StemoniX

Enabling Medicine to Work the First Time

Application Summary

Disease Modeling with iPSCs to Accelerate Drug Discovery

Rett syndrome (RTT) **is a rare autosomal dominant neurodevelopmental disorder arising from spontaneous mutations in the MECP2 gene on the X chromosome.** Individuals with RTT experience severe neurological complications including progressive loss of motor skill, speech, and behavioral functions. To identify potential therapeutics for treating Rett syndrome, we generated and screened iPSC-derived microBrain 3D spheroids from healthy control and patient donors to identify compounds and target pathways that rescued the patient derived microBrain 3D-RTT phenotype.

microBrain 3D and microBrain 3D-RTT show similar structural and cellular composition.

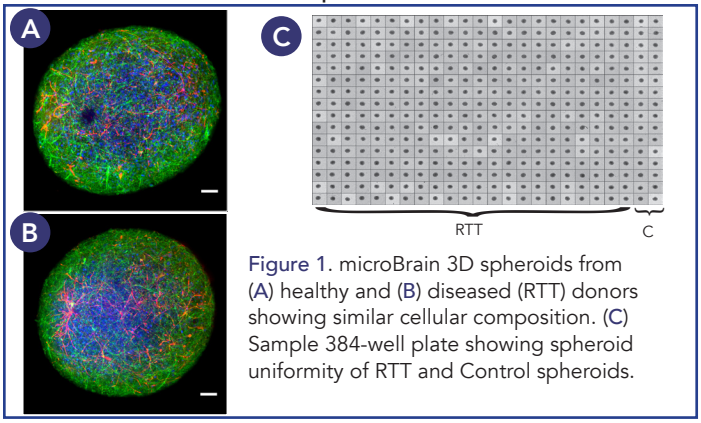

Figure 1. microBrain 3D spheroids from (A) healthy and (B) diseased (RTT) donors showing similar cellular composition. (C) Sample 384-well plate showing spheroid uniformity of RTT and Control spheroids.

Phenotypic differences were identified between healthy and disease spheroids. RTT spheroids showed altered electrophysiology and decreased neurite outgrowth.

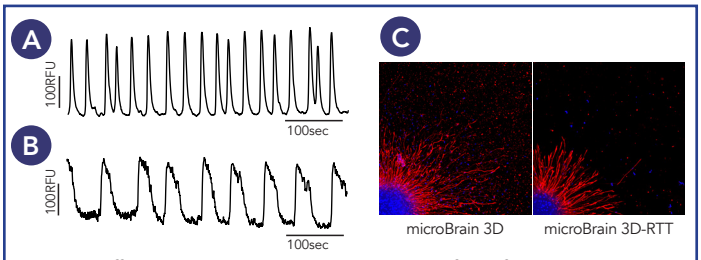

Figure 2. Differences in the electrophysiological profiles of (A) microBrain 3D and (B) microBrain 3D-RTT spheroids. (C) Comparison of neurite outgrowth.

Phenotypic screening of microBrain 3D-RTT spheroids identified compounds that 'rescued' the disease phenotype.

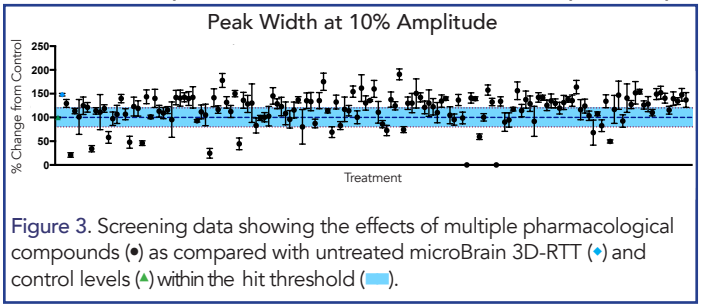

Figure 3. Screening data showing the effects of multiple pharmacological compounds (•) as compared with untreated microBrain 3D-RTT (♦) and control levels (▲) within the hit threshold (▬).

Hit identification and prioritization by multiparametric analysis allows differentiation between compounds with no, partial, and near complete phenotypic rescue.

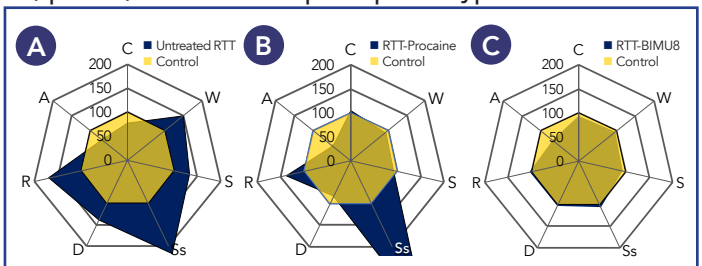

Figure 4. Multiparametric fingerprints for (A) control microBrain 3D and untreated microBrain 3D-RTT, (B) procaine, and (C) BIMU8. Note the near complete rescue of the RTT phenotype by BIMU8.

Multiple target pathways and potential development approaches were identified with the native human neurobiology of microBrain 3D-RTT.

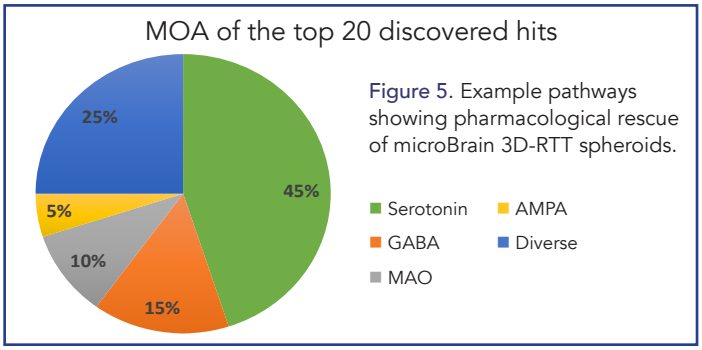

Figure 5. Example pathways showing pharmacological rescue of microBrain 3D-RTT spheroids.

microBrain 3D technology

- *Enables* iPSC-based disease modeling and high throughput screening.
- *Provides* native human biology to uncover multiple potential therapeutic pathways.
- *Accelerates* drug discovery by combining disease models and HTP screening in a single, relevant human-based preparation.

For more information on this or other custom disease models, please contact us at info@stemonix.com

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