PREFACE

The next generation of biomaterial development

As defined by Park & Lakes (2007), a biomaterial is a material that replaces either a tissue within the body or a function of the body. The development of novel biomaterials is an iterative process that involves the creation of increasingly safer, more reliable, more inexpensive and more physiologically appropriate replacements for damaged or diseased human tissues. In their article entitled ‘Third-generation biomedical materials’, Hench & Polak (2002) described three generations of biomaterials that had been developed to that point. In the first generation of biomaterial development, individuals used materials in their local environments for replacing tissues that were lost to damage or disease. Several early civilizations used synthetic materials for treatment of skeletal defects; for example, Black et al. (1982) described the use of metallic implants by ancient Egyptian and Etruscan civilizations for fixation of fractures, as well as for treatment of other skeletal injuries. Rodriguez et al. (2007) noted that a skull was found in Perú dating to 2000 BC, in which a bony defect had been treated using a thin gold plate. According to Park & Bronzino (2003), rapid developments in the use of biomaterials took place shortly after Lister (1867) described the aseptic surgical technique in his thesis ‘On the antiseptic principle in the practice of surgery’. Prior to that time, the absence of effective mechanisms to prevent infection at the surgical site severely limited the use of medical implants. In the late nineteenth century, several surgeons experimented with the use of metallic and natural biomaterials for the treatment of skeletal defects. For example, Hansmann (1886) was the first surgeon to describe the use of metal plates and screws for subcutaneous fixation of bone. According to Eyron-Lewis et al. (1992), the first hip-replacement surgery occurred in 1890, when Themisocles Gluck replaced a tuberculous knee joint with a hinged prostheses fashioned from ivory. In the early twentieth century, several classes of metallic and polymeric biomaterials were adopted for use in medical applications. For example, Venable et al. (1937) used an in vivo study involving a canine model to demonstrate that ion transfer occurred between dissimilar metals within in the body. This study also showed that a cobalt-based alloy (vitallium) exhibited low levels of corrosion; this alloy remains a fixture in orthopaedic surgery to this day. Bothe et al. (1940) demonstrated in an in vivo study involving a feline model that titanium was well tolerated by the surrounding tissues and that bone grew into contact with titanium. It should be noted that innovations

One contribution of 14 to a Theme Issue ‘Advanced processing of biomaterials’.
were not limited to novel uses of metals. For example, Kolff & Scribner (2002) demonstrated the clinical use of an artificial kidney known as a ‘rotating drug artificial kidney’ in 1943; this first haemodialyzer was fashioned out of cellophane tubing. Harold Ridley used the first intraocular lens, which was fabricated out of rigid polymethylmethacrylate, for cataract treatment in 1948 (Apple & Sims 1996). The goal during the first generation of biomaterial development was the creation of materials that exhibited inert behaviour when placed in the body. Surgeons sought materials that provided (i) appropriate mechanical properties for the intended use, (ii) corrosion resistance, and (iii) an absence of injurious effects such as carcinogenicity, toxicity, allergy and inflammation. In the second half of the twentieth century, materials scientists began to partner with physicians in order to develop novel biomaterials that were specifically designed for use within the human body. During this time, biomaterials were created that promoted specific responses by the surrounding tissues. One example of this type of material is a bioactive ceramic called hydroxyapatite. Calcium phosphate (Ca$_{10}$(PO$_4$)$_6$(OH)$_2$) is similar in chemical structure to the mineral component of human bone. According to Ducheyne (1994), bioactive ceramics, such as hydroxyapatite, bond to bone, as well as promote bond formation when placed in bone tissue. Maxillofacial implants, orthopaedic implants and dental implants are plasma-sprayed with hydroxyapatite coatings in order to obtain fixation between the implant and the surrounding bones (Dhert 1994; Petit 1999). Resorbable polymers are another class of second-generation biomaterials. The most prominent use of resorbable polymers is in drug-eluting stents that are used to maintain patency of the coronary arteries; as noted by Hassan (2008), over four million of these devices have been implanted around the world. In these devices, cytostatic agents, cytotoxic agents, antithrombotic agents and/or anti-inflammatory agents are incorporated within resorbable polymeric matrices. According to Kukreja et al. (2008), pharmacological agents are released from the polymer into the surrounding tissues after implantation. At the present time, which is referred to as the third generation of biomaterial development, biomaterials are being created that promote or inhibit specific cell activities. Current biomaterial research efforts involve the development of materials that promote an ‘appropriate host response for a given application’; the definition for the word ‘biocompatibility’ developed by Williams (1999) reflects this change in emphasis. For example, artificial tissues being fabricated by placing cells within scaffold materials, which help guide cell proliferation and differentiation. Efforts are underway, as described by Madurantakam et al. (2009), to develop scaffold materials with nanoscale features that mimic the natural extracellular environment. One significant roadblock to the development of artificial tissues is the dearth of scaffold materials that enable nutrient transport and support cell proliferation. In many cases, growth of cells ceases in artificial tissues at a thickness of only four to seven cell layers. Kretlow & Mikos (2008) noted that scaffold materials with morphologies that provide improved nutrient diffusion are required in order to develop artificial tissues with appropriate sizes for clinical use.

