Chapter 5

Overview on Biocompatibilities of Implantable Biomaterials

Xiaohong Wang

Additional information is available at the end of the chapter

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1. Introduction

A biomaterial is any material that comprises whole or part of a living structure or biomedical device which performs, augments, or replaces a natural function to improve the quality of life of the patients [1]. Over the past fifty years biomaterials has been developed as a science with various forms of implants/medical devices, and have been widely used to replace and/or restore the function of traumatized or degenerated tissues or organs. As a life-saving and life-improving option for countless patients, biomaterials have been paid more and more attention during the last decade. Only in the United States, more than 13 million implant/medical devices implanted annually. As a result, the impact factor of the journal of "Biomaterials" has boomed from 2.489 to 7.404 from the year 2001 to 2012.

The implant/medical device scope of biomaterials ranges from simple implants like intraocular lenses (which restore sight to millions of cataract patients every year), sutures, wound dressings, decellular matrices, bone plates, joint replacements to more complex materials like biosensors, catheters, pacemakers, blood vessels, artificial heart (that provide both mechanical and biological functions in a body), left ventricular assist devices and prosthetic arterial grafts. According to the resources and properties biomaterials can be assorted into autografts, allografts, organic polymers, such as natural collagen, fibrin, chitosan, hyaluronan, heparin, cellulose, and synthetic polyurethane (PU), polyester, metal, such as aluminium, steel, titanium, inorganic salts, such as calcium phosphate, hydroxyapatite, and their compounds or derivatives. There are more than one hundred different biomaterials which have been applied *in vivo*. All biomaterials when implanted into a body initiate a host response that reflects the first steps of tissue repair. The host/biomaterial interactions which follow implantation of any prosthesis or device are a series of complex events that have not been well defined. Generally, host reactions following implantation of biomaterials include

injury, blood–material interactions, provisional matrix formation, acute inflammation, chronic inflammation, granulation tissue development, foreign body reaction, and fibrosis/fibrous capsule development [2]. There are numerous types of host responses to a broad spectrum of biomaterials.

When considering a biomaterial for implantation or medical use, the first and most important requirement is nontoxic, nonimmunogenic, chemically inert/active, and acceptable by the human body. Biocompatible in most cases means that the biomaterials must not form thrombi in the blood system, result in tumors in the surround tissues, or be immediately attacked, encapsulated, or rejected by the body [3]. According to the host responses to implantable biomaterials, there are many different kinds of biocompatibilities, including local tissue responses, such as necrosis, repulsion, infection, inflammation, calcification, scar, cyst, amalgamation, thrombus, tumor, cancer, and whole body responses, such as fever, toxicity, circulation impediment, nerve anesthesia, malformation, etc. The overall biocompatibilities including cyto-compatibility, hemo-compatibility, and tissue-compatibility, are often evaluated using histological sections, cell markers, and metabolite measurements. Sometimes, polymers with similar chemical characteristics behave differently in certain situations. For example, polyethylene and ultrahigh molecular weight polyethylene behave differently as orthopedic biomaterials for knee and hip replacement [4]. Until present, most of the implantable biomaterials trigger acute or/and chronic inflammatory responses in the body. These reactions can totally black a biomaterial and even lead to huge disasters or personal misfortunes. Among the numerous types of host responses, early interactions between implants and inflammatory cells are probably mediated by a layer of host proteins on the biomaterial surface. Franz and coworkers have described several typical host responses of implantable biomaterials (Figure 1) [5]. This model can be used as a reference for evaluation of an implantable biomaterial when it is implanted shortly *in vivo*.

In this chapter, I will focus on the *in vivo* host responses about twenty common used biomaterials which cover nearly every tissue and organ in human body. Advanced biologic techniques have been employed in determining the mechanisms behind observed macroscopic or microscopic responses. An understanding of the molecular and cellular events which occur in response to implantable biomaterials may allow us to manipulate responses and design more biocompatible, bioactive and functional biomaterials for clinical applications, such as regenerative medicine and controlled releasing drugs.

2. Allografts

Allograft (also called homograft) is a tissue/organ graft from one individual to another of the same species with a different genotype [6]. It has been successfully used in various medical procedures for more than 150 years. Approximately 1500000 allografts are transplanted each year for a variety of life-saving and life-enhancing surgeries. For example, skeletal grafts for patients with bone defects from cancer or traffic accidents; cornea transplants to help restore sight; heart valves to replace damaged heart tissues; skin grafts to save the lives of burn victims, and tendon replacements to help people with more active lives [7].

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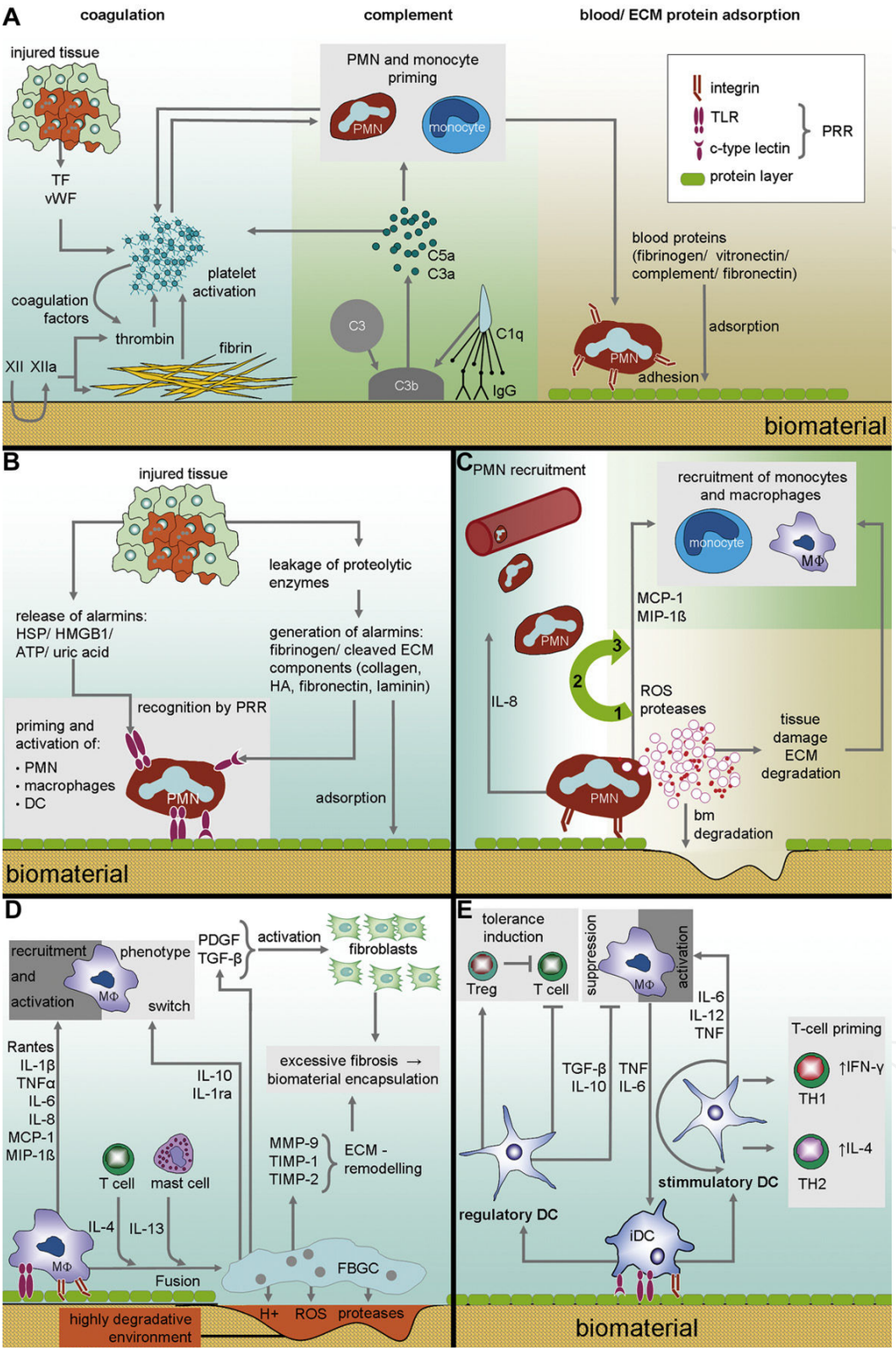

Figure 1. Immune response toward biomaterials. (A) Adsorption of blood proteins and activation of the coagulation cascade, complement and platelets result in the priming and activation of polymorphonuclear leukocytes (PMNs), monocytes and resident macrophages. (B) Danger signals (alarmins) released from damaged tissue additionally prime the immune

cells for enhanced function via pattern recognition receptor (PRR) engagement. (C) The acute inflammatory response is dominated by the action of PMNs. PMNs secrete proteolytic enzymes and reactive oxygen species (ROS), corroding the biomaterial surface. Interleukin (IL)-8 released from PMNs enhances PMN influx and priming. In the transition from acute to chronic inflammation, PMNs stop secreting IL-8 in favor of cytokines promoting immigration and activation of monocytes and macrophages. (D) Macrophages are the driving force of chronic inflammation. Constant release of inflammatory mediators like tumor-nekrose-faktor alpha (TNFα), IL-6, and monocyte chemotactic protein (MCP)-1 results in permanent activation of macrophages. Fusion-inducing stimuli like IL-4 and IL-13 promote the fusion of macrophages to foreign body giant cells (FBGCs,) which form a highly degradative environment on the biomaterial surface. Furthermore, FBGC promote extracellular matrix (ECM) remodeling and fibroblast activation resulting in excessive fibrosis and biomaterial encapsulation. (E) Macrophage-derived cytokines and pattern recognition receptor engagement activate dendritic cells (DCs) on the biomaterial surface. Depending on the nature of the stimulus, DCs mature to either immunogenic or tolerogenic subtypes, amplifying or suppressing the inflammatory response [5].

Compared with autografts which come from the same bodies and are only available in limited amounts, allografts are more readily available and accompany with less risk and postoperative morbidity. The healing times is therefore shorter and less painful for a patient with no second surgical site is required (as there is when an autograft is utilised). Currently, the use of allograft tissues is increasingly popular all over the world, with widespread orthopaedic surgeons and debilitating musculoskeletal conditions. Nearly one tissue/organ donor can save or improve the lives of up to 60 people. Especially, Musculoskeletal Transplant Foundation, the world's largest tissue bank, provides allograft tissue and biologic solutions for ligament reconstruction [8]. Meanwhile bone and soft tissue allografts from the Steri-Graft™ line has been in existence for over 13 years and has helped doctors and their patients with over one hundred thousand successful transplantations. Before transplantation, a blood sample from the donor is normally tested in case any infected diseases, such as human immunodeficiency virus (HIV), Hepatitis, and Syphilis [9].

Specially, decellularized tissue/organ matrices derived from allografts have been used since the 1940s to support tissue repair and replacement. Their popularity has grown sharply during the last decade with the advent of tissue engineering [10]. At present, decellularized tissues/organs have been successfully used in a variety of tissue/organ regenerative medicines. The efficiency of cell removal from a tissue/organ is dependent on the origin of the tissue/organ and the specific physical, chemical, and enzymatic methods that are used. Each of these treatments affects the biochemical composition, tissue ultrastructure, and mechanical behavior of the remaining extracellular matrix (ECM) scaffold, which in turn, affect the host response to the material [11].

3. Collagen and gelatin

Collagen is one of the most prevalent proteins in the connective tissue of animals and constitutes approximately 25% of total body protein in vertebrates. It therefore is an important biomaterial in medical, dental, and pharmacological fields. After the immunogens in the collagen molecules are dislodged, collagen has excellent biocompatibilities either *in vitro* or *in vivo*. Collagen is capable of being cross-linked into solid or lattice-like gels. Resorbable forms of collagen have been used to dress oral, skin or some of the other soft tissue wounds,

for closure of graft and extraction sites, and to promote healing [12]. During *in vivo* implantation, collagen irritates slight inflammation accompanying with some scar tissues.

