# CDKL5 Program of Excellence
# 2022 Pilot Grant Program

**Project Title:** "Utilizing patient iPSC-derived neurons to determine the functional consequences of longer cilia in CDKL5 Deficiency Disorder (CDD)"

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The landscape for therapeutic development in neurodevelopmental disorders was transformed by the seminal discovery by Shinya Yamanaka that a patient's skin or blood sample can be transformed into stem cells (called induced pluripotent stem cells, or iPSCs) that can in turn be transformed, or differentiated, into brain cells (also known as neurons and glia) to develop human preclinical in vitro model systems. We are applying this technology to advance the understanding of CDKL5 Deficiency Disorder (CDD), a neurodevelopmental disorder in which there are few therapeutic options beyond the management of symptoms, which includes seizures, visual impairment, intellectual disability, and other developmental delays. Previous studies in rodents found that an organelle structure in neurons, called cilium, is elongated with loss of CDKL5. The signaling mechanisms involved in cilia development are known to be critical for neuron development, but it is not known how changes in cilia structure affects the ability of neurons to respond to developmental cues and whether this plays a role in the functional consequences of CDKL5 loss in neurons. Here, we propose to use CDD patient-derived iPSCs to generate neural progenitors (developmental precursors to neurons) and mature neurons to see if CDD-derived cells are deficient in their ability to respond to signaling molecules involved in regulating these developmental pathways. The proposed studies will help determine if these pathways contain potential druggable targets for modulating deficits in CDD-derived neurons.