc, Sanofi

Dr. Jacobs spoke about their recent qualitative study of motor function limitations and adaptations in pediatric patients with GM1 and GM2 Gangliosidoses. Their study goals were to evaluate the challenges associated with both gross and fine motor function loss and the adaptions and supportive therapies used. Their perspectives were from the caregivers of these pediatric patients and data were collected by interviewing the caregivers. All caregivers indicated that these patients had issues with most gross motor functions like walking, jumping and reaching. Fine motor function loss was also indicated, including problems with drawing, buttoning and brushing teeth. Most of the patients used mobility adaptations, like a wheelchair or a walker, and supportive therapies such as physical, occupational, and speech therapy. It was concluded that there was substantial loss in both gross and fine motor function and mobility adaptions and physical and speech therapies were commonly used by these pediatric patients.

Elise Townsend, DPT, PhD, MGH Institute of Health Professions

Dr. Townsend presented her collaborative work with Dr. Michael Kiefer, DPT, PhD building a novel clinical rating scale to help determine meaningful changes in infants with GM2. The goal of their

work is to develop a scale that is brief and family-friendly, can be used for virtual and clinic visits, and measures functions that are most important to caregivers. Ultimately, it is intended to provide an appropriate endpoint for clinical trials. They collected data by interviewing families about health-related functions such as communication, feeding, vision, hand and arm use, and gross motor function. Currently, they are testing the Infantile GM2 clinical rating scale and actively recruiting participants with infantile GM2 that are under 5 years of age. They have an urgent need for newly diagnosed young infants. Participation requires 30-minute zoom visits every 45-90 days and the completion of an online survey of symptoms and function before these visits.

Mathias Schmidt, PD, PhD, JCR USA

Enzyme replacement therapy for GM2 gangliosidosis was the topic of a talk by Dr. Schmidt of JCR Pharmaceuticals' U.S. company, JCR USA. JCR Pharmaceuticals has a long history of developing therapeutic agents for multiple lysosomal storage diseases and currently they have developed and are testing a new therapy for GM2 gangliosidosis, called JR-479. This therapeutic agent utilizes their J-Brain cargo technology that enables the HexA enzyme to pass the blood brain barrier. Studies of JR-479 in mice with GM2 gangliosidosis are showing some promising results and more pre-clinical studies are under way.

Michael Przybilla, PhD, University of Minnesota

Dr. Przybilla submitted a brief video about his research at the University of Minnesota, which focuses on gene therapy and gene editing for lysosomal disorders. In mice models of GM2 and GM1, his proprietary system gene editing (PSG) approach resulted in higher levels of enzyme and improvement in both behavioral function and disease pathology. Currently, his lab is focused on getting enough enzyme from the liver into the brain. He has submitted grants for funding and plans to move toward an Investigational New Drug (IND) application with the FDA or (IND-enabling studies).

Christian Freitag, MD, Chief Medical Officer at Azafaros

Although Dr. Freitag was unable to attend in person, he provided a video update on the nizubaglustat program at Azafaros. Gisela Linthorst, the company's Head of Patient Engagement and Advocacy, was present and available for questions. Two studies were discussed, including the PRONTO study and the RAINBOW study. PRONTO is a prospective longitudinal study of neurological disease in patients with the late-infantile or juvenile onset of GM1 or GM2 gangliosidoses. It has 31 patients enrolled, data are being collected, and the results are intended to support the future development of a clinical trial of nizubaglustat. The RAINBOW study is a phase II clinical study to evaluate the safety, tolerability, pharmacokinetics, and pharmacodynamics of nizubaglustat in patients with GM2 or Niemann-Pick disease Type C (NPC). It is a randomized 12-week study that had 13 patients with GM2 and NPC enrolled, all from Brazil. Two patients have since dropped out, and this study is ongoing. An 18-month phase III study with nizubaglustat in GM1, GM2, and NPC patients is in the planning stages currently.

