# CDKL5 Program of Excellence
# Pilot Grant Program

**Application Title:** CDKL5 deficiency disorder cortical organoids for drug testing and reversibility potential

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The lack of live human brain cells for research has slowed progress toward understanding the mechanisms underlying the CDKL5 deficiency disorder. A human model using reprogrammed patient somatic cells offers an attractive alternative as it captures a patient's genome in a stem cell state. Scientists in the Muotri lab can coax these stem cells into brain organoids or "mini-brains". These self-assembled, tridimensional structures mimic early stages of neurodevelopment of that individual in the lab. When comparing mini-brains from CDKL5 mutation carrying individuals to those derived from family-related non-affected individuals, we observed several alterations in neurons carrying the mutant CDKL5 gene. Thus, the disease-in-a-dish approach allows for progressive time-course analyses of target cells, offering a unique opportunity to investigate the cellular and molecular alterations before symptomatic onset. Here, we propose to test the efficacy of promising compounds in CDKL5-mutant mini-brains. Working with several patients is also important for understanding how brain cells derived from diverse human genetic backgrounds respond to specific drugs. Finally, we also plan to confirm reversibility of the disease condition by correcting the genetic mutation in this human model, as a proof-of-principle for future gene therapies.