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*J. R. Soc. Interface* 2008 **5**, 1137-1158  
doi: 10.1098/rsif.2008.0151

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## REVIEW

# Biomaterials in orthopaedics

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At present, strong requirements in orthopaedics are still to be met, both in bone and joint substitution and in the repair and regeneration of bone defects. In this framework, tremendous advances in the biomaterials field have been made in the last 50 years where materials intended for biomedical purposes have evolved through three different generations, namely first generation (biointer materials), second generation (bioactive and biodegradable materials) and third generation (materials designed to stimulate specific responses at the molecular level). In this review, the evolution of different metals, ceramics and polymers most commonly used in orthopaedic applications is discussed, as well as the different approaches used to fulfil the challenges faced by this medical field.

**Keywords:** biomaterials; orthopaedics; tissue engineering; bioactive materials; biodegradable materials; biointer materials

## 1. INTRODUCTION

Bone and joint degenerative and inflammatory problems affect millions of people worldwide. In fact, they account for half of all chronic diseases in people over 50 years of age in developed countries. In addition, it is predicted that the percentage of persons over 50 years of age affected by bone diseases will double by 2020 (Bone and Joint Decade's Musculoskeletal Portal 2007, <http://www.boneandjointdecade.org>). These diseases often require surgery, including total joint replacement in cases of deterioration of the natural joint. Besides, numerous bone fractures, low back pain, osteoporosis, scoliosis and other musculoskeletal problems need to be solved by using permanent, temporary or biodegradable devices. Therefore, orthopaedic biomaterials are meant to be implanted in the human body as constituents of devices that are designed to perform certain biological functions by substituting or repairing different tissues such as bone, cartilage or ligaments and tendons, and even by guiding bone repair when necessary.

During most of the twentieth century, the availability of materials for the elaboration of implants was the same as for other industrial applications. Indeed, pioneer surgeons designed their implants using materials available and with a successful record of industrial use such as in chemistry, energy, mechanical and aerospace. Since the human body consists of a highly corrosive environment, very stringent requirements are imposed on the candidate materials' properties. Consequently, the first generation of biomaterials consisted of easily available materials of industrial use,

that were required to be as inert as possible in order to reduce their corrosion and their release of ions and particles after implantation. Mechanical properties also play a leading role in the selection of candidate materials for implant manufacture. The concept of biocompatibility, associated with a set of *in vitro* and *in vivo* standardized tests, was introduced in order to assess the biological behaviour of synthetic materials.

When trying to understand the evolution of biomaterials research and their clinical availability during the last 60 years, three different generations seem to be clearly marked (Hench & Polak 2002): biointer materials (first generation), bioactive and biodegradable materials (second generation), and materials designed to stimulate specific cellular responses at the molecular level (third generation). These three generations should not be interpreted as chronological, but conceptual, since each generation represents an evolution on the requirements and properties of the materials involved. This means that at present, research and development is still devoted to biomaterials that, according to their properties, could be considered to be of the first or the second generation. The materials that each new generation brings in do not necessarily override the use of those of a previous one. The present review is not meant to be a historical account of biomaterials used in orthopaedics. This review aims to set the point of view on the biomaterials evolution and not on the orthopaedic application or the type of device. This evolutionary perspective, along with the three generations, may provide a clearer insight into how biomaterials research and evolution set up the ground for the design and development of innovative devices for improved

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solutions to orthopaedic clinical problems. First-generation materials are still successfully used in a wide range of applications. Third-generation materials will open new possibilities of treatments and applications, but they are not meant to substitute plainly the materials from previous generations.

## 2. FIRST GENERATION

In engineering design, the selection of a material for a specific application is governed by matching the material properties with the requirements of this application. In the case of biomaterials, biological requirements have to be added to the common ones (mechanical, chemical and physical). Consequently, concepts such as foreign body reaction (particularly due to wear debris), stress shielding, biocompatibility, and, more recently, bioactivity and osteoinduction have been gradually introduced as requirements for biomaterials in the design of implantable devices.

When synthetic materials were first used in biomedical applications, the only requirement was to 'achieve a suitable combination of physical properties to match those of the replaced tissue with a minimal toxic response of the host' (Hench 1980). They were the 'first-generation biomaterials', according to Hench's classification, because they were 'inert' so as to reduce the immune response and the foreign body reaction to a minimum.

### 2.1. Metallic materials

The first metallic materials successfully used during the twentieth century in orthopaedic applications were stainless steel and cobalt–chrome-based alloys. Ti and Ti alloys were introduced by the 1940s. NiTi shape memory alloys appeared by the 1960s and they seemed to open a whole new range of applications, due to their special mechanical behaviour, but the properly unsolved allergenic effect of Ni has hampered their use.

The first really successful substitutive joint prosthesis was the total hip prosthesis developed by Charnley in the very late 1950s (Charnley 1960). This was a cemented prosthesis with a stem made of stainless steel.

Stainless steel materials are resistant to a wide range of corrosive agents due to their high Cr content (more than 12 wt%), which allows the formation of a strongly adherent, self-healing and corrosion resistant coating oxide of  $\text{Cr}_2\text{O}_3$ . Several types of stainless steel are available and the most widely used for implant manufacture is austenitic stainless steel. In order to be austenitic at room temperature, stainless steel needs to contain a certain amount of austenite stabilizing elements such as Ni or Mn. The stainless steel most widely used in clinical applications is AISI 316L that contains 0.03 wt% C, 17–20 wt% Cr, 12–14 wt% Ni, 2–3 wt% Mo and minor amounts of nitrogen, manganese, phosphorus, silicon and sulphur (table 1).

Stainless steel is widely used in traumatological temporary devices such as fracture plates, screws and hip nails among others, owing to their relatively low cost, availability and easy processing. Their use in

orthopaedic joint prosthesis is restricted because other metallic alloys such as Ti-based and Co–Cr-based alloys exhibit superior mechanical and corrosion properties. At present, new austenitic stainless steel with high Cr content (over 20%), where Ni has been partially substituted by Mn and with a high N content (between 0.3 and 0.4%), is being used in joint prosthesis. N stabilizes the austenitic phase and induces an increase in both the corrosion resistance and the mechanical properties (yield stress). This is a clear example of new materials with an improved performance that have been developed chronologically during the second generation, but that from a conceptual point of view belong to the first generation.

The wear resistance of austenitic stainless steel is rather poor and this is the reason why the metal-on-metal pairs in joints such as the hip (femoral head and acetabular cup) were discarded, because of high friction and the large number of wear debris particles that were produced, which led to a rapid loosening. This is one of the main reasons why the Co–Cr–Mo alloy (ASTM F75, Vitallium) was introduced in hip prostheses (McKee & Watson-Farra 1966; Walker & Gold 1971). Co–Cr alloys have been also successfully used in combination with polyethylene (PE) in the fabrication of artificial disc prostheses such as the SB Charité artificial disc replacement system (Punt *et al.* 2008). Co–Cr-based alloys exhibit an excellent corrosion resistance, even in chloride environments, that they combine with a good wear resistance. Their mechanical properties are also superior, most significantly their fatigue strength. These materials have a high elastic modulus (220–230 GPa) similar to that of stainless steel (approx. 200 GPa), and an order of magnitude higher than that of cortical bone (20–30 GPa). On contact with bone, the metallic devices will take most of the load due to their high modulus, producing stress shielding in the adjacent bone. The lack of mechanical stimuli on the bone may induce its resorption that will lead to the eventual failure and loosening of the implant (Huiskes *et al.* 1992; Bauer & Schils 1999). The range of Co–Cr alloys used in clinical applications includes wrought and cast alloys. Among the wrought alloys those containing 33–37 wt% Ni (ASTM F562, MP35N) are widely used in orthopaedic devices (table 1).

Ti and its alloys, originally used in aeronautics, became materials of great interest in the biomedical field, due to their excellent properties that include a moderate elastic modulus of approximately 110 GPa, a good corrosion resistance and a low density (approx. 4700 kg m<sup>−3</sup>).

It was after Branemark (Branemark *et al.* 1964) discovered what he named the osseointegration phenomenon for Ti implants that the exploration of dental and surgical applications of Ti alloys started. Titanium and its alloys are able to become tightly integrated into bone. This property significantly improves the long-term behaviour of the implanted devices, decreasing the risks of loosening and failure.

