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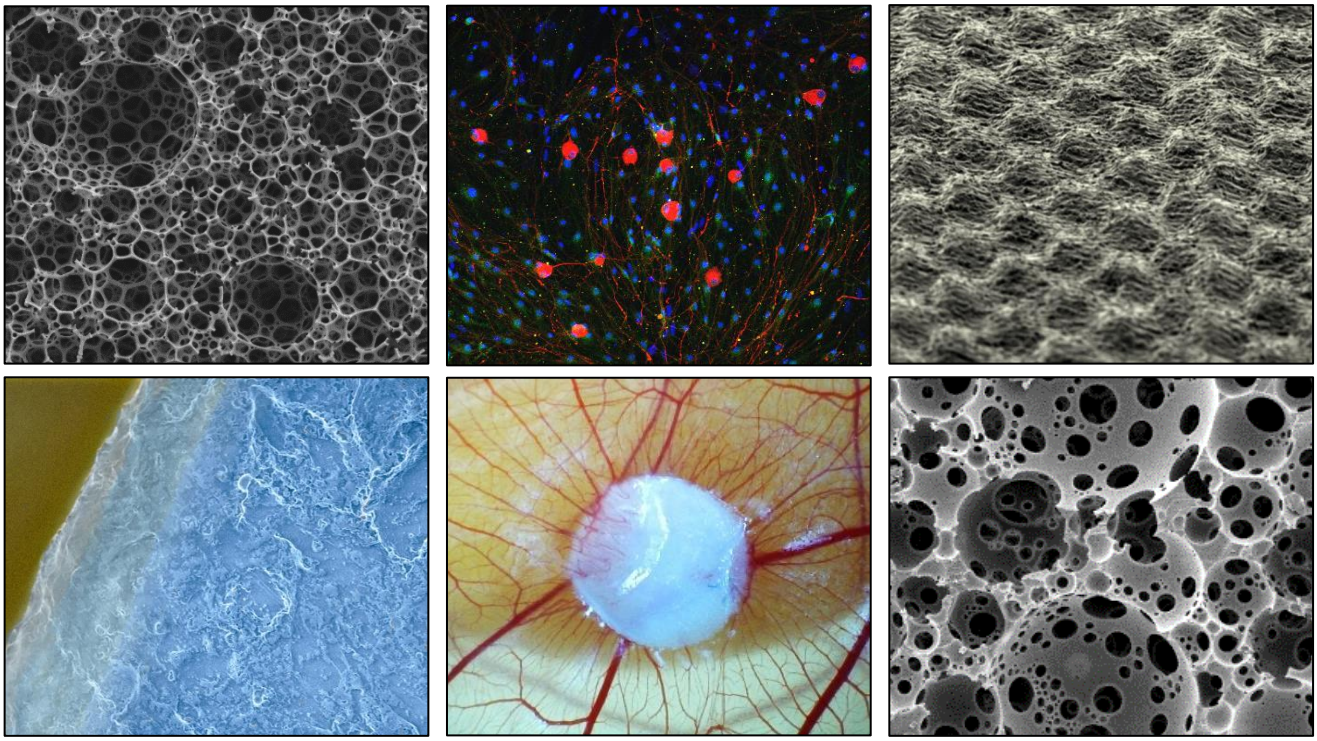

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MICROFLUIDIC-BASED 3D BIOPRINTING TO FABRICATE BLOOD VASCULATURE

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Introduction

The most substantial healthcare challenge facing the UK is the inevitable transition towards ageing population. Organ transplantation as the gold-standard treatment has saved many lives and millions of pounds for the NHS; however, every day, 4 people in the UK die while on the waiting list. The development of new and effective artificially engineered organs and tissue grafts without the need for immunosuppression will therefore be necessary to ensure we maintain and improve the healthcare nationally and globally. 3D extrusion-based bioprinting has emerged as a promising 3D printing technology for development of more advanced and functional organs and tissues, as well as drug development, and 3D in vitro disease models[1,2]. However, current developments are not able to recapitulate the heterogeneity and complexity of organs and tissues (Fig. 1A). Recent studies[1,2] have demonstrated the potential use of microfluidic-based 3D printing by allowing more control and precision over the organisation of biomolecules, cells and material thus, enabling fabrication of complex 3D constructs. However, the traditional fabrication method for such devices is labour-intensive and expensive, limiting its widespread use. Herein, we proposed an agile and novel manufacturing pipeline based on COntinously Varied Extrusion (CONVEX)[3] design approach in extrusion-based printing to develop integrated 3D-printed microfluidic chip nozzles, based on microfluidic mixers and hydrodynamic flow focusing components (Fig. 1B) with the potential to fabricate blood vessels.

