Human iPSC-based blood–brain barrier models as predictive tools for CNS drug development

Catarina M. Gomes[1,2], Elisabetta Traggiai[2], Andreas Hierlemann[1], Agostino Cirillo[2], Mario Modena[1]
[1]D-BSSE, ETH Zurich, Basel, Switzerland, [2]BioMedical Research, Novartis Pharma AG, Basel, Switzerland

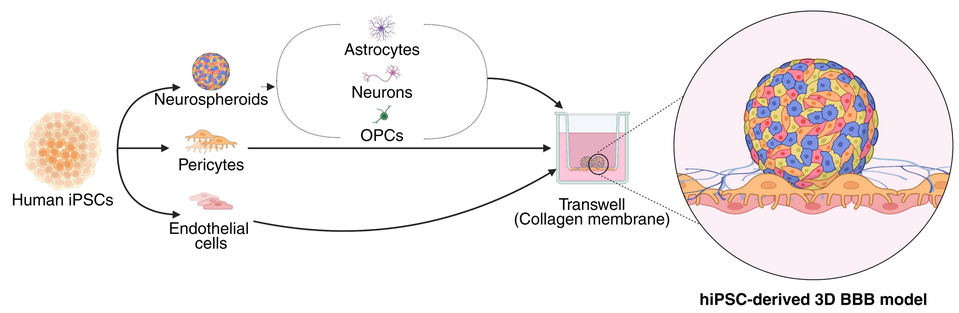
1 Introduction

The human blood–brain barrier (BBB) is a highly specialized and dynamic multicellular interface that strictly regulates molecular and cellular exchange between the systemic circulation and the central nervous system (CNS). Modeling the BBB still relies greatly on animal models, although these do not fully recapitulate human-specific neurovascular interactions and CNS drug permeability, which limits their predictive value for translational research.

2 Aim

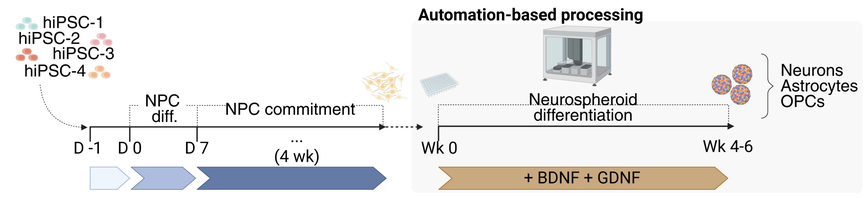
Develop a robust hiPSC-derived model that recapitulates key cellular, structural and functional features of the native barrier.

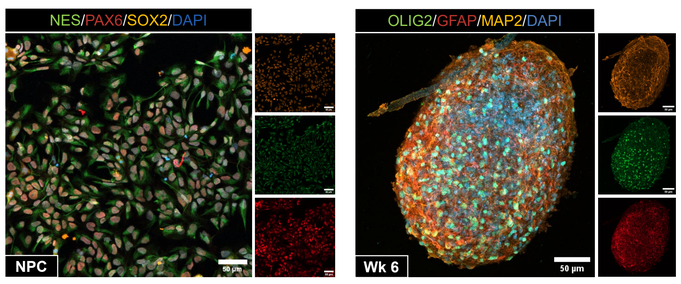
3 Experimental strategy



4 Results

4.1 Neurospheroid platform

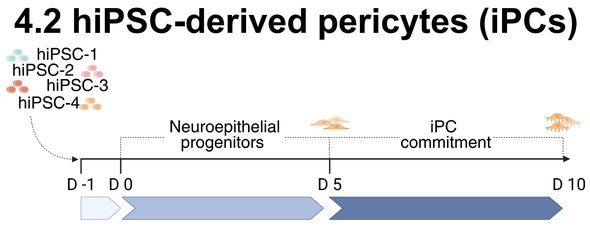


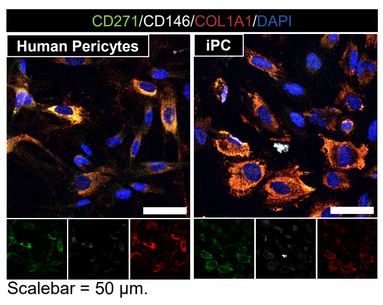


Acquired in a Zeiss LSM 980 – Airyscan 2/MP (inverted), 32X objective (water immersion). Scalebar = 50 µm.

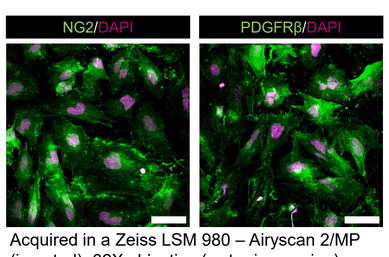
- Neurospheroids contain neurons, astrocytes, and oligodendrocyte progenitor cells (OPCs).
- The platform enables robust, high-throughput, and semi-automated generation of a hiPSC-derived 3D CNS model.

4.2 hiPSC-derived pericytes (iPCs)

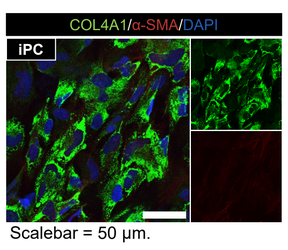




Scalebar = 50 µm.