A collagen sponge obtained from Beijing Yierkang Biengineering Development Center China was implanted subcutaneously in rats for time periods up to 8 weeks (Figure 2) [13]. One week after implantation, slight inflammation with some lymphocytes, myofibrils and fibroblasts were observed. The appearance of myofibrils and fibroblasts indicated that scar tissue was developed (Figure 2A). Two weeks after implantation, fibrous tissue was formed with scattered macrophage and lymphocyte cells in the fibrous layer. Newly formed blood vessels appeared in the implant site while the collagen sponges were completely resorbed (Figure 2B). Four weeks after implantation, the thin fiber layer had changed into wavelike scar tissue and tightly connected with the surrounding muscles. Capillaries were evident in the new fibrous scars (Figure 2C). Six weeks after implantation, scar tissue in the collagen samples was mature (Figure 2D). Eight weeks after implantation, the wave-like scar tissue in the collagen samples became thinner with some lipocytes and vacuoles (Figure 2E) [13].

Collagen compounds, such as collagen/chitosan, collagen/hyaluronan, have been investigated extensively during the past several decades. The biocompatibilities of these compounds depend largely on the incorporated constituents. For example, a corneal collagen crosslinked with riboflavin and ultraviolet radiation-A has been used for keratoconus repair of a 29-year-old woman with some good results [14]. In some instances, it is more competing to use a compound to improve the mechanical properties of the collagen based biomaterials. For example, a porous implantable dexamethasone-loaded polylactide-co-glycolide (PLGA) microspheres/collagen glucose sensors [15] and a mitomycin C (MMC) delivery system (MMC-film), incorporating polylactide (PLA)–MMC nanoparticles in a composite film from blends of collagen–chitosan–soybean phosphatidylcholine (SPC) with a mass ratio of 4:1:1 have been explored with no sign of internal infection and fibrous encapsulation in any animals after 20 days of implantation [16].

Gelatin is a mixture of peptides/proteins produced by partial hydrolysis of collagen extracted from the skin, boiled crushed bones, connective tissues, organs and some intestines of animals such as domesticated cattle, chicken, horses hooves, and pigs [17]. Gelatin possesses a better biocompatibility than its ancestry collagen. Alloimplants of bone matrix gelatin are effective in the treatment of bone defects with a low risk of complication such as rejection or infection [18]. Aqueous gelatin solution is an amorphous natural hydrogel in which cells can be encapsulated, extruded and deposited at desired positions. Unlike collagen hydrogel, gelatin hydrogel holds a special gelation property around 20℃. In Tsinghua University the author's own group, this property has been explored extensively for rapid prototyping (RP) (or additive manufacturing) of three-dimensional (3D) complex geometrical structures with computer-aided design channel models [19-24]. Until now, a hybrid hierarchical 3D construct consisting both synthetic polyurethane PU and natural cell/ gelatin-based hydrogel with interconnected macro-channels has been produced via a double nozzle RP technique at a low temperature (-28℃). These constructs have demonstrated excellent in vivo biocompatibilities [23,25]. This technique holds the potential to be widely used in the future complex tissue/organ manufacturing areas.

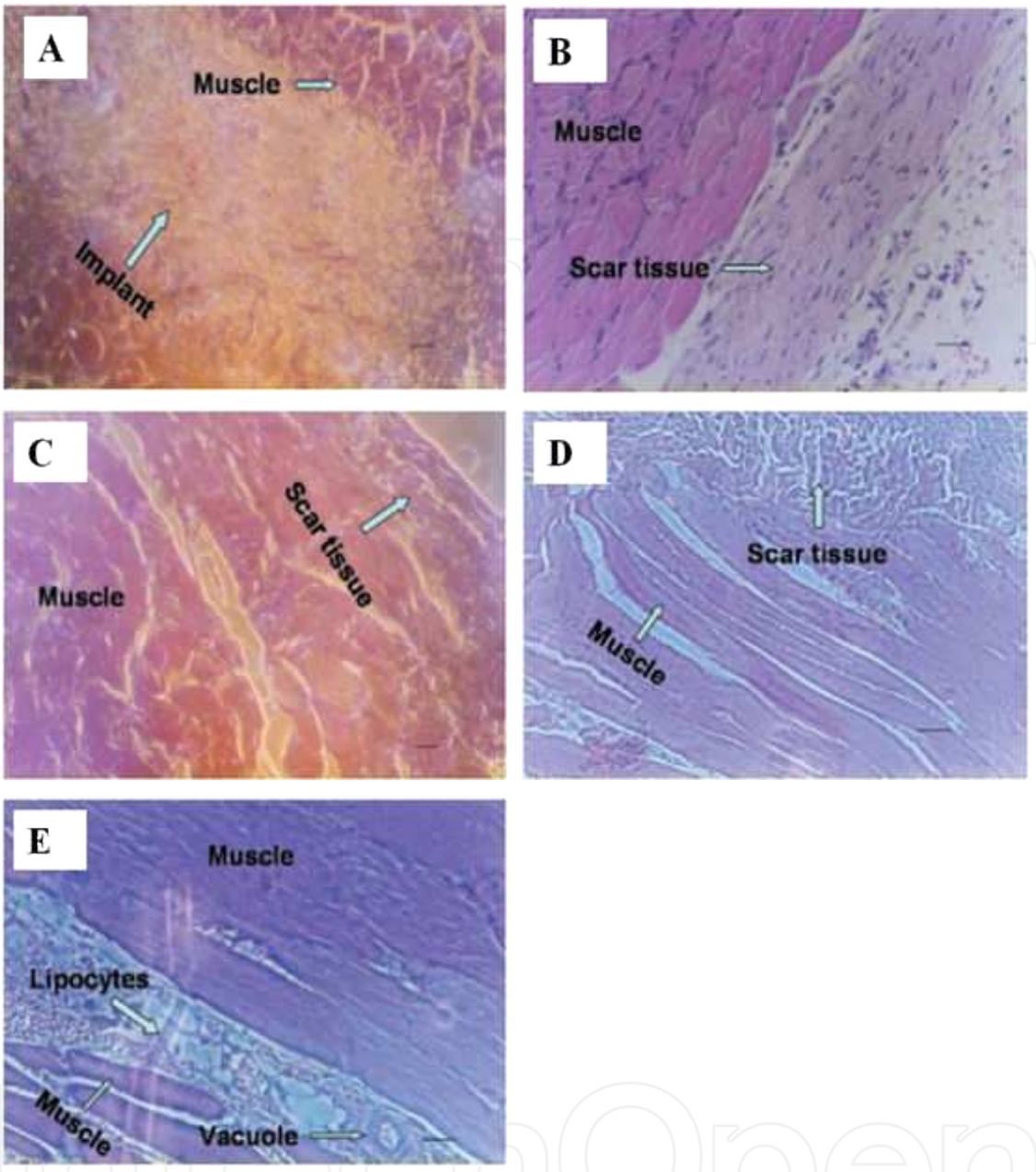

Figure 2. Light-microscope evaluation of the tissue response to collagen sponges with hamatoxylin-eosin (HE) staining: (A) 1 week after implantation; (B) 2 weeks after implantation; (C) 4 weeks after implantation; (D) 6 weeks after implantation; (E) 8 weeks after implantation. The scale bar indicates a distance of 50μm in (A), (C), and (D), and a 25μm in (B) and (E) [13].

Combination of gelatin microspheres/scaffolds with other biomaterials, such as collagen, alginate, chitosan, hyaluronan, and fibrin has also been explored extensively. For example, a gelatin microsphere containing basic fibroblast growth factor and preadipocytes, is essential to achieve a engineered fat tissue [26]. A PLGA microparticles containing an anticancer agent paclitaxel was formulated for the treatment of lung cancers [27]. Gelatin hydrogel incorporating hepatocyte growth factor induced angiogenic change around the implanted hy-

drogel [28]. A silk fibroin/gelatin composite scaffold was implanted into subcutaneous pockets on male Sprague-Dawley rats with a slight inflammation reaction. By day 30, the scaffold had been completely infiltrated and organized by fibroblasts and inflamed cells. The greater the gelatin concentration in the scaffold, the faster the degradation rate [29].

4. Fibrin

Fibrin (also called Factor Ia) is a fibrous, non-globular protein involved in the clotting of blood. It is formed from fibrinogen by the protease thrombin, and is then polymerised to form a hemostatic plug or clot (in conjunction with platelets) over a wound site [30]. The clot fibrin can be naturally degraded by proteolytic enzymes from the fibrinolytic system, such as plasmin [31,32]. *In vivo*, fibrin(ogen) plays an important role in hemostasis, inflammation, signal transduction, platelet activation, wound healing, osteoinductive and angiogenesis [33-36]. The food and drug administration (FDA) in American has approved commercially made fibrin sealants in 1998 [37].

During the last decade, autologous fibrin-based matrices have demonstrated great potential as being used as tissue engineered replacements, such as heart valves [38-40], cartilages [41], and blood vessels [42]. Immunohistochemistry and ECM assay demonstrated that the fibrin scaffolds can be completely absorbed *in vivo* in about 3 months with low granulomatous inflammation (Figure 3) [43-46]. Farhat and coworkers have evaluated whether a fibrin glue spray technique enhances cell seeded acellular matrix (ACM) repopulation in a porcine bladder model. The *in vivo* central fibrosis results indicated that while fibrin glue enhanced cellular organization on ACM *in vitro*, factors supporting seeded cell survival are lacking [47].

On the other hand, spatio-temporal controlled delivery of bioactive molecules within fibrin has been expanded rapidly. Various states of fibrin, such as scaffold, sheets, microparticles and fibrin-coated drug particles have been used as drug delivery systems [48,49]. Growth factors, such as vascular endothelial growth factor (VEGF) and transforming growth factor-β (TGF-β) can easily bind to the fibrin molecules and be controlled released subsequently by diffusion [50-56]. In the future, autologous fibrin may play an important role in customized clinical applications, such as anti-immune drug delivery systems and human tissue/organ constructions to avoid any negative host reactions [57].

5. Dextran and its derivatives

Dextran, a high-molecular-weight polymer of d-glucose, formed by sucrose enzymes on the cell surface of certain lactic acid bacteria in the mouth adhere to the tooth surfaces and produce dental plaque. Uniform molecular weight dextrans (named for their average molecular weight) from Leuconostoc mesenteroides with specific preparations has been used for over 50 years in plasma volume expansion, thrombosis prophylaxis, peripheral blood flow enhancement and for the rheological improvement of, for instance, artificial tears [30,58]. Dex-

trans with an average molecular weight of 1000 to 2 million g/mol are commercially available for research purposes [59]. Two preparations of dextran with lower fractions (40000 and 70000 g/mol) are suitable for nontoxic clinical use [60]. However, high fractions of dextrans can produce erythrocyte aggregation, impaired microcirculation, and a clinical picture akin to shock and certain other diseases.

