APPLICATION HIGHLIGHT

Multivascular Networks and Functional Intravascular Topologies within Biocompatible Hydrogels

OVERVIEW

Modeling multidimensional vascular networks is a notoriously difficult task, especially when considering the complex functions they perform within organ systems. Modeling mechano-biological and organ systems within an in vitro environment has become an emerging field that holds great promise on clinical studies. In this study, the researchers optimized the hydrogel bioinks using food-grade additives to create various vasculature models representing pulmonary and circulatory organs while modeling mechanobiological systems. The feasibility of the DLP printing method on generating complex vasculatures and the biocompatibility of the hydrogels used in the built structures were evaluated. Additionally, the research examined the biocompatibility of hydrogels, including the viability of populated cells and tissue implantation in vivo.

MATERIALS AND METHODS

To successfully model microvascular structures in vivo, the researchers employed a custom-designed DLP system, akin to the Allevi BioLight printer.

- Custom-designed DLP bioprinter;
- PEGDA 6 kDa 20 wt%, with tartrazine as the photoabsorber due to its low toxicity and high availability

RESULTS

Solid organs contain distinct fluid networks that are physically and chemically entangled to provide the complex extracellular microenvironment that defines multicellular life. The ability to fabricate such multivascular topologies within biocompatible and aqueous environments holds great potential in the fields of biomaterials and tissue engineering.

Creating hydrogels to demonstrate functional intravascular topologies

The researchers' first step was to examine different intravascular topologies, such as a 3D bicuspid intravascular valve. The team successfully printed and operated the bicuspid valve, which exhibited responses to flow directions and dynamic responses (Figure 1).

When anterograde and retro-grade pulsatile flows were applied, the valve leaflets responded rapidly and dynamically to promote the formation of stable mirror image vortices in the valve sinuses (Fig. 1, right).

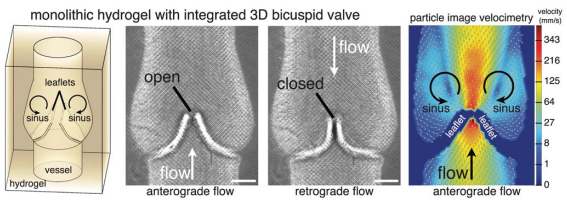

Figure 1

Tidal ventilation and oxygenation in hydrogels with vascularized alveolar model topologies

By using fractal topology algorithms, non-intersecting vascular networks were created for human red blood cells to flow through a helical channel equidistantly around an oxygen tube (Fig. 2, left). Collection of perfused red blood cells showed significantly higher SO_2 and PO_2 relative to deoxygenated RBCs loaded at the inlet and negative control gels ventilated with humidified nitrogen gas (Fig. 2, top right).

Design and generation of functional distal lung subunit model

To extend this work closer to a scalable lung-mimetic system, the team used a mathematically generated alveolar vascular network to create a fully functional pulmonary model (Fig. 3). They demonstrated that tidal ventilation resulted in bidirectional RBC flow and was able to successfully and efficiently oxygenate the blood. This model was able to withstand over 10,000 cycles of ventilation while still transferring gas into the blood cells, presenting great potential for scalable future designs.

Rapid biomanufacturing of cell laden hydrogel "organ chips" and noninvasive characterization of cellular activity

The team designed a cell laden hydrogel workflow they utilized for the production of tissue constructs containing mammalian cells (Figure 4). This workflow could be adapted to create lung-mimetic architectures by populating the hydrogel with human lung fibroblasts in the bulk of the interstitial space and human epithelial-like cells in the airway, which could facilitate the development of a hydrogel analog of a organ-on-a-chip lung design. The team tested viability and functionality of human mesenchymal stem cells (hMSCs) that have been bioprinted with their custom made DLP bioprinter (with mixtures of PEGDA and GelMA) and indicated that the protocol 1) supports rapid biomanufacturing, 2) can maintain the viability of mammalian cell lines, 3) supports the normal function and differentiation of primary human stem cells, 4) and provides an experimentally tractable means to explore stem cell differentiation as a function of soluble factor delivery via vascular perfusion.

