Scalable 3D-Printed Synthetic Vasculature Platform for Oxygen and Nutrient Delivery in 3D Tissue Models

by

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The absence of functional vasculature limits the viability, scalability, and physiological relevance of 3D tissue models. Stem cell-derived organoids serve as powerful platforms for modeling development, disease, and therapeutic response, but suffer from diffusion-limited transport that leads to necrotic core formation and restricted maturation. Existing approaches to improve transport, including spinning cultures, slicing, and endothelial co-culture, offer only partial solutions and often compromise tissue architecture or scalability. Engineered vascularization efforts have faced limitations in resolution, perfusion control, or mechanical robustness. To address these challenges, we developed a synthetic vasculature platform integrated with a perfusion system to enable continuous delivery of oxygen and nutrients.

First, we developed photocurable resin formulations for two-photon polymerization (2PP) to fabricate perfusable, porous, and mechanically robust vascular structures. For *in vitro* use, we optimized a PEGDA-PETA resin with a non-functional porogen to achieve cytocompatibility, tunable porosity, and high-resolution vascular features. For potential *in vivo* applications, we formulated a custom flexible monomer blend with enhanced elongation at break and burst pressure, yielding mechanical properties closer to native vasculature. Then, we engineered a modular, tissue-agnostic perfusion platform with tunable geometries, compatible with diverse tissue systems and differentiation protocols. We used computational modeling to guide perfusion parameters for sustained oxygen delivery during long-term culture. Finally, we validated the platform by integrating it with early-stage brain organoid differentiation, which reduced necrotic core formation, preserved ventricular-like architecture, and maintained populations of proliferative neural progenitors. Single-cell RNA sequencing and metabolomics revealed reduced cellular stress, increased mitochondrial activity, and a metabolic shift from glycolysis to oxidative phosphorylation.

These advances establish a scalable and adaptable approach for vascularizing 3D tissues. While this work focused on brain organoids, the system is compatible with various tissue models and may inform the development of immune-isolating or pre-vascularized constructs for regenerative medicine. By combining engineered materials, high-resolution 3D printing, and continuous perfusion, this platform addresses key transport limitations in 3D tissue cultures and provides a foundation for future translational applications.

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