Developing a scalable hiPSC-derived blood-brain barrier model

Studying barrier opening by microbubbles and focused ultrasound

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Introduction

One of the major challenges in curing cognitive disorders is the blockage of therapeutics by the blood-brain barrier (BBB).

Transient barrier opening using microbubbles driven into oscillation by focused ultrasound is a promising technique. However, mechanisms remain elusive, partly due to differences in physiology and anatomy between lab animals and humans.

This research aims at developing a human BBB model using scalable techniques and materials for testing transient opening of the BBB for drug passage using microbubbles and focused ultrasound.

Targets of the project:

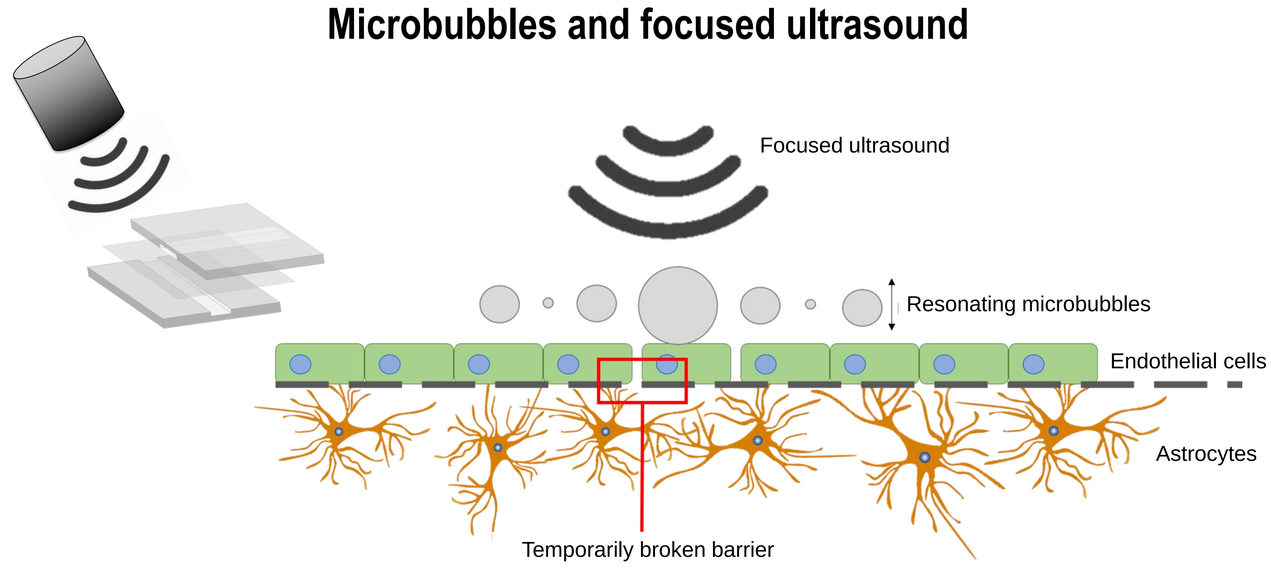
→ BBB model using stemcell-derived spheroid-on-chip.

- In suspension astrocyte differentiation protocol.
- Characterization of astrocytes.
- Test cell viability on the scalable BBB chip.

→ Testing barrier function and transient opening of BBB.

- Optimize coculture and monitor barrier.
- Develop and test microbubble producer and injector.

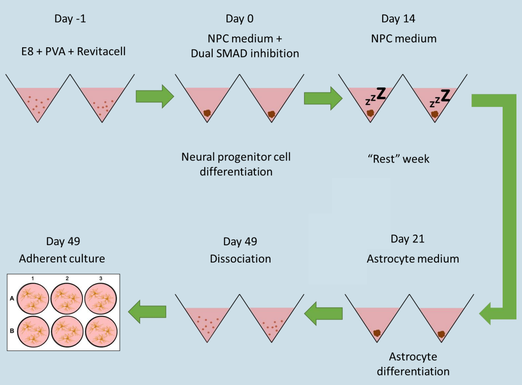
Microbubbles and focused ultrasound

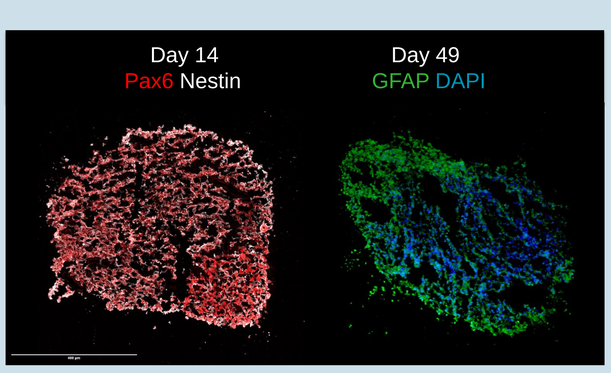


1. Astrocyte differentiation in suspension

For scalability, a workflow that is fully in suspension is preferred so it can be applied to a bioreactor.

Staining of neural progenitor cell markers Pax6 and Nestin at day 14 and astrocyte marker glial fibrillary acidic protein (GFAP) at the end of differentiation (day 49) were positive.

