Penn Medicine

the orphan disease center

CDKL5 Program of Excellence
2019 Pilot Grant Program

Project Title: "CDKL5 Syndrome cortical organoids for drug testing and reversibility potential" (2017)

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We have built the first human model to understand how CDKL5 mutations impact brain development. Starting from human pluripotent stem cells, the Muotri lab has developed a unique 3D protocol to generate functional brain organoids. At the cellular and molecular levels, these organoids mimic the gene expression and cellular diversity/organization found in the human fetal brain. At the functional level, we can detect brain oscillatory waves, strongly suggesting that the neural connectivity networks self-assembled as expected. Importantly, these brain organoids can be created from cells derived from CDKL5 Deficiency Syndrome patients and healthy subjects (controls). When compared to organoids derived from controls, brain organoids carrying different CDKL5 mutations displayed several molecular and cellular phenotypes, indicating eventual therapeutic opportunities for this syndrome. For the continuation project, we will take advantage of the human brain organoid model to test for pharmacological interventions and gene therapy approaches, as well as to validate some of the molecular targets of CDKL5 in human neural cells.