Microfluidics-Based Approaches for Vascularized Tissue and Organ Constructs

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Introduction

One of the principal challenges in the tissue engineering and regenerative medicine has been the need for establishment of a functional vasculature for engineered tissues and organs, as well as for in vitro models and extracorporeal organ assist devices. A promising approach towards addressing this challenge has been the use of microfluidics technology to form bifurcated networks of microchannels that mimic the architecture of organ vasculature. Here we report on progress towards microfluidics-based vascular networks that provide physiologic levels of pressure, flow and wall shear stress, and on fabrication technologies capable of producing vascular geometries with smooth flow paths that are amenable to confluent seeding with endothelial and smooth muscle cells. These technologies are useful for a range of applications including in vitro models for discovery, extracorporeal organ assist devices, and biodegradable scaffolds for engineered tissue constructs.

Materials and Methods

Computational Fluid Dynamic (CFD) models were used to design bifurcated microvascular networks with transport properties similar to those of physiologic vasculature. Large, dense, space-filling networks with uniform levels of flow and wall shear stress, comprising vast capillary networks closely spaced to provide sufficient tissue oxygenation, were generated and translated into mask layouts for photolithographic pattern transfer onto silicon wafer masters for scaffold construction. These silicon masters were used for replica molding with a range of scaffolding and device materials, including polystyrene (PS), PolyDiMethylSiloxane (PDMS), and bioresorbable polymers including PolyGlycerol Sebacate (PGS), silk fibroin (SF) and PolyEster Amide (PEA). Conventional BioMEMS fabrication technology utilizing epoxy resin photolithographic patterning was employed to produce bifurcated networks with rectangular channels, all of the same depth, in a large scaffold structure. In order to realize circular microchannels ranging in diameter from capillaries to large vessels, a novel fabrication technology based on electroplated masters was developed and applied to the formation of PS devices. Alternative round channel formation techniques utilizing xenon difluoride (XeF2) etching of silicon masters was also used to form round, smooth microchannel networks. A silicon master formed using XeF2 etching to produce rounded channels with smooth transitions between vessels of differing dimensions is shown in Figure 1.

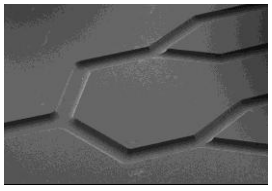

Figure 1. *Silicon master mold etched with XeF2 to produce round channels.*

Results

Microchannel networks produced in PS using electroplated silicon master molds have been endothelialized with primary human umbilical vein endothelial cells (HUVECs) to form confluent endothelial layers on channel surfaces (Figure 2.) In Figure 3, microfluidics fabrication technology has been utilized to form vascular networks in a resorbable polymer (SF), which has then been seeded with human dermal microvascular endothelial cells (HDMVECs) to form a confluent layer.

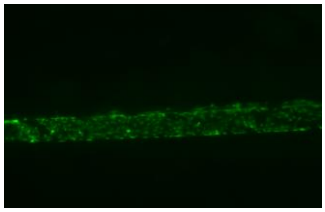

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Figure 2. *Calcein AM stain of endothelial layer seeded on intraluminal surface of micromachined channel in PS scaffold.*

Figure 3. *Endothelial cell seeding of bifurcated vessel network in bioresorbable SF scaffold.*

Discussion and Conclusions

Microfluidic technologies have been used to produce vascular network structures with a range of cross-sectional geometries and with smooth transitions and flow paths capable of reducing the potential for blood damage and thrombosis. These approaches form the basis of in vitro models comprising vasculature, engineered respiratory assist devices, and microvascularized biodegradable scaffolds for engineered tissue constructs and organ replacement.

References

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