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Chapter

Biomedical Implants for Regenerative Therapies

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Abstract

Regenerative therapies aim to develop novel treatments to restore tissue function. Several strategies have been investigated including the use of biomedical implants as three-dimensional artificial matrices to fill the defect side, to replace damaged tissues or for drug delivery. Bioactive implants are used to provide growth environments for tissue formation for a variety of applications including nerve, lung, skin and orthopaedic tissues. Implants can either be biodegradable or non-degradable, should be nontoxic and biocompatible, and should not trigger an immunological response. Implants can be designed to provide suitable surface area-to-volume ratios, ranges of porosities, pore inter-connectivities and adequate mechanical strengths. Due to their broad range of properties, numerous biomaterials have been used for implant manufacture. To enhance an implant's bioactivity, materials can be functionalised in several ways, including surface modification using proteins, incorporation of bioactive drugs, growth factors and/or cells. These strategies have been employed to create local bioactive microenvironments to direct cellular responses and to promote tissue regeneration and controlled drug release. This chapter provides an overview of current bioactive biomedical implants, their fabrication and applications, as well as implant materials used in drug delivery and tissue regeneration. Additionally, cell- and drug-based bioactivity, manufacturing considerations and future trends will be discussed.

Keywords: biomaterials, bioactive biomedical implants, stem cells, drug delivery, manufacturing

1. Introduction to bioactive implants

Implants are man-made devices that are fabricated for the implantation inside body to replace or support a biological structure, together with delivering drugs and monitoring body functions. They can remain in the body temporarily or permanently [1]. To date, biomedical implants are used not only as sensory devices [2]; brain and neural devices including neuronal, cochlear and retinal implants [3, 4]; subcutaneous implants [5]; cardiovascular devices such as vascular grafts, stent, heart valves, pacemakers [3]; sutures and wound dressings [6]; spinal [7] and dental implants [8]; cosmetic [9] and structural implants [10] including rods, braces, craniofacial, hip and knee replacements; but also as ophthalmic devices including glasses and contact lenses as well as insulin delivery devices [6].

In recent years, scaffolds made of synthetic or natural polymers were developed to regenerate damaged or deteriorated tissues, or to deliver drugs to specific locations. Scaffolds are three-dimensional (3D) structures that mimic the native extracellular matrix (ECM) of tissues and provide a substrate for cell adhesion and proliferation.

These biomedical implants can be made of bioactive materials. The term "bioactive" means that a material can affect its surrounding tissue biologically. Scaffolds can include molecules that promote a biological response in the region where they are implanted. Moreover, cells can be included in these scaffolds to promote healing and regeneration, as they naturally secrete growth factors and cytokines [11].

The risks related to the surgery during the placement or removal of the implant include infection and implant failure. Also, inflammation reaction against the material or rejection needs to be taken into consideration [1]. Here, we report what it is known about bioactive biomedical implants, their desired properties and their applications, focusing on the techniques and materials used for their fabrication. We further provide an overview of cell-based and drug-based implants, implant manufacture and its considerations.

2. Biomaterials for implants in drug delivery and regenerative therapies

To assist native tissue regeneration or/and replacement, implants are made of biomaterials, which support cell and tissue growth through cell adhesion, proliferation and differentiation, prevent unwanted cell and tissue growth, tailor tissue response and prevent immunological responses [12].

Biomaterials have been used for controlled drug delivery systems, sutures and adhesives including biodegradable and non-biodegradable materials, cardiovascular grafts, reconstructive and orthopaedic implants, ophthalmic devices such as corneas and contact lenses, and dental implants [13]. Various types of materials have been used to produce biomedical implants. These include bioceramics, polymers, metals and composites, which are further discussed below. **Table 1** summarises current biomedical applications for biomaterials.