Passage Bio

Moderator Allison Bradbury read the following company statement**: "***In December, Passage Bio shared that they have paused enrollment of new participants in the Imagine-1 study of PBGM01, an*

investigational gene therapy, for GM1 gangliosidosis while they explore partnership opportunities for the continued advancement of the program. During this time, Passage remains committed to patient safety and all children currently enrolled in the clinical trial have continued to receive ongoing care and support. Passage remains optimistic about the potential of the Imagine-1 program for patients and looks forward to sharing further information with the community when they can."

IntraBio

IntraBio has a New Drug Application (NDA) for IB1001 for the treatment of Niemann Pick disease Type C which has been accepted for filing by the US Food and Drug Administration (FDA). The application has been given a Prescription Drug User Fee Act ("PDUFA") date of September 24, 2024, and the company anticipates hearing the outcome of the application at this time. As such, a representative from IntraBio did not present, and moderator Allison Bradbury read the following company statement:

"As part of the regulatory process and due to very strict compliance laws which limit what can be shared about a drug while it is formally under NDA review, IntraBio is unable to present at external engagements such as our annual conference. While we understand that it may be disappointing to not have an update this year, we want to emphasize the positive implications of this: the acceptance of IntraBio's NDA for NPC underscores the Agency's dedication to advancing treatments for rare diseases with huge, unmet medical need, such as GM2 Gangliosidosis.
The company has continued to keep NTSAD updated on all milestones and will continue to do so."

Queens University

Moderator Allison Bradbury read the following company statement**:** "*A phase 1/2 infantile GM2 gene therapy trial was initiated in 2021, conducted at Queens University in Kingston, Ontario, Canada, and sponsored by Taysha Gene Therapies. It had been inactive. Earlier this year, Taysha gave the license for this trial to Queens University. Currently, Dr. Jagdeep Walia and his colleagues at Queens University are pulling together data on the children who were dosed since 2021 and are hoping to secure funding and restart the trial in the near future. When there is more to share about this trial, Dr. Walia has offered to speak to our community. Meanwhile, he is open to answering any questions via e-mail. He may be reached at Jagdeep.Walia@kingstonhsc.ca or NTSAD can connect you with him."*

Terry Flotte, MD, University of Massachusetts

Dr. Flotte presented updates on the clinical trials of AAV gene therapy that UMASS is currently working on. He highlighted some of the many clinical gene therapy trials they have performed in the past and focused on one for patients with GM2. Results have shown that gene therapy using a 2-vector approach (HexA and HexB), although not preventing the disease, could deliver a functional enzyme with biological effects, accompanied by a decrease in GM2 levels. Remarkable preservation of feeding behavior was observed in multiple treated infants. Some of the challenges with this work include achieving a global distribution of the enzyme, the overall safety of the vector, including dose and route of administration, and efficacy endpoints. They are currently working on a single bicistronic HexA/HexB vector that they hope will be an even better therapeutic option.

Cyndi Tifft, MD, PhD, National institutes of Health (NIH)

Dr. Tifft presented updates on the IV Gene Therapy for Type I and Type II GM1 gangliosidosis. In May, 2019 the NIH team launched an intravenous delivery AAV9 gene therapy trial for Type 1(infantile) and Type II (late-infantile and juvenile) GM1. They have treated a total of 12 patients: 10 with Type II and 2 with Type 1 disease. The presentation focused on type II patients. The primary outcome measure of this Phase I/II trial is safety and there have been no serious adverse events attributable to the study drug. In addition, the team has seen increases in b-gal enzyme activity in CSF to the level of normal age-matched control subjects that are stable out to 3 years in the earliest treated patients. They have also seen decreases in GM1 ganglioside in CSF but not to the level of healthy controls. The decreases have been stable over 3 years for the earliest treated patients. Clinically, most patients have remained stable with declines in 3 of the patients who were further along in their disease. The patient who was pre-symptomatic has had consistent improvements. This is true for measures on the Vineland Adaptive Behavior Scale and on the Clinical Global Impressions Scale. With these encouraging results the NIH team with their UMass colleagues are planning a second trial with recommendations from FDA on outcomes that, if achieved, could lead to an application for drug approval.