Implementation of iPSC-derived Cell Types to Advance the Development of Organ-on-a-Chip Model Systems

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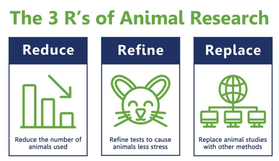
Value from Innovation

OVERVIEW: Drug development should be human-centered

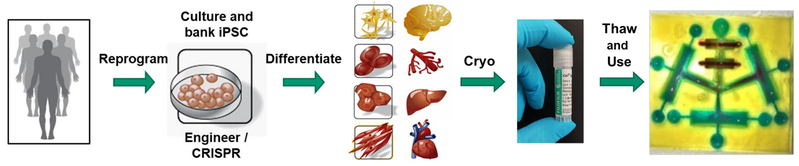
Too many drug failures in past 20+ years



Many reasons to reduce animal testing

FDA Modernization Act 2.0

In 2022, the FDA Modernization Act 2.0 ended the long-standing mandate that required drugs to be tested on animals before they are tested in humans. This change also authorized the use of alternative technologies to reduce the reliance on animal testing. These accepted options can be grouped into four different categories: 1) cell-based assays, which include human induced pluripotent stem cells (iPSC); 2) 3D organoids & spheroids; 3) "organ chips"; and 4) computer models, which covers AI, machine learning, and bio-simulation. This poster will focus on the combination of iPSC-derived cell types (e.g., iCell® products) and organ-on-a-chip (OoC) systems.



Human iPSC are a promising new alternative to animal models since they offer more physiological relevance, meaningful drug responses, and opportunities for "disease-in-a-dish" studies. When highly specialized cell types generated via human iPSC technology (such as iCell® products) are paired with cutting-edge organ-on-a-chip technologies, this approach is gaining increased traction as the best hope for improving the pre-clinical pipeline for new therapeutics.

Commercially available organ-on-a-chip platforms

SYNVIVO
Curiochips®
aimbiotech
BiomimX
THE BEATING ORGANS-ON-CHIP
emulate
CN-BIO
AlveoliX
In-vitro models inspired by nature
Jananda™
In vitro solutions for in vivo results
NETRI
PROVIDING ORGANS-ON-CHIP FOR THE INDUSTRY
4Dcell
EXPLORE BETTER.
AxoSim
Human Data, Faster.
MIMETAS
the organ-on-a-chip company

The development of OoC systems has revolutionized in vitro research, offering dynamic, physiologically-relevant platforms that enable the creation of multi-cellular models that closely mimic the structure and function of native human organs. A critical requirement of such OoC systems as they evolve and improve the scalability, complexity, and throughput, is that they maintain consistency.

There are now many providers out there with commercially available options for organ-on-a-chip technology. Our goal here is to support the integration of iPSC-derived cells into various OoC platforms to reshape research across neuro-science and broader biomedical fields, bridging the gap between pre-clinical studies and clinical outcomes.

iCell® Blood-Brain Barrier (BBB) Kit – an Isogenic Tri-culture of Human Cells

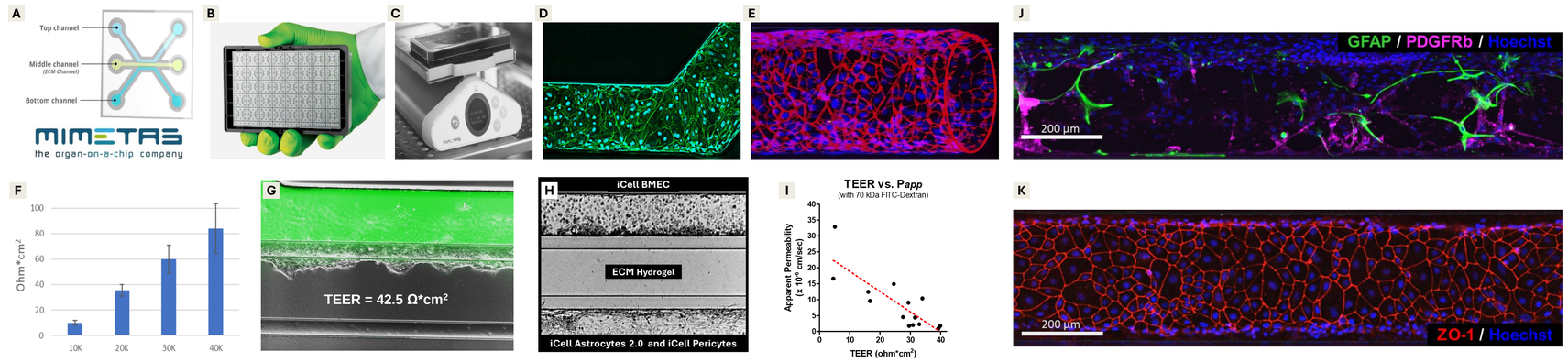


Figure 1. (A) MIMETAS is an organ-on-a-chip company based in the Netherlands; (B) the OrganoPlate® platform technology is a microfluidic 3D tissue culture plate that is membrane-free and generates perfusion without pumps and tubing from (C) the OrganFlow® rocker that provides continuous medium flow in the incubator; (D) iCell BMEC were cultured in the top channel and immunostained for ZO-1 (green) and Nuclei (blue); (E) Lumen formation with the BMEC could be imaged by confocal imaging and Z-stacking. The OrganoTEER® instrument enables impedance-based TEER measurements in the OrganoPlate and (F) these data show that increasing seeding densities of BMEC results in higher TEER values; (G) BMEC can also form robust cell barriers that prevent FITC-dextran molecules from passing through; (H) the isogenic tri-culture iCell BBB kit was established on the OrganoPlate 3-lane 40 device, and (I) TEER measurements vs. apparent permeability was plotted from Day 5 experiments. The Papp was calculated from the permeation rate of FITC-labeled dextran (70 kDa). As expected, there was a linear negative correlation because when the integrity of the BBB is high, the TEER values are also high, and the permeability is low. R^2=0.6775, with significant correlation P value = 0.0003. (J) Images from the bottom channel with iCell Astrocytes 2.0 and Pericytes stained for GFAP (green) and PDGFRb (magenta), and BMEC again in the top channel stained for ZO-1 (red). Hoechst=nuclei=blue.

