Blood-brain barrier on-a-chip for high-throughput barrier and transport studies

Arya Lekshmi Nair[1,2], Jeroen Heijmans[1], Tania M. Fowke[1], Rumaisha Annida[1], Ka Yen Liu[1], Arnaud Nicolas[1], Maria Pontier[1], Wouter Strijker[1], Remko van Vught[1], Henriëtte Lanz[1], Helga E. de Vries[2], Nienke R. Wevers[1]

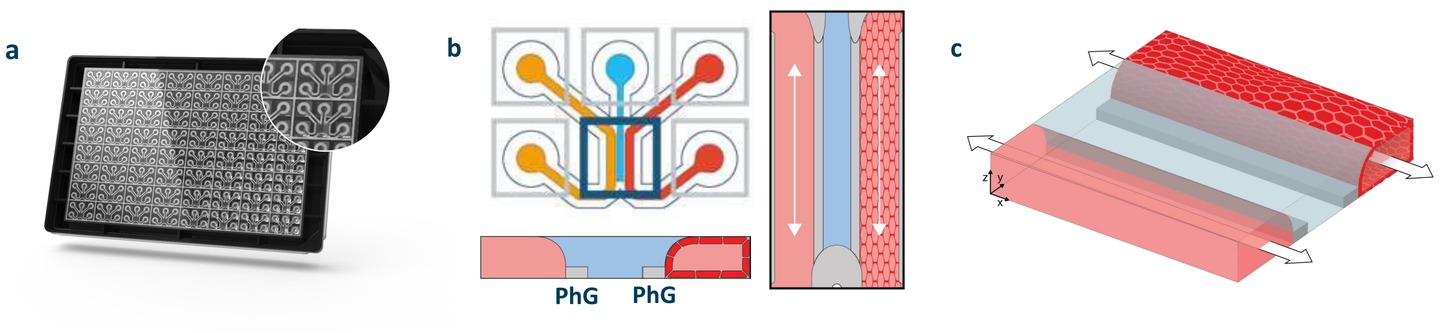
[1]MIMETAS BV, Oegstgeest, The Netherlands; [2]Department of Molecular Cell Biology and Immunology, Amsterdam UMC-VUmc, Amsterdam, the Netherlands

BBB model summary

A key aim of in vitro blood-brain barrier (BBB) research is to provide biologically relevant, predictive, and easy-to-use human models for applications such as toxicity and transport. We present a 3D microfluidic primary human brain microvascular endothelial cell (HBMEC) BBB model with relevant junction and transporter expression, tight and selectively permeable barriers, response to known toxicants, and suitability for high-throughput, on-chip TEER measurements.

Building a BBB model in the OrganoPlate®

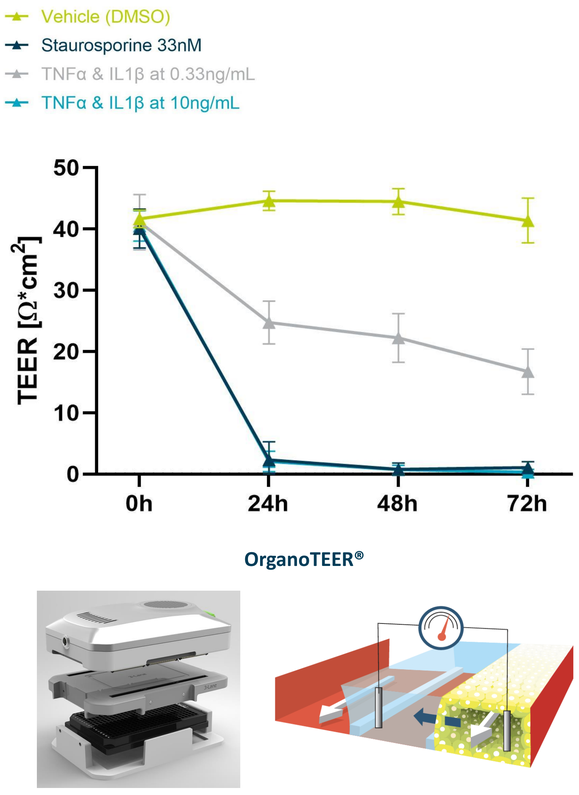
The OrganoPlate is a 3D culture plate with up to 64 (3-lane configuration) microfluidic tissue chips built into a standard 384 well plate. Extracellular matrix (ECM) gels are patterned in microfluidic channels using PhaseGuides™. After gelation of the ECM, HBMECs are seeded in the perfusion channel. The plate is placed on the MIMETAS OrganoFlow® rocker, and under perfusion cells form functional 3D microvessels within 6–7 days. Microvessels are accessible from both apical and basolateral sides, making them highly versatile for assays.



