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Letter to the Editor

Novel techniques of engineering 3D vasculature tissue for surgical procedures

Dear Sir

In the UK annually 225,0000 procedures are carried out involving the replacement blood vessels.[1] In the US, annually there are 400,000 coronary graft procedures carried out alone.[2] Further to this, there are 8-million patents with outlying artery diseases requiring a vessel bypass procedure and 500,000 with end stage renal failure patients requiring heamodialysis access vessels.[1–3] Arterial bypass surgical procedures are of critical importance, with (i) autologous grafting from an internal artery, (ii) intra-thoracic artery, (iii) sephaneous vein or radial artery and (iv) synthetic polytetrafloro ethylene polymers, becoming key surgical technologies over the years. Due to the high demand, there is a significant requirement for the sustainable bio-manufacture of replacement blood vessels for use to augment operative procedures.

Current technologies which involve prosthetics and autografts, are key methods in repairing large and medium vessels with a diameter of between 5 and 10mm. This is possible because as blood flows, hemodynamics reduces the issues of blood coagulation. However, small-diameter autogenous and prosthetic expanded polytetrafloro ethylene grafts are severely limited.[4] For wider vessels, current autografting procedures still offer significant difficultly. Significant advancement was made by Weinberg and Bell in 1986[5] who first engineered vascular grafts from living tissue. This key research was the elemental clinical application of vascular tissue engineering. Although clinical success of novel methods for producing tissue-engineered large-diameter vascular grafts have been made. However, the requirement for translatable research to operating theatre and the necessity of small-diameter vessel has not yet been achieved.

Tissue engineered vessels are limited in their capability to provide treatment for the needs of patients with complicated anatomies and for younger patients who will outgrow an implant. In order to be able to bioengineer vascular tissue systems, there needs to be four key components (i) a viable source of cells, (ii) supporting biocompatible materials, (iii) specific growth factors and (iv) an accurate biofabrication technique employed to fabricate a 3D vessel structure. The complexity comes from the fact that there is the requirement for smooth muscle cells to be incorporated into the scaffold with endeotheal cells. These have an important function in the maintenance of homeostasis as well as vascular remodeling processes after transplantation.

The key principle technologies used for blood vessel tissue engineering are shown in Fig. 1. The key technologies are those of engineered scaffold, decellularized scaffolds and 3D Printing technology, through the deposition of biological materials. The pathological location and blood vessel type dictates the thickness of the individual layers. The cellular composition of each layer has a specific role to play in maintaining vascular homeostasis. Meanwhile the endothelium layer provides a semi-permeable barrier for the diffusion of nutrients, oxygen and metabolic waste products, that happens between circulating blood and the bodies own cells.

Research has also been carried out to isolate (i) endothelial cells, (ii) smooth muscle cells and (iii) fibroblasts, all from a vein biopsy. MSC's and ASC's also have multi-differentiation potential. This enables them to differentiate into both endothelial cells and smooth muscle cells. Endothelial progenitor cells (EPC), have also shown paramount proliferation and angiogenesis properties. These cells can be sourced from the bone marrow using a simple outpatients' procedure.

Using these cells as a baseline, coupled with recent advances in automated 3D bioprinting processes provide a panacea method towards engineering blood vessels. These vessels can be manufactured to have complex geometries, reproducibility and biological properties relevant to specific patients. Continuous extrusion bioprinting can be used to generate tissue systems that are precise and specific. The ability to maintain a stable flow during the bioprinting process in response to applied stress can be controlled based upon the bioinks rheological properties. Stabilization post bioprinting is also achieved by physical, click chemistry or chemical crosslinking. This is required to ensure that the post bioprinted construct maintains the required high resolution.

As bioprinting technology evolves then vessel architectures consisting of multiple specific rings can be controlled to produce tissues with key mechanical and physiological properties. Due to the specific need of blood vessels to have microstructural complexity, extrusion-based bioprinting methods offer a high degree of potential to create viable living constructs. These can be bio-manufactured to have a specific size, required to make vessel constructs which have optimum mechanical properties.

This technology has key advantages which may potentially be used to lead towards clinical translation of tissue engineered constructs to the operating theatre.

