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EDITORIAL

Regenerative medicine, tissue engineering and vascular surgery: twenty first century clinical challenges

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Cardiovascular disease remains one of the leading causes of death and illness in man. Currently available vascular prosthetic devices are associated with significant risks of infection, thromboembolism, degeneration and growth failure, especially in younger patients. Because of such problems, several groups of researchers are seeking to engineer human organs and tissues capable of replacing diseased and damaged native cardiovascular tissues [1]. Tissue engineering, defined as "an interdisciplinary field that applies the principles of engineering and life sciences towards the development of biological substitutes that restore, maintain, or improve tissue function", offers the possibility of providing a true biological substitute with patient-specific properties [1, 2]. Vascular tissue engineering applies engineering principles and techniques to restore the structure and function of pathologically altered molecules, cells, and tissues of blood vessels [3]. The major advantage of tissue-engineered cardio-vascular tissues lies in their ability to grow, remodel, and repair in vivo without rejection. Moreover, such biological tissue-engineered substitutes provide patients with an alternative source of vascular conduits especially in cases where shortage of autologous and diseased veins is a problem. In essence, tissue-engineered cardiovascular devices offer the possibility of developing a patient-specific implantable device with the potential of growing alongside native tissue without the risk of rejection [4].

The key components for developing processed biological tissues are cells, scaffolds, growth factors, hormones and nutrients, and a biologic environment provided by bioreactors [4]. Several methodologies for constructing blood vessel replacements with biological functionality have emerged. The most common strategies include the use of cell-seeded gels, cell self-assembly, cell-seeded biodegradable synthetic scaffolds and xenogeneic acellular materials [5].

It has been more than two decades since Weinberg and Bell [6] introduced the innovative concept of developing a vascular graft from living tissue. Their graft combined synthetic and biological components; it was made of collagen integrated with Dacron mesh, smooth muscle cells and a functioning endothelium. Recent advances in cellular, scaffold and bioreactor technologies indicate that the goal of producing purely tissue-engineered vascular tissues with no synthetic components is now achievable and devices may soon be available for clinical use [7, 8]. Nevertheless, a number of significant problems remain to be resolved before biological vascular grafts can be used routinely in the management of vascular disease.

McAllister and colleagues [9] have recently reported the successful implantation of a completely biologic tissue-engineered graft for vascular access in ten patients with end stage renal disease receiving haemodialysis. Patency rates at 1 and 6 months were 78 and 60%, respectively. This is the first encouraging result of the use of a tissue-engineered vascular graft in a clinical setting. McAllister et al. used the cell self-assembly technique (as opposed to cell-seeded gels or cell scaffold technology) for the construction of their tissue-engineered vessel. In this approach, first described by L'Heureux in 1998 [10], human tissue-engineered vessels are constructed by taking advantage of the natural ability of

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cells to produce their own extracellular matrix (ECM). Briefly, human fibroblasts extracted from patient biopsy samples were cultured to form 15 sheets of living fibroblasts with associated ECM. These sheets were rolled over a stainless steel mandrel to allow them to fuse. After 10 weeks of culture the vessels were air-dried and the lumen seeded with endothelial cells. Total production time for the graft ranged between 6 and 9 months. Seven days prior to surgery, the lumen of the vessel was seeded with autologous endothelial cells and preconditioned to both flow and pressure. Tissue-engineered vascular grafts were then delivered to the clinic in a sealed, insulated, impact resistant container and transplanted. Grafts with an average length of 23.2 cm (range 14–30 cm) were implanted into nine patients (one patient was excluded prior to implantation because of gastrointestinal haemorrhage) and were assessed for both mechanical stability and effectiveness during the safety phase (0–3 months) and after haemodialysis was started. While the patency rates were good, it was possible to use the implanted graft for haemodialysis for longer than 12 months in only three patients [9].

There are some advantages to using the cell-self assembly technique used by McAllister et al. Firstly, the tissues are completely autologous so that the grafts are non-immunogenic and non-thromobotic. Secondly, as the graft develops its own matrix and does not require an external scaffold, there are no concerns about the use of xenogenic scaffolds, especially cross infection. Moreover, the high cell yield prior to in vivo implantation of the graft ensures excellent ECM synthesis and deposition. The major limitation to the technique is the long culture time required and this will limit their clinical application, especially in an emergency. Other areas of concern are the very high cost of production, the requirement for patient specificity and the lack of off-the-shelf availability.

An alternative approach for developing tissue-engineered vessels is to utilise fibrin gel and bioreactor technology. Fibrin gel offers a number of advantages over cell self-assembly [5, 11]. Fibrin has many inherent characteristics making it an ideal material for endothelial and smooth muscle cell adherence and it produces autologous extra cellular matrix. However, the main obstacle to the use of fibrin is its intrinsic weakness. The newer bioreactors closely mimic the natural physiological environment of blood vessels and can be used to produce tissue-engineered vessels under physiological conditions. The low burst pressure of fibrin gel matrices is being examined by many researchers as well as in our laboratory at CABER. Naturally occurring and synthetic ECM matrix materials are now being combined to link the key biologically active components such as fibrin gel to mechanically stronger synthetic polymers such as polyurethane. Already these approaches are showing promise [12].

In June 2010 the Tissue Engineering and Regenerative Medicine International Society (TERMIS) annual European chapter conference will be held in Galway**.** To accomplish its mission, the Society brings together the international scientific community engaged or interested in the field of tissue engineering and regenerative medicine and promotes education and research within the field through regular meetings, publications and other forms of communication. The society also serves as an international forum to promote the informed discussion of challenges and therapeutic benefits of the application of tissue engineering and regenerative medicine technologies.

Vascular tissue engineering is a rapidly developing discipline and likely to become a major modality for the treatment of advanced cardiovascular disease. Encouraging preliminary results both in vitro and in vivo show that vascular engineering is now well established. While we are not very far from the time when the use of engineered cardiovascular tissues will become an integral part of vascular surgical practice, regulatory approval (CE marking and FDA approval) are also challenges for adoption of these very promising approaches.

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