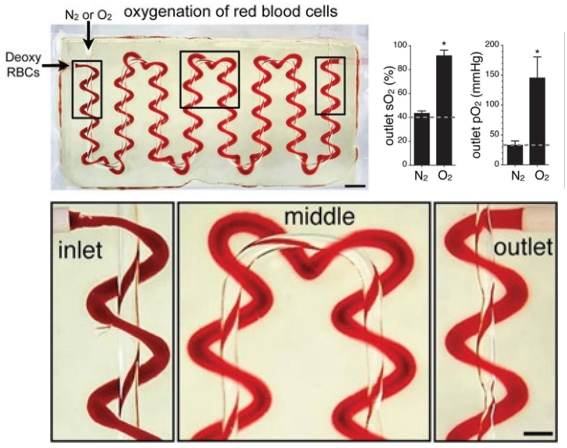

Figure 2

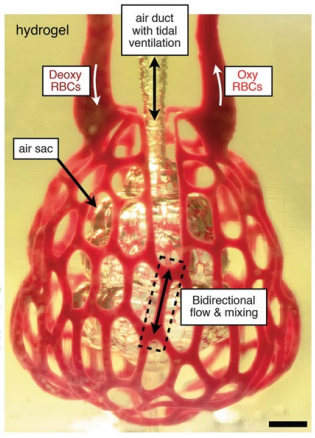

Figure 3

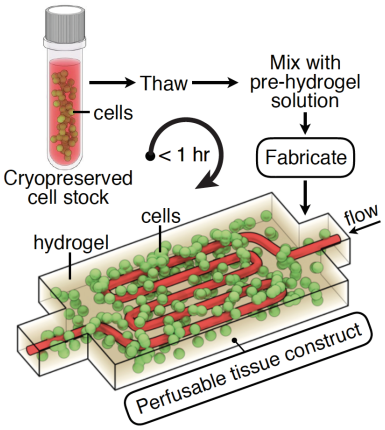

Figure 4

Engraftment of functional hepatic hydrogel carriers

In addition to successfully modeling organ systems, the study also focused on the biocompatibility of the hydrogel formulation with living cells and tissue for therapeutic transplantation. To further demonstrate the viability of the hydrogel formulation, the researchers implanted various hepatic hydrogel aggregate carriers into mice (Figure 5). The results concluded that the albumin promoter activity was enhanced by 60 times after 14 days, and was in fact a viable method of implantation. Furthermore, upon gross examination of tissues after resection, hydrogel carrier tissues appeared to have more integration with host tissue and blood.

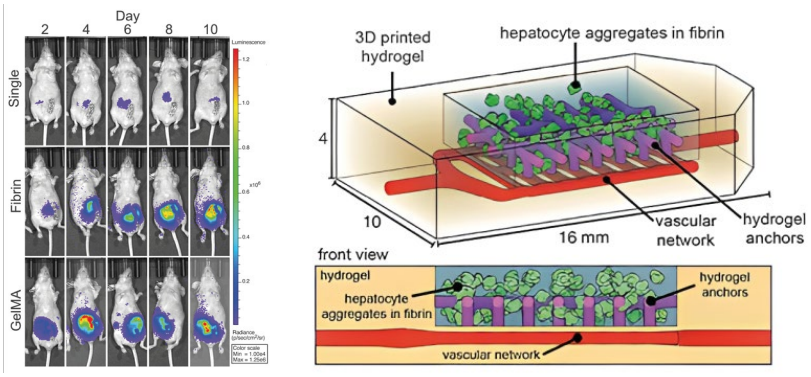

Figure 5

• SUMMARY

The work demonstrated the vast opportunities that are possible within the field of cell research and in vitro organ modeling. Using DLP printers such as the Allevi BioLight, researchers and organizations are able to design and create extremely detailed micro-architecture, providing an approach to address longstanding design limitations in tissue engineering that have hindered progress of preclinical studies. With various bioink options and extremely customizable print settings, the BioLight offers the ideal solution suitable for any task to the highest level of detail.

The multitude of benefits that 3D bioprinting technology offers in in vitro disease modeling from a) enabling the **creation of complex, physiologically relevant tissue models** that more closely mimic human organ systems than traditional 2D cell culture methods to b) the production of **highly reproducible and standardized tissue constructs, improving the accuracy and reliability of experimental results**. Development in the field of 3D bioprinting platform for **high-throughput drug screening**, enables the rapid screening of numerous compounds and potentially **accelerating the development of new treatments for various diseases** in the foreseeable future. **3D bioprinting is a valuable tool that has revolutionized the field of in vitro disease modeling and has the potential to significantly impact the development of novel therapies.**

REFERENCE:

Grigoryan, Bagrat, et al. "Multivascular Networks and Functional Intravascular Topologies within Biocompatible Hydrogels." Science (New York, N.Y.), vol. 364, no. 6439, May 2019, p.458, https:// doi.org/10.1126/SCIENCE.AAV9750.