Penn Medicine
Orphan Disease Center

CDKL5 Program of Excellence
Pilot Grant Program

Application Title: Identifying a Neural Circuit Readout for CDKL5 Disorder

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CDKL5 disorder is an X-linked, monogenetic disease that results in early-onset epileptic seizures and persistent intellectual disability. Mouse models of CDKL5 disorder recapitulate behavioral phenotypes seen in human patients, but not the prominent seizure phenotype. Given this discrepancy, we propose to address three questions: 1) Do *Cdkl5* mutant mice show alterations in seizure susceptibility? 2) Could spontaneous seizures be suppressed by the genetic background of different mouse strains? and 3) Do mice lacking *Cdkl5* display features of epilepsy at the neural circuit level? We plan to assess seizure susceptibility in two independent mouse models of CDKL5 disorder, a knockout and a patient mutation knockin, in mice with different genetic backgrounds. In collaboration with Dr. Douglas Coulter at Children's Hospital of Philadelphia, we also plan to examine excitation-inhibition balance in wild-type versus CDKL5-deficient neural networks *in vivo* in mice. Our goal is to identify reliable neural circuit markers of seizure susceptibility that can be reciprocally validated in mice and in human. These markers can serve as potential readouts for future drug and compound screens targeting CDKL5 disorder, and are imperative for the assessment of novel therapeutics in both preclinical and clinical trials.