Expanding the iPSC-derived BBB → Neurovascular unit

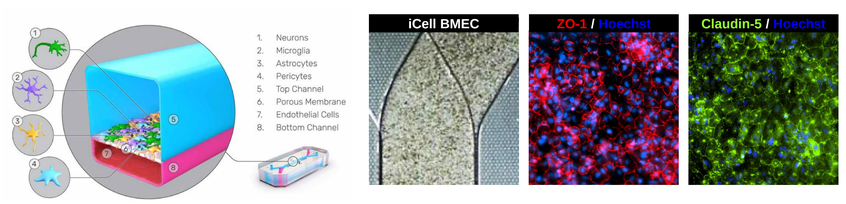


Figure 2. Emulate (Boston, MA) has developed the Brain-Chip to study human physiology and disease in a comprehensive model of the neurovascular unit. Preliminary testing of the iCell BBB kit on this platform focused on overcoming the challenges of implementing a new micro-physiological system into an iPSC-based workflow. Some challenges were identified (cell detachment, bubbles, and how to deal with non-viable cells post-thaw, etc.), but as shown above, improved cell marker staining was observed for ZO-1 and Claudin-5 after culturing on the chips with dynamic flow. Additional work is needed, but these results are promising and Emulate has firsthand experience supporting such a model system.

ALS Disease modeling with iCell® Motor Neurons

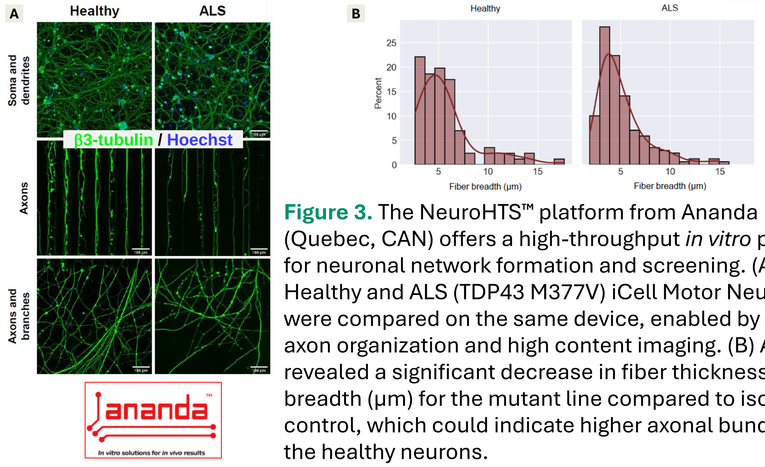


Figure 3. The NeuroHTS™ platform from Ananda Devices (Quebec, CAN) offers a high-throughput *in vitro* platform for neuronal network formation and screening. (A) Both Healthy and ALS (TDP43 M377V) iCell Motor Neurons were compared on the same device, enabled by parallel axon organization and high content imaging. (B) Analysis revealed a significant decrease in fiber thickness or breadth (µm) for the mutant line compared to isogenic control, which could indicate higher axonal bunding in the healthy neurons.

Organ-on-a-chip technology enhances the functional activity of iCell® Sensory Neurons

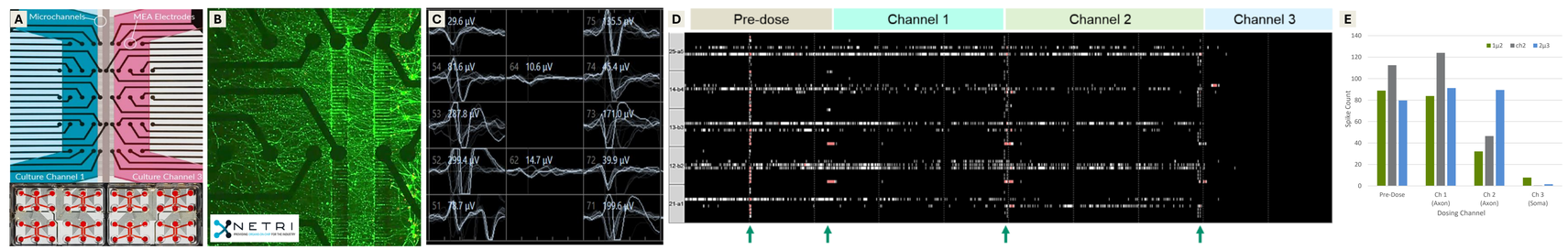


Figure 4. (A) The DuaLink microelectrode array (MEA), a compartmentalized microfluidics device by NETRI (Lyon, France) , is compatible with the Maestro MEA system from Axion Biosystems. (B) iCell Sensory Neurons were plated into channel 3 of the device where neurites readily grow and project through the microchannels over time. Pictured here are sensory neurons stained with the live cell dye Calcein AM on DIV 29. Image courtesy of NETRI. (C) Spontaneous action potentials were detected by the electrodes embedded under the microchannels less than 2 weeks post-plating. (D) iCell Sensory Neurons were dosed with Lidocaine (1 mM) in each individual channel. All spike activity was silenced when the drug was added to Ch 3, which is where cells were seeded initially. Time between doses was ~90 sec, and artifacts from touching the plate are indicated by the arrows. (E) Data suggest the effects of lidocaine are primarily observed when applied to the cell soma.