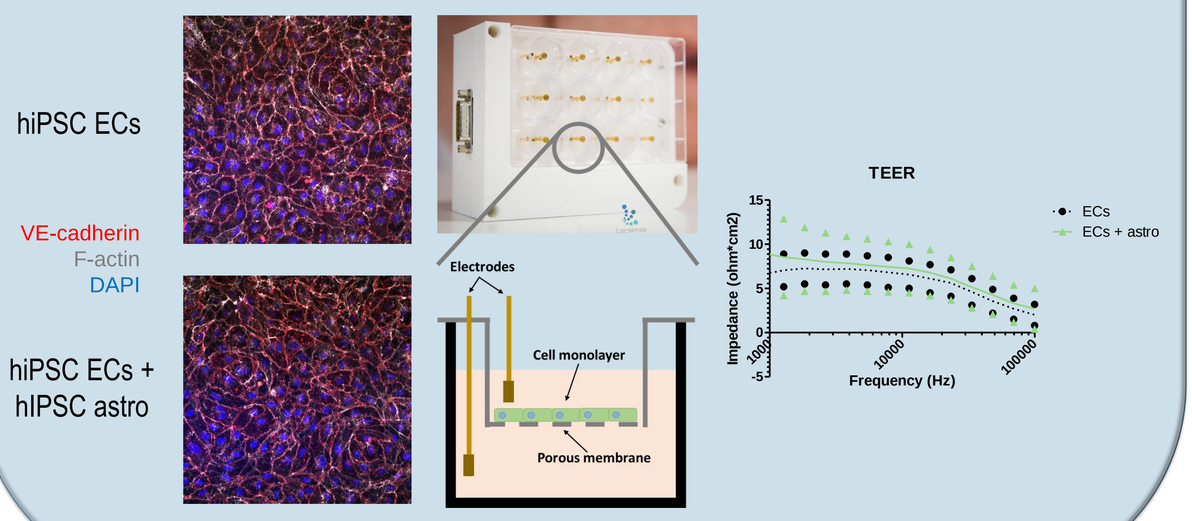




2. Barrier function in coculture

Coculture of hiPSC-derived endothelial cells and astrocytes were optimized in a transwell.

Monoculture and coculture have similar barrier function in EGM2 medium.

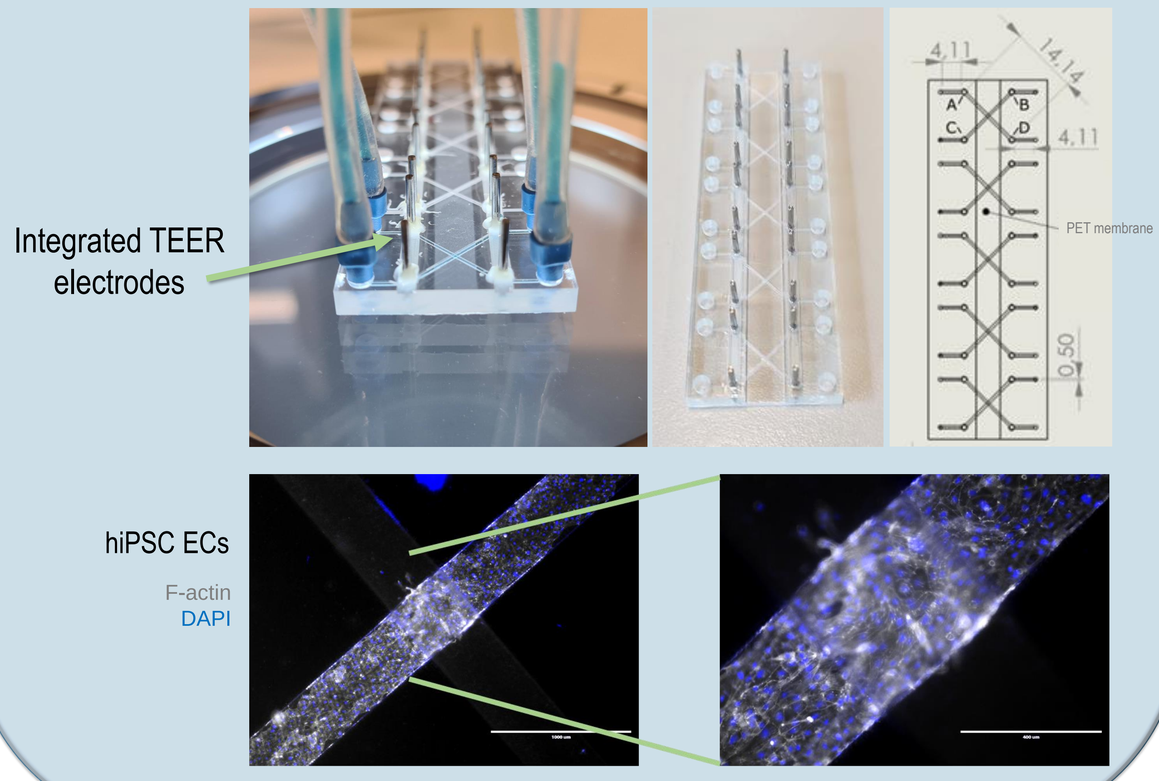


3. First steps toward a BBB on chip

The BBB chip is fabricated in cyclic olefin copolymer for scalability. The top and bottom channel is separated by a PET membrane with 3 µm pores.

Micronit is working towards making the chip commercially available after the end of the project.

hiPSC-derived endothelial cells showed good survival after 4-day culture on a rocking platform.



Conclusion

The protocols of hiPSCs culture and astrocyte differentiation in suspension were characterized and can be implemented in further upscaling.

The devices were constructed using scalable techniques that can be implemented in industry.

First steps were made in developing a BBB model for evaluation of transient barrier opening by microbubbles and focused ultrasound.