SPECIAL ISSUE ON BONE TISSUE ENGINEERING

We are delighted to introduce this Special Issue of the Journal of Engineering in Medicine devoted to Bone Tissue Engineering. The Editorial Board of Engineering in Medicine considered this area of tissue engineering to be developing fast and thus of interest to their readers. We hope that we have collected together a set of papers that will enable readers of this journal to develop their knowledge of this area.

The idea of being able to get the body to grow new bone under suitable conditions is not new. 100 years ago here in Glasgow Sir William Macewan was implanting a series of materials into the body to get bone to regenerate [1]. Figure 1 shows the results of a canine experiment where he resected $1^1/_8$ inch (28.6mm) of the radius including the periosteum and firmly inserted a glass tube into the medulla. The specimen was collected 8 weeks and 5 days later and shows that firm union of the radius has occurred and that two-thirds of the glass tube is filled with new bone. Figure 2 shows one of the histological sections from this experiment showing osteoblasts lining the repair site and new blood supply being provided. In the succeeding 100 years the materials have been optimised, both in terms of mechanical properties and their chemistry, the collection and expansion of cells *in vitro* has been improved and the importance of mechanical stimulation and the release of growth factors has been realised.

This issue of the journal starts with two clinical papers on the major clinical requirements for new bone formation, in orthopaedics and dentistry. Dominic Meek and colleagues from here in Glasgow have considered bone as a biological material to be replaced and how it re-forms. They consider the currently used bone graft materials of both natural and synthetic origin. They present data indicating the number of potential applications of a successful bone tissue engineered implant. Francis Hughes and collaborators from King's College London have provided the dental view. They have concentrated on periodontal disease which occurs in 15% of the population and is the major cause of tooth loss. Here the biological tissues have an excellent ability to repair, providing the dentist can provide the appropriate environment for the tissue to be re-formed. A membrane is required that excludes bacteria and intruding tissues, yet allows nutrients into the area where new bone and periodontal ligament is required. Again, the newly forming tissue is strongly controlled by bone morphogenic proteins and other bioactive molecules.

From the clinical opinions on the needs and potential applications of bone tissue engineering, we progress to four papers on potential scaffolds for bone tissue engineering. Liz Tanner has reviewed composite scaffolds based on polymers and ceramics or glasses. It seems that the combination of similar materials to those making up bone material do give the optimal mechanical and biological properties, but that the fully optimised material has not yet been produced. Julian Jones and colleagues from Imperial College London consider bone tissue engineering scaffolds based on bioactive glasses, working from Bioglass® developed by Larry Hench. Sol-gel and melt derived scaffold glasses are compared using a range of characterisation techniques and the manufacturing parameters have been optimised. These bioglass scaffolds have been shown to be bioactive by soaking in simulated body fluid and by *in vitro* testing with human osteoblasts. Vincenzo Guarino and Gino Ambrosio from the University of Naples "Frederico II" describe their manufacture of polycaprolactone scaffolds using thermally induced phase separation or melt co-continuous polymer blending combined with salt leaching to produce high porosity scaffolds with good pore interconnection. Zhanfeng Cui and colleagues at the University of Oxford describe their work developing a bilayer scaffold to replace cartilage and subchondral defects, using electrospun collagen-polylactic acid composites with nano sized hydroxyapatite reinforcement for the subchondral bone layer. They have optimised both layers in terms of morphology and mechanical and surface properties, by controlling the manufacturing variables.

Figure 1 The sample of Macewan's "glass tube experiment" held in the Hunterian Museum in the University of Glasgow. A canine radius and ulna 8 weeks and 5 days after a section $1^{1}/_{8}$ inch (28.6mm) long was removed from the radius. A small glass tube was inserted firmly into the distal medulla. Firm union of the radius has occurred and the distal two-thirds of the tube is filled with osseous tissue (from the collection of the Hunterian Museum, University of Glasgow).

The next five papers all consider the interaction of cells with the surfaces with which they are reacting during cell culture or *in vivo*. Prakash Jayakuma and Lucy Di Silvio start by introducing us to the cell biology of bone including the cell types, especially progenitor cells and methods of ossification and remodelling bone. They then give examples of how these cells can be stimulated using scaffolds and soluble factors and implications for improving for example bone graft. It is now considered that a key cell feature to focus on in biomaterials development in order to stimulate osteogenesis is the focal adhesion. Manus Biggs and Matt Dalby thus consider these important cell features and how they can be manipulated by scaffold materials and micro and nanoscale surface features.

In the future it is likely that stem cell biology will underpin tissue engineering strategies. Riocahrd Oreffo and colleagues focus on the skeletal stem cell, generally termed mesenchymal stem cells, from the bone marrow. As we discover new mesenchymal stem cell niches and understand that the cells have different characteristics and potentials it is becoming increasingly important to differentiate between these cells. This paper discusses the

