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Editorial

Special Issue: Design of Bioreactor Systems for Tissue Engineering

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Tissue engineering and, more broadly, regenerative medicine is moving into a phase where we are seeing potential therapies moving 'slowly but surely' from the laboratory into the clinic, *i.e.*, from research to the clinic and into manufacturing. The numbers of cells required for cell therapy protocols can vary from tens of millions, to billions [1], and it is widely considered that such cell numbers can be produced in bioreactor systems. Thus, the bioreactor is becoming a key tool for culturing clinical numbers of human cells and the regenerative medicine industry will become increasingly reliant on such systems at the centre of cell therapy production and tissue engineering.

This Special Issue of *Processes* contains papers in the area of "Design of Bioreactor Systems for Tissue Engineering". Here we showcase the diversity and advances in research that contribute to developing effective systems for the culture and controlled differentiation of stem cells, or the combination of cells and biomaterials into functional tissue.

Bioreactors are a mature technology in the more traditional biotechnology and bioprocessing industries, but in regenerative medicine they are still developing. There is an observable evolution to bioreactor systems technology in tissue engineering: their use as a research tool for cell culture; innovative modifications to enable 3D tissue culture and the provision of mechanical stimuli; a maturing of our understanding to enable rational modelling, design and optimisation of bioreactor systems. This evolution is reflected in the papers we have published in this Special Issue of *Processes*.

The primary role for the use of bioreactors has been as a research tool and as a technique to facilitate cell culture. This Special Issue contains a comprehensive review of bioreactor systems, as applied to human bone tissue production. Sladkova and de Peppo [2] report how bioreactor systems have helped to advance the culture of cells on scaffolds. They discuss the principle types of bioreactors, considerations of their design and physiological relevance, and the perspectives for clinical translation.

Continuing the theme of the use of bioreactors as a research tool, Kabiri *et al.* [3] describe how a fourteen channel bioreactor device can be used to study cell migration, and have used it to investigate the migration rates of bone marrow-derived MSC and MCF-7 breast cancer cells towards each other. Papantoniou *et al.* [4] report their work on the application of Design of Experiments methodology to evaluate bioreactor operating conditions and the effects on osteogenic gene expression. This approach exemplifies the holistic approach of using engineering methodologies to evaluate cell biological behaviour to better evaluate potential manufacturing processes. Finally, in this theme, the culture of clinically-relevant cartilage constructs in a scaffold-free system using a perfusion bioreactor is reported by Gilbert *et al.* [5]. This system is used to test the hypothesis that full thickness perfusion will accelerate the maturation of the cartilage tissue seeded with porcine chondrocytes.

A further development has been through innovations with bioreactors and their systems to improve cell and tissue culture, to introduce 3D architecture into nascent tissue, and to stimulate cells and tissue with external stresses. Naing *et al.* [6] exemplify this theme in their work where a multi-axis bioreactor has been used to mechanically stimulate human dermal fibroblasts in collagen scaffolds to mimic *in vivo* behaviour. There is much promise in the use of such bioreactors, but a key challenge is the optimisation of the stimuli and the operating conditions.

Vocal fold cells *in vivo* are subject to vibration. Klemuk *et al.* [7] have developed a multiwell disc secured to a rheometer to study a range of frequency, acceleration and shear stresses in this novel bioreactor. Their paper describes a modelling approach to understanding the performance of this bioreactor in combination with the use of four recoil materials of known stiffness. Also along this theme: Laurent *et al.* [8] report the design of a tension-torsion bioreactor to impart mechanical forces on growing ligament tissue; Goodhart *et al.* [9] describe the use of a unique bioreactor to apply cyclic strain to fibroblasts cultured on a woven scaffold; and a novel "hourglass"-type chamber for seeding cells onto scaffolds is illustrated by Hennig *et al.* [10].

More recently, the use of bioreactors has started to mature, there are some common configurations and a rational bioreactor design is emerging. These approaches are improving consistency and reliability and allow tissue engineers to carry out design and modelling to provide robust clinical and manufacturing tools. Perfusion bioreactors are a common configuration for tissue engineering. Donato *et al.* [11] have developed a mathematical model to enable the optimisation of hollow cylindrical constructs and the direction and magnitude of perfusion flow to ensure cell oxygenation and culture. A reaction-diffusion model for the transport and uptake of nutrients into tissue constructs is reported by Aristotelous *et al.* [12].

A key challenge in tissue engineering is consistent and even seeding and culture of cells. Schulte *et al.* [13] have developed an all-in-one system for seeding, conditioning and perfusion of vascular cells. This system has been tested with polyurethane and collagen scaffolds and human saphenous vein fibroblasts and endothelial cells. Design requirements for bioreactors are maturing and are normally centred on fluid mechanics and mass transfer: an example of the state-of-the-art is reported by Mattei *et al.* [14]. This paper discusses oxygen-shear stress trade-offs and glucose consumption in cell constructs. Another mature bioreactor type is the spinner flask that is widely used in tissue construct seeding and cell culture. Ismadi *et al.* [15] describe the characterisation of the fluid flow field in spinner flasks using particle image velocimetry. The study provides an overview of the

fluid structure within the spinner flask and the results quantify the range of stresses for the given impeller speeds.

There is a virtuous cycle of bioreactor development and evolution. As researchers discover new uses for bioreactors, or develop new reactor types for research, they will subsequently see the need for modification, leading to a more quantitative understanding to aid design and manufacture. In conclusion, bioreactors have moved on from simply being alternatives for conventional cell culture; we are using them uniquely for stimulating cells to stem cell differentiation or to condition tissue. The papers in this Special Issue are examples of how the field is moving forwards and gives some insights into where bioreactors in regenerative medicine will be positioned in the future.

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