Commercially pure Ti (CP Ti), grade 4 (ASTM F67) and Ti6Al4V (ASTM F136) are the most common

Table 1. Summary of different metallic materials used or developed for orthopaedic applications, including their elastic modulus, yield strength and ultimate strength.

material	principal alloying elements (weight %)	elastic modulus (GPa)	yield strength (MPa)	ultimate strength (MPa)
stainless steel 316L	balance Fe 17–20 Cr 12–14 Ni 2–3 Mo max 0.03 C	205–210	170–750	465–950
CoCrMo F75	balance Co 27–30 Cr 5–7 Mo max 2.5 Ni	220–230	275–1585	600–1785
MP35N	balance Co 33–37 Ni 19–21 Cr 9–10.5 Mo			
Ti grade 4	balance Ti max 0.4 O	105	692	785
Ti4Al6V	balance Ti 5.5–6.5 Al 3.5–4.5 V	110	850–900	960–970
Ti6Al7Nb	balance Ti 6 Al 7 Nb	105	921	1024
Ti35Nb5Ta7Zr (TNZT)	balance Ti 35 Nb 5 Ta 7 Zr	55	530	590
NiTi	55.9–56.1 Ni	20–70 (martensite)	50–300 (martensite)	755–960
TiNb	balance Ti 25–40 Nb	70–110 (austenite)	100–800 (austenite)	—
		60–85	—	—

titanium alloys used in orthopaedics (table 2). For CP Ti, four grades are available according to oxygen content. CP Ti grade 4 contains the highest amount of oxygen, up to 0.4 per cent, and consequently, the highest tensile and yield strengths (Ratner *et al.* 2004).

The excellent corrosion resistance of Ti and Ti alloys is due to the formation of an adhesive  $\text{TiO}_2$  oxide layer at their surface. Other surface properties such as wear are very poor due to the low shear resistance of Ti and Ti alloys.

CP Ti, typically with single-phase alpha microstructure, is currently used in dental implants, while Ti6Al4V, with a biphasic alpha–beta microstructure, is most commonly used in orthopaedic applications. The Al and V alloying elements stabilize the alpha–beta microstructure, and improve the mechanical properties, in relation to CP Ti (typically twice the yield and ultimate strength values of CP Ti). These properties can be modulated by heat treatment and mechanical working. Despite Ti and Ti alloys combining a range of excellent properties, i.e. mechanical properties, corrosion resistance, fatigue–corrosion resistance, low density and relatively low modulus, their processing is not easy whether it is machining, forging or heat treating.

Some studies have pointed out V as a potential cytotoxic element (Friberg *et al.* 1979; Steinmann 1985;

Thompson & Puleo 1996; Daley *et al.* 2004). Recent advances have been made in order to overcome these concerns by developing new titanium alloy compositions (Long & Rack 1998). Particularly, Ti6Al7Nb and Ti5Al2.5Fe, with properties similar to Ti6Al4V but V-free, and TNZT alloys, based on the Ti Nb Ta Zr system to achieve minimum elastic moduli and excellent biocompatibility, should be pointed out. The Ti35Nb5Ta7Zr and its variant Ti35Nb5Ta7Zr0.4O show elastic moduli values as low as 55 and 66 GPa. This new generation of Ti alloys is at present under development and investigation, and it does not seem to be commercialized yet. Here is again an example of first-generation biomaterials being developed when third-generation biomaterials are already in use.

Aside from these conventional metallic materials, another type appeared in the 1960s when the shape memory effect was discovered in NiTi alloys by Buehler & Wang (1967). The shape memory effect is the ability of a material to recover its shape upon heating after having been ‘plastically’ deformed. The effect takes place by the transition from a low-temperature microstructure to a high-temperature one. Stress-induced martensite is responsible for the superelastic behaviour exhibited by shape memory alloys. Their elastic recoverable strain can reach up to 10 per cent, while for elastic metallic materials it is

Table 2. Summary of the metallic, ceramic and polymeric biomaterials used in orthopaedic applications.

material	orthopaedic applications	references
<i>metals</i>		
stainless steel (316, 316L)	fracture plates, screws, hip nails	
Co–Cr–Mo alloys	prostheses stems, load-bearing components in total joint replacement	McKee & Watson-Farra (1966) and Walker & Gold (1971)
HA-coated Ti alloys	hip and knee prostheses, screws and pins for bone fixation	Sun <i>et al.</i> (2001)
Ti6Al4V	prostheses stems	Long & Rack (1998)
TNZT alloys (Ti–Nb–Zr–Ta)	<i>under investigation</i>	Long & Rack (1998)
NiTi	internal fixator for long bone shafts, spinal correctors, vertebral spacer anchoring of prostheses and staples	Duerig <i>et al.</i> (1996), Shabalovskaya (1996) and Chu <i>et al.</i> (2000)
Ni-free shape memory alloys	<i>under investigation</i>	Suzuki <i>et al.</i> (2006)
<i>ceramics</i>		
high alumina ceramics	orthopaedic load-bearing applications	Christel <i>et al.</i> (1988)
ISO alumina standard 6474	dental implants	Christel <i>et al.</i> (1988)
PSZ	alveolar ridge augmentations otolaryngological coatings for tissue ingrowth maxillofacial reconstruction	
<i>calcium phosphate cements</i>		
R cement	cleft palate apical barrier	Driessens <i>et al.</i> (2002)
H cement	periodontal pockets filling periapical	Ginebra <i>et al.</i> (2007)
biopex	alveolar bone augmentation bony defects	Kurashina <i>et al.</i> (1997)
bonesource	periodontal osseous defects repair of large periodefects periapical surgery	Chow <i>et al.</i> (1991)
calcibon=biocement D		
cementek		
fracture grout		
KyphOs		
mimix		
Norian SRS		
rebone		
$\alpha$ -BSM=biobon=embark		
<i>bioglasses</i>		
45S5 BG	maxillofacial reconstruction	Filho <i>et al.</i> (1996)
45S5.4F BG	middle-ear reconstruction	Jedlicka & Clare (2001)
45B15S5 BG	dental implants	Hench <i>et al.</i> (1975)
52S4.6 BG	percutaneous access devices junction of spinal vertebrae	Filgueiras <i>et al.</i> (1993)
S45P7		Andersson <i>et al.</i> (2004)
55S4.3 BG		
<i>glass-ceramics</i>		
KGC ceravital	dental implants	Bromer <i>et al.</i> (1977)
KGS ceravital	maxillofacial reconstruction	Ohtsuki <i>et al.</i> (1991)
KGy213 ceravital	vertebral prosthesis devices iliac crest prostheses	Gross <i>et al.</i> (1988)
A/W GC		
MB GC		
Bioverit		
<i>polymers</i>		
polymethacrylic acid (PMMA)	acrylic bone cements	Kokubo <i>et al.</i> (1987) Höhland <i>et al.</i> (1985) Gummel <i>et al.</i> (1983)
<i>polyethylene (PE)</i>		
	anchoring of hip prostheses vertebroplasties and kyphoplasties liner of acetabular cups in hip arthroplasties	Lewis (1997a), Phillips (2003) and Lewis (2006)
	tibial insert and patellar components in total knee arthroplasties	Fisher & Dowson (1991) and Lewis (1997b)

(Continued.)

Table 2. (Continued.)

material	orthopaedic applications	references
polydimethylsulphoxide (PDMS)	replacement for small joints in hand and foot	Abel <i>et al.</i> (1998)
polypropylene (PP)	bone fixation devices	Marcolongo <i>et al.</i> (1998)
polysulphone (PS)	bone fixation devices, total joint arthroplasties	Charvet <i>et al.</i> (2000)
polycarbonate (PC)	bioabsorbable fixation devices and bone regeneration	
polyglycolic acid (PGA)	drug delivery	Rokkanen (1998) and Middleton & Tipton (2000)
polylactic acid (PLA)	bioabsorbable fixation devices and bone regeneration	Rokkanen (1998) and Middleton & Tipton (2000)
polycaprolactone (PCL)	drug delivery	
polydioxanone (PDS)	bioabsorbable devices for bone regeneration	Hutmacher <i>et al.</i> (2000)
	bioabsorbable fixation devices	
	bone regeneration	

approximately 0.1 per cent. In addition, the shape memory alloys can exhibit an elastic modulus as low as 30 GPa in the martensitic state, while it ranges between 70 and 110 GPa in the austenitic phase (Duerig & Pelton 1994; Ryhänen 1999). Therefore, their use in load-bearing applications seems more adequate than other metallic materials. Their ability to deliver a uniform compressive stress after the recovery of a prestrain upon heating could make them useful in applications such as staples for osteotomies, fracture repair (Chu *et al.* 2000), internal fixators for long bone shafts, spinal correctors, vertebral spacers and anchoring of prostheses (Duerig *et al.* 1996). Finally, the almost constant force they can produce over a very large displacement in their pseudo-elastic behaviour could be also beneficial for bone distraction devices.

