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Stereolithography-based 3D printing of micro-channels for vascularized hydrogels

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Introduction: Construction of three-dimensional (3D) soft biomaterial scaffolds for long-term cell culture is crucial to the field of tissue engineering and regenerative medicine^[1]. Adequate vascularization to ensure oxygen and nutrient supply to the tissue cells of engineered 3D cell cultures is widely considered the most important barrier in the field^[2]. Thus, fabrication of freely definable channel structures inside hydrogels as arteriole and venule analogs is of particular interest. Soft hydrogels recapitulate the mechanics and hydration of the native extracellular matrix. However, fabrication of hydrogel scaffolds with required structural detail, stability, and complexity remains challenging despite recent progress in 3D fabrication methods^[3]. Stereolithography is a promising technique for fast, high resolution 3D printing of polymer materials in a layer-by-layer fashion, but commercially available starting materials for stereolithography are mostly incompatible with biological environments^[3]. Here, we report on the manufacture of 3D biocompatible hydrogel scaffolds at sub-200 μm resolution using projection-based stereolithography combined with photochemical post-modification with cell adhesive peptides to address the challenge of synthetic vasculature.

Materials and Method: Poly(ethylene glycol) (PEG) hydrogels were 3D printed by light-induced solidification of an aqueous pre-polymer solution (PEG-diacrylate 700 Da, lithium acylphosphinate as photoinitiator, Quinoline Yellow as photoabsorber) using a commercial stereolithography system (envisionTec Micro). Printed hydrogels were further post-functionalized with an RGD-containing peptide by conjugating acrylated peptide onto the hydrogel through unreacted acrylate groups from PEG-diacrylate. An endothelial cell line (CRL 2922) was cultured on the printed structures and monitored for viability, adhesion and proliferation.

Results: Figure 1a shows a top-view of four printed closed channels of square cross-sectional profile with dimensions from 100 to 400 μm (channel entrances at the bottom of the micrograph) while Figure 1b displays the respective channels in cross-section after sectioning of the block. Figure 2 shows phase contrast microscopic images of the samples with (w/ RGD) or without RGD (w/o RGD) at two different magnifications (10x and 20x objectives) after cell culture for 8 h, 24 h, and 48 h, respectively.

Discussion: We optimized the printing configuration by manipulating both optical properties (proximity effects) and material properties (composition of pre-polymer solution). Optimization allowed printing of hydrogel blocks with internal channel structures approaching arteriole dimensions (100 μm cross-section). Cell culture showed high compatibility of peptide-functionalized hydrogels to CRL 2922 cells in terms of cell viability. In addition, cells adhered much better and proliferated much faster when cultured on functionalized hydrogels compared to non-functionalized ones.

Conclusion: Channel structures of arteriole/venule-sized dimensions could be fabricated in 3D printed hydrogels at sub-200 μm resolution through an optimized printing configuration. Compared to conventional channel fabrication methods such as hydrogel bonding and sacrificial molding^{[4],[5]}, our approach features a single automated process at high resolution that few methods can achieve in soft hydrogel materials with full 3D design freedom. Bio-functionalization of printed hydrogels enabled culture of CRL 2922 endothelial cells as an excellent candidate for the manufacture of 3D microvascular scaffolds with endothelial cells lining the synthetic vascular wall for tissue engineering.

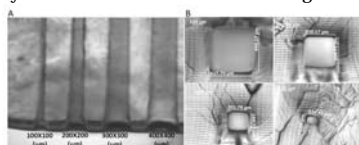


Figure 1. A) Microscopic image (2.5x objectives) of top view of printed channels inside hydrogel. B) Microscopic image (10x objectives) of cross-sections of printed channels inside hydrogel.

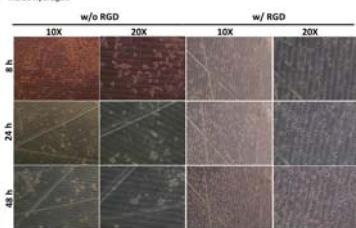


Figure 2. Microscopic images (10x and 20x) of hydrogels modified with or without RGD peptide, both seeded with CRL 2922 cells after 8, 24 and 48 h of incubation.

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