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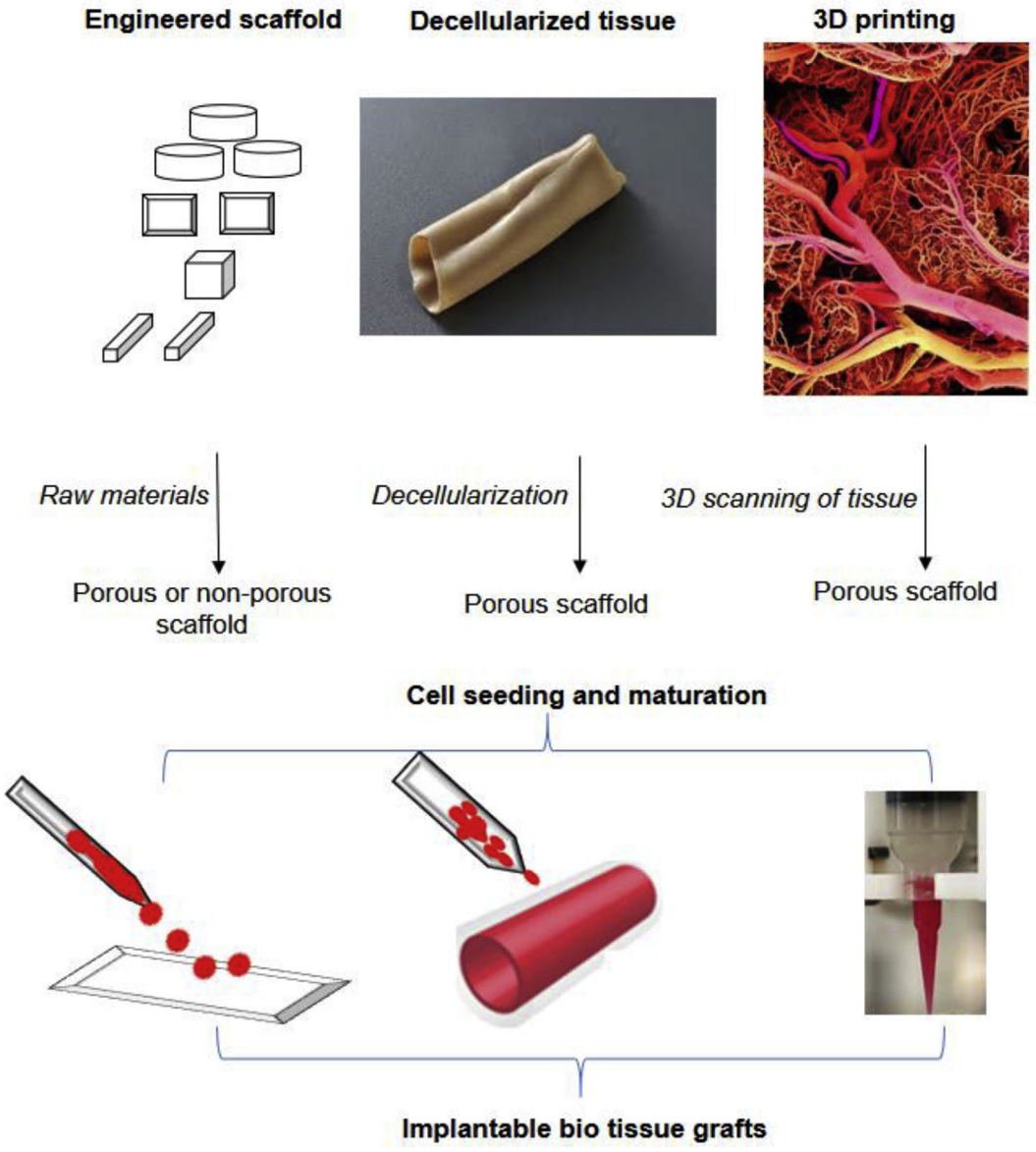

Fig. 1. The three current approaches used for blood vessel tissue engineering, including (a) engineered scaffold (b) decellularized tissue and (c) 3D printing/bioprinting processes.

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Daniel Thomas[a,*], Deepti Singh[b]
[a] *3Dynamic Systems Tissue Engineering, Heol Ty Gwyn, UK*
[b] *Department of Ophthalmology, Schepens Eye Research Institute, Harvard Medical School, Boston, MA, 02114, USA*

[*] Corresponding author.
E-mail addresses: daniel.thomas@engineer.com (D. Thomas), deepti_singh@meei.harvard.edu (D. Singh).

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