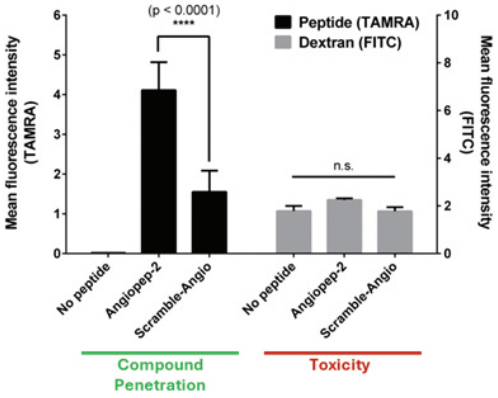


Figure 1: Angiopep-2 traverses BBB spheroids without compromising barrier integrity.

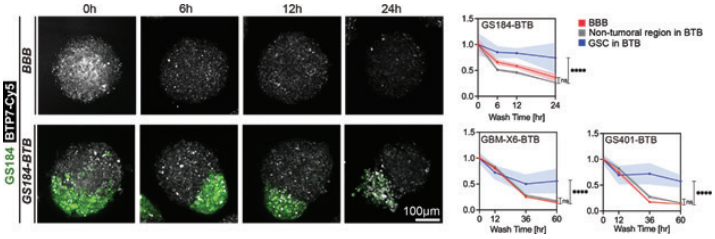
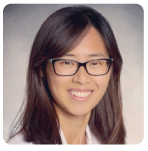


Figure 2: Brain-tumor targeting peptide BTP-7 permeates BTB assembloids and is selectively retained in tumor niches.

Breaking Barriers: Human Blood-Brain Barrier and Blood-Tumor Barrier Models De-risk CNS Drug Discovery



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The impermeability of the blood–brain barrier (BBB) and the heterogeneity of the blood–tumor barrier (BTB) remain major bottlenecks in translating promising therapeutics into effective treatments for central nervous system (CNS) diseases and brain malignancies. To overcome the longstanding challenge of poor translational predictability in preclinical studies, we have engineered a next-generation suite of self-assembling human 3D assembloids that accurately model both the physiological BBB and malignant BTB. These models are designed for high-throughput, high-fidelity screening, enabling rapid, mechanism-informed de-risking of CNS therapeutics.

The BBB assembloids self-organize within just 2-3 days from primary human brain endothelial cells, vascular pericytes, and astrocytes. The resulting structures feature an astrocytic core enveloped by a continuous endothelial–pericyte surface that consistently exhibits high expression of tight-junction proteins and robust transporter activity. This model has been rigorously validated to rapidly identify compounds with true BBB penetrance and discriminate them from non-penetrant compounds.

Complementing this platform, our BTB assembloids integrate patient-derived glioblastoma (GBM) stem cells (GSCs) with the same vascular constituents to recreate the compromised tumor vasculature often observed in vivo and in clinical GBM specimens. Thousands of BTB organoids can be formed in parallel, while preserving the genetic landscape of the originating tumors. Transcriptomic and functional profiling of these models reveals enhanced stemness, mesenchymal transition, invasiveness, angiogenesis, which are phenotypes that have been confirmed in orthotopic models and clinical GBM samples. The assembloids enable simultaneous evaluation of drug delivery and therapeutic response.

Together, these modular platforms provide a unified, scalable toolkit for 1) unbiased discovery of brain-penetrant modalities, 2) mechanistic insights into BBB and BTB biology, and 3) accelerated, risk-mitigated development of neuro-oncology therapeutics. Our approach bridges the preclinical-to-clinical divide and opens a fast lane for translational success in CNS drug development.