CDKL5 Program of Excellence
2025 Pilot Grant Program

Project Title: "Development of a tau hyperphosphorylation assay in CDKL5 deficiency disorder iPSC-derived neurons"

PI: Jedd Hubbs, PhD

Institution: Boston Children's Hospital

Therapeutic development for neurodevelopmental disorders requires teamwork across many disciplines from preclinical tool development to clinical trial readiness with natural history studies. We aim to develop better preclinical models to improve translation of preclinical findings to the clinic by screening in cells that are most similar to the cells affected in the target disease. We are leveraging Shinya Yamanaka's discovery that a patient's skin or blood cells can be transformed or induced to become stem cells (called induced pluripotent stem cells, or iPSCs). These cells can then be directed to become brain cells (such as neurons and glia). In addition to using brain cells, the feature (or endpoint) of the cells that is leveraged for drug screening should be relevant to patient biology. We have previously found that iPSC-derived neurons from patients with CDKL5 Deficiency Disorder (CDD) are more active than healthy control neurons, something that reflects seizure activity of patients with CDD and can be used to identify compounds that improve seizure burden. However, it's not clear that improving seizure burden will improve other patient outcomes, including deficits in movement or learning and memory. Here, we propose to use CDD patient iPSC-derived neurons to develop a novel assay or screening tool for CDD. In CDD neurons, a protein called tau becomes excessively modified, which destabilizes neuronal scaffolding and disrupts protein transport inside neurons. We hypothesize this plays a role in both the seizures and developmental delays in CDD by disrupting neuronal connectivity. Our goal is to screen FDA-approved compounds to understand whether this endpoint can be reversed in CDD neurons and whether this can be used for future screens as a novel endpoint.