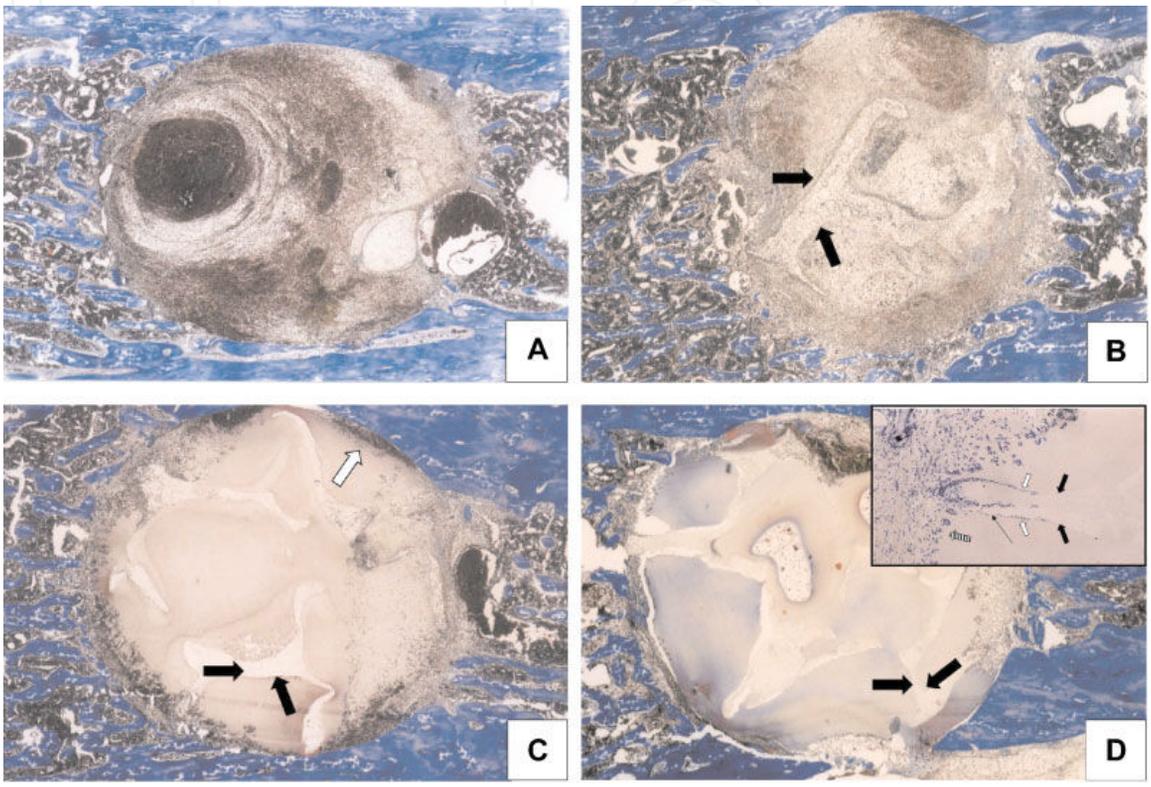

Figure 3. Eleven-day Masson's trichrome (MT) staining sections of a fibrin scaffold. (A) Untreated defects and (B) defects containing empty scaffolds were filled with new bone tissue. However, no reparative bone was observed in the center of defects containing (C) scaffolds filled with fibrin (low T) and (D) scaffolds filled with fibrin (high T). (Inset) Patches of multinucleated giant cells (striped arrow) were observed at the scaffold interface in all scaffold-containing groups. Black arrows point to areas occupied by the scaffold, whereas white arrows point to the advancing bone front. Field width 5.2 mm, inset field width 0.2 mm [46].

During 1990-1994, extensive toxicologic evaluations indicate that small-volume infusions of 7.5% NaCl/6% dextran 70 (HSD) at the proposed therapeutic dose of 4 mL/kg, present little risk as implantable biomaterials [61,62]. Dextran hydrogels have offered good opportunities as protein delivery systems or tissue engineering scaffolds because of an inherent biocompatibility [63]. The hydrophilic, soft and rubbery properties of the dextran hydrogels ensure minimal tissue irritation and a low tendency of cells and proteins to adhere to the hydrogel surface [59]. Althogh dextran itself is not toxic, some of the methods used for crosslinking the polymer may result in toxic byproducts. For example, the toxicity of dialdehyde crosslinked dextran/gelatin hydrogel can be detected in fibroblast and endothelial cell cultures. Subcutaneous implantation studies in mice showed that the foreign body reaction seen around the implanted hydrogel samples was moderate and became minimal upon increas-

ing implantation time [64]. A methacrylate-derivatized dextran hydrogel also shows good *in vitro* biocompatibilities [65].

More recently another effect of dextran, namely that of antithrombogenesis, has been recognized [66]. Dextran sulfate, a dextran derivative, its effects on coagulation has already been proven [67]. It has been reported that dextran sulfate has been found to activate the polymerization of fibrin monomer, ATIII, conversion of prekallikrein to kallikreinand fibrinolysis. Kallikrein, the conversion of fibrinogen to fibrin appears to be inhibited by dextran sulfate. These effects are, *inter alia*, concentration dependent [67,68]. Meanwhile, a dextran sulphate sodium model of colitis has demonstrated several correlations of this biomaterial with human inflammatory bowel disease [69]. Furthermore, a lauric acid modified dextran-agmatine bioconjugate (Dex-L-Agm) was prepared by 1,1'-carbonyldiimidazole activation and the nucleophilic reaction between tosyl of tosylated dextran and primary amine of agmatine was found to be highly cytocompatible without causing hemolysis and red blood cell aggregation [70].

6. Hyaluronan

Hyaluronan (also called hyaluronic acid or hyaluronate, HA) is a natural anionic, viscoelastic and hygroscopic glycosaminoglycan, discovered in 1934, by Karl Meyer and his assistant, John Palmer in the vitreous of bovine eyes [71]. As one of the chief components of the ECM, hyaluronan distributes widely throughout connective, epithelial, and neural tissues. It is unique among glycosaminoglycans in that it is nonsulfated, forms in the plasma membrane instead of the Golgi, and can be very large in molecular weight (often reaching the millions) [72]. HA plays several important organizational roles in the ECM by binding with cells and other protein components through specific and nonspecific interactions [73] and is responsible for various functions within the ECM such as cell growth, proliferation, differentiation, migration [74], and even some malignant tumors [76].

Basically hyaluronan is a highly non-toxic, non-antigenic and non-immunogenic polysaccharide, owing to its high structural homology across species, and poor interaction with blood components [77,78]. The FDA in American has approved the use of hyaluronic acid for certain eye surgeries, such as cataract removal, corneal transplantation, and detached retina [79]. People take hyaluronic acid for various joint disorders (lubricant agents), lip fillers, "youth fountains", and even wound healing catalysts [80]. Nowadays various hyaluronan hydrogels have been used to delivery drugs and cell growth factors [81,82]. There are some evidence show that fragmented hyaluronan stimulates the expression of inflammatory genes by a variety of immune cells at the injury site. With the protein-bonding abilities, hyaluronan fragments signal through both Toll-like receptor (TLR) 4 and TLR2 as well as CD44 to stimulate inflammatory genes in inflammatory cells. Hyaluronan presents on the epithelial cell surface can provide protection against tissue damage from the environment by interacting with TLR2 and TLR4 [83-85]. It is well known that accumulation and turnover of ECM components are the hallmarks of

tissue injury. Current model of hyaluronic acid appear in the early stages of wound healing is to physically make room for white blood cells, which mediate the immune response and at least in part, reduce collagen deposition and therefore lead to reduced scarring [86]. This hypothesis is in agreement with the research of West and coworkers, who have showed that in adult and late gestation fetal wound healing process, removal of HA results in fibrotic scarring [87].

HA can be modified through several different ways, such as chemically esterify its carboxylic groups with some types of alcohol. The physico-chemical properties of the new biopolymers allow the preparation of many biomaterials with different biocompatibilities for various medical applications [88]. Shen and coworkers implanted hyaluronan hydrogel and periodate oxidated hyaluronan hydrogel in ischemic myocardium and found rapid degradation rates, low quantity of inflammation-mediating cells, thin fibrous capsules with dense blood vessels around the hydrogels at week 2 [89]. Praveen and coworkers used HA/polyvinyl alcohol (PVA) coating membrane to minimize the problems related to protein deposition and fibrous tissue formation on an implanted glucose sensor [90]. HA hydrogels modified with laminin could support cell infiltration, angiogenesis, and simultaneously inhibit the formation of glial scar after being implanted into the lesion of the cortex [91]. Compared with pure gelatin hydrogen, HA/gelatin composite has a better compatibility and contiguity with the surrounding brain tissue with no inflammatory reaction and fibrous encapsulation [92]. Intravitreal implants of hyaluronic acid esters represent useful biocompatible and biodegradable properties for a potential drug delivery system in the treatment of posterior segment ocular diseases [93]. A crosslinked HA hydrogel that contained a covalently bound derivative of the anti-proliferative drug MMC was synthesized and evaluated *in vitro* and *in vivo*. This hydrogel has strong potential as anti-fibrotic barriers for the prevention of post-surgical adhesions [94]. Two injectable thiolated HA derivatives were coupled to four alpha, beta-unsaturated ester and amide derivatives of poly(ethylene glycol) (PEG) 3400 and were found that the encapsulated cells can retained their original fibroblast phenotype and secreted ECM in vivo [95]. A fibrin/HA composite gel with autologous chondrocytes has been synthesized for tracheal reconstruction. Histologically, the grafts showed no signs of inflammatory reaction and were covered with ciliated epithelium [96].

7. Heparin

Heparin (from Ancient Greek ηπαρ (hepar), liver), a highly sulfated glycosaminoglycan, is widely used as an injectable anticoagulant, and has the highest negative charge density of any known biological molecule [97]. Heparins are involved in different pathways of the coagulation cascade with anticoagulant, antithrombotic, profibrinolytic, anti-aggregative, as well as anti-inflammatory effects [98]. As stated in the fibrin section, the primary anticoagulant effect of heparin is through the suppression of thrombin-dependent amplification of the coagulation cascade, and inhibition of thrombin-mediated conversion of fibrinogen to fibrin [99].

Heparin holds the ability to relieve pain, inhibit clotting and inflammation, restore blood flow, enhance healing, and can be a useful addition to a range of available treatments for burn wounds [100]. Unfractioned heparin exhibits a broad spectrum of immunomodulating and anti-inflammatory properties, by inhibiting the recruitment of neutrophils and reducing pro-inflammatory cytokines in the treatment of inflammatory bowel disease [101]. Low-molecular-weight heparin can reduce or prevent development of signs/symptoms associated with post-thrombotic syndrome [102]. Heparin has been widely used to form an inner anticoagulant surface on various experimental and medical devices such as membranes [103,104], tubes and renal dialysis machines [105,106].

Although heparin is used principally in medicine for anticoagulation, its true physiological role in the body remains unclear. Blood anti-coagulation is usually achieved by heparan sulfate proteoglycans which derive from endothelial cells stored within the secretory granules of mast cells and only released into the vasculature at sites of tissue injury [107]. Rather than anticoagulation, the main role of heparin may be defense at such sites against invading bacteria and other foreign materials [108]. A thiol-modified heparin in the Extracel-HP® mimics heparan sulfate proteoglycans also normally presents in the ECM and regulates the *in vivo* growth factor release for a functional microvessel network development [109]. A well-known adverse effect of heparin therapy is thrombocytopenia, a serious, immune system–mediated complication with significant mortality (Figure 4) [110-112].

8. Alginate

Alginate, is a salt of alginic acid (medical-dictionary.thefreedictionary.com), and an anionic polysaccharide distributed widely in the cell walls of brown algae, where it, through binding water, forms a viscous gum (Wikipedia, the free encyclopedia). Sodium alginate (composed of mannuronic and guluronic (G) dimmers) is a biocompatible and biodegradable polymer, and has been widely used in cell encapsulation technology, though the biocompatibility of the alginates in relation to their composition is a matter of debate [113]. In the molecules of sodium alginate the primary block guluronic acid contains available carboxylic acid groups that allow the alginate to be reversibly crosslinked by divalent cations, such as Ca^{+2} and Mg^{+2}, to form a relatively stable hydrogel [114,115]. Clinically, water-soluble alginates are useful as materials for dental impressions. Calcium alginates have been widely used as a base material to encapsulate glucose-sensing pancreatic islets that secrete insulin into the lymphatic system to reverse the effects of insulin-dependent diabetics [116]. Some investigators have utilized alginates to promote the viability of encapsulated cells [117]. Alginate-poly-L-lysine-alginate (APA) microcapsules continue to be the most widely studied device for the immuno-protection of transplanted therapeutic cells [118]. Alginate-chitosan-alginate (ACA) microcapsules have been developed as a device for the transplantation of living cells with protein adsorption onto the surface of microcapsules immediately upon implantation [119].