However, there is a problem of allergy and toxicity for NiTi alloys associated with the release of Ni ions. The concern of Ni toxicity and potential carcinogenicity has limited the use of NiTi alloys in Europe and the USA, but they have been successfully used for more than 20 years in Russia (Shabalovskaya 1996) and China (Chu *et al.* 2000) for biomedical devices. In order to overcome this problem, several alternative Ni-free alloys, mainly Nb-based, are currently under development from the material science side although their long-term biological performance will have to be assessed (Suzuki *et al.* 2006).

Osseointegration being a very relevant issue for the anchorage of implants in the surrounding bone, great effort is being made in the design and optimization of biomaterials' surfaces. Advances in the study of the interactions between biological entities (proteins and cells) and surface materials have pointed out the essential role of biomaterial surface parameters such as roughness (Meyle *et al.* 1993; Chesmel *et al.* 1995; Healy *et al.* 1996; Thomas *et al.* 1997; Anselme *et al.* 2000; Boyan *et al.* 2001), wettability (Morra & Cassinelli 1997; Webb *et al.* 2000) and electrostatic charges (Shelton *et al.* 1988; Healy *et al.* 1996; Qiu *et al.* 1998). As a result, a wide variety of surface treatments are applied to most metallic implants before their implantation. The effect of surface physical properties such as topography on cell behaviour is a rather recent

concept that has allowed rationalizing the well-known effect that roughness has on osseointegration and that has been very well analysed in the case of dental implants. Treatments of passivation (Masmoudi *et al.* 2006; mainly by acid etching) and roughening (Aparicio *et al.* 2003; Schuh *et al.* 2004; Gil *et al.* 2007; shot peening and blasting) are the most commonly employed methods for dental implants.

## 2.2. Ceramic materials

When reviewing the first-generation ceramic biomaterials, the most commonly employed are alumina, zirconia and several porous ceramics. These non-metallic inorganic materials have a limited range of formulations. The microstructure is highly dependent on the applied manufacturing process (maximum temperature, duration of the thermal steps, purity of the powder, size and distribution of the grains and porosity) and it has a clear and direct effect on both the mechanical and biological properties.

One of the pioneering applications of bioceramics consisted of replacing the traditional metallic femoral heads of hip prostheses by high-density and highly pure alumina ( $\alpha$ -Al<sub>2</sub>O<sub>3</sub>; Boutin 1972). Later, ceramic materials were also used for the acetabular cups, showing excellent wear rates, excellent corrosion resistance, good biocompatibility and high strength (Hench & Wilson 1993). This meant a significant improvement in relation to conventional PE cups, responsible for wear debris release that induces a foreign body reaction and eventual osteolysis. Nevertheless, ceramic material components suffer from early failures due to their low fracture toughness. Therefore, important efforts have been made to improve the material quality by modifying the production processes and design requirements. Ceramic materials are widely used in total hip arthroplasties either as femoral heads articulated against PE, or as acetabular cups in the alumina-on-alumina combination.

Alumina has been used for nearly 20 years owing to its low friction and wear coefficients. Alumina hip prosthesis components must be perfectly spherical and congruent, making surface finish a crucial step to limit

friction and wear. Moreover, serious problems of stress shielding, due to a very high elastic modulus (380 GPa) compared with cancellous bone, appear in elderly patients with osteoporosis or rheumatoid arthritis and lead to the loosening of the alumina acetabular cup. This is the reason why a widely accepted combination consists of using alumina for the head of the hip joint, while the acetabular component is made of ultrahigh molecular weight PE (UHMWPE).

Zirconia is one of the ceramic materials with the highest strength suitable for medical use. Extremely low wear (less than 0.1 mm<sup>3</sup> per million cycles) has been reported for zirconia femoral heads articulated against alumina inserts for hip prostheses under normal laboratory hip simulation conditions. This bearing combination has been introduced into clinical use (Villermaux 2000). In addition, zirconia is extremely hard with excellent mechanical properties for hip replacements.

Highly porous ceramics have been developed in order to promote bone ingrowth and to induce prosthesis stabilization. However, mechanical requirements will determine the porous behaviour for low loaded or unloaded bearing applications.

The calcium carbonate skeleton of certain corals mimics trabecular bone. This fact has led to the replication or reproduction of these structures with different ceramic materials. In this sense, replamine-form preparation of Al<sub>2</sub>O<sub>3</sub> and hydroxyapatite (HA) were described in detail by White *et al.* (1975) with acceptable results.

Alumina and zirconia can also be foamed during solidification with a foaming agent such as CaCO<sub>3</sub> that produces porous generating gases (Peroglio *et al.* 2007). However, the risk of mechanical collapse increases with porosity, according to the Ryshkewitch equation:  $\sigma = \sigma_0 \cdot e^{-cp}$  (Ryshkewitch 1953), where  $\sigma$  is the compression strength;  $\sigma_0$  is the compression strength of the bulk non-porous material;  $c$  is a constant; and  $p$  is the porosity volume fraction.

Finally, because highly porous materials expose a larger surface to the environment, their compression strength can be affected by ageing.

### 2.3. Polymers

Some examples of polymer biomaterials of the first generation are silicone rubber, PE, acrylic resins, polyurethanes, polypropylene (PP) and polymethylmethacrylate (PMMA).

Acrylic bone cements have played and still play a key role in the anchorage of prostheses to the surrounding bone in cemented arthroplasties. Charnley (1960) introduced the self-polymerizing PMMA bone cement into contemporary orthopaedics where he took the idea from dental cements with the help of the chemist D. Smith. This cement is constituted on the one hand by a powder phase consisting of prepolymerized PMMA, an initiator (to catalyse the polymerization process) and a radiopacifier (BaSO<sub>4</sub> or ZrO<sub>2</sub>), and on the other hand by a liquid phase formed by MMA monomer, an accelerator reagent and a stabilizer. These two components are mixed into a paste that

after the polymerization of the monomer hardens and eventually sets.

Owing to the nature of the PMMA bone cement, it provides an excellent primary fixation of the prosthesis, but it does not promote a biological secondary fixation. Moreover, even if from the biomaterials point of view, PMMA bone cements perform adequately, several drawbacks are associated with their use: residual monomer may go into the blood supply producing a fat embolism, the large exotherm in setting may produce thermal necrosis of the surrounding bone, the shrinkage of the cement during polymerization produces gaps and loss of contact between the cement and the prosthesis and between the cement and the bone, the difference in stiffness between the metallic prosthesis and the bone may induce overstress or overstrain that may produce fractures in the cement and the release of cement particles that by interacting with the surrounding tissues may induce an inflammatory reaction. The ceramic radiopacifier particles reduce the mechanical properties up to 10 per cent due to the discontinuities that they introduce in the cement matrix. This is the reason why new opacifiers based on organic iodine compounds have been investigated (Artola *et al.* 2003). Despite these significant drawbacks, acrylic bone cements are still clinically used with a good rate of success. One of the reasons is that surgeons and material scientists have combined their effort to greatly improve the surgical technique and material performance from the time when acrylic bone cements were initially used. Monomer cooling, vacuum mixing and injecting devices have significantly improved the cements' microstructure and their mechanical properties. Moreover, the very good knowledge about the pros and cons of these materials, as well as the available choice of alternative solutions for implant anchorage that surgeons have on their hands, allows them to be used only in those applications where they can exhibit a superior clinical performance. More recently, acrylic cements have been used in vertebroplasty and kyphoplasty, two surgical procedures aimed at augmenting the strength of weakened vertebral body, in order to stabilize it and restore it (Phillips 2003; Bono & Garfin 2004). In the case of vertebroplasties and kyphoplasties, the same formulations as for cemented arthroplasties are still used, including several formulations with a higher concentration of radiopacifier (Kuhn 2000; Carrodeguas *et al.* 2002).

