Penn Medicine

the orphan disease center

CDKL5 Program of Excellence
2019 Pilot Grant Program

Project Title: "High-throughput drug screening platform for CDD cortical organoids"

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CDKL5 deficiency disorder (CDD) is caused by mutations in the cyclin-dependent kinase-like 5 gene, a member of a highly conserved family of serine-threonine kinases. Much effort has been made in order to develop effective therapies for controlling seizures and improve patient's quality of life, but it is still hampered by the limited knowledge of CDKL5's role and the lack of screening models. The unavailability of live human brain cells for research has blocked progress toward understanding mechanisms behind mental disorders. Pluripotent human stem cells have been successfully generated from early-stage human embryos or by cellular reprogramming methods (iPSCs) and can give rise to various cell types. In this context, iPSC-derived three-dimensional cortical organoids can ultimately serve as a valid predictive pre-clinical translational model for studying disease mechanisms. Our group already generated cortical organoids to unveil the molecular basis of CDD electrophysiological phenotypes in a low-throughput fashion. In a complementary approach, StemoniX develops and manufactures human iPSC platforms for pharmaceutical drug discovery and research in a high-density screening plate (-384well format) with a single spheroid per well. Each spheroid is composed of mature cortical neurons and astrocytes and displays spontaneous synchronized neuronal activity, readily detectable in the form of calcium oscillations. This advanced 3D neural platform displays highly consistent functional performance across independent wells and plates, which enables their use to investigate the effect of compounds on neural activity in a highly reproducible fashion. Therefore, on a collaborative basis, we will generate a 3D screening platform to identify potential targets able to ameliorate functional alterations of CDD neurons that will be further validated in cortical organoids. We genuinely believe that our efforts will profoundly impact the knowledge about CDD therapy and will push the field to the next level.