CHEMICAL ENGINEERING

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Monday, June 29, 2020

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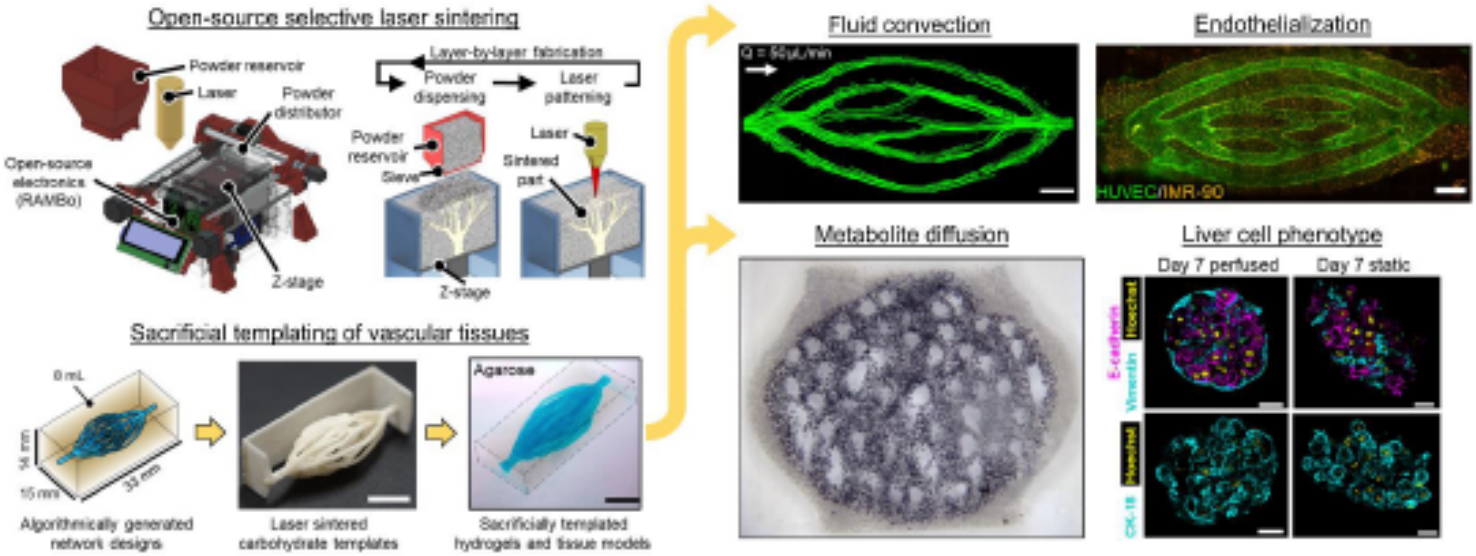
Generation of Engineered Tissues with Biomimetic Vascular Networks through Sacrificial Templating

ABSTRACT: Metabolic function in mammalian tissues is sustained by the delivery of oxygen and nutrients as well as the removal of waste through complex, three-dimensional (3D) networks of hierarchically organized blood vessels. However, fabrication of such 3D vascular networks within engineered tissues remains one of the greatest challenges facing the fields of biomaterials and tissue engineering. Sacrificial templates have proven useful for patterning perfusable vascular networks in engineered tissues, but such templates have been constrained in architectural complexity by fundamental limitations in the extrusion-based 3D printing techniques which have been used to fabricate them.

We hypothesized that these architectural limitations could be overcome by creating sacrificial vascular templates using the methodology of selective laser sintering (SLS), a specialized 3D printing process which uses the energy from a laser to 3D print solid structures from powdered raw materials. To this end, we developed an open-source SLS system in our lab and demonstrated its capacity to pattern biomimetic and highly branched scale models of vascular topology. We next sought to adapt SLS fabrication to be compatible with biocompatible and water-soluble materials which could be used sacrificially and in the presence of fragile cells. We identified and characterized formulations of carbohydrate powders which are compatible with SLS, and we introduced post-processing steps which improve the surface quality of laser sintered carbohydrate templates. We further demonstrated laser sintering of carbohydrates into elaborate branched structures, including algorithmically-generated biomimetic branching networks with a tree-like morphology, which we term dendritic networks.

Laser sintered carbohydrate templates were used to pattern perfusable vascular networks in a range of materials including natural and synthetically-derived biocompatible hydrogels, which can support cells in both the lumenal and parenchymal spaces. We leveraged this methodology to establish a complete pipeline

encompassing generative vascular design, additive fabrication, perfusion culture, and volumetric spatial analysis of model tissue performance. Specifically, we identify heterogeneous zones of metabolic activity that emerge in perfused cell-laden hydrogels and we demonstrate that dendritic vascular networks can sustain cell metabolism deep within model tissues greater than 1 cm thick. We also seed endothelial cells, characterize convective transport through dendritic networks, and explore strategies to modulate the dynamics of changing cell densities within perfused gels. Finally, in collaboration with Kelly Stevens (UW Bioengineering), our joint team demonstrated that perfusion culture through dendritic networks can support the survival and function of primary hepatocyte cultures. This approach for rapid design and biofabrication of engineered volumetric tissues offers an experimental strategy for interrogating the relationship between vascular network architecture, metabolite transport, and tissue function (Kinstlinger et al. Nature Biomed. Eng. (Accepted, in press)).



BIOGRAPHY: Ian Kinstlinger is a senior PhD student and NIH Fellow at Rice University in the Bioengineering department. As a member of the Microphysiologic Systems Engineering and Advanced Materials Lab (PI: Dr. Jordan Miller), his doctoral research has been centered around understanding the interplay between vascular architecture, transport, and function in engineered tissues. After developing a platform biofabrication technology to scalably engineer complex branching vascular networks within soft and cell-laden biomaterials, Ian has focused on understanding how such networks can be used to support the survival and metabolic function of large and densely cellularized model tissues. He is also an avid "maker" and supporter of open-source technologies to advance science; throughout his doctoral studies, he has developed a suite of low-cost, open-source hardware tools for vascular tissue engineering. Ian plans to graduate from Rice in summer 2020 and transition to postdoctoral research. Prior to his PhD, he completed his undergraduate degree (B.S. Biomedical Engineering) at Washington University in St. Louis.

LECTURE 1:00 - 2:00 Zoom
Networking Hour on Zoom Following

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