CDKL5 Program of Excellence
2018 Pilot Grant Program

Project Title: "High Content Screen to identify drug targets for the neuronal manifestations of CDKL5 deficiency"

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CDKL5 Deficiency Disorder (CDD) is a neurological syndrome caused by mutations in the cyclin-dependent kinase-like 5 (CDKL5) gene characterized by early-onset epileptic infantile spasms, cognitive disabilities, and drug-resistant epilepsy. A key role for CDKL5 in neuronal maturation and function is underscored by the fact that it is highly expressed and developmentally regulated in the brain. In addition, neuronal CDKL5 has been implicated in the control of neuronal morphology and synaptic function. Together, the detrimental central nervous system (CNS) clinical manifestations and the lack of a complete understanding of the CDKL5-dependent cellular mechanisms represent urgent unmet needs to uncover the molecular basis for CDD and identify therapeutic interventions. Despite the very limited knowledge on the molecular mechanisms underlying CDD, previous work has indicated an interplay between CDKL5 and primary cilia.

Primary cilia are sensory cellular antennae with a key role in brain homeostasis and development. In the CNS, they are thought to orchestrate the morphological and the physiological maturation of newly generated neurons and deletion of cilia in adult-born neurons results in defects in dendritic refinement and synapse formation. Mutations in genes required for cilia assembly and/or function underlie ciliopathies, which are a broad spectrum of disorders with severe neurodevelopmental outcomes including intellectual disability and various neurological deficits. Previous work found an association between CDKL5 and cilia. Consistent with these previous findings, our preliminary data indicate an altered ciliation in the hippocampus of Cdkl5 knockout mice. Here we propose to gain insights into the role of CDKL5 in neurons by testing the hypothesis that CDKL5 is a novel ciliary gene with a role in neuronal maturation and function. For this purpose, we will perform a phenotypic screen in rat Cdkl5-deficient neurons to identify small molecule compounds that rescue the neuronal cilia phenotype. We believe that our unbiased phenotypic screen approach will likely provide important insights into the cell biology of CDD and potentially identify novel drug-target candidates of CDKL5.