Engineering of functional cardiac tissue based diagnostic platforms that can mimic physiological function

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RESEARCH PROBLEM

Modelling human cardiac physiology using two-dimensional (2D) *in vitro* methods, while informative, does not adequately represent the *in vivo* state. New methods are required to more accurately represent the three-dimensional (3D), *in vivo*, cardiac environment to thereby better model cardiac events and the diagnosis thereof. This requirement has seen the development of 'bioinspired 3D structures' such as, 3D cell culture models, smart hybrid tissues, organ-on-a-chip systems and body-on-a-chip systems [1-4].

To create the required functional cardiac tissue platform, an '*ex-vivo*' cardiac model approach, is being adopted, with a degree of biological fidelity to mimic 3D cardiac tissue for analysis of myocardial function.

RESEARCH OBJECTIVE

The research objective will be fulfilled by:

1. Tissue engineering (TE) knowledge and skills associated with (bio-)scaffold formation, will be used to create a 3D environment for cardiomyocytes using (i) polycaprolactone (PCL) as a hard tissue model for the outer containment of cardiomyocytes and (ii) hydroxypropylcellulose (HPC) as a soft tissue model with cardiomyocytes embedded within the print.

2. 3D printing will be used to create a form of ex-vivo cardiac tissue model with the ability to react to electrical and mechanical stimuli.

3. Cardiac events will be created using a dynamic system whereby, stimuli inputs can be controlled and reactionary outputs can be measured.

RESEARCH TO DATE

A literature review has been carried out at the nexus between 'lab-on-a-chip' and '3D-scaffolds' for cardiac tissue model applications.

A multi-partner review publication with a working title "Ex-vivo cardiac models: progress, principles and applications in the period 2015-2020" is under consideration.

A new 3D-printer, Allevi 2 Bioplotter (Allevi Inc., PA, USA), with melt extrusion capability has been installed and initial items produced, see Figure 1.

KEY FINDINGS

3D-printed hard tissue components should have 'concertina' attributes to allow for 'flex' to mimic the anisotropy structure of cardiac tissue and to aid cardiomyocyte cell signalling. These structures have also been referred to previously as 'accordion-like honeycombs', see Figure 2 [5].

In addition to the mechanical support offered by the hard tissue model, there should be a soft tissue component, such as a hydrogel, to offer fluid mechanics to maintain cell health.

There is a potential gap in the commercial market for a method to replicate the effects on molecular, electrical and mechanical properties of cardiac tissue for diagnostic testing.

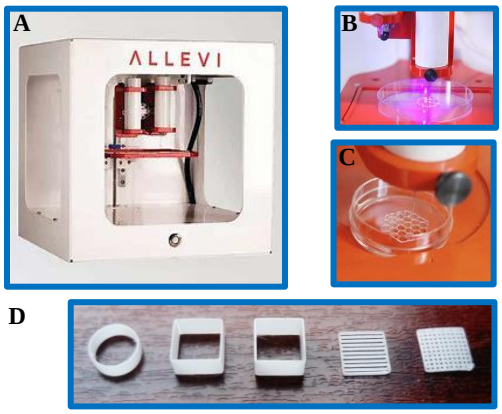

Figure 1 Images of Allevi 3D-printer with melt extrusion capability (A-C). A range of initial 3D-scaffolds of PCL hard tissue, from left to right, 10 mm cylinder, 10 mm cube, 10 mm cube (repeat), 10 mm cube with inset geometry of lines and 10 mm cube with inset geometry of a grid (D).

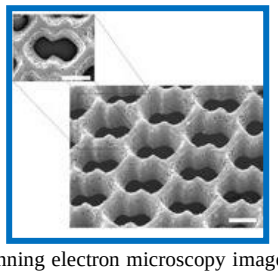

Figure 2 Scanning electron microscopy image of 'accordion-like honeycombs' with anisotropic structure for cardiac tissue engineering, created by Engelmayr *et al.* [5].

REFERENCES

1. Charbe *et al.*, World of Clinical Oncology. 8(1): 21-36. 2017.
2. Feiner & Dvir, iScience. 23(2): 1-14. 2020.
3. Zhang *et al.*, Nature Reviews Materials. 3: 257-278. 2018.
4. Sung *et al.*, Analytical Chemistry. 91(1): 330-351. 2019.
5. Engelmayr *et al.*, Nature Materials. 7(12): 1003-1010, 2008.