CDKL5 Program of Excellence
2021 Pilot Grant Program

Project Title: "Systems Analysis of the CDKL5-Deficiency Disorder (CDKL5-DD) Cerebrospinal Fluid Proteome"

PI: Victor Faundez, MD, PhD

Institution: Emory University

CDKL5 deficiency disorder (CDD) is a distinct and devastating genetic disease dominated by early neurological symptoms. The promise of cures and treatments, either genetic or drug-based, is still elusive. Evaluating therapies requires at hand robust biomarkers capable of informing us about disease severity and whether brain tissue has been 'repaired' by a therapy (target engagement). We posit that the collection of all proteins in a biological sample, or proteome, offers unique possibilities to identify quantitative biomarkers in cerebrospinal fluid. In this application, we will use our experience with *Cdkl5-/y* and *Mecp2-/y* mouse tissues and fluids. We propose to quantify simultaneously the expression of thousands of proteins in cerebrospinal fluid from a mouse model of CDD and controls to define a CDD pathological proteome. We focus on cerebrospinal fluid because it is accessible and amenable to longitudinal sampling in patients. Importantly, we have learned that potential biomarkers identified in the cerebrospinal fluid proteome of the *Mecp2-/y* mice cannot be revealed simply by exploring the brain proteome from these mutant animals. Thus, cerebrospinal and brain proteomes are not overlapping but complementary. This discovery is of central relevance for CDD biomarker discovery as it indicates that identification of biomarkers in cerebrospinal fluid requires their direct study. In this application, we will test the idea that there are *Cdkl5-/y* cerebrospinal disease biomarkers yet to be discovered that elude their identification by studying the *Cdkl5-/y* brain tissue proteome.