National Tay-Sachs & Allied Diseases Association, Inc.

PI: Jiang, Xuntian

Progress Report - LAY SUMMARY

August 1, 2019 – January 31, 2020

Oligosaccharide Biomarkers for Disease Progression and AAV Therapeutic Efficacy in GM1Gangliosidosis

A major challenge for developing treatments for GM1 gangliosidosis (GM1) disease is difficulty in evaluation of efficacy. This is complicated by limited patient numbers, and heterogeneity in age, severity, and stage of disease progression. Biomarkers that reflect disease status could provide a valuable surrogate endpoint for assessment of treatment effect and reasonably predict clinical benefit. We have identified an oligosaccharide (carbohydrate whose molecule is composed of a relatively small number of monosaccharides) biomarker that was referred as to H3N2b and significantly elevated in the urine, cerebrospinal fluid (CSF) and plasma from GM1 patients and brains from GM1 cat model. This biomarker in GM1 cat brains was reduced in response to gene therapy. These results suggested that H3N2b was a sensitive biomarker for disease severity and progression and for assessing treatment efficacy. The goal of this project is to evaluate this marker as a surrogate outcome measure of treatment for GM1. This project will provide a much-needed tool for assessing GM1 disease severity and therapeutic efficacy.

The H3N2b and its deuterated analog d_6-H3N2b (6 hydrogen atoms in H3N2b are replaced by heavier stable isotope deuterium atoms) as internal standard are important to develop a fully-validated FDA compliant assay for accurate and precise measurement of this biomarker in clinical samples, however, they are not commercially available. We prepared H3N2b in small quantity in a pilot study in the first year. In the first 6 months of second year, we scaled up the synthesis of H3N2b and its internal standard, and obtained crude H3N2b (2.5 g) and d_6-H3N2b (1.2 g). They are contaminated with 23% isomeric interferences. We developed a high performance liquid chromatography method for purification of H3N2b and d_6-H3N2b. We have obtained 0.55 g of H3N2b with chromatographic purity > 99%. Currently we are purifying d_6-H3N2b, and expect to obtain at least 50 mg of d_6-H3N2b (> 95% chromatographic purity) by March 2020.

After completing purification of d6-H3N2b, we will develop FDA-compliant clinical assays for the oligosaccharide biomarker, determine the relationship between oligosaccharide biomarker levels and disease severity using biospecimens and clinical data collected in the NIH natural history study, and evaluate the response of oligosaccharide biomarker to AAV gene therapy through quantification of the biomarker in urine, plasma, and CSF collected in Phase 1/2 trial.