PE, and more specifically UHMWPE, is particularly attractive for applications such as the liner of acetabular cups in total hip arthroplasties, in the tibial insert and patellar component in total knee arthroplasties and as a spacer in intervertebral artificial disc replacement. Its unique properties of high abrasion resistance, low friction and high impact strength, excellent toughness and low density, ease of fabrication, biocompatibility and biostability make it an ideal candidate (Fisher & Dowson 1991; Sutula *et al.* 1995). However, wear will take place and the wear debris will lead to undesirable effects. It has been recently shown that gamma-ray sterilization enhances the rate of production of particles produced during the wear

process. These particles produce an inflammatory reaction in the surrounding tissues that may end up as granulomatous lesions, osteolysis and bone resorption (Maloney & Smith 1995). In order to overcome these problems, new processing and sterilization techniques have been developed and continue under study. They are specifically addressed to reduce the fraction of low molecular weight chains in the polymer, the orientation and compaction of the polymer chains and the modification and hardening of the surface of the UHMWPE-bearing components.

Medical grade silicone elastomers have been widely used in the replacement of diseased small joints. The idea of replacing the small joints of the hand with silicone implants was first introduced by Swanson in the mid-1960s (Swanson 1968). Arthroplasties of the metacarpophalangeal and metatarsophalangeal joints are most commonly practiced in severe pained rheumatoid arthritis treatments (Abel *et al.* 1998). Silicone implants have proved to reduce pain effectively, correct ulnar drift in fingers and slightly improve the functional range of motion (Kirschenbaum *et al.* 1993). Implant mechanics are the main limitations of these flexible implants: the most important clinical complication related to silicone implants is fracture (Blair *et al.* 1984; Bass *et al.* 1996). Other drawbacks include subluxation, bone erosion, loosening and implant abrasion (Hirakawa *et al.* 1996). A key issue in the success of silicone-based implants lies in the appropriate design of the device mimicking the normal characteristics of the joint (El-Gammal & Blair 1993; Wilson *et al.* 1993).

Carbon fibres have also been used in orthopaedics as biomaterials of the first generation. They have been mainly used to reinforce polymers. These composite materials have been tested with good results and rare failure for spine surgery (Tullberg 1998). They have also been studied for different applications such as total hip replacement and internal fixation. Carbon–carbon prostheses for long-term middle-ear implantation have also been applied with satisfactory results (Adams *et al.* 1978; Adams & Williams 1984; Podoshin *et al.* 1988). Nevertheless, the main concern with these implants is their release of carbon debris into the surrounding tissues. It has been shown that they elicit adverse cell response in some cases, such as collagenase synthesis (Olson *et al.* 1988), cell detachment and lysis (Brandwood *et al.* 1992) and the release of cell-activating factors that then activate other cells in the culture (Greis *et al.* 1994). Consequently, this means that the use of these materials should be kept under scrutiny unless carbon debris release is avoided.

Polyester and polytetrafluoroethylene (Goretex) have been used for cruciate ligament prostheses, but their clinical performance was not good enough to become currently used by orthopaedic surgeons (Dürselen *et al.* 1996).

Polymer matrix composite materials reinforced with ceramic particles or fibres, aiming for an inert behaviour, have been also developed, although from a chronological point of view they appeared later in time, coexisting with the development of biomaterials of the second and third generations. One of the main

applications sought was for osteosynthesis of bone plates and screws. The main strategies consisted of reinforcing polymeric matrices of polyetheretherketone, PE or polysulphone (PS) mainly with carbon or glass fibres (Evans & Gregson 1998; Ramakrishna *et al.* 2001). Carbon fibre-reinforced composites present a lower rigidity in comparison with metallic biomaterials, which is closer to that of cortical bone (Lewandowska-Szumiel *et al.* 1999). These non-resorbable composite materials are designed to be stable in *in vivo* conditions without changes in the stiffness of the devices with implantation time. Since these composites contain fully polymerized and reacted thermoplastic polymers, no complications associated with the toxic effect of monomers can be expected. These materials can be shaped according to surgery requirements, although in certain applications such as bone plates, the stiffness and lack of ductility of these materials do not allow the surgeon in the operating theatre to give the final bend or shape in order to adapt it to the anatomy of the patient.

A common feature of first-generation biomaterials is that after implantation a layer of diverse unspecific proteins is adsorbed on their surface. The effect of such different proteins adsorbed in different configurations results in unspecific signalling to the cellular environment. The consequence is that a layer of fibrous tissue grows on the material surface, and with time the implant becomes totally encapsulated by such fibrous tissue. The development of bioactive interfaces eliciting a specific biological response and avoiding any fibrous layer has been one of the main driving forces in second-generation biomaterials.

### 3. SECOND GENERATION

The second generation of biomaterials should be considered to have appeared between 1980 and 2000, and was defined by the development of bioactive materials' ability to interact with the biological environment to enhance the biological response and the tissue/surface bonding, as well as by the development of bioabsorbable materials' ability to undergo a progressive degradation while new tissue regenerates and heals. Bioactivity refers to any interaction or effect that materials exert on cells with the aim of leading or activating them to specific responses and behaviours. Mineralization and binding between the bone tissue and the implant is one of the most currently known processes to increase bioactivity in bone repair and fixation applications. Bioactive biomaterials designed for bone fixation, repair and regeneration led to the *in vivo* deposition of a layer of HA at the material surface. By the mid-1980s, these bioactive materials had reached clinical use in a variety of orthopaedic and dental applications, including several bioactive glasses (BGs), ceramics, glass–ceramics and composites. However, there are other methods to induce materials' bioactivity. These methods rely on the modification of surfaces with adsorbed proteins and tethered polymers and biomolecules that promote certain cell responses depending on the final application.

### 3.1. Ceramics

The most common ceramic materials can be classified as BGs, glass-ceramics and calcium phosphates (CaPs) both as ceramics and cements. The application of these materials as bone substitutes started around the 1970s (De Groot 1974; Jarcho *et al.* 1976; Alkao *et al.* 1981; El Gannham 2005) and have been mainly used as bone defect fillers (Vogel *et al.* 2001). The similarities between the bone mineral phase and their structural and surface features are accountable for their good bioactive properties, enabling binding to the bone with no mediation of a fibrous connective tissue interface (Meffert *et al.* 1985; Schepers *et al.* 1991). Bioactive ceramics have been reported to be biocompatible and osteoconductive.

HA ( $\text{Ca}_{10}(\text{PO}_4)_6(\text{OH})_2$ ),  $\beta$ -tricalcium phosphate ( $\beta$ -TCP,  $\text{Ca}_3(\text{PO}_4)_2$ ), their derivatives and their combinations are the most commonly used ceramics. Depending on their synthesis process, these materials show different physical and chemical properties (El Gannham 2005). HA shows good bioactive properties; however, its chemical stability reduces its solubility rate in comparison with other CaPs such as TCPs. In fact, after implantation HA may remain integrated into the regenerated bone tissue, whereas TCPs are completely reabsorbed (Takahashi *et al.* 2005; Ginebra *et al.* 2006).

There is a range of suitable CaPs (amorphous CaP (ACP), OCP,  $\alpha$ -TCP,  $\beta$ -TCP, CDHA, HA, TTCP and occasionally FA) that can be used as CaP cements (CPCs). These materials are injectable, harden inside the damaged bone tissue and generate low heat transfer that avoids the premature death of surrounding cells (Ginebra *et al.* 1997; Takagi *et al.* 1998).

Silicon plays an essential role in bone formation; indeed, silicon ions are known to be involved in the calcification process of young bones (Carlisle 1970). Thus, the presence of silicon in biological ceramics and glasses has a significant effect in the osteogenesis process. In fact, it has been demonstrated that the incorporation of silicon into apatites induces the formation of a higher amount of bone tissue than non-doped apatites (Patel *et al.* 2002). Moreover, silicon improves materials' bioactivity by leading the formation of Si-OH groups on the material surface. These groups trigger the nucleation and formation of apatite layers on the surface improving the material-bone bonding.