Materials and Methods

FullControl GCode designer software[4] was used to extrude a single layer of acrylonitrile butadiene styrene (ABS) with complex passive mixer component using an Ender 3 3D printer. The ABS channels were cast into polydimethylsiloxane (PDMS) before flushing with acetone. To achieve co-axial hydrodynamic flow focusing of calcium chloride-Pluronic solution by 2wt% sodium alginate solutions, the calcium chloride channel had a smaller diameter than sodium alginate channels (Fig.1B).

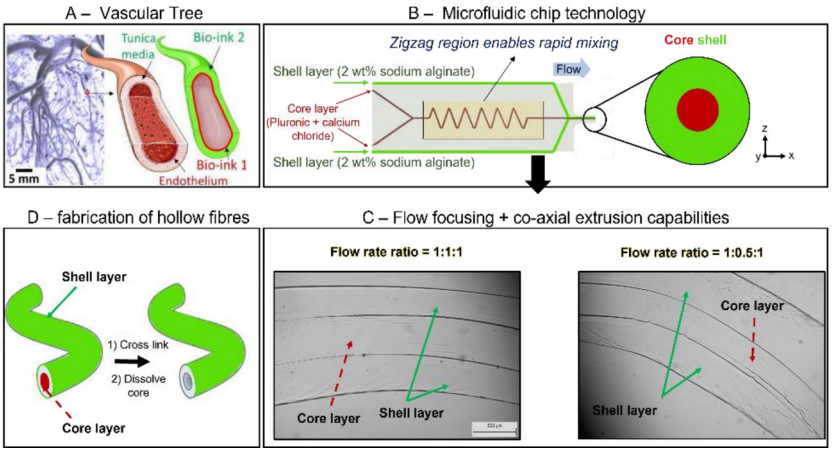

Figure 4: To recreate natural blood vessel (A), a novel microfluidic chip nozzle for extrusion printing platform developed (B). Optical micrographs indicated the flow focusing and co-axial extrusion capabilities of the newly developed nozzle (C). The hollow fibres obtained by removing the core layer after cross linking (D).

Results and Discussion

Direct GCode scripting allowed to incorporate complex passive mixer region (zigzag region. Fig.1B), enabling on-fly mixing of two fluids (core fluid with red dye). Furthermore, flow-focusing capabilities was achieved through cross junction design, resulting in dynamic variation of the diameter of the core fluid (30-40% of total width of channel) by changing the flow rates of shell bioink (Figure 1C). The important aspect of the newly developed 3D printed microfluidic nozzle was fabrication of multi-shell hollow fibres similar to that of the blood vessel. The core bioink layer maintained its structure since sodium alginate (shell layer) cross-linked upon extrusion inside the calcium chloride bath. Although few microfluidic printhead with co-axial extrusion capability are commercially available, the diameter of core fluid cannot be varied dynamically to imitate the changing diameters of blood vessels. On the other hand, our agile manufacturing pipeline is capable of fabricating 3D-printed microfluidic rapidly and consistently at significantly lower cost suitable for recreation of the complexity of blood vessels.

Conclusions

An agile manufacturing pipeline has been developed to fabricate novel microfluidic chip nozzles suitable for 3D bioprinting of complex tissues and organs. Microfluidic chip nozzles allowed dynamic and precise control of the diameter of core/shell hydrogels. Future work will integrate the microfluidic chip nozzle on a 3D printer to fabricate complex 3D structures containing cells.

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