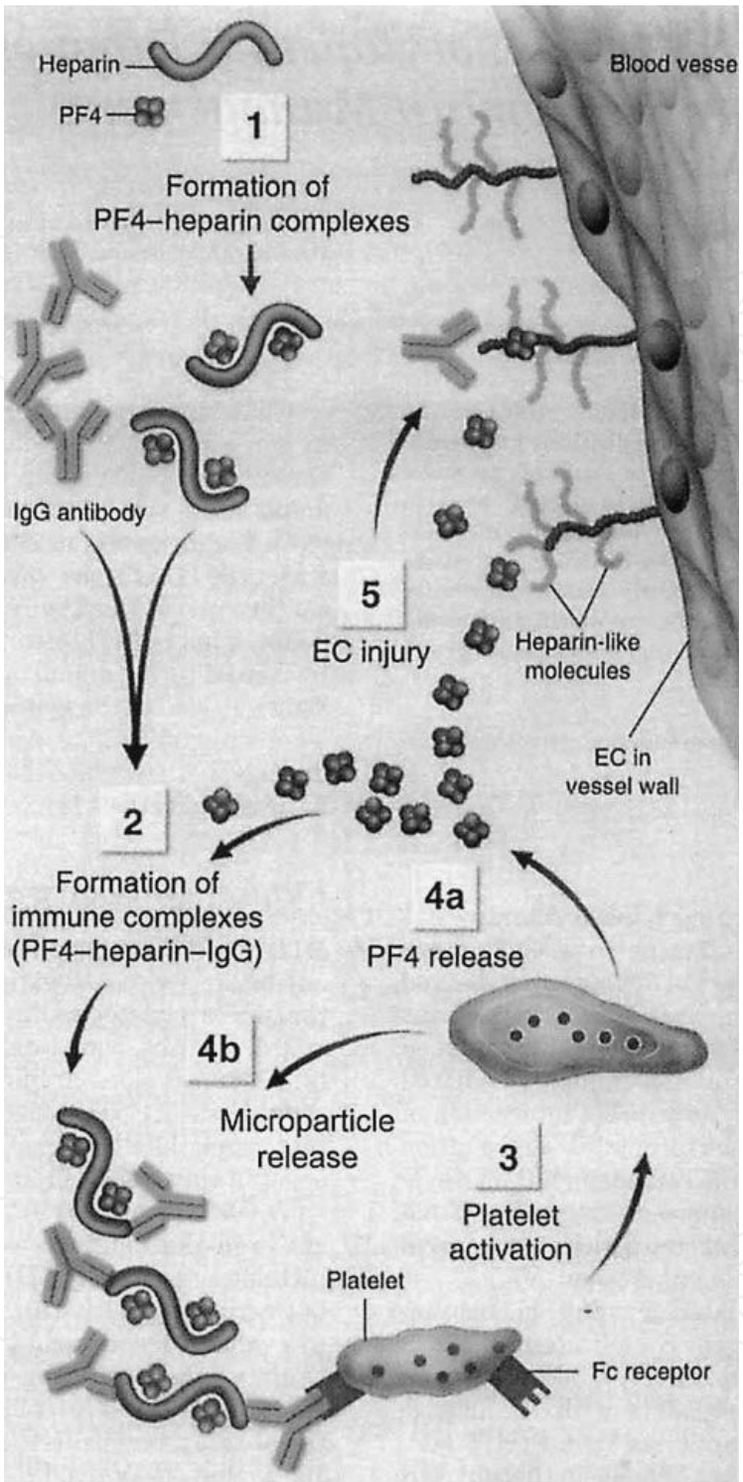

Figure 4. Model of pathogenesis of heparin-induced thrombocytopenia (HIT). Heparin binds with Platelet factor 4 (PF4), which exposes neoepitopes on PF4 and leads to antibody production (1). Heparin-PF4-IgG immune complexes form (2), and IgG in multimolecular complex triggers platelet activation via binding to Fc receptors (3). Activated platelet releases additional PF4 (4a) and prothrombotic platelet microparticles (4b). Thrombotic risk is further promoted by binding of PF4 to heparin-like molecules on endothelial cells (EC), contributing to immune system–mediated endothelial damage (5) [112].

9. Chitin, chitosan and their derivatives

Chitosan is a naturally occurring linear polysaccharide, consisting of glucosamine and N-acetyl-glucosamine, normally made of deacetylated chitin which is the structural polymer found in the shells of crabs and shrimp (lobster, squid, some yeast and mould), by N-deacetylation using strong alkali [120]. More than 40 years have lapsed since this biomaterial had aroused the interest of the scientific community around the world for its potential biomedical applications [121]. Until now chitosan possess a number of commercial and biomedical applications in wound dressing, drug delivery and tissue engineering. For example, chitosan based scaffold biomaterials have demonstrated versatile properties to promote the epithelial and soft tissue regeneration in the body [122,123]. Chitosan patches in various sizes that have been cleared by the FDA are a topical hemostat for moderating severe bleeding. Nevertheless, an obvious disadvantage of this implantable, absorbable biomaterial is that chitosan initiates serious host inflammation reactions (Figure 5) [13,124]. Additionally, chitosan is bioadhesive and has the ability to transiently open tight junctions in the nasal epithelia, thereby permitting drugs to diffuse through this barrier. Advantages of this nasal route of administration include: a higher permeability of the nasal mucosa than in the gastrointestinal tract; a low degree of pre-systemic metabolism; and a high level of patient compliance, compared to injectable systems [125].

It is very interesting that when the number of N-acetyl-glucosamine units in a chitin/chitosan mixture is higher than 50%, the biopolymer is termed chitin. 50% deacetylated chitosan has a less inflammation reaction than the others when they are implanted *in vivo* [126]. Cross-linking of chitosan membrane using genipin and some other chemical agents can increase the membrane's ultimate tensile strength but significantly reduced its strain-at-fracture and swelling ratio [127]. In the author's own group, an ammonia treated chitosan sponge was implanted subcutaneously in rats for 8 weeks (Figure 5). One week after implantation, the chitosan sponges were entirely retained and wrapped with a layer of purulent cells. The purulent cells had infiltrated the outside chitosan sponges (Figure 5A). Two weeks after implantation, the encapsulated purulent layer was enlarged at the periphery of chitosan sponges. More acute inflammatory cells had infiltrated the chitosan sponges and there was no sign of biodegradation of the chitosan sponges (Figure 5B). Four weeks after implantation, the chitosan sponges still maintained their porous structure. A much thicker purulent layer and more acute inflammatory cells were found around or in the chitosan sponges (Figure 5C). Six weeks after implantation, most of the chitosan still maintained their scaffold integrity with numerous interspersed purulent cells. Some purulent cells even formed large channels throughout the chitosan sponges (Figure 5D). Eight weeks after implantation, purulent cell infiltrations had further increased in the chitosan sponges. Some collapsed matrix structures were detected at the outer margins of the implants and more channel structures were found between the remnants of chitosan lamellae (Figure 5E).

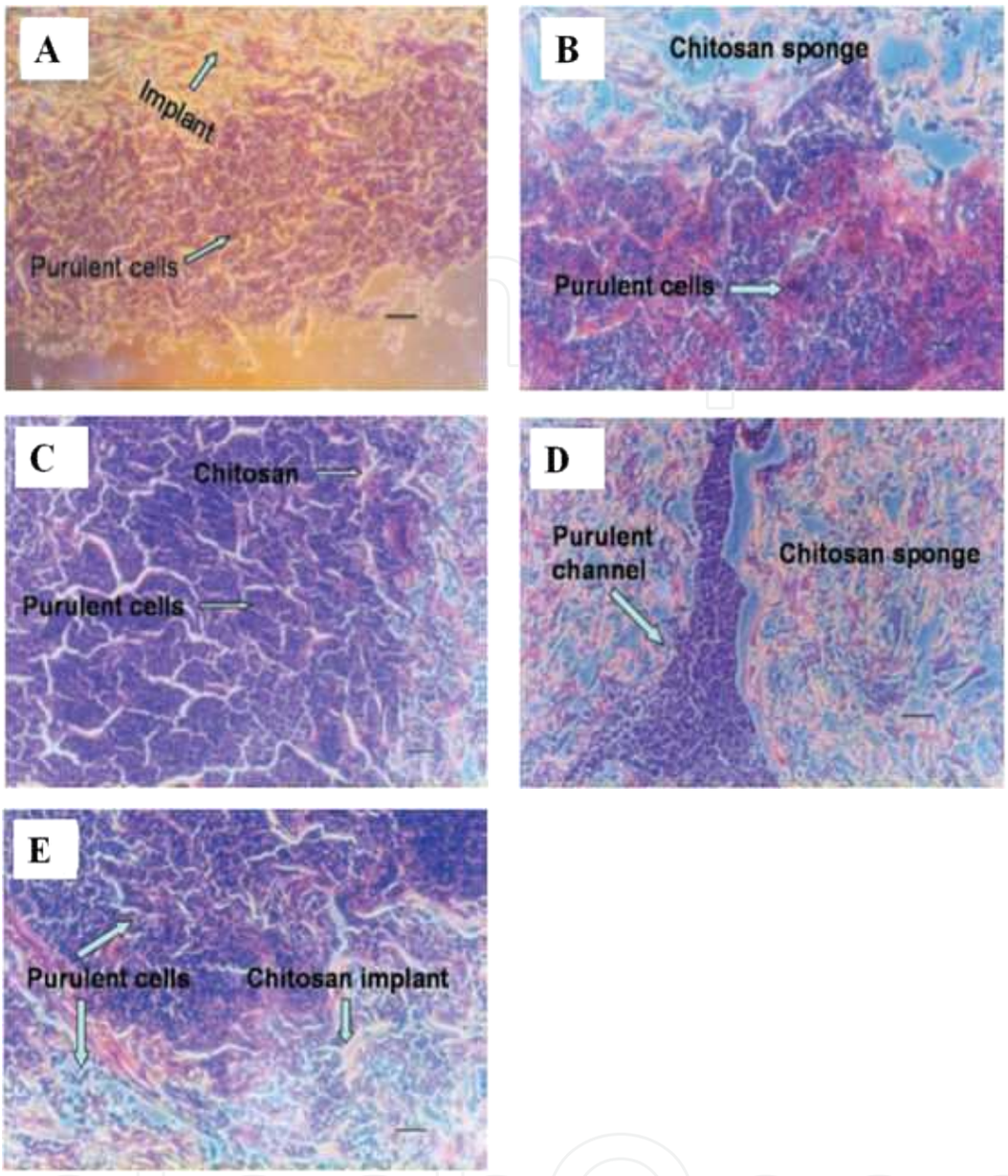

Figure 5. Light-microscope evaluation of the tissue response to chitosan sponges with HE staining: (A) 1 week after implantation; (B) 2 weeks after implantation; (C) 4 weeks after implantation; (D) 6 weeks after implantation; (E) 8 weeks after implantation. The scale bar indicates a distance of 50 μm in (A), (C), and (D), and a 25 μm in (B) and (E) [13].

