Figure 1. BBB organoids. (a) Spatial distribution of NVU cells in BBB organoid. (b) VEGF disrupts tight junctions (ZO-1) and increases organoid permeability to dextran. (c) P-gp efflux pump inhibition increases influx of rhodamine-123 (P-gp substrate). (d) Transcytosis of angiopep-2 (a BBB-permeable peptide).
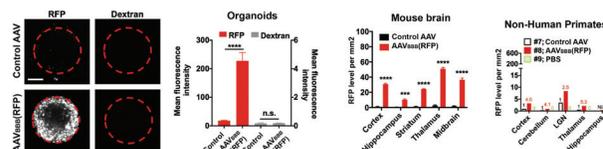

Figure 2. Translation of permeability of a novel BBB-penetrant AAV variant in BBB organoids to mouse and non-human primate models.

3D Human Blood-Brain-Barrier Organoids for Modeling Therapeutic Delivery to the CNS

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Dr. Cho's work focuses on designing precision medicines with improved tumor-killing efficacy. In conjunction with that work, her lab has pioneered an organoid platform to model the blood-brain-barrier. This innovative and accessible approach addresses limitations of current 2D models, offering the potential for significant improvements in screening and analysis of brain-penetrant drugs.

The inability of most therapeutics to cross the blood–brain barrier (BBB) is a major roadblock to effective treatment of diseases in the central nervous system (CNS). In vitro BBB models continue to play critical roles in prioritizing CNS drug candidates prior to in vivo studies. However, brain endothelial cells (BECs) tend to rapidly dedifferentiate and lose their BBB characteristics when they are grown as monolayer cultures, resulting in the lack of expression of key BBB modulators and leaky paracellular barrier function. The mid-throughput 2D transwell BBB model is used widely, though it is associated with several limitations including barrier leakiness and loss of BBB marker expression. 3D microfluidic BBB systems have been developed to better simulate the BBB morphology, however these devices have limited throughput and require either purchase of a commercial device or construction of one, making them relatively inaccessible to many laboratories.

We have developed a high-throughput, versatile and robust 3D human BBB organoid platform for studying BBB functions and modeling therapeutic delivery. These miniature organoids are formed through the self-assembly of neurovascular unit cells co-cultured under low-adherence condition: Human BEC encase the organoid outer surface together with associating human brain pericytes (HBP), while the core consists mostly of human astrocytes (HA) (Fig. 1a).

The organoids are easy to culture, made from highly accessible cells, and reproduce key BBB biological characteristics and functions, as well as predict drug permeability. We show that the surface of the organoids recapitulates key BBB features, such as: 1) Tight junctions that exclude fluorescent dextran of various molecular weights (Fig. 1b), 2) Functional drug efflux pumps such as P-glycoprotein (Fig. 1c), 3) Receptor mediated transcytosis (Fig. 1d) to facilitate entry of specific molecules, and 4) Lipid transporter and transcytosis inhibitor MFSD2A. Furthermore, as in vivo rodent models continue to face challenges in the field with interspecies differences, we have recently demonstrated that the permeability of a novel AAV-based vector for gene delivery translates from organoids to both mice and non-human primates (Fig. 2). These data highlight the BBB organoid model as a promising in vitro screening tool to mitigate failure risk at a later state of drug development.