PhD Open Days

Engineering a Thalamocortical Assembloid-on-a-chip to Model Circuit Dynamics in SYNGAP1-related encephalopathy

PhD Program in Bioengineering and Biosciences

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BACKGROUND

SYNGAP1-related encephalopathy (SYNGAP1)

- Rare neurodevelopmental disorder (NDD), caused by *de novo* missense or loss of functions mutations in *SYNGAP1* gene.
- *SYNGAP1* encodes a synaptic RasGAP protein (SynGAP1) which acts as a negative regulator of excitatory synaptic strength by inhibiting RAS and RAP pathways, essential for modulating AMPA receptor trafficking during synaptic plasticity.

Clinical Features

- Intellectual Disability
- Autism Spectrum Disorder (ASD)
- Epilepsy
- Sleep problems
- Speech & walking impairments
- Behavior impairments
- **Sensory Processing Impairments (SPI)**

Poorly studied and understood

~100 % Hallmark of SYNGAP1

Auditory, visual, tactile hyper and hypo- responsiveness

(high pain thresholds, acute touch avoidance…)

QUESTION

Is SPI more than a subjective change in feeling?

Could proper processing of external stimuli be essential for modulating the cortical circuits required for higher-order cognition?

Abnormal processing of external stimuli may be a primary mechanism driving broader cognitive deficits, such as:

ASD

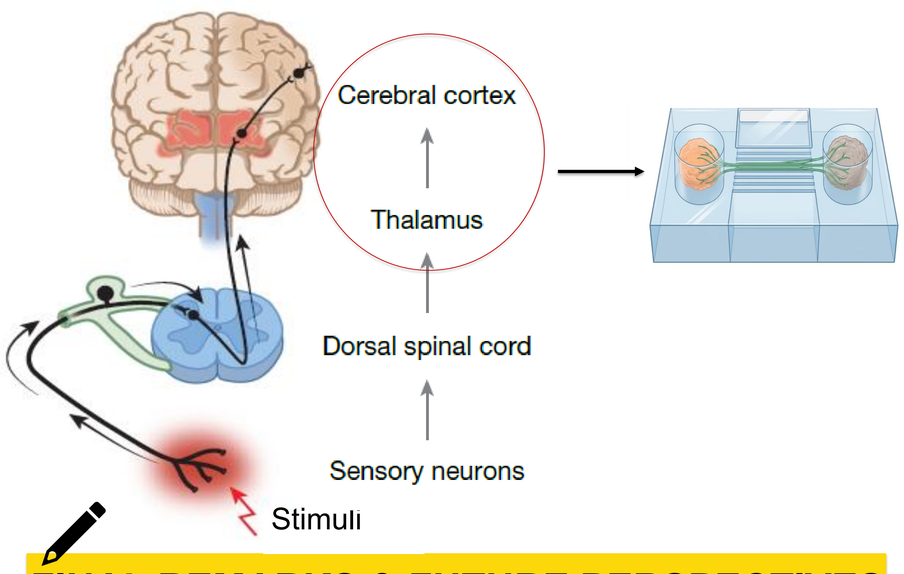
Behavioral adaptation and learning deficits

Maladaptive behaviors (e.g., risky behaviors, self-injury).