Several BGs containing  $\text{SiO}_2$  as network former and  $\text{Na}_2\text{O}$ ,  $\text{CaO}$  and  $\text{P}_2\text{O}_5$  as modifying oxides such as the bioglass (45S5) developed by Hench in the 1970s, and glass-ceramic compositions are able to stimulate tissue regeneration by inducing the formation of surface active layers (Anderson & Kanganiemi 1991; Ohtsuki *et al.* 1991; Neo *et al.* 1993; Cao & Hench 1996). According to Hench (1991), bioactive materials are able to form a carbonated HA (CHA) bone-like layer on the surface. The crystallization of the ACP film occurs by incorporating  $\text{OH}^-$  and  $\text{CO}_3^{2-}$  from the solution to form a CHA layer. Several BG formulations have been developed by both the melt process and the sol-gel process (Hench *et al.* 1998). These bioglass formulations induce bone growth three times faster than HA

(Fujishiro *et al.* 1997). Approximately 10 hours after implantation, there is a combination of adsorption and desorption processes of proteins and growth factors to trigger the osteogenic cascade and cell differentiation. In approximately 100 hours, stem cells differentiate to form osteoblasts, which generate an extracellular matrix (ECM) to form a new bone. Finally, CaP matrix crystallizes to enclose bone cells (osteocytes). It has been shown that a large surface area in BGs, silica gel and glass-ceramics (larger than  $40-80 \text{ m}^2 \text{ g}^{-1}$ ) provides a high amount of silanol (Si-OH) terminations, which are adequately flexible to match the crystal cell of CHA and therefore might act as nucleation sites for it (Karlson *et al.* 1989; Kokubo 1991). Furthermore, Li and co-workers observed that abundant  $\text{OH}^-$  groups and a negative zeta potential were required to nucleate CHA on the gel (Li & Zhang 1990; Li *et al.* 1994a,b). Thus,  $\text{Ca}^{2+}$  is deposited on the surface and induces phosphate precipitation. It was also shown that  $\text{SiO}_2$  and  $\text{TiO}_2$  gels were able to induce the nucleation of CHA owing to their negative charges at physiological pH. Conversely,  $\text{Al}_2\text{O}_3$  is positively charged at pH 7 and inhibits CHA nucleation (Li *et al.* 1994a,b).

Besides  $\text{SiO}_2$ ,  $\text{P}_2\text{O}_5$  has also been used as a network former, while alkaline earth metals (e.g.  $\text{MgO}$  or  $\text{CaO}$ ) or alkali metals (e.g.  $\text{Na}_2\text{O}$  or  $\text{K}_2\text{O}$ ) act as network modifiers allowing the modification of the inner interface environment through ion exchange. In several cases,  $\text{TiO}_2$  has also been used as a modifier to enhance reticulation within the glass network (Clement *et al.* 2000; Navarro *et al.* 2003). Owing to their poor mechanical properties, low tensile strength and very low fracture toughness, BGs are not suitable for load-bearing applications. Conversely, BGs were successfully used in low load-bearing material applications for bone repair in dental and orthopaedic surgery (Ogino *et al.* 1980; Schepers *et al.* 1991; Stanley *et al.* 1997). BG surfaces have also been modified to enhance their bioactivity by coating them with adhesive proteins such as fibronectin to promote cell adhesion (García *et al.* 1998).

### 3.2. Metals

None of the metallic materials used in orthopaedics is bioactive *per se*. However, two approaches can be considered to obtain bioactive metals. The first one consists of coating the surface of the implant with a bioactive ceramic (HA and BGs). The second one is to chemically modify the surface of the material so as to obtain the deposition of a bioactive ceramic *in vivo* or to induce proteins and cell adhesion and other tissue/material interactions.

Some of the coating methods of the first approach include electrophoretic deposition (Ducheyne *et al.* 1990), plasma spraying (De Groot *et al.* 1990; Thull & Grant 2001), radio frequency or ionic ray sputtering (Cook *et al.* 1988), laser ablation (Clères 1999; Serra *et al.* 2001) or hot isostatic pressure (Hero *et al.* 1994). None of these methods produce covalent links with the substrate, and the majority are not cost-effective. However, HA coating by plasma spray deposition is at

present the most common method used for clinical applications. In this process, HA in its plasma state (greater than 1000°C) is projected against a colder material metallic surface (100–150°C). By cooling down rapidly, a mechanical interaction is created between the ceramic and the substrate. However, this method presents some drawbacks such as difficulties in controlling the final composition of the ceramic (Yan *et al.* 2003), crystallinity of the coating (Fazan & Marquis 2000), structure of the HA which is thermally unstable, heterogeneities between the substrate and the coating (air bubbles) and residual stresses in the ceramic coating (Wang *et al.* 1993). All these factors may produce failure of the coating, during the life in service of the implant (Mann *et al.* 1994). Extensive information about these drawbacks and their possible consequences are reviewed in the literature (Sun *et al.* 2001).

In the second approach, various methods based on chemical modifications have been developed to obtain apatite or other CaP material layers on metallic surfaces, creating a direct chemical link between the substrate and the coating. These methods have been mainly developed for CP Ti and Ti alloys.

The first method consists of a thermochemical treatment developed by Kokubo *et al.* (1996), which consists of etching the surface of the material with an aqueous solution of NaOH, followed by a heat treatment at 600°C. This results in a thin titanate layer able to form a dense bone-like apatite layer when placed in a physiological medium. An alternative method developed by Ohtsuki *et al.* (1997) is based on a chemical etching with hydrogen peroxide containing small amounts of tin chloride at 60°C. Another method consists of dipping the material in a sol–gel solution previously prepared at 0°C, followed by a thermal treatment at 500°C (Li & de Groot 1993). Other methods consist of the attachment of self-assembled monolayers (SAMs) designed with a functional group at their end, which is able to induce the nucleation of a CaP (Campbell *et al.* 1996; Tanashi & Matsuda 1997; Wheeler *et al.* 1997). A final strategy used consists of the precalcification of the metallic surfaces by successive immersion in solutions of Na<sub>2</sub>HPO<sub>4</sub> and Ca(OH)<sub>2</sub>, after a two-step chemical etching with a mixture of HCl and H<sub>2</sub>SO<sub>4</sub> followed by immersion in NaOH boiling solution (Wen *et al.* 1997).

The mechanisms involved in the nucleation and growth of a CaP layer on this bioactive surface, *in vitro* and *in vivo*, are not fully understood. Among the surface parameters that seem to play a critical role in apatite deposition are the electrostatic charges and zeta potential, density of hydroxyl groups and structure of TiO<sub>2</sub> oxide (Li *et al.* 1994a,b; Cho *et al.* 1995; Uchida *et al.* 2003).

Other surface modification methods to improve the bioactivity of metallic surfaces were also studied. Methods ranging from dip-coating techniques to formation of SAMs and tethering polymer chains to the surface were developed to affect the adhesion of cells, to influence proliferation and differentiation rates and to achieve more stable long-term material/tissue integration (Blawas & Reichert 1998; Scotchford *et al.* 1998). In this context, covalent chemical binding of

polymers and biomolecules has been achieved through silanized titania surfaces, using amino- and carboxyl-directed immobilization mainly through glutaraldehyde chemistry, and photochemistry by ‘grafting to’ biomolecules with a photoactive group (Colloiu *et al.* 1993; Xiao *et al.* 1998, 2001).

### 3.3. Polymers

This second generation was characterized by the development of resorbable biomaterials that displayed a controlled chemical breakdown and the resorption of the polymer chains. Biodegradable polymers of synthetic and natural origin such as polyglycolide (PGA), polylactide (PLA), polydioxanone (PDS), poly( $\epsilon$ -caprolactone) (PCL), polyhydroxybutyrate (PHB), polyorthoester, chitosan, poly(2-hydroxyethyl-methacrylate) (PHEMA), hyaluronic acid and other hydrogels were extensively studied during this period. The concept of bioabsorbable material was introduced in the 1960s by Kulkarni *et al.* (1966, 1971). In the last decades, these materials have been used in many orthopaedic applications such as bone substitution, repair of bone fractures (including ligament fixation), cartilage, meniscus and intervertebral disc. They are found as sutures, rods, screws, pins and plates (Ciccone *et al.* 2001).

When from a mechanical point of view a polymeric device can be used instead of a metallic one, the use of bioresorbable implants has several advantages over the use of traditional metallic ones. Biodegradable implants reduce the stress shielding effect, eliminate subsequent surgeries that may be necessary to remove the metallic implant, and enable post-operative diagnostic imaging, avoiding artefacts from metals.

Many macromolecular compounds are bioabsorbable, but only a few have the required properties for internal bone fixation devices. PLA, PGA and PDS have been the most widely used for such purposes.