We are currently witnessing the development of artificial tissues with macroscale, microscale and nanoscale features that match those of their natural counterparts. This volume describes several technologies for processing biomaterials with unique biological functionalities.
One area that is receiving renewed interest in the biomaterial community is the use of naturally derived materials for medical applications. For example, silk, the product of the domestic silkworm, has been used as a suture material for nearly 100 years (Halsted 1913). In recent years, chitosan, a polysaccharide derived from crustaceans, has found clinical use as a haemostatic agent (Rao & Sharma 1997; Cox et al. 2009). In addition, proteins obtained from the blue mussels have recently been considered for use as alternatives to conventional acrylate-based adhesives (Doraiswamy et al. 2008). In this issue, Ko et al. (2010) describe the use of polysaccharide-based naturally derived polymers, such as alginate, agarose, cellulose and chitosan, as scaffolds for tissue engineering. Their work demonstrates that hydrogels of naturally derived polymers exhibit good cell compatibility, as well as porosity appropriate for cell ingrowth. Yannas et al. (2010) discuss the use of type I collagen–glycosaminoglycan scaffolds in tissue regeneration. Type I collagen–glycosaminoglycan scaffolds with gradients in their physico-chemical properties have recently been developed. In addition, scaffolds with paucidisperse pore sizes have been demonstrated. Giocondi et al. (2010) describe the use of apatitic biomineral calcium hydrogen phosphate dihydrate, which is also known as brushite, in resorbable biomedical cements; the relationship between brushite atomic-step motion and incorporation of additives, as well as other processing parameters by means of in situ scanning-probe microscopy, are evaluated. Katti et al. (2010) discuss modification of Na-montmorillonite clay with three unnatural amino acids; they demonstrate the biocompatibility of Na-montmorillonite clay and clay-modified chitosan/polygalactouronic acid/hydroxyapatite using in vitro assays. Wegst et al. (2010) use freeze casting in order to fabricate materials with complex structures; it is anticipated that this technology will enable the development of the multi-level hierarchical composite structures seen in nature.