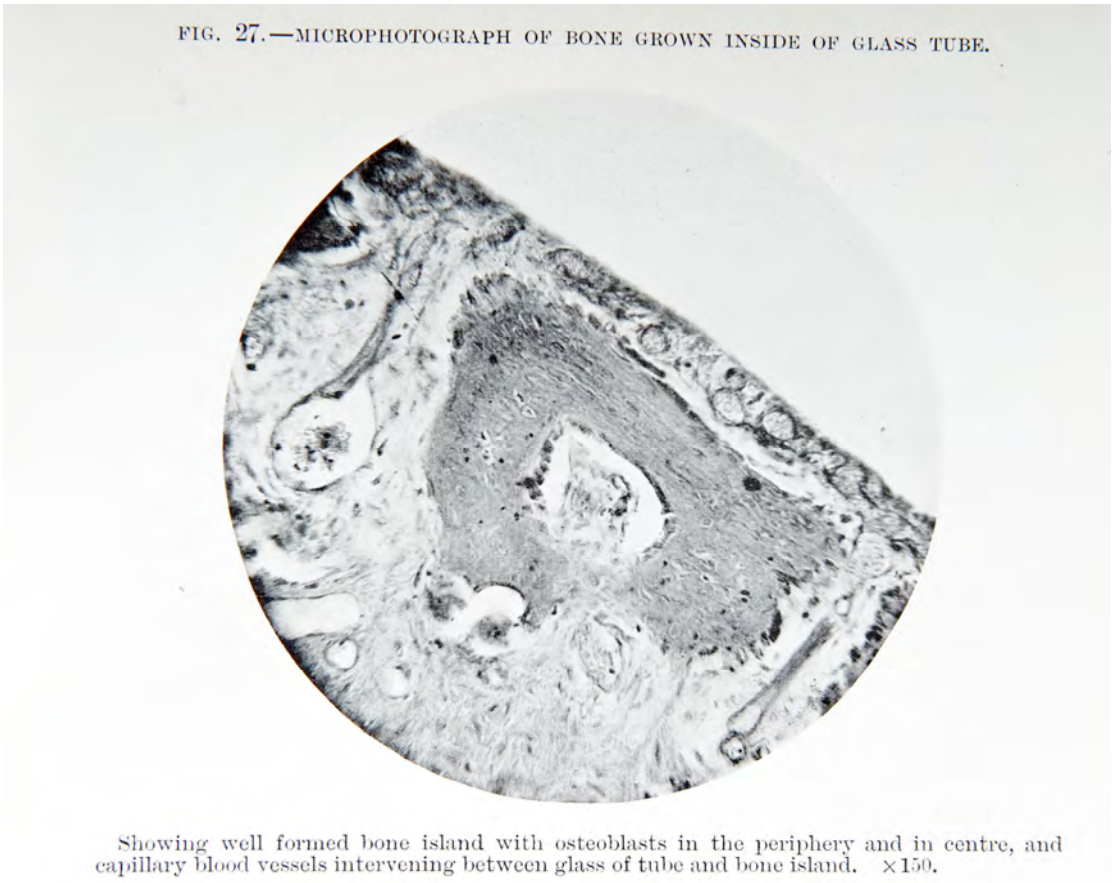

Figure 2 Drawing of a histological section of the new bone formed during the "glass tube experiment" showing osteoblasts lining the healing site along with the formation of new capillary blood vessels to support the regenerating bone growth (from Macewan [1] reproduced with the assistance of Special Collections, University of Glasgow Library).

identification, multipotentiality and use of the cells in bone regeneration. It also considers appropriate *in vivo* models for stem cell research in bone therapy.

Karine Anselme and co-workers have provided two important papers considering two sides of cell response to surface chemistry and topography; physico chemistry and then cell biology both of which are equally important. Their first paper considers definition and characterisation of surface features and how they can be applied in implantology. Their second considers protein absorption, adhesion formation and then direct mechanotransdution through the cytoskeleton and nucleoskeleton and indirect biochemical signalling and thus how surface features can influence intracellular behaviour.

The above group of papers consider the target cells for bone tissue engineering and how to engineer the surface to give targeted cell response. The last four papers look at an equally important point and all consider the response of bone cells or potential bone cells to their biomechanical environment. Gwen Reilly and John Haycock and others discuss the role of fluid flow on bone matrix protein production. Cells *in vivo* are not in a static *in vitro* cell culture environment, rather, biological fluids move leading to flow around the cells. The cells respond strongly to their biomechanical environment and this can be exploited during tissue engineering. This original paper compares the *in vitro* and *in vivo* environments and then shows, for the first time, that hyaluronan and CD44 have roles in mechanotransducing fluid flow signals to collagen output from the cells. Clearly, understanding of the stimulation of cell signalling events will be key to developing appropriate bioreactor systems for the culture of cell seeded bone scaffolds. Bioreactor cell culture, where both nutrients and mechanical cues can be delivered to growing constructs *in vitro*, are a cornerstone of tissue engineering.

Alicia El Haj and Sarah Cartmell consider the design of the bioreactors. The ultimate goal of tissue engineering is to grow new tissues and organs *in vitro* as off the shelf replacements for damaged or diseased tissues. Clearly static culture cannot provide this. Their paper reviews spinner, rotary, perfusion, compression and magnetic bioreactors, as well as monitoring of growing tissues during culture.

Finally, we have two papers from Mark Thompson and co-workers which consider mechanobiology firstly *in vitro* and then *in vivo*. Their *in vitro* paper develops new ideas such as stretching the cells and also builds on ideas in the aforementioned papers such as fluid flow and stimulating in 3D. The *in vivo* paper is rather different and focuses instead on whole bone loading, *in vivo* imaging of local mechanical environment and whole tissue healing and modelling of the *in vivo* situation.

Thus the papers presented progress from the clinical requirements through materials science to biology before bringing all these factors together in the development of appropriate biomechanical environments to encourage cells to grow and develop. We hope that you enjoy reading this selection.

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Reference

1 **Macewan, W.,** The Growth of Bone – Observations on osteogenesis, an experimental enquiry in the development and reproduction of diaphyseal bone, Pub James Maclehouse and Sons, Glasgow, 1912.