Also in this author's own group, a series of bone repair materials were fabricated by adding three chitosan derivatives, such as phosphorylated chitin (P-chitin), phosphorylated chitosan (P-chitosan), and disodium (1→4)-2-deoxy-2-sulfoamino-β-D-glucopyranuronan (S-chitosan) into two kinds of biodegradable calcium phosphate cements (CPCs). All the chitosan derivatives can greatly improve the mechanical properties and reduce the biodegradation rates of the CPCs. At least six totally different tissue responses were detected when the implants were examined in tibial and radial defects of rabbits. Large bone defect (9 mm in

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length for radii and 3 mm in depth and diameter for tibias) repair in rabbits with the P-chitosan incorporated CPCs exhibits excellent tissue compatibilities with no any adverse or negative effects, such as fibrous encapsulation, osteolysis, hyperplasia, and inflammation, no matter the concentrations of P-chitosan is high or low (Figure 6) [128,129]. Tissue responses to P-chitin are highly sensitive (Figure 7) [130,131]. Three different bone formation types in the resorption lacuna of the P-chitin incorporated CPCs due to the P-chitin concentrations were found during the 22 weeks implantation. The first is that with low P-chitin content trabeculae formed directly from the implant (Figure 7A). The second is that with middle P-chitin content cartilages formed from the outside of fibers before they turned into trabeculae (Figure 7B, 7C). The third is that with high P-chitin content callous formed from the outside of fibers before they turned into trabeculae (Figure 7D, 7E). P-chitin content has a negative relationship with the biodegradation rate of the cements. However, the degradation rates are compatible with the ingrowth of trabeculae. A mild foreign-body reaction in the high P-chitin content sample during the first three time spans did not impair its placement by a newly formed bone. The generally properties of these biomaterials have met the main requirements for bone repair (Figure 7) [130,131]. Different from the above mentioned bone repair types, tissue responses to water-soluble S-chitosan, prepared from chitin by successive N-deacetylation, specific carboxylation at C-6 and sulfonation, was rather obtuse. No inflammation or other negative response was found in the S-chitosan containing samples (S-CPCs). After 4 weeks implantation, newly formed trabeculae contacted with the implant directly in the lower S-chitosan sample, while a thin layer of fibers formed between the newly formed bone and the implant in the higher S-chitosan samples [132,133]. These results indicate that the concentrations and functional groups in a linear polysaccharide play a key role in determining the ultimate biocompatibilities of an implantable biomaterial. In addition, as a derivative of chitin, chitosan initiates blood coagulation while S-chitosan inhibits blood coagulation when they are used as hemo-contact biomaterials.

Recently, chitosan and its derivatives have been widely used in skin wound, burn and disease treatments. For instance, a chitosan-gelatin-hyaluronic acid scaffold was found flexible with good mechanical properties when it was used as artificial skin substitutes [134]. A bacterial cellulose synthesized by Acetobacter xylinum and modified by chitosan was found to be optimal in providing wound dresses with a moist environment for wound healing [135]. When an artificial chitosan skin regenerating template was implanted subcutaneously it showed a similar inflammatory pattern as Integra, a two-layer skin regeneration system, constructed of a matrix of crosslinked fibers [136,137].

With the combination with other natural polymers, such as collagen, gelatin, hyaluronan, fibrin, the strong host inflammation reactions of chitosan can be reduced to a certain degree. It was found that a bioactive glass-chitosan composite containing 17% (wt%) chitosan produced by a freeze-drying process and implanted in the femoral condyl of an ovariectomised rat can promote a highly significant bioactive and osteoinductive property [138-140]. The ultimate biocompatibility of a chitosan compound depends largely on the ratio of the different components. Host tissues, such as smooth muscle and hepatic tissue have a similar response to the chitosan containing collagen/chitosan mixtures [141]. A collagen/chitosan matrix

crosslinked by agent 1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide in a N-hydroxysuccinimide and 2-morpholinoethane sulfonic acid buffer system has exhibited improved blood and cell compatibilities than the pure chitosan samples [142,143].

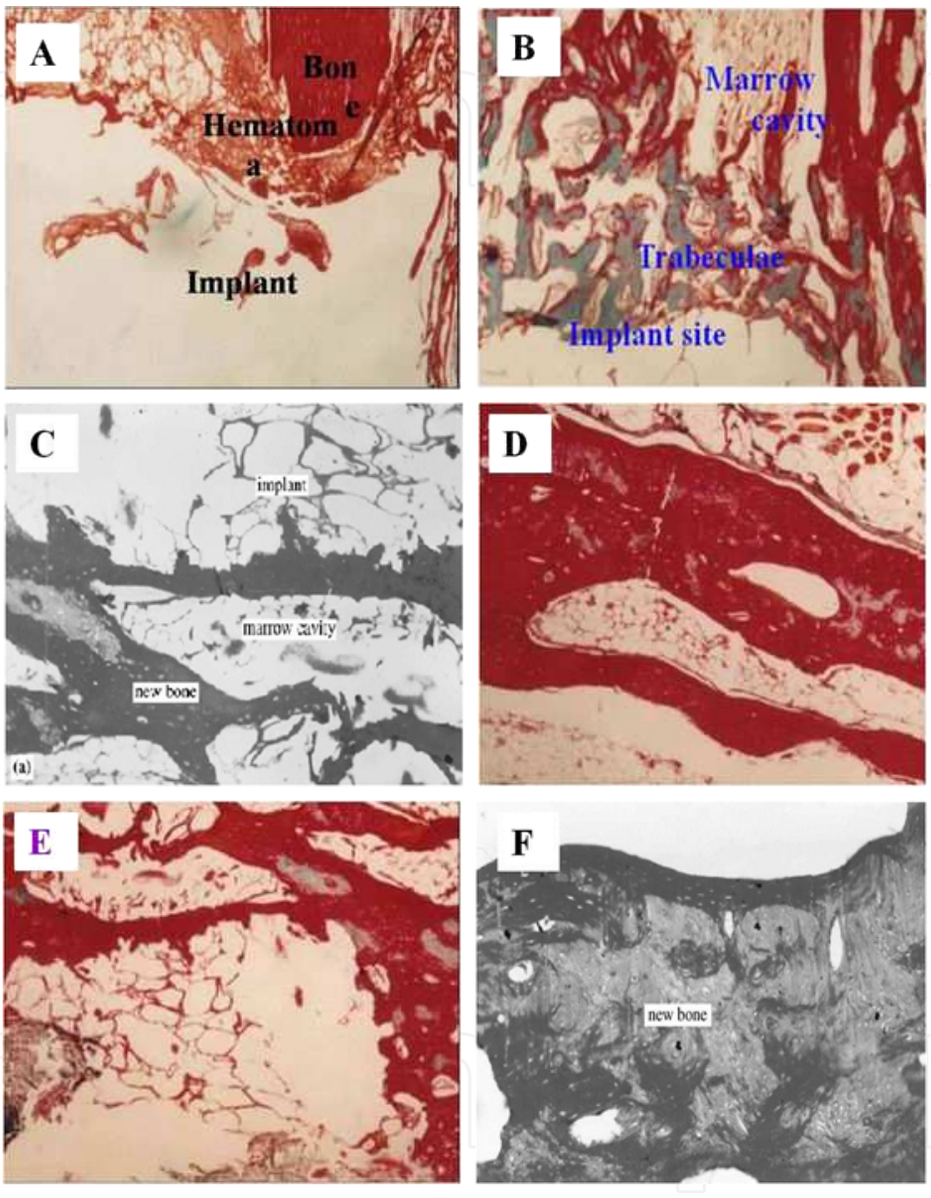

Figure 6. Tissue responses to the P-chitosan incorporated CPC specimen at different time points with MT staining. (A) 1 week after implantation in the high P-chitosan content (0.12 g/mL) sample with very little hematoma. (B) 4 weeks after implantation in the high P-chitosan content (0.12 g/mL) sample newly formed woven bone clearly appeared with tightly bonding between the implant and host bone. No macrophage was found around the implant. The implant was directly changed into new trabeculae after degradation. (C) 12 weeks after implantation newly formed long bone in the low P-chitosan content (0.02 g/mL) sample. (D) 12 weeks after implantation newly formed long bone in the middle P-chitosan content (0.07 g/mL) sample. (E) 12 weeks after implantation newly formed long bone in the high P-chitosan content (0.12 g/mL) sample. Trabeculae formed after the implant was gobbled up (infiltrated) by body fluid. Clear evidence of remodeling around the implant surface was displayed. (F) 22 weeks after implantation the newly formed dense trabeculae in the high P-chitosan content (0.12 g/mL) sample [129].

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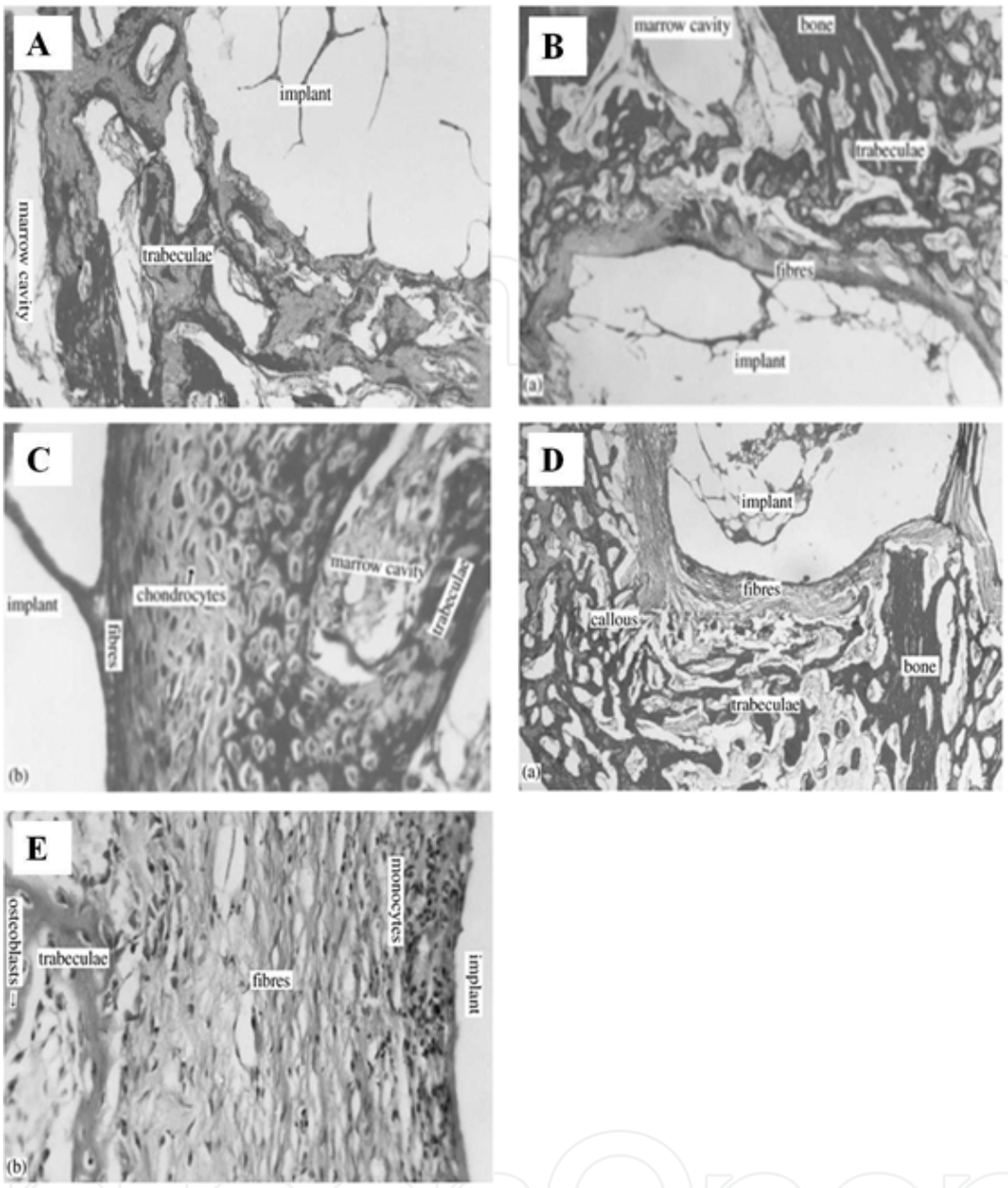

Figure 7. Tissue responses to the P-chitin incorporated CPC specimen 4 weeks after implantation. (A) P-chitin: 0.02 g/mL with MT staining. Magnification ×100. (B) P-chitin: 0.08 g/mL with MT staining. Magnification ×40. (C) A magnification of (B) with MT staining. Magnification ×400. (D) P-chitin: 0.14 g/mL with MT staining. Magnification ×40. (E) A magnification of (D) with HE staining. Magnification ×400 [131].