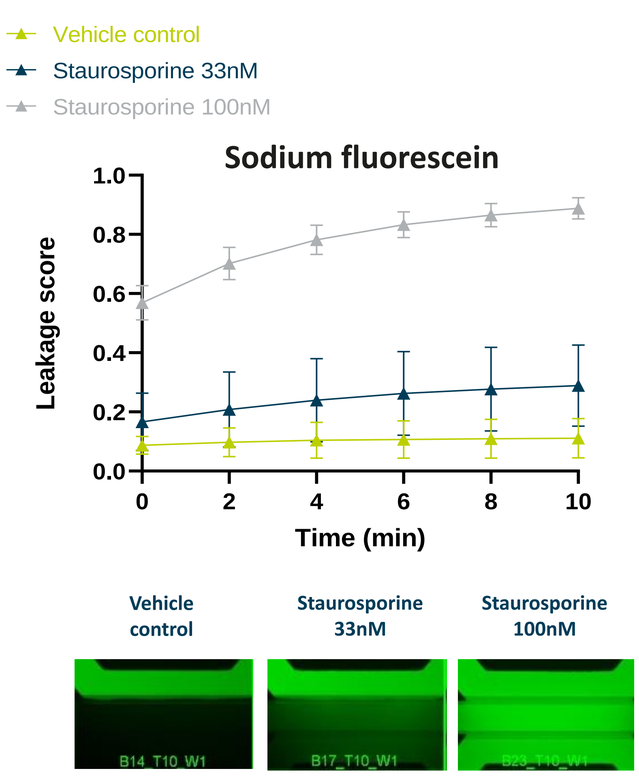
The OrganoPlate 3-lane 64 platform (a) and chip layout (b). The plate contains 64 microfluidic chips with 3 adjacent channels (lanes) in the observation window. The PhaseGuides™ (PhG) allow for gel patterning without the use of artificial membranes between the channels. c) 3D schematic of a tubular culture in the OrganoPlate.

Compound-induced barrier disruption in primary brain endothelial cells

HBMEC microvessels show a time- and dose-dependent response to staurosporine and cytokine exposure, measured with the OrganoTEER® platform and fluorescent permeability assays.



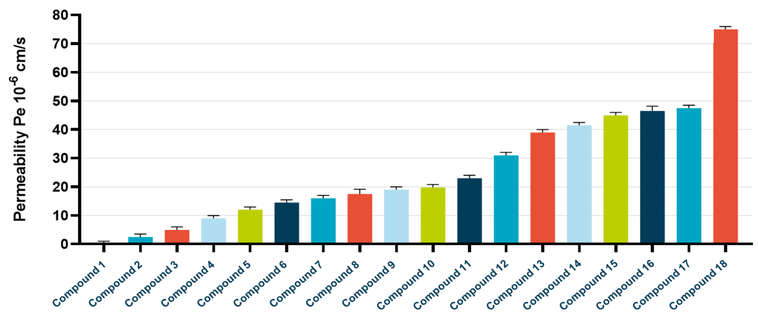
Time-lapse TEER measurement of primary human brain microvascular endothelial cells (HBMEC) exposed to staurosporine or TNFα and IL1β in the 3-lane 64 platform.



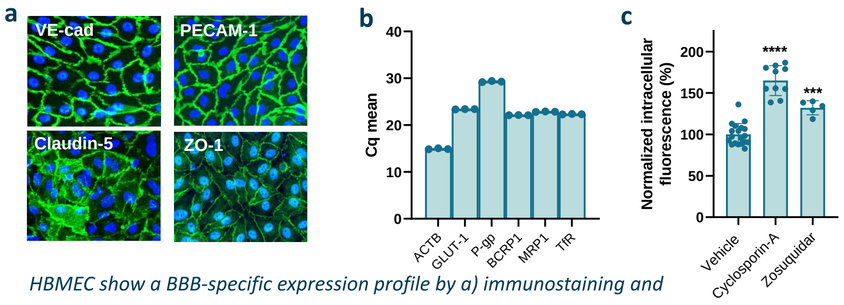
Permeability measurement of HBMEC exposed to staurosporine in the 3-lane 40 platform. Leakage score: fluorescence ratio of gel / cell channel.

Small molecule transport

The HBMEC model can be used to measure and rank small molecule permeability. 18 compounds were perfused through the lumen and measured by mass spectrometry after 1h. Control compounds digoxin (#2) and propranolol (#17) show low and high permeability, respectively.



Gene expression & transport function



HBMEC show a BBB-specific expression profile by a) immunostaining and b) quantitative PCR, and c) show P-gp activity using the calcein-AM uptake assay.

This work is supported by the Innovative Medicines Initiative 2 Joint Undertaking (JU) under grant agreement No 807015. This JU receives support from the European Union's Horizon 2020 research and innovation programme and EFPIA. This work was also supported by the European Union´s Horizon 2020 research and innovation programme under grant agreement 667375 (CoSTREAM), and under the Marie Skłodowska-Curie grant agreement No. 813294 (ENTRAIN).

Literature

Gijzen L et al. (2020). An intestine-on-a-chip model of plug-and-play modularity to study inflammatory processes. SLAS Technol. 25 (6): 585-597

Wevers NR et al. (2021). Modeling ischemic stroke in a triculture neurovascular unit on-a-chip. Fluids Barriers CNS, 18 (59).

Visit us at mimetas.com
More questions? Contact us via support@mimetas.com