The mechanical strength of bioabsorbable polymeric implants has been enhanced by using the self-reinforcing process. This approach consists of reinforcing the polymer matrix with oriented fibres or fibrils of the same material. This self-reinforcing strategy for PLA (SR-PLA) and PGA (SR-PGA) has been clinically studied and used since 1984 (Törmälä 1992; Waris *et al.* 1994).

Bioabsorbable fixation can be used in the treatments of a variety of fractures, namely glenoidal rim, proximal humerus, lateral humeral condyle, medial condyle of the humerus, olecranon, radial head, distal radius, hand, femoral head and neck, femoral condyles, patella, tibial condyles, talus, calcaneus, metatarsal bones, phalanges of the toes and malleolar fractures (Rokkanen 1998). Bioabsorbable devices are also currently used in the fixation of bone in osteotomies, arthrodeses and other reconstructive surgery. Bioabsorbable self-reinforced PLA, self-reinforced PGA and PDS pins can be used to fix distal chevron osteotomy (Barca & Busa 1997); PLA staples are used in foot surgery (Burns 1998; Burns & Varin 1998). The fixation of ruptures of the ulnar collateral ligament of the thumb, which is a common sports injury, can be

done using bioabsorbable devices. PLA arrows and plugs are also used in the fixation of the knee meniscus bucket-handle lesions and dislocations of the shoulder (Albrecht-Olsen *et al.* 1993; Pihlajamäki *et al.* 1994).

Bioabsorbable implants for spinal surgery are rather recent in comparison with the applications mentioned previously (Vaccaro *et al.* 2003). Some applications such as interbody cages elaborated with PLA for specific spinal fusion applications, bioabsorbable ramp type interbody spacers for posterior lumbar interbody fusion procedures and the use of PLA screws for anterior cervical decompression and fusion processes have been successfully reported (Brunon *et al.* 1994; Subach *et al.* 1999; Van Dijk *et al.* 2002). The stabilization of posterolateral lumbar fusion using facet joint fixation with PLA bioabsorbable rods has also been studied (Johnson *et al.* 1997).

Bioabsorbable polymers are usually processed following similar procedures as those used for thermoplastics. They can be melted and extruded, moulded by injection or compression or solvent cast, but the presence of moisture must be carefully controlled, because their hydrolytic sensitivity leads to a significant decrease in the material's molecular weight. Therefore, the polymer has to be kept completely dry before thermally processing, and its contact with moisture during the processing must be avoided. The effect of several processing parameters on polymers' degradation during processing has been reported by Von Oepen & Michaeli (1992) and Michaeli & Von Oepen (1994).

Biodegradability is mainly originated by hydrolysis of the polymer chain backbone and to a lesser extent by enzymatic activity (Vert & Li 1992; Li & McCarthy 1999). Degradation times depend on multiple factors such as polymer crystallinity, molecular weight, thermal history, porosity, monomer concentration, geometry and the location of the implant. In an aqueous environment, water penetrates the bulk of the polymer sample and attacks preferentially the chemical bonds of the amorphous phase, shortening the polymer chains (Gopferich 1996). Crystalline regions remain and temporarily support the physical properties of the device until water disrupts and attacks crystalline regions. In a second stage, enzymatic attack of the bulk takes place (Li & Vert 1994). Degradation inside the device is accelerated due to the presence of the acidic degradation products that autocatalyse the degradation process of the material. After degradation, the hydrophilicity of the monomer increases as well as the amount of acidic end groups. These factors together with a lower crystallinity and size of the device and a higher amount of reactive hydrolytic groups in the polymer backbone accelerate the degradation process (Grizzi *et al.* 1995; Middleton & Tipton 2000). This type of degradation is known as 'bulk degradation' (Li & Vert 1994; Li 1999). In the case of PLA and PGA, the final products of the polymer degradation are the acidic monomers (lactic acid and glycolic acid, respectively) that are enzymatically converted and used in the metabolic pathway of the tricarboxylic acid cycle that takes place in the mitochondria. The final products are

ATP, water and CO<sub>2</sub> that are excreted by the lungs and kidneys (Brady *et al.* 1973; Agrawal *et al.* 1995).

Chitosan, PHEMA, PEG and hyaluronic acid are among the most relevant hydrogels studied of this second generation of biomaterials. Hydrogels' structure and properties are attributed to the bonding of hydrophilic macromolecules by means of covalent hydrogen and ionic bonds that form a three-dimensional network that is able to retain large amounts of water in their structure. These types of polymers have been mainly used in cartilage, ligaments, tendons and intervertebral disc repair applications (Ambrosio *et al.* 1996).

Self-reinforcing is not the only method used to strengthen polymer materials. Hydrogels such as PHEMA, which is a highly biocompatible, permeable and hydrophilic hydrogel, have been combined with PCL and reinforced with PGA and PET fibres and studied for potential use as tendon and ligament prosthesis (Migliaresi *et al.* 1981; Davis *et al.* 1991; Ambrosio *et al.* 1998). The incorporation of PCL and PET fibres into a PHEMA matrix has been studied as an alternative to previous intervertebral disc prosthesis made from metals and metallic-polymer systems (Taksali *et al.* 2004).

Composite materials reinforced with ceramic particles or fibres, both biodegradable and inert can be considered to have been developed during the last 30 years. The inert ones can be considered as first-generation materials and they have been already described.

Most bioabsorbable composites for bone repair applications were developed following the so-called bone-analogue concept proposed by Bonfield *et al.* (1981) and Bonfield (1988). It is necessary to point out that in the case of Bonfield's composite, as well as some others, the concept is a bioactive non-biodegradable material: HAPEX consists of a PE matrix reinforced with HA particles. HA acts as the bioactive agent that promotes osteoblast attachment, while PE, the matrix, is a stable, non-biodegradable inert polymer. It is worth mentioning that HAPEX has been successfully commercialized for middle-ear implant applications and to date it has been implanted in over 300 000 patients with very successful outcomes. In the case of bioabsorbable composites, the bioabsorbable polymer matrix is reinforced with a bioactive reinforcing phase such as HA, several CaPs and BGs (Kasuga *et al.* 2003; Kunze *et al.* 2003; Jaakkola *et al.* 2004; Navarro *et al.* 2005). The aim is to obtain a material with mechanical properties similar to those of bone that can form bioactive bonding with bone tissue and where the degradation process matches the healing period of the fracture or lesion. The adhesion between the components of the two phases is one of the main concerns that need to be solved. The most effective strategy to improve adhesion at the interface between the organic matrix and the inorganic reinforcement is to chemically modify both phases in order to create a biocompatible chemical bonding between them. Some natural polymers such as hyaluronic acid, collagen and chitosan have proved to have some intrinsic bioactive effect in some tissues such as cartilage tissue. Polymers' bioactivity depends on the functional groups and binding sites available at the material surface. Thus,

polymers' bioactivity can be also improved by coupling certain polymers and biomolecules to their surface as in the case of metals and ceramic materials. For the second-generation biomaterials, polymer surface modification has been mainly achieved by physisorption of proteins and peptides on the surface, by dip-coating and by amino- and carboxyl-directed immobilization of biomolecules (Ma *et al.* 2002). Polymers' surfaces have also been modified biochemically to induce their mineralization with HA layers (Kato *et al.* 1996).

#### 4. THIRD GENERATION

The third-generation biomaterials are meant to be new materials that are able to stimulate specific cellular responses at the molecular level (Hench & Polak 2002). For these biomaterials, the bioactivity and biodegradability concepts are combined, and bioabsorbable materials become bioactive and vice versa. These materials' properties should merge with their ability to signal and stimulate specific cellular activity and behaviour. Temporary three-dimensional porous structures that stimulate cells' invasion, attachment and proliferation, as well as functionalized surfaces with peptide sequences that mimic the ECM components so as to trigger specific cell responses are being developed (Hutmacher *et al.* 2000; Temenoff & Mikos 2000; Agrawal & Ray 2001). Deliveries of biochemical factors and medical drugs, as well as control of cell behaviour through mechanotransduction are some fields of interest.