Current advances in some drug delivery systems make it possible to improve the therapeutic efficacy and minimized the side effects associated with toxicity of the drug. Chitosan has shown promise in the development of non-parenteral delivery systems for challenging drugs. For example, a 5-Fluorouracil (5-FU) loaded scaffold composed of chitosan fibers were prepared by a modified wet spinning technique [144]. Thermosensitive hydrogel composed of chitosan and glycerophosphate is proposed to be the potential candidate of *in situ* gel-forming implant for long-term drug delivery [145]. However, unpredictable body re-

sponses to the chitosan systems as stated above can complicate their applications to some degree. The composite chitosan-collagen-soybean phosphatidylcholine film impregnated with MMC-PLA-nanoparticles for treatment of hepatocellular carcinoma in mice has exhibited some special characteristics compared with pure chitosan delivery systems. In vivo, the growth of the tumors were inhibited considerably and dose-dependently by the MMC-film ($P<0.05$) with no any signs of vice reactions, such as inflammation, infection, and fibrous encapsulation after 20d of implantation [16,146,147]. Thus a careful balance between the immune reaction and drug effectiveness is needed when a chitosan pertaining template is used for biomedical applications.

10. Polyglycolide (PGA), Polylactide (PLA) and poly(Lactic-co-Glycolic Acid) (PLGA)

Polyglycolide also named polyglycolic acid (PGA) is a biodegradable, thermoplastic polymer and the simplest linear, aliphatic polyester which contains the ester functional group in it's main chain [148]. It can be prepared starting from glycolic acid by means of polycondensation or ring-opening polymerization. PGA has been known since 1954 as a tough fiber-forming polymer. Owing to its hydrolytic instability, its use has initially been limited [149]. *In vivo*, PGA initiates a marked host reaction around the implantations. This leads to the development of a foreign body response that comprises an initial acute inflammatory phase and a subsequent chronic inflammatory phase. For example, when a synthetic PGA scaffold seeding with adult-derived or somatic lung progenitor cells from mammalian lung tissue was implanted in an immunocompetent host, a serious foreign body response totally altered the integrity of the developing lung tissue [150].

Polylactic acid or polylactide (PLA) is another thermoplastic aliphatic polyester derived from renewable resources, such as corn starch, tapioca products, and sugarcanes [30]. A poly(L-lactide) (PLLA) coil stent has ever been implanted in pigs with no stent thrombosis and late restenosis [151]. However, PLA, as well as PLLA, and poly(D,L-lactide) (PDLA), induces a strong inflammatory response when they are implanted in the body due to their acidic products [152]. Aframian and coworkers implanted tubular PLLA, PGA coated with PLLA (PGA/PLLA), or nothing (sham-operated controls) in Balb/c mice either beneath the skin on the back, and found that inflammatory reactions were shorter and without epithelioid and giant cells in the sham-operated controls. Tissue responses to PLLA and PGA/PLLA scaffolds are generally similar in areas subjacent to skin in the back and oral cavity. Biodegradation proceeded more slowly with the PLLA tubules than with the PGA/PLLA tubules. No significant changes in clinical chemistry and hematology were seen due to the implantation of tubular scaffolds. [153]. It was reported that, after the PLLA segments were swallowed *in vivo* by phagocytes, cell damage and cell death were obvious. The highest numbers of necrotic cells were observed on day 2 [154]. These reactions can result in an unexpected risk for patients and have strongly limited in clinical applications of this kind of biomaterials.

To date, numerous strategies have been investigated to overcome body reactions induced by this kind of biomedical devices [155]. As a result, most of the PLA, PLLA, and PDLA have been used as a composite or compound with some other biomaterials. For example, a PLLA and poly(ethylene oxide) (PEO) blend has been prepared by mechanical mixture and fusion of homopolymers [156]. A biodegradable star-shaped 8 arms PEG-b-PLLA block copolymer was synthesized by Nagahama and coworkers to create a novel implantable soft material with drastically lowered crystallinity, increased swelling ability, and desirable mechanical properties [157,158].

Currently PGA, PLA and their copolymers, such as poly(lactide-co-caprolactone) (PLCA), poly(glycolide-co-caprolactone) (PGC), and poly (glycolide-co-trimethylene carbonate) are widely used as biomaterials for the synthesis of absorbable sutures and tissue engineering scaffolds in the biomedical field [159,160]. For example, a resorbable PLGA bone fixation implanted in craniofacial patients in 1996 resulted in 0.2 percent significant infectious complications, 0.3 percent device instability, and 0.7 percent self-limiting local foreign-body reactions [161]. As long-term implants, the toxicity of the accumulated acidate products made the situations even worse [162]. Until the present, most of the implanted PGA, PLA and PLGA related biomaterials still encounter an immune tissue response due to tissue trauma during implantation and the presence of foreign body reactions [163]. Surface coating has become one of the research hot points for the implantable devices with poor biocompatibilities. For instance, the biocompatibilities of some artificial polymer devices, such as heart valves, stents and vascular prosthesis that come into contact with bodily tissues or fluids particularly blood, have been improved by Venkatraman and coworkers with endothelialization surface layers [164,165].

Similarly, when a polyvinyl acetate (PVA)/PLGA microsphere was implanted into the subcutaneous tissue of rats, acute inflammation with neutrophils was found at day 3. Chronic inflammation with multinucleate giant cells, fibrosis, and mixed inflammatory cells was found at day 30. Mineralization around the implant was found at day 60 [166]. On the contrary, a dexamethasone/PLGA microsphere system can suppress the inflammation reaction by a fast releasing of dexamethasone [167]. A highly monodisperse and smooth PLGA-paclitaxel microspheres against malignant brain tumors were fabricated using an electrohydrodynamic atomization (EHDA) process [168]. In addition, PLA, PGA and PLGA can be tailored to meet mechanical performance and resorption rates required for applications ranging from non-structural drug delivery applications, nanoparticles (nanofibers), to resorbable screws and anchors [169,170].

11. Polycaprolactone (PCL)

Polycaprolactone (PCL) is a biodegradable polyester with a low melting point of around 60°C and a glass transition temperature of about −60°C. It is commonly used as an additive for resins or starch to improve their processing characteristics, lower their costs, and change their properties (e.g. impact resistance), or as a plasticizer in the manufacture of special pol-

ymers (e.g. Pus) [30]. PCL has been approved by the FDA for specific applications, such as a drug delivery devices, sutures, or adhesion barriers. It has been widely used as a scaffold material for tissue engineering with mismatched mechanical properties and slow degradation rate [171,172]. In rats the *in vivo* degradation of PCL is about 3 years [173].

Various categories of drugs have been encapsulated in PCL, in microsphere, nanosphere or bulk states, for targeted drug delivery and for controlled drug release [174-176]. For example, a PCL scaffold modified by grafting nerve growth factor (NGF) and Tirofiban (TF) has been used as nerve conduits to promote the regeneration of sciatic nerves [177]. Low molecular weight PCL pieces can be ingested and digested ultimately by phagocyte and giant cell without any cumulate vice-products (Figure 8) [178-180].

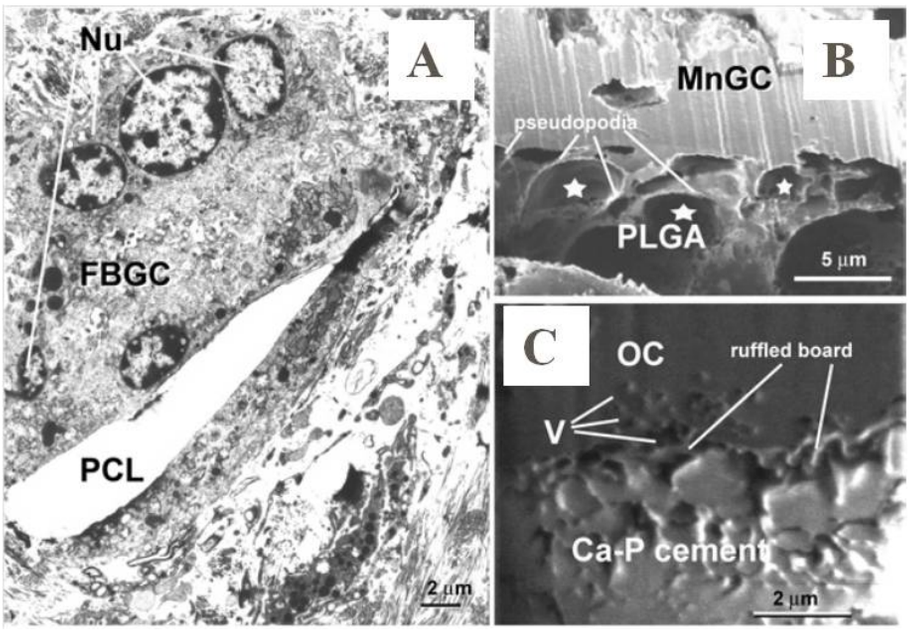

Figure 8. Micrographs illustrating extracellular degradation of biomaterials by macrophage fused multinuclear giant cells. (A) A foreign body giant cell (FBGC) engulfed a fragment of poly(epsilon-caprolactone), PCL polymer *in vivo*. Nu, nuclei of FBGC. The PCL polymer was dissolved during sample preparation. Transmission electron microscopy (TEM), bar = 2 μm. (B) *In situ* cross-section of the interface between a multinuclear giant cell (MnGC) and PLGA film. Note the pseudopodia of the MnGC penetrated deep inside the surface of PLGA film and formed sealed compartments. PLGA polymers are eroded within the compartments. Focused ion beam (FIB) microscopy, bar = 5 μm. (C) *In situ* cross-section of the interface between an osteoclasts-like cell (OC) and calcium phosphate cement. Note the typical ruffled board of OC and vesicles (V) secreting from OC to the sealed extracellular space. FIB microscopy, bar = 2 μm [162].

12. Polyurethane (PU)

PU is a series of biomaterials that contains urethane radical and offers the greatest versatility in compositions and properties of any family of polymers. Especially, a few specific elastomeric PU compositions have demonstrated a combination of toughness, durability, biocompatibility and biostability for being used as implantable medical devices, which is not

achieved by any other available materials [181]. Because urethane is available in a very broad hardness range (e.g. eraser-soft to bowling-ball-hard), it allows the engineer to replace rubber, plastic and metal with the ultimate goals in abrasion resistance and physical properties. During the last half century, PUs have become and remained the most valuable implantable elastomers for uses requiring toughness, durability, biocompatibility and biostability [182]. With their inherently stable in the body environment, some of the PUs have been widely used in medical applications such as synthetic heart valves, vascular grafts, and pacemaker electrodes. However, these usages of PUs have been limited by three major complications: calcification, thrombosis, and chemical degradation [183].

In the 1970s and 1980s as the PUs became recognized as the blood contacting material and were used in a wide range of cardiovascular devices in long-term implants, they fell under scrutiny with the failure of pacemaker leads and breast implant coatings in the late 1980s. According to the manufacturer's report, high voltage coil fracture and PU defects were the predominant causes of lead failure [184,185]. During the next decade PUs had been extensively researched for their relative sensitivity to biodegradation and the desire to further understand the biological mechanisms for *in vivo* implantation [186,187]. Some investors have seeded autologous sheep blood outgrowth endothelial cells (BOECs) on a cholesterol (Chol)-modified PU (PU-Chol) heart valve leaflet to result in an intact, shear-resistant endothelium that would promote resistance to thrombosis [188]. Because of the complex behavior of implantable PUs in the body environment, special attention to the choice of the constituted components must be paid for designing and manufacturing the PU-containing devices. Subsequent treatment during sterilization, storage, implantation, *in vivo* operation and explantation also determine the performance and provide the means for assessing the efficacy of the PUs implants [189].