SCOPE

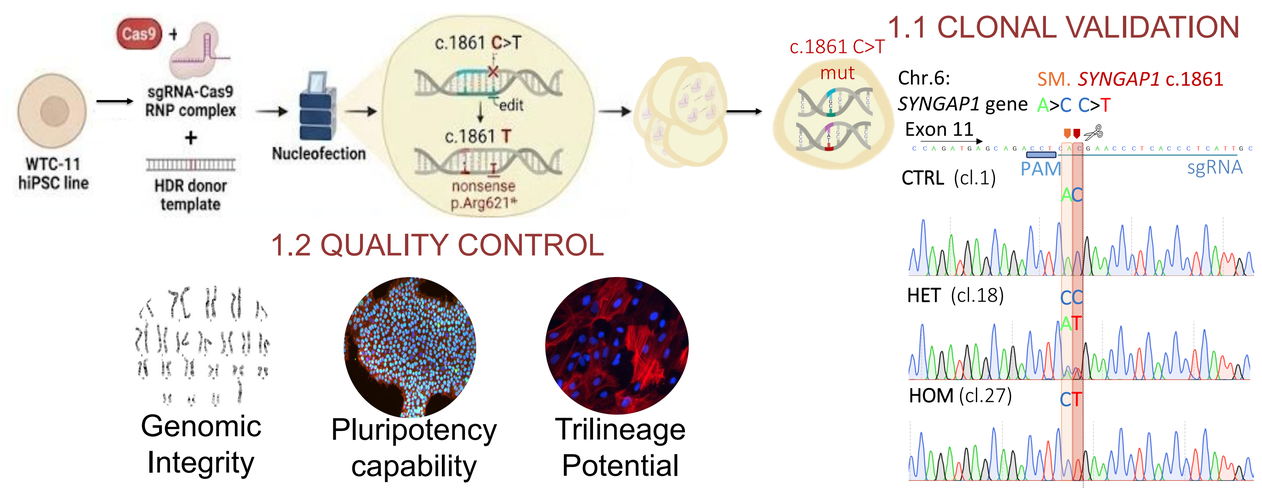
In a haploinsufficient SynGAP1 mouse model, altered sensory processing is linked to thalamocortical circuit dysregulation, directly impairing behavioral adaptation and learning.

Engineering a Thalamocortical Assembloid-on-a-chip to model circuit dysfunction in SYNGAP1 using gene edit human induced pluripotent stem cells (hiPSCs) harboring a patient-specific mutation.

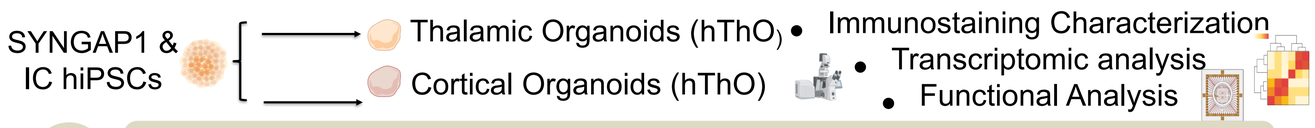


STRATEGY & RESULTS

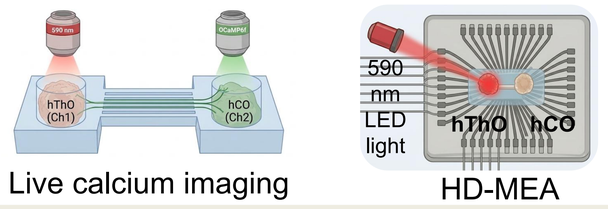
1 Generation of an isogenic SYNGAP1 c.1861C>T hiPSC model by gene editing



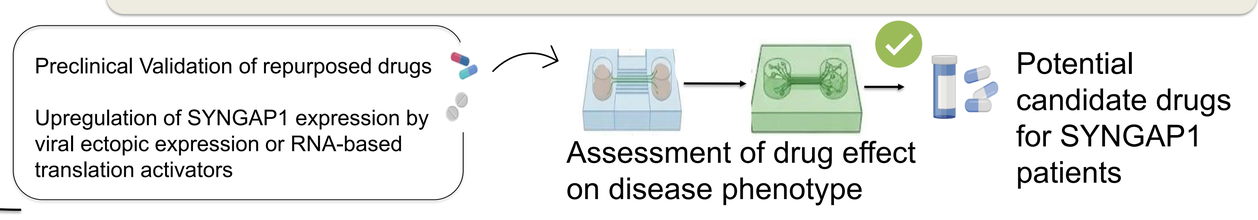
2 Modeling SrE in Brain Region-Specific Organoids



3 Engineering the Thalamocortical Assembloid-on-a-chip



4 Validation of the Thalamocortical assembloid-on-a-chip as a plataform for Drug Testing



FINAL REMARKS & FUTURE PERSPECTIVES

Successfully generated a hiPSC isogenic model of the c.1861C>T *SYNGAP1* mutation via CRISPR-Cas9 homology-directed repair (HDR), comprising unedited, heterozygous, and homozygous clones

This platform offers unprecedented physiological fidelity for modeling SPI in SYNGAP1, advancing neural biomarker discovery and targeted sensory therapies. Additionally, it can capture absence seizures, a key feature of thalamocortical dysfunction in SYNGAP1

Beyond SYNGAP1, this workflow provides a human-relevant, high-throughput NAM alternative to animal models for other NDDs (e.g., ASD) characterized by thalamocortical dysconnectivity

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