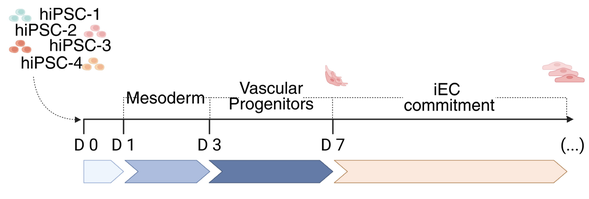
Acquired in a Zeiss LSM 980 – Airyscan 2/MP (inverted), 32X objective (water immersion). Scalebar = 50 µm.



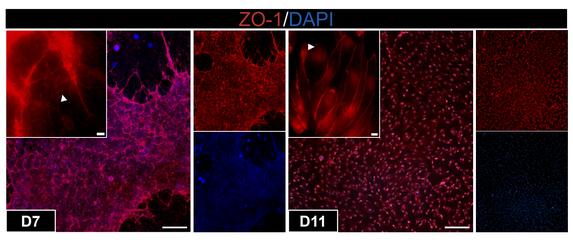
Scalebar = 50 µm.

- iPCs express key brain pericyte markers (NG2, PDGFRβ, amongst others) and show low expression of the mural cell marker α-SMA.

4.3 hiPSC-derived endothelial cells (iECs)

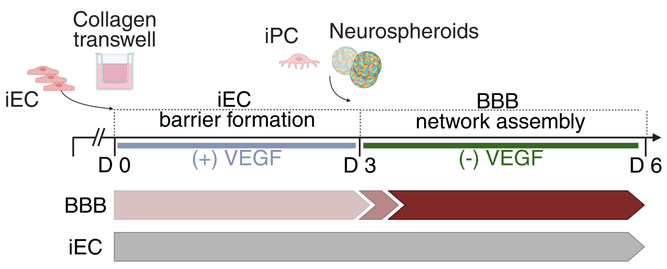


- iEC express ZO-1 at the early vascular progenitor stage (day 7) and display an elongated morphology in the absence of flow.

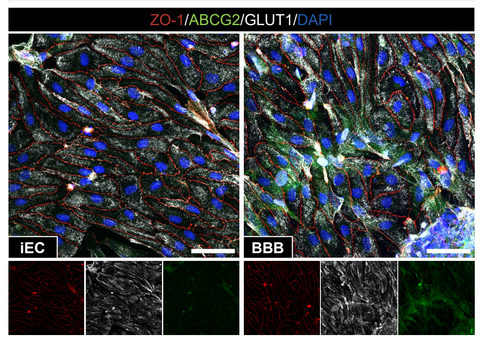


Acquired in a widefield microscope, Nikon Eclipse Ti2-E (inverted). Scalebar = 10 (zoom-in images) and 200 µm.

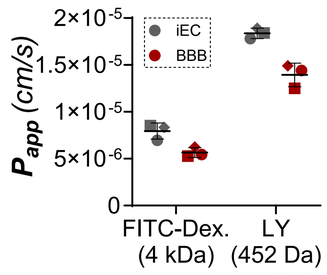
4.4 A fully hiPSC-derived BBB model



iEC-BBB phenotype

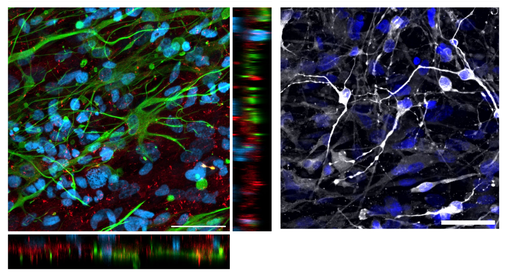


BBB permeability



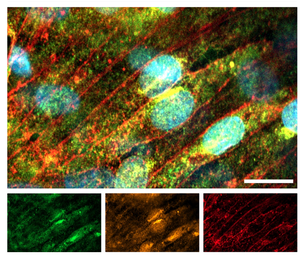
Data are presented as mean ±. SD. Points represent 3 biological replicates. P_{aap} is measured using Spark (Tecan) plate reader.

Neural compartment phenotype



Acquired in a Zeiss LSM 980 – Airyscan 2/MP (inverted), 32X objective (water immersion). Scalebar = 50 µm.

Brain shuttle protein expression



Scalebar = 50 µm.

- iECs express brain microvascular endothelial markers, including tight junction protein ZO-1, transporters (ABCG2, GLUT1), and shuttle proteins (TfR, CD98hc). The iEC-BBB model exhibits reduced permeability to small molecules, compared to monoculture controls.
- Neurons and astrocytes display a homeostatic-like morphology under BBB co-culture conditions.

5 Conclusion

The hiPSC-derived BBB model system provides a human-relevant platform for investigating drug transport, neurovascular interactions, and potentially BBB dysfunction in neurodegenerative diseases. It is ultimately aimed at accelerating preclinical development of CNS-targeted therapeutics.

Partner/Sponsor:
NOVARTIS

Contact:
Catarina M. Gomes | catarina.monteiro@bsse.ethz.ch
ETH Zurich, D-BSSE
www.bel.ethz.ch