The most prominent disadvantages of PUs being used as artificial heart valves include mineralization, environmental stress-cracking and oxidation. While the mechanisms of these forms of degradation are not fully understood, an awareness of their causes and effects that leads to all of the long-term functionality is required for the sophisticated PU-based devices of today and tomorrow [190-191]. Over the last half century, extremely efforts have been paid in the biomedical research field to improve the biocompatibilities and biodurability of the PU implants, but only resulted in very little clinical effects [192-194].

In the later l990s a number of new bioresorbable materials with all the versatility of PUs in terms of physical properties and biocompatibility have been yielded. AorTech Biomaterials was set up in 1997 to commercialise a range of medical grade PUs developed by the Australian research group (Commonwealth Scientific and Industrial Research Organization, CSIRO). The company estimates that the worldwide market for surgical heart valve products is worth more than $1bn (€705 m) and to be growing at a rate of 8% a year. Meanwhile, the market for catheter-delivered heart valves is worth around $200 m (€141 mm) [195]. In the authors' own group in Tsinghua University, China, a novel PU made of PCL, PEG, and 1,6-hexmethyldiisocyanate has been synthesized. The hydrolytic degradation property of the PU can be highly tuned by changing the composition and structure of copolymers, such as PEG and PCL. When this kind of PU was used as a small-caliber (1.2 mm inner diameter)

vein and nerve repair grafts it demonstrated excellent antithrombogenicity and superior biocompatibility (Figure 9) [196,197].

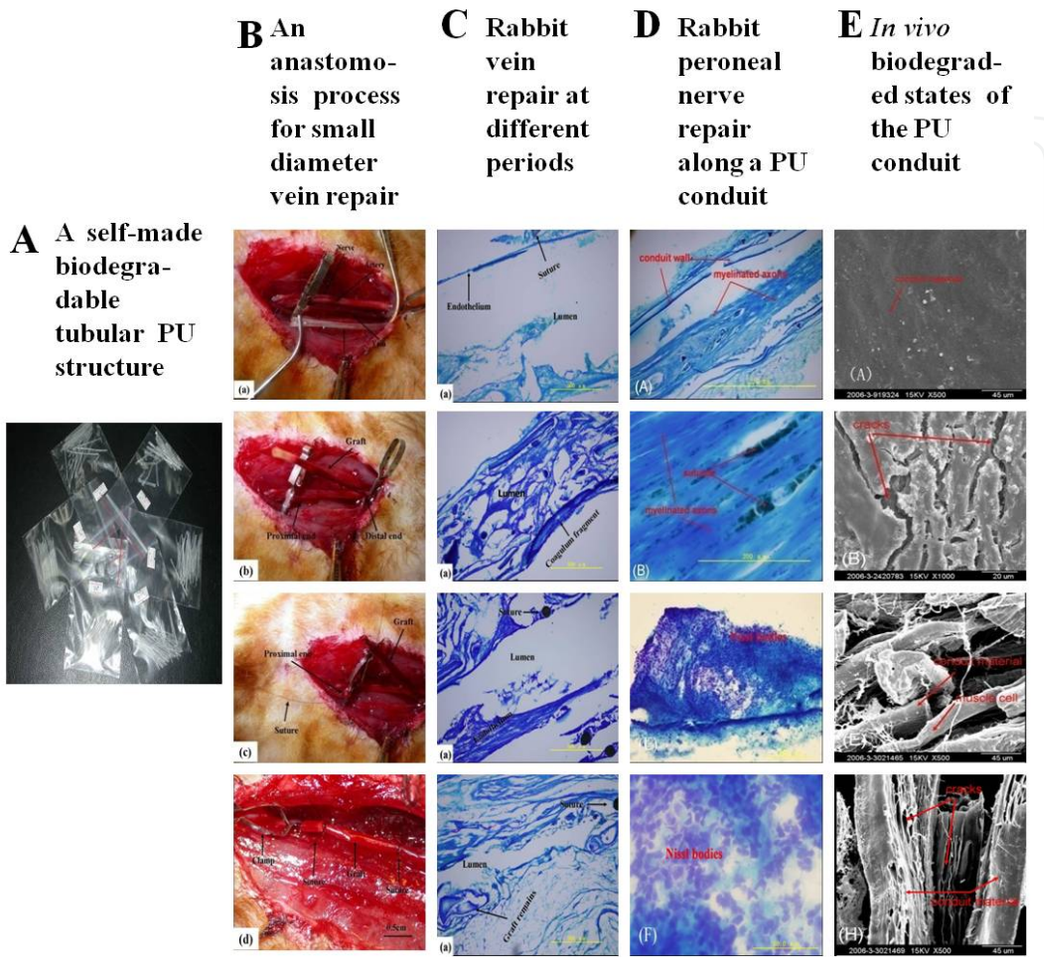

Figure 9. An implantable small-diameter nerve and blood vessel repair PU conduit. (A) PU conduits with different inner diameters. (B) The PU conduit was connected to the vein of a rabbit. (C) The vein defect repair processes with a very thin layer of fibrin-platelet deposition. (D) The nerve repair processes in rabbits with growing myelinated axons. (E) The PU conduits degraded gradually *in vivo* in 12 weeks [196, 197].

13. Polytetrafluoroethylene (PTFE)

Polytetrafluoroethylene (PTFE), Discovered in 1938 by Roy J. Plunkett, is a synthetic high-molecular-weight compound consisting wholly of carbon and fluorine with numerous applications [198]. The best known brand name of PTFE is Teflon made by DuPont Co. It is insoluble in all normally used organic solvents, not biodegradable *in vivo* and can suffer high temperatures as 260 ℃ permanently. Clinically, PTFE has been widely used as a large blood vessels repair materials.

A 5 year research using PTFE-Gore-Tex grafts mainly for superficial femoral occlusion has been conducted. The majority of the grafts were inserted in an elderly poor risk group of patients with critical ischaemia of the lower limb. The overall cumulative patency at 2 years was 29% falling to 18% at 5 years. Perioperative angiographic indicated that inflammatory reaction is the only risk factor significantly affecting the cumulative graft patency. The presence of diabetes was found to have a significant detrimental effect on limb salvage [199]. A permanently implantable left ventricular assist device, made of Dacron velour, Teflon felt, and Teflon-coated polyester fiber sutures, has been tested in chronic animal experiments. *In vivo* experiments demonstrated that all components elicited mild to moderate inflammatory reactions. Tissue responses to PTFE are rather passivated. Hematocele occurred only when the components were implanted in the aorta with direct blood contact and exposed to arterial blood pressures [200]. An 8 cm long PTFE prosthesis was implanted into defects of the abdominal aorta of dogs, and the following changes were found: the blood flow through the vascular prosthesis induced a shortening of the blood clotting time and a slight increase in the prothrombin consumption. It has a favourable effect of the sealing of pores in the prosthesis and covering its internal surface with a fibrin membrane [201].

14. Silicone

Silicon is a metal in the same column as carbon in the periodic table with the symbol Si and atomic number 14 [30]. It is the most abundant element on earth and does not occur naturally in its pure metallic state. Dimethylsiloxane is the building block for most medical-grade silicone products, including breast implants. This FDA Grade Silicone sheeting is commonly used in applications where food or consumables are present. For more than 20 years silicone miami breast implants have gone through a lot of changes since their first uses. After the mid-1980s many reports concerns the rupture rate of the thinner-shell products, the risk of subsequent breast cancer, and the connective-tissue diseases or symptoms in women with silicone gel-filled breast implants appeared. In the United States a moratorium (in place since 1992) on the use of these prostheses has been maintained by the pressure of overwhelming litigation. At the same time, Australian authorities also restricted the availability of silicone breast implants. Huge damages awarded by United States courts forced Dow Corning, manufacturer of a large percentage of breast prostheses, to file for Chapter 11 bankruptcy in May 1995 [202].

As with any implantable medical devices or drugs, the risk of possible adverse effects must always be weighed against the ability to provide benefits. A great deal of safety research combined with more than 40 years of clinical experience has proven the efficacy and relative safety of the silicone gel breast implants. A rough estimate of implant shell rupture rate is ~10% at 10 years with both biocompatibility and biodurability problems [203]. A fibroconnective tissue capsule was found around all the samples [204]. The capsule formed around implanted mammary prosthesis is highly differentiated and organized, consisting of three layers: interface layer in three variations, intermediate fibrous layer of dense rough collagen fibers and light elongated cells with oval nucleus between them and adventitious layer. Be-

tween the fibers of the interface and the middle strata intra- and extracellular silicone droplets and bulks were observed, representing the location where further pathological processes can take place [205]. It is said by Dr. Sidney Wolfe, director of Public Citizen's Health Research Group, in a statement that: "Public Citizen continues to oppose the FDA's 2006 decision to return silicone breast implants to the market for cosmetic use in women for augmentation. The agency's newer information about the risk of implant-associated lymphoma and the previously known risks are serious enough to warrant advising women against having these implanted."

On March 9, 2012 a new silicone breast implant, which joins the two other silicone breast implants on the market - one made by Allergan and the other by Mentor, was approved by the FDA of the United States of America. Recommended monitoring after initially silicone breast implantation is 3 years and then every two years thereafter. In a review Roach and coworkers concern the importance of length and time on physicochemical interactions between living tissue and biomaterials that occur on implantation. The review provides detailed information on material host interactions, dynamic material/cell surface states, surface chemistry and topological roles during the first stage of implant integration, namely protein adsorption. Generally, after the first contact of material with host tissue a state of flux due to protein adsorption, cell adhesion and physical and chemical alteration of the implanted material is followed (Figure 10) [206]. This model can answer many questions concerning the conformational form and bound proteins and therefore has instruction meanings in new implantable biomaterial design field.

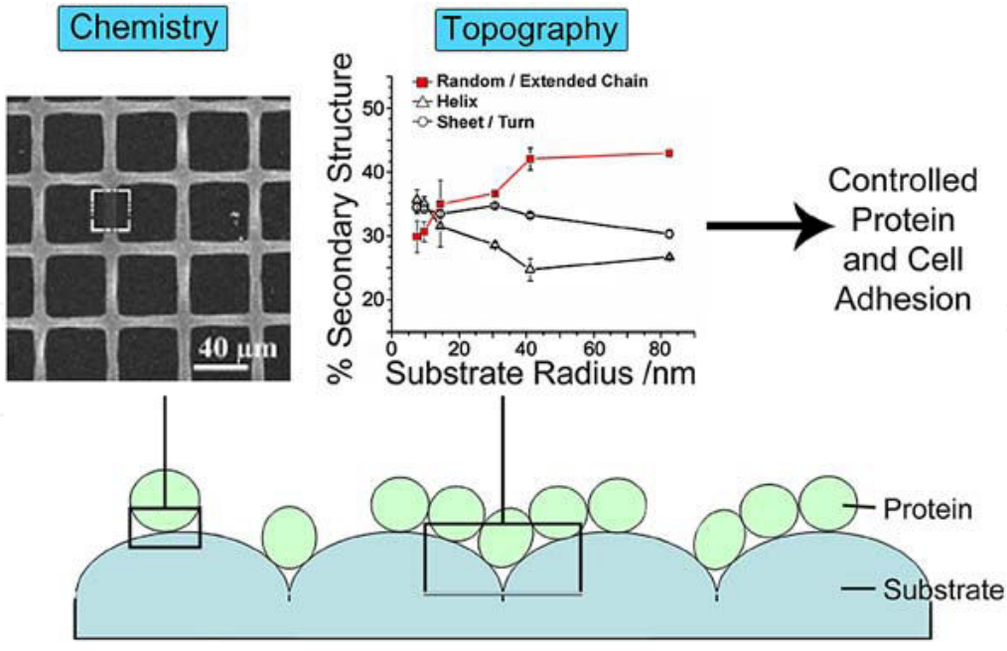

Figure 10. Schematic of protein–surface interactions: Chemistry—adsorption onto biotinylated stripes which appear white, whilst adsorption is hindered on square oligoethylene-glycol regions, the white box shows an intentionally bleached area Topography—albumin adsorption onto hydrophilic silica spheres of varying dimensions as a model of surface curvature [206].