In recent years, several computer-aided additive and subtractive methods for processing biomaterials have been developed. These techniques may be used to develop prostheses with patient-specific attributes, scaffolds for tissue engineering, as well as small-scale medical devices (Doraiswamy et al. 2006). For example, anatomical data obtained from computed tomography, magnetic-resonance imaging and other medical-imaging techniques may be used to guide computer-aided additive or subtractive processes in order to fabricate patient-specific prostheses. A prosthesis may be fabricated that exhibits an appropriate geometry, size and weight for treatment of a given patient. Small-scale features may be incorporated into the prosthesis in order to promote tissue ingrowth (Ovsianikov et al. 2007). For example, He et al. (2006) recently used computed tomography data and realistic surgical models created by means of rapid prototyping in order to fabricate ‘exact-fit’ implants for clinical examination; implants were fabricated by means of computer numerical controlled machining. In this issue, Burg et al. (2010) describe the use of rapid prototyping to create artificial tissues, including breast tissue. Murr et al. (2010) use an additive manufacturing approach known as electron beam melting in order to fabricate complex functional mesh arrays; these materials may be useful in orthopaedic prostheses, including knee and hip implants. Dahotre et al. (2010) describe the use of laser-based direct melting techniques and optical interference techniques for creating microscale textures on titanium alloys. The relationship between texture, wetting and in vitro
biocompatibility is examined. Doraiswamy & Narayan (2010) discuss the use of laser micromachining to create scaffolds for vascular tissue networks. Concentric three-ring structures were fabricated for differential adherence and growth of cells. Fritsch et al. (2010) describe the use of mathematical models in order to examine the relationships between porosity, stiffness and strength in ceramic tissue-engineering scaffolds.

Recent efforts have also focused on the development of nanostructured materials for use in several medical applications, including prostheses and implantable biosensors. Nanostructured materials contain features with dimensions in the 1–100 nm range. According to Narayan et al. (2004), recent advances in the development of nanostructured materials for medical applications have taken place owing to two complementary forces. First, there is a natural evolution from development of microstructured materials to development of nanostructured materials as novel processing and characterization techniques become available. Second, nanostructured materials may participate in nanoscale interactions between biological molecules, including antigen– antibody interactions, protein assembly and signal transduction (Lee et al. 2009). Nanostructured biomaterials may be processed either using top-down methods, which involve the fabrication of nanostructured materials out of conventional bulk materials, or bottom-up methods, which involve self-assembly of small-scale components into large-scale functional constructs. In this issue, Venugopal et al. (2010) discuss electrospinning nanofibres of natural polymers and synthetic polymers. These materials can be used to imitate the topography and architecture observed in human tissues. Their study demonstrates that nanofibres promote adhesion, differentiation and proliferation of cells. These materials were combined with hydroxyapatite in order to create an artificial extracellular matrix for the development of artificial bone tissue. Narayan et al. (2010) examine functionalization of nanoporous alumina membranes by means of atomic layer deposition. These membranes are similar to the natural filters in the kidney that allow water and small waste molecules to pass into the urine, but prevent proteins and cells from passing into the urine. In this study, zinc oxide coatings and platinum coatings were deposited on nanoporous alumina membranes using atomic layer deposition. The pores of the PEGylated platinum-coated membranes remained free of fouling after exposure to human platelet-rich plasma. The zinc oxide-coated membranes demonstrated activity against Escherichia coli and Staphylococcus aureus bacteria. Verma et al. (2010) examine preparation of tissue-engineering scaffolds from nanocomposites containing chitosan, hydroxyapatite and polygalacturonic acid using freeze-drying methods.

The development and use of biomaterials is expected to dramatically increase over the coming decades as a result of ageing populations in Europe, China, Japan and the USA. The medical-device industry relies on the development of advanced ceramics, metals, polymers and composites in order to create sophisticated replacements for damaged and diseased tissues. For example, clinical use of drug-eluting cardiovascular stents has markedly expanded over the past decade owing to the development of resorbable polymers that release pharmacological agents in order to prevent artery closure; flexible wire meshes that maintain patency of the artery; and flexible polymers that expand the artery. It is hoped that this special issue will stimulate interactions among the numerous stakeholders...
involved in the development of biomaterials, including physicians, surgeons, engineers and biologists, and will promote future research activities in this rapidly developing area.

Roger J. Narayan
Joint Department of Biomedical Engineering,
University of North Carolina and North Carolina State University,
Raleigh, North Carolina, USA
E-mail address: roger_narayan@msn.com

References


