

CDKL5 deficiency disorder (CDD) is an X-linked, intractable, early-onset seizure disorder without an effective treatment. In addition to seizures, mutations in the CDKL5 gene cause neurodevelopmental delays, motor dysfunction, and autistic behaviors. To identify compounds that may help restore normal function, scientists at UCSD used a custom StemoniX microBrain 3D model derived from a patient with CDD.

microBrain 3D can represent specific patient phenotypes.

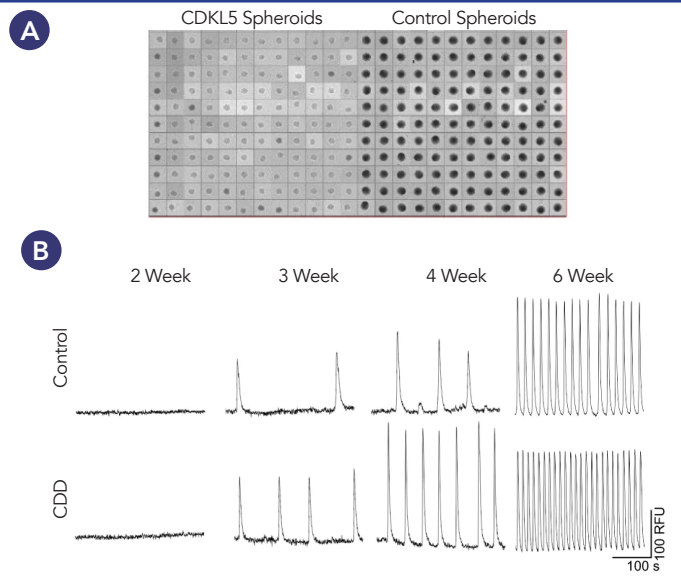


Figure 1. (A) microBrain 3D spheroid platforms were generated from patient-derived and control iPSCs. Brightfield staining shows differences between neurosphere shape and size. (B) Spontaneous activity of both control and diseased spheroids was measured at 2, 3, 4, and 6 weeks. CDD spheroids showed a higher activity level than control spheroids beginning at week 3.

Platform design allows for rapid screening and analysis.

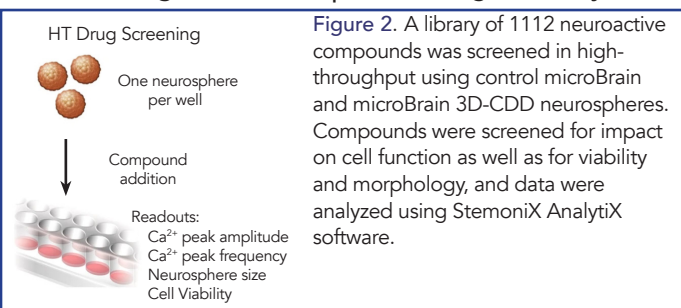


Figure 2. A library of 1112 neuroactive compounds was screened in high-throughput using control microBrain and microBrain 3D-CDD neurospheres. Compounds were screened for impact on cell function as well as for viability and morphology, and data were analyzed using StemoniX AnalytiX software.

AnalytiX analysis rapidly quantifies spheroid function.

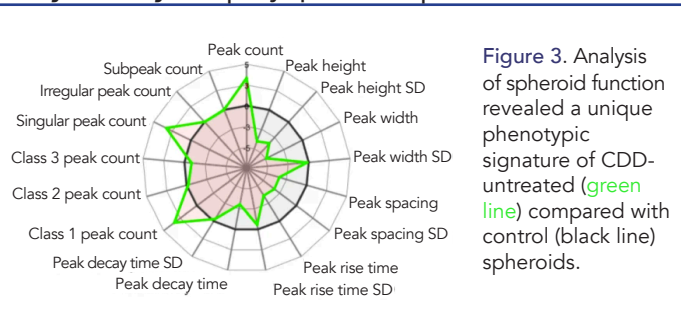


Figure 3. Analysis of spheroid function revealed a unique phenotypic signature of CDD-untreated (green line) compared with control (black line) spheroids.

Recovery analysis identifies the most effective compounds.

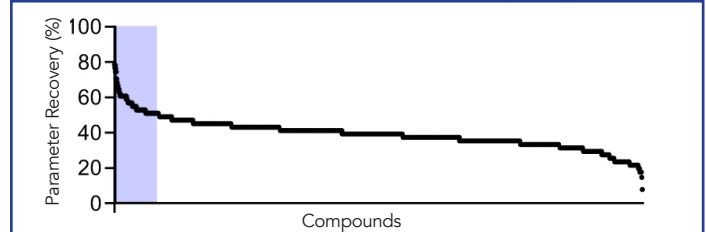


Figure 4. AnalytiX scalar perturbation of parameter recovery identified the top 25 compounds (blue) with more than 60% rescue of the functional parameters shown in Figure 3.

Functional rescue is multiparametric and dose dependent.

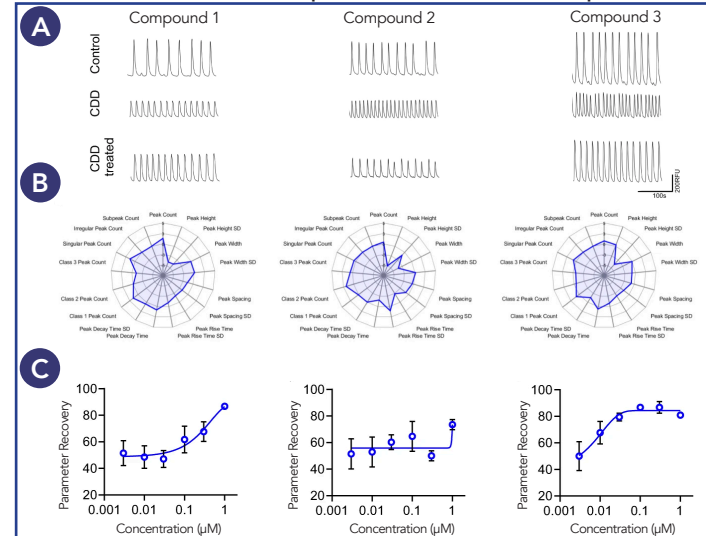


Figure 5. (A) microBrain and microBrain 3D-CDD activity before and after compound addition. (B) Spider plots showing restored function of microBrain 3D-CDD following treatment with each of three representative compounds. (C) Dose-response curves for each of the three compounds showing percent parameter recovery.

microBrain 3D spheroids

- Identify new targets and hits using custom platforms and high-throughput screening.
- Are highly adaptable and can be created from healthy and patient populations.
- Enable rapid, high-throughput drug discovery and functional rescue across multiple cellular processes.
- Place human biology at the front of CNS-based drug discovery.

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