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Tissue engineering

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Guest Editorial:

Tissue Engineering

This special theme seeks to highlight the recent trends and innovative developments in tissue engineering (TE). The development of TE as an area of study has been rapid in the last one decade and, its definition is very broad depending on each individual's interpretation of the subject. For example, Freed and Novakovic [1] interpreted TE as having three major components: metabolically active cells, polymeric micro-carriers (scaffolds) and bioreactors. However, one may also view TE as a technology for culturing functional cells and tissues which, in particular, aims to create an *in vitro* environment that regulates cells and tissues development and maintenance *in vivo*. In general, topics of TE research can include but are not limited to cellular fate processes, methods of tissue characterization, tissue culture methods including TE bioreactors, biomaterials, three dimensional tissues like assemblies, design methods for TE scaffold, characterization of cell-scaffold material interactions, etc. Apart from these areas, research work on multi-scale analysis, mass transport and fluid flow in TE systems, and optimization methods for tissue culture systems are also found.

Engineering artificial tissues is a complicated multidisciplinary area. However cell seeding is considered as the first step in engineering a tissue. The cells need support for growth and therefore scaffolds are provided. Similarly, nutrients and other chemicals (e.g., vitamins) are needed for growing tissues. In this process, several bioreactors are applied to enhance the cell seeding ability and mass transport such as flask spinning bioreactor and perfused bioreactors such as hollow fiber membrane bioreactor. Cell species and cell seeding density both can effect on tissue development and they continue to be topic of intense research. The scaffolds provide three-dimensional structures which permit cellular differentiation and tissue growth while bioreactors support a culture environment providing an *in vitro* environment that fulfill requirements for spatially uniform cell seeding and proliferation. As the demands of TE products increase from different aspects of both academic and clinical appliance, people have engaged in lots of effort to investigate suitable scaffolds and bioreactors; enormous selections of TE systems/devices are therefore available now.

It is of course an enormous task to bring many different aspects of TE in a single journal issue. Nevertheless, the six papers included highlight how traditional engineering (particularly chemical engineering) can be applied in addressing TE problems.

Song et al [2] determined the feasibility of co-culturing hematopoietic stem/progenitor cells (HSPCs) and mesenchymal stem cells (MSCs) derived from human umbilical cord blood (UCB) using cytodex-3 microcarriers. Currently, the potential of using the MSCs for clinical purpose are extensively being explored at many laboratories in the

world. The authors of this paper showed that UCB-hematopoietic stem cells (HSCs) and UCB-MSCs could be harvested simultaneously after their *ex vivo* culture. In addition, the two different types of cells could be easily separated by sedimentation after the co-culture due to the distinct weight differences between cytodex-3 microcarriers (containing adherent MSCs) and the suspended HSCs. The results of the paper are very promising.

Among the papers selected for publications, two are related to the development of novel biomaterials for TE. In these papers, the properties of the materials were investigated in detail, indicating the potential application of the materials in bone TE. Nawawi et al [3] have synthesized novel manganese-doped biphasic calcium phosphate (Mn-doped BCP) powders via sol-gel technique. The Mn-doped BCP powders were studied for their phase behaviour at different concentrations of Mn and calcination temperatures (500–1200°C). The authors used the X-ray diffraction (XRD) to reveal the presence of hydroxyapatite (HA) and β -tricalcium phosphate (β -TCP) phases in the materials. They also used other methods to characterise the materials, such as thermogravimetric analysis for any loss of materials. On the other hand, Fadli et al.[4] study the influence of dispersant concentration on the physical properties of porous alumina ceramics formed by the protein foaming–consolidation method. The paper presents the preparation method in detail. For example, it details the fact that the authors prepared slurries of alumina powders, yolk, and dispersant by rigorously stirring the mixture for 3h with an alumina-to-yolk ratio of 1:1 in weight and dispersant concentration of 0.01–0.05 wt.%. The authors discuss how the properties of the slurry (e.g., density) can be controlled as well as measurements of pore size distribution of the developed biomaterials.

The paper by Xia et al [5] assayed the effect of E-cadherin coating on the differentiation of hair follicle derived cells toward neurogenic lineage. In particular, they used E-cadherin coating system to culture embryonic undifferentiated cells to maintain stem-cell self-renewal function and cell proliferation potential. The results of the paper were found to be promising. The paper demonstrated that culturing mouse out root sheath (ORS) on E-cadherin-coated dishes could lead to neuronal cell morphology change of part of the ORS cells. Also, elongated cell morphology with fine cell processes connecting to nearby cells became significant in the subpopulation of the cells that strongly adhered to the coated culture dish. These results deserve further studies and should point towards new directions.

The above three papers focused on one of the core issues in TE, i.e., the effect of biomaterial and surface modification on cell behavior and tissue construction. On a slightly different context, the paper by Ellis and Chaudhuri [6] evaluates the morphologies of hollow fibre membrane scaffolds fabricated from six commercial poly(lactide-co-glycolide) (PLGA) polymers with different lactide: glycolide (PLA : PGA) molar ratios. This paper responds to the fact that the morphological characteristics of scaffolds are fundamental to their use for cell culture in regenerative medicine

applications. The authors demonstrated that the molecular weight, PLA:PGA ratio and PDI are key factors in deciding the desired PLGA membrane morphology. The paper demonstrated the use of a number of chemical engineering techniques (e.g., porosity measurements) for TE systems.

The potential for numerical simulations in TE was demonstrated in the paper by Nassehi et al [7]. They reported a model for simulating the micro-hydrodynamics of liquid/air flow inside membrane pores using a continuous penalty finite element scheme. Membranes are used extensively in TE systems such as hollow fiber membrane bioreactors, and, as such, their accurate characterization is of utmost importance. In this paper, a modelling approach was presented which combines the features of an air/water two-phase flow systems with flexibility and accuracy. The volume of fluid (VOF) method was applied to track the motion of the gas-liquid interfacial boundaries as an approach to monitor the repulsion of the wetting liquid from the pores to detect their bubble pressures and then determine the pore size. The developed model was used to predict the outcome of bubble point tests for a range of inlet boundary conditions (e.g. pressures). The results obtained in the work compared well with the experimental data, indicating the ability of the developed model to accurately predict the bubble point pressure.

Although the papers in this special issue highlighted a number of recent advances, the field of TE is constantly evolving and with time, there will be need to investigate new problems, such as nanotechnology and smart materials and their applications in TE.

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