The third generation of biomaterials appeared approximately at the same time as scaffolds for tissue engineering applications started to be developed. Tissue engineering emergence is boosted as an alternative potential solution to tissue transplantation and grafting. The use of allografts, autografts and xenografts presents several limitations, namely donor site scarcity, rejection, diseases transfer, harvesting costs and post-operative morbidity (Fernyhough *et al.* 1992; Banwart *et al.* 1995; Goulet *et al.* 1997). Tissue engineering and regenerative medicine are recent research areas exploring how to repair and regenerate organs and tissues using the natural signalling pathways and components such as stem cells, growth factors and peptide sequences among others, in combination with synthetic scaffolds (Hardouin *et al.* 2000). In addition to the combination of the basic tissue engineering triad (cells, signalling and scaffold), there are some processes such as angiogenesis and nutrients delivery that are crucial to stimulate tissue regeneration and must take place right after implantation.

Although tissue engineering has emerged as a very brilliant alternative to overcome many existing problems related to the current use of autografts, allografts and xenografts, its implementation as part of a routine treatment for tissue replacement is controversial. At present the angiogenesis problem has not been solved. Besides, tissue engineering involves cells' manipulation which is not a simple and straightforward issue, and represents a main drawback for the generalized use of this technique in a hospital. In spite of that, tissue

engineering is a very promising strategy that opens numerous possibilities of study and research in the field of regenerative medicine.

Tissue engineering is a multi- and interdisciplinary field that involves the complementary effort of the engineering, chemistry, physics and biology fields. Engineers, chemists and physicists will have to focus on the improvement and development of new materials and processing technologies, new surface treatments and characterization techniques, bioreactors and cell seeding methods. From the biology side, new cell sources will have to be found as well as new isolation and expansion methodologies. Furthermore, new biomolecules such as growth factors and peptides involved in cell differentiation, angiogenesis and tissue formation processes will have to be developed. Finally, surgeons will have to enhance and develop new surgical procedures, probably minimally invasive, in order to overcome present limitations.

Scaffolds understood as three-dimensional porous structures need to fulfil the following criteria in order to be used in tissue engineering (Spaans *et al.* 2000; Boccaccini *et al.* 2002).

- The material must be biocompatible and its degradation by-products non-cytotoxic.
- The scaffold must be biodegradable and should resorb at the same rate as the tissue is repaired.
- The scaffold must possess a highly interconnected porous network, formed by a combination of macro- and micropores that enable proper tissue ingrowth, vascularization and nutrient delivery.
- The mechanical properties of the scaffold must be appropriate to regenerate bone tissue in load-bearing sites. Moreover, the material must keep its structural integrity during the first stages of the new bone formation.

Both natural and synthetic polymers have been used in the development of new three-dimensional scaffolds for bone, cartilage, ligament, meniscus and intervertebral disc tissue engineering. In particular, synthetic biodegradable polymers have attracted special attention because they enable a better control of their physico-chemical properties and also because they have been successfully used in clinical applications. PLA, PGA, PCL and PHB are the most widely studied polymers for bone tissue engineering purposes. PLA, collagen and silk have been studied as potential materials for ligament tissue engineering (Guarino *et al.* 2007). A combination of PCL and hyaluronic acid has been developed for meniscus tissue engineering with promising results (Chiari *et al.* 2006). Hyaluronic acid, polyglactin (Marijnissen *et al.* 2002), collagen, fibrin, alginates, chondroitin sulphate photocrosslinked hydrogels and glycosaminoglycans are also under study for cartilage and intervertebral disc (nucleus pulposus) tissue engineering applications (Cancedda *et al.* 2003; Revell *et al.* 2007). In addition, decalcified (or demineralized) bone matrix (DBM) is currently being used successfully in various clinical applications as an alternative to autografts (Mellonig 1996; Caplanis *et al.* 1998; Groeneveld *et al.* 1999; Russell & Block 1999;

Wang *et al.* 2007). It is commercially available from different manufacturers as an allergenic human freeze-dried bone graft (Wang *et al.* 2007), and is generally used for filling bone defects. Moreover, due to its similarity with natural bone, DMB has been demonstrated to be an efficient carrier for bone morphogenetic proteins (BMP), which are growth factors that enhance bone formation (Canter *et al.* 2007). In fact, DMB is also used as a delivery system, and in combination with BMPs, particularly with rhBMP-2, constitutes an excellent osteoinductive bone graft (Peel *et al.* 2003).

The combination of bioactivity and biodegradability is probably the most relevant characteristics that encompass third-generation biomaterials. The bioactivation of surfaces with specific biomolecules is a powerful tool that allows cell guidance and stimulation towards a particular response. The aim is to mimic the ECM environment and function in the developed scaffold by coupling specific cues in its surface. Thus, cell behaviour including adhesion, migration, proliferation and differentiation into a particular lineage will be influenced by the biomolecules attached to the material surface.

Biodegradable composite scaffolds combining biodegradability and bioactivity offer unique advantages in the tissue engineering field. The incorporation of an inorganic phase into a bioabsorbable polymer matrix modifies the mechanical behaviour of the porous structure (Navarro *et al.* 2004b), modifies the degradation pattern of the polymer and also enhances the bioactivity of bone tissue engineering scaffolds (Spaans *et al.* 2000; Navarro *et al.* 2005).

In the case of cartilage, some natural polymers, namely collagen and hyaluronic acid, possess inherent biological cues that allow chondrocytes to interact with hydrogel scaffolds. Alginate, chitosan and other synthetic hydrogels have been modified with growth factors such as transforming growth factor (TGF)- $\beta$ 3, adhesion proteins and peptide sequences such as RAD, ELK and EAK among others, which can increase the expression and synthesis of cartilage-specific ECM proteoglycans and promote cell–material interactions (Holmes 2002; Na *et al.* 2007). Scaffolds intended for ligament regeneration have been functionalized with RGD motifs to stimulate cell attachment and proliferation as well as to increase the production of ECM proteins (Guarino *et al.* 2007).

Numerous elaboration techniques and approaches to the development of three-dimensional scaffolds that combine biodegradability and bioactivity are currently under study (Coombes & Heckman 1992; Mikos *et al.* 1993; Mooney *et al.* 1996; Wake *et al.* 1996). Each preparation technique confers particular and different structural characteristics to the scaffold. Therefore, the choice of the technique depends on the requirements of the final application. Some of the most promising techniques for the processing of such scaffolds are gel casting, solvent casting and particulate leaching, laminated object manufacturing, phase separation, gas saturation, fibre bonding and membrane lamination among others (Yang *et al.* 2001). Recently, a new three-dimensional braiding technology for the fabrication of biodegradable PLLA scaffolds for ligament replacement

has been developed (Laurencin & Freeman 2005). The micro- and macrostructure of the scaffolds depend strongly on the processing technique. Pore distribution, interconnectivity and size are of paramount importance in order to guarantee proper cell proliferation and migration, as well as tissue vascularization and diffusion of nutrients. According to Klawitter & Hulbert (1971) a pore size between 100 and 350  $\mu\text{m}$  is optimum for bone regeneration. Probably, a comprehensive assessment of the ability of a three-dimensional scaffold to allow cell viability and capacity of ECM production is to evaluate its permeability. Moreover, it seems that it would be advisable to evaluate the transport properties of oxygen and nutrients inside the scaffold in order to assess whether they will be able to reach cells seeded inside them.

Some ceramics and glasses have been used for the elaboration of porous scaffolds. As in the case of polymers, a high degree of macro-, micro- and nanoporosities is needed. In addition, the degradation rate of the biomaterial and the regeneration rate of the tissue must be equilibrated in order to enable a proper bone turnover process (Artzi *et al.* 2004).

Current research is focused in nanocrystalline structures (Ferraz *et al.* 2004), organic–inorganic composites, fibres (Aizawa *et al.* 2005), microspheres (He *et al.* 2007), three-dimensional ACP scaffolds (Tadic *et al.* 2004), HA (Deville *et al.* 2006), tuned porosity microstructures (Tampieri *et al.* 2001) and hierarchically organized structures (Furuichi *et al.* 2006).

Recently, the introduction of undifferentiated bone marrow stromal cells into a hydrogel containing CaP particles in suspension (Trojani *et al.* 2006) has resulted in an injectable cement composite mixed with living cells. The *in vivo* results obtained after the implantation of this material in mouse have shown a good vascularization and integration into the host tissue.

In addition, BG–ceramics elaborated from CaP degradable glasses as well as BGs, and CPC foams have been used as templates for *in situ* regeneration with very promising results (Gong *et al.* 2001; Yuan *et al.* 2001; Almirall *et al.* 2004; Navarro *et al.* 2004a; Ginebra *et al.* 2007).

