CDKL5 Program of Excellence
2021 Pilot Grant Program

Project Title: "Defining ciliary signaling and targets in CDKL5 Deficiency Disorder"

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CDKL5 deficiency disorder (CDD) is defined by loss of the CDKL5 kinase, an enzyme thought to phosphorylate and regulate cellular signaling substrates. Currently, the activities of CDKL5 are not well understood, nor well-linked to the neurological deficiencies found in patients. A new hypothesis links CDKL5 to signaling concentrated in the primary cilium. The cilium is a microtubule-based structure connecting neural and endocrine receptor signals outside the cell to neural signaling important for cognitive and motor function. This proposal will first focus on validating the "ciliary hypothesis" for CDKL5 by first discovering CDKL5 interacting regulatory proteins and substrates, and key proteins from related diseases like Rett syndrome to build a CDD protein interactome. Using superresolution microscopy and signaling assays, we will test links from CDD interactome proteins to ciliary trafficking and signaling to discover how CDKL5 couples to neural signaling. Further work will profile the localization and signaling of >20 known ciliary G-protein coupled receptors in the brain of CDKL5 KO versus normal mice or CDKL5 KO iPS cells. These tests will link molecular changes in specific drugged GPCRs to CDKL5 deficiencies created in iPS cells or mice. By identifying known, "therapy-ready" GPCR targets altered in CDD, we seek to define actionable targets for immediate clinical use.