Beside the breast implants a silicon-silk transistor about one millimeter long and 250 nanometers was created. So far the technique has been tested on mice with no adverse effects. Electrical, bending, water dissolution, and animal toxicity studies suggest that this approach might provide many opportunities for future biomedical devices and clinical applications [207]. A silicone catheter attached to a 2-5 x 1-3 cm stainless steel chamber with a self sealing injection port had been intravenously for antimicrobial chemotherapy. Peripheral venous access had become unsatisfactory in all of patients, and six had required central venous catheterisation [208]. More recently, a silicon-based neural probe with microfluidic channels was developed [209].

Origins of controlled release of implantable drug delivery dates back to 1964 when silicone implants were used to prolong a drug effect. Over 40 years, the progress to a safe, effective and acceptable implant system has been slow. The critical factors in implant research which need to be addressed include: erodibility, reproducibility, lack of irritation and carcinogenicity, lack of dose dumping, duration and pulses. While it is possible to surgically implant and remove drug-containing devices or polymeric matrices, the requirement for such intervention could have a significant negative impact on the acceptability of a product candidate. In recent years, two implant systems have been approved for human use; (a) a silicone-based device (Norplant^{R}), and (b) a system based on lactide/glycolide copolymers to release a luteinizing hormone - releasing hormone (LHRH) agonist for treatment of male reproductive tract tumours. This drug delivery approach is very appealing for a number of classes of drugs, particularly those that cannot be given via the oral route, and drug candidates whose therapeutic index is relatively large [210].

15. Aluminium (or aluminum) and ceramics

Aluminium (or aluminum) is the third most abundant chemical element (after oxygen and silicon in the boron group) with symbol Al and atomic number 13. It is one of the typical metals which has been widely used as hard tissue repair materials with unique properties, such as strong mechanical strength, not soluble and degradable in body fluid under normal circumstances, combined in over 270 different minerals, low density (weight) and corrosion resistances [211]. It is generally accepted that metallic implant materials with higher strength/modulus ratios are more favorable for hard tissue repair due to a combined effect of high strength and reduced stress-shielding risk [212].

Al alloys, such as Al-silicon (Si), Al-platinum, and Al-titanium (Ti) are widely used in implantable engineering structures and components where light weight or corrosion resistance is required except for blood-contacting surfaces [213,214]. For example, an implantable double-sided electrode microdevices, called flexible nerve plates, with a prototype of Al layer could reduce the number of insertion sites and thereby the insertion trauma during implantation of neural prostheses [215]. A Ti-6Al-4vanadium (V) alloy was selected as the ceramic-to-metal seal because its excellent mechanical properties and favorable biocompatibility [216]. The first-generation of implantable left ventricular assist devices (LVADs) were Ti-Al-

vanadium alloy pulsatile, volume-displacement pumps. The modern LVAD era began with the introduction of the HeartMate X (vented electric) VE in 1998 [217]. These devices can provide excellent circulatory support and improve survival until heart transplantation. However, they have many application limitations, such as a large volume, an excessive surgical dissection, a large diameter driveline, a noisy pump operation, and particularly a limited mechanical durability. Other complications include bleeding, infections and thromboembolic events. During the succeeding decade, vast improvements in pump design resulted in a new crop of LVADs, whose attributes are transforming LVAD therapy into a kind of standard of care for end-stage heart failure [218]. LVAD therapy has now evolved into a solution which is strikingly superior to optimal medical therapy [219, 220].

It was reported that changes in the porous hydroxyapatite and Al oxide orbital implant densities may correspond to healing and maturation of soft tissues surrounding and penetrating the implants [221]. The thermal oxidation behavior of Al ion implanted Ti nitride films has been studied in dry oxygen atmosphere and found that Al implantation caused the oxidation rate of TiN films to slow down at the initial stage of oxidation [222]. Until recently, there is limited evidence regarding comparative effectiveness of various hip implant bearings, especially metal on metal or ceramic on ceramic implants compared with traditional metal on polyethylene or ceramic on polyethylene bearings [223].

For clinical applications, it is an important character that the metal devices do not cause mental or body uncomfortable reactions, such as delaminate or infiltrate ions to the surround tissues. For example, a defibrillator is a medical device that generates and delivers a shock to the heart of someone in cardiac arrest. Although this device can save lives, there are risks involved, for both the patient and the first responders. One risk associated with defibrillator use is that of burns. Certain transdermal medication patches contain aluminum backings, and when they come in contact with the defibrillator paddle, can cause minor burns to the patient. Accidental shocks to others can occur when first responders accidentally contact with the patient who is being defibrillated. The only objects that should touch the patient during treatment are the defibrillator paddles held by the administrator of the procedure. Sometimes internally implanted defibrillators discharge shocks when they are unnecessary. When this occurs, it can cause pain and promote a dangerous heart rhythm. In addition, the event can be emotionally disturbing and frightening. Doctor can recalibrate the device to minimize the risk of additional unnecessary shocks, and offer suggestions on how to manage these rare events [224].

A ceramic is an inorganic, nonmetallic solid material possessing strong mechanical properties prepared by the action of heat and subsequent cooling [30]. The uses of ceramics have been revolutionizing the biomedical field in deployment as implants for humans during the past three decades. In the search to improve the biocompatibility and mechanical strength of skeletal implant materials, attention has been directed towards the potential use of ceramic composites [225]. Since 1975 alumina ceramic has proven its bioinertness and have been accepted in biomedical applications, some alumina ceramic, such as Al2O3 has been characterized with high hardness and high abrasion resistance. Noiri and coworkers evaluated the biocompatibility of alumina-ceramic material histopathalogically for eight weeks by im-

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planting in the eye sockets of albino rabbits with no signs of implant rejection or prolapse of the implanted pieces. After a period of four weeks of implantation, fibroblast proliferation and vascular invasion were noted. By the eighth week, tissue growth was observed in the pores of the implants [226].

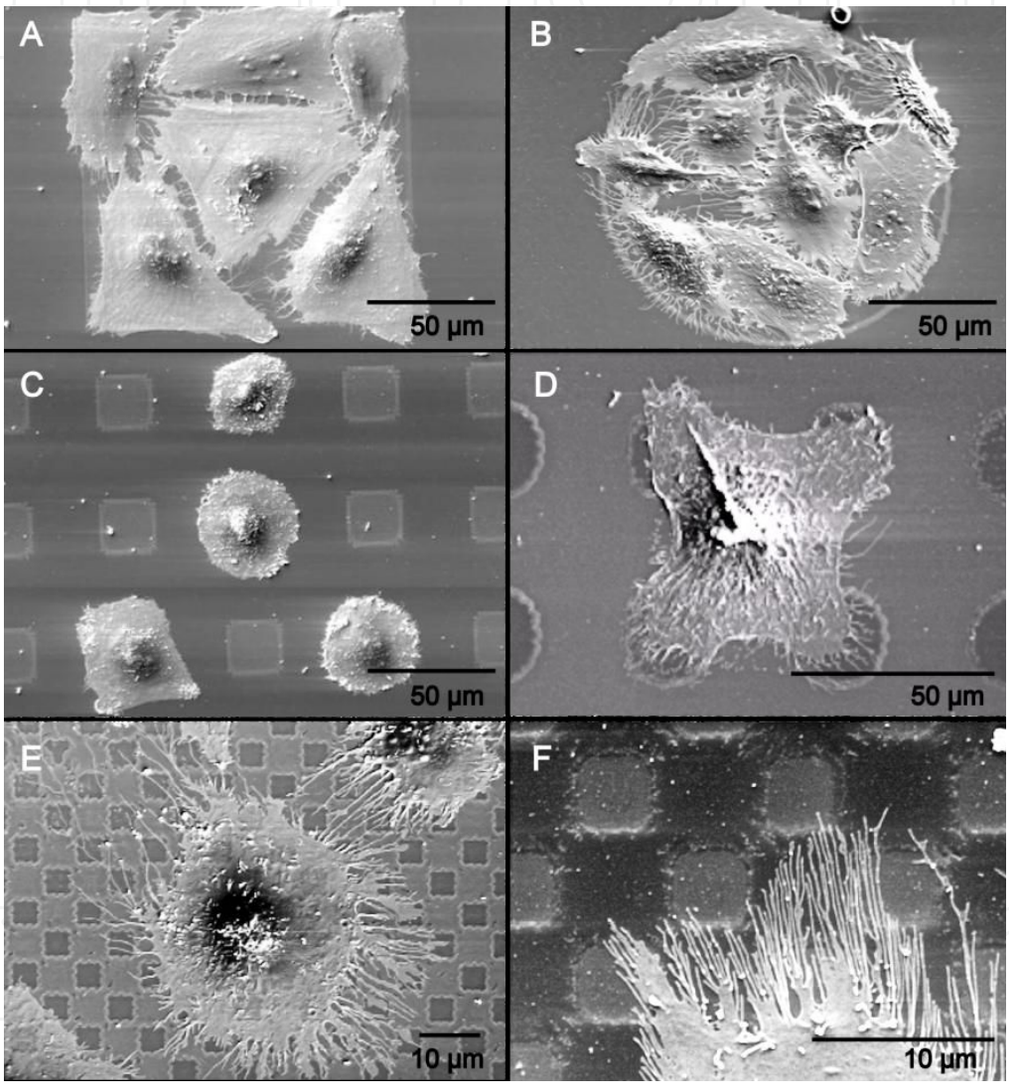

Figure 11. Scanning electron microscopy (SEM) images of SaOS-2 cells cultured for 48 h on micropatterned Ti (A-D) and diamond-like carbon (DLC) (E, F) surfaces. Large-sized (125 µm) squared (A) and circular (B) features facilitated the adhesion of several cells on one Ti island with the cells aligning themselves along the edges of the cell-friendly material. The cells adhering to mediumsized Ti islands no longer conformed strictly to the geometrical shape of the patterns (C) but particularly on circularly patterned surfaces, star-like cellular morphologies appeared (D). On small-sized inverse DLC samples, the cell bodies non-selectively covered large micro-patterned areas (E), but their filopodia clearly showed a preference for DLC trying to avoid bare Si circles (F) [222].

16. Conclusion remarks

Biocompatible is a vital important aspect for an implantable biomaterial. Among the numerous types of host responses to a broad spectrum of biomaterials, those with no adverse or negative effects, such as, fibrous encapsulation, osteolysis, hyperplasia, and inflammation are among the most expectant ones. As advances are made in biomaterial science and technology, new implants/medical devices will be continually explored, alternatives to conventional implants will become more and more effective, and hence more and more attractive. In an effort to provide the best clinical outcomes for the patients, we need to develop the best candidates with minimum invasive surgery times and unnecessary health risks. In the future, design and manufacture immuno or low-immuno implantable biomaterials according to or mimicking the patients' own ingredients, such as blood components, ECMs, tissues and organs, will be possible. For an implantable biomaterial biocompatibility should be always put into the primary importance position no matter it is used as a temporary scaffold, a permanent template, or a drug delivery vihicle.

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Author details

Xiaohong Wang[1,2,3]

Address all correspondence to: wangxiaohong@tsinghua.edu.cn

1 Key Laboratory for Advanced Materials Processing Technology, Ministry of Education & Center of Organ Manufacturing, Department of Mechanical Engineering, Tsinghua University, Beijing, P.R. China

2 Business Innovation Technology (BIT) Research Centre, School of Science and Technology, Aalto University, Aalto, Finland

3 State Key Laboratory of Materials Processing and Die & Mould Technology, Huazhong University of Science and Technology, Wuhan, P.R. China

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