Metals have also been used in the development of porous structures for bone tissue engineering. The development of porous metallic scaffolds (metallic foams) for bone tissue engineering and drug delivery applications has mainly been focused on titanium and titanium alloys (Assad *et al.* 2003a,b; Li *et al.* 2002, 2006, 2007; Yeh & Sung 2004).

Despite the numerous studies on the manufacture and design of metallic foams (Körner & Singer 2000; Banhart 2001), works dealing with the *in vitro* or *in vivo* behaviour of this type of materials are still scarce. Titanium fibre meshes (86% porosity and a 250  $\mu\text{m}$  average pore size) have been used for the *ex vivo* culture of rat bone marrow stromal cells, under static and dynamic conditions (flow perfusion bioreactor), and subsequent implantation in cranial defects in rats (Sikavitsas *et al.* 2003; Van den Dolder *et al.* 2003). These scaffolds have also found application as delivery systems for transforming growth factor  $\beta$ 1 (TGF- $\beta$ 1) and have been used to repair rabbit cranial defects

(Vehof *et al.* 2002). Titanium foams tested *in vitro* with human osteoblasts have shown osteoblast colonization and differentiation into mature bone cells, and consequently could be appropriate materials for spine fusion and other applications (St-Pierre *et al.* 2005; Müller *et al.* 2006). In fact, some authors even claim the osteoinductive action of these materials (Takemoto *et al.* 2006; Tognarini *et al.* 2008).

Porous tantalum is also being successfully used clinically in several orthopaedic applications. Its high volumetric porosity, low elastic modulus (it can be as low as 3 GPa) and good frictional characteristics make tantalum foam an ideal candidate for weight-bearing applications such as total joint arthroplasty (Levine *et al.* 2006). Moreover, tantalum has an excellent *in vivo* biocompatibility and can become bioactive via a simple chemical treatment (Miyazaki *et al.* 2001).

The main concerns with these unresorbable scaffolds are related to their permanent implantation in the body that can trigger risks of toxicity caused by the accumulation of metal ions due to corrosion (Rubin & Yaremchuk 1997), the premature failure due to poor wear properties, and the higher elastic modulus compared with bone, which leads to heterogeneous stress distributions.

Bioresorbable foams of magnesium have been developed as a new alternative for bone graft substitutes. By adjusting their porosity, an elastic modulus similar to that of cancellous bone can be achieved (Wen *et al.* 2001). In addition, magnesium scaffolds have shown good osteoinductive properties (capable of osteogenesis; Maeda *et al.* 2007).

Research on shape memory metallic foams is currently carried out, especially with NiTi alloys, so as to reduce stress shielding and increase the wear resistance of conventional porous titanium scaffolds. Gu *et al.* (2006) have studied the *in vitro* behaviour of porous NiTi in contact with osteoblasts while Unger *et al.* (2004) have obtained preliminary results on the cytocompatibility of porous NiTi scaffolds with endothelial cells for angiogenesis. As such, all these metallic materials belong to the first generation. The innovation lies in the porosity, although a fibrous layer between the metal and the ECM growth inside the pores should be expected. Thus, as mentioned above, when discussing strategies for improving metal bioactivity, a proper treatment of the material surface may help to avoid this problem and create a direct bonding with the tissue.

Since cell adhesion is mediated by protein–cell interactions via biological recognition of protein sequences by transmembrane cell receptors, with specific sequences that enhance cell attachment (arginine–glycine–aspartic acid (RGD)), the design of biomaterials is now focused on biological stimulation. Some of the most commonly employed strategies are the functionalization of biomaterial surfaces using proteins and peptides that mimic the ECM chemistry, in particular RGD sequences (Garcia *et al.* 1997; D'Avi *et al.* 1998; Dee *et al.* 1999; Hersel *et al.* 2003), and the addition of growth factors into the scaffold composition for a controlled delivery to the surrounding cells. For this last approach, various growth factors have already been used: fibroblast growth factor (FGF), platelet-derived

growth factor and insulin-like growth factor, TGF, BMPs, interleukins and interferons (Nathan & Sporn 1991; Ripamonti & Tasker 2000).

Surface bioactivation can be achieved by functionalizing surfaces with different biomolecules by applying a variety of methods where both chemical bonding and physical adsorption take place. Some of these methods are an update and evolution of some of the methods already explored at the end of the second generation of biomaterials. During the third generation, dip-coating techniques are still used, but some more sophisticated 'bottom-up' and 'top-down' techniques are also developed to engineer surfaces with high specificity levels. Additionally, the synthesis and tailoring of new biomolecules for specific applications occur during this third generation. The development of more complex biopolymers and biomolecules such as elastin-like biopolymers including peptide sequences that induce mineralization and cell adhesion, or self-assembled amphiphilic peptides that include cell signalling cues could provide the answer (Rodríguez-Cabello *et al.* 2007; Sargeant *et al.* 2008).

Therefore, it is predictable that in the short and medium term, future trends in biomaterials will involve the active interaction between chemistry and biology and will be more and more focused on achieving their combination with biological entities in order to obtain a totally viable biological environment.

## 5. CONCLUSION

In the last 60 years, biomaterials for orthopaedic applications have moved from materials available for different industrial applications into the development of materials with abilities to interact with the biological environment and to elicit specific biological responses. Most of the problems that orthopaedic surgery has to face have not basically changed, and are practically the same that orthopaedics had to face 50 years ago; however, the choice of possible solutions has been greatly expanded because new materials allow the design of innovative devices. The possibility to regenerate tissues or organs could not be undertaken with the materials of the first generation. The possibility to modify and control surface properties at the micro/nano level constitutes one of the major breakthroughs, because it opens a whole new range of strategies seeking the desired interaction with the biological environment. In certain instances, the regeneration of a musculoskeletal tissue can be considered, either after an early diagnosis of some pathology or after an accident or an operation where part of the tissue has been lost or a resection has been made. In such cases, the aim of regenerative medicine will be either to implant a smart biomaterial that is able to stimulate stem cells existing in their niches or to use cellular tissue engineering strategies, where a construct developed inside a bioreactor and consisting of a scaffold, patient's cells and initial ECM developed by them, is implanted in the patient's body that recognizes it as its own tissue. One of the main ideas behind the different approaches reviewed in the literature consists of developing functionalized bioabsorbable polymeric, CaP or

composite substrates or scaffolds able to stimulate cell activity, i.e. adhesion, proliferation and differentiation, with the aim that differentiated osteoblasts produce bone ECM. Most of these approaches meant for bone regeneration require still solving the necessary angiogenesis in the newly growing ECM, expected to become healthy bone tissue. Here again, the combination of knowledge of materials scientists and biologists should allow the development and synthesis of materials and biomolecules with the right chemistry and structure to stimulate endothelialization as well as the formation of blood vessels.

In many other circumstances, like fractures, large resections, joint malfunctions, spinal pathologies and other situations, repair or substitution will be the main requirement. This means that different devices and prostheses will still be needed as permanent implants. In this sense, it is difficult to foresee in the short or medium term that metals and alloys can be avoided in relevant load-bearing applications: the evidence seems to point out that titanium alloys will still be needed for osteosynthesis applications, like bone plates where no osseointegration into bone is desirable. The consequence is that the use of biomaterials of the first generation cannot be discarded, and in general, it can be said that biomaterials from the three generations have a relevant role to be played. For those cases where the aim is the integration of the implant in the surrounding tissue, bioactive surfaces are developed by different means: functionalization with different molecules, surface coatings or layers such as CaPs and others like metallic porous structures.

The final comment that seems necessary to introduce is that, in many instances, the biological assessment of modified or functionalized surfaces, as well as three-dimensional scaffolds is carried out *in vitro* by means of cell cultures. However, the conclusive assessment can only come from *in vivo* testing. Besides extracellular fluids, there is blood contact and inflammation that play the leading role in the outcome of the final implant behaviour.

The main conclusion seems to be that there is still sophisticated materials science to be developed in order to match the biological complexity at the molecular level. However, the task of tailoring the biomaterials' surfaces for at least some of the different purposes of implant integration and tissue regeneration seems a feasible challenge in the future, probably at midterm by the synergistic interdisciplinary work of materials science, engineering, biology, chemistry, physics and medicine.

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