Application	Material	References
Ophthalmic applications (contact lenses, intraocular lenses)	Silicones, hydrogels	[14]
Cardiovascular applications (vascular prostheses, artificial valves, stents, cardiac-assisted pumps, blood bags and catheters)	Polymers, metals and ceramics; polyurethane (PU); polyesters (PE); polybutesters (PBE); polypropylene (PP) and PTFE; stainless steel	[15–21]
Central nervous system and peripheral nervous system (scaffolds for nerve regeneration)	Polycaprolactone (PCL), silk, collagen	[11, 22–26]
Orthopaedic applications (total hip replacement, hip arthroplasty, total knee arthroplasty, bone screws, orthodontic brackets and wires; bone fillers and scaffolds as bone replacements)	Chromium, cobalt, molybdenum, nickel, titanium and zirconium alloys, ultrahigh molecular weight polyethylene (UHMWPE), Ti-6Al-4V, ceramic-coated steels, stainless steel, copper; natural polymers like collagen, chitosan, alginates, synthetic polymers, ceramics like bioglasses, hydroxyapatite and beta-TCP; poly(L-lactic acid) (PLLA); poly(lactic acid), poly(lactic-co-glycolic acid) (PLGA), polycaprolactone (PCL)	[11, 12, 14, 27–33]

Table 1.
Examples of biomedical applications for currently used biomaterials.

2.1 Bioceramics

Ceramics are chemically inert and possess low thermal and electric conductivity as well as physical properties, which make them a suitable material glass for biomedical implants [34, 35]. Bioceramics are osteoinductive and osteoconductive and possess mechanical properties like native bone. Their use as biomedical implants prevents the transmission of diseases and immunogenicity. To date, bioceramics are utilised for dental, periodontal, maxillofacial and orthopaedic applications [36]. In comparison to non-resorbable bioceramics, degradable ceramics exhibit lower mechanical strength. Their chemical and physical composition determines their biological response [37].

Ceramics produced from aluminium, zirconium and titanium oxides possess bending, tensile and compressive strength at least 3 times higher than natural bone and are used mainly for pin-type dental implants and root- and endosteal plate forms [38]. The first zirconia implants were reported in the 1970s. These implants exhibited the ability to integrate into bone tissue, accumulate less plaque and provide improved aesthetics compared to titanium implants [39, 40]. Hence, titanium-zirconium alloys, also called Straumann Roxolid or Roxolit (TiZr1317), are often used as dental implants due to their enhanced mechanical properties and osseointegrative properties that are often used as dental implants [41].

Calcium phosphate-based bioceramics such as tricalcium phosphate (TCP) are similar in chemical composition to the inorganic phase natural bone tissue. TCP exhibits better biodegradation, restorability and bioactivity *in vivo* than hydroxyapatite and is commonly used for orthopaedic, dental and maxillofacial applications. Complete resorption of orthopaedic implants fabricated from TCP was reported after up to 2 years in the rat tibia and for the formation of cancellous bone [42].

Amorphous or low crystalline hydroxyapatite (HAp) is bioactive and bioresorbable. The preparation of synthetic HA at high temperatures results in high crystallinity. Biodegradation and resorbability of HAp are very slow. HAp bioceramics are commonly used for small defects in the case of bone loss or fractures of the tibia, calcaneus and vertebra. HAp is not employed for load-bearing bone applications because of its poor mechanical properties. The modification of HAp with strontium, magnesium and silicon ions resulted in enhanced mechanical and biological properties [43]. Improved bioresorbability was achieved by zinc—[44] and manganese—[45] substitution of HAp.

Dicalcium phosphates (DCP) are biodegradable ceramics composed of calcium phosphates and water. DCPs are widely added to material compositions to modify their physical properties. Dehydrated DCP is known as brushite, which is used in tibial plate and distal metaphysis bone fractures [46].

Historically, ceramics have been used as dental and orthopaedic implant materials. However, compared to other material classes, ceramics have not been used extensively as implant materials due to their limited load-bearing capacity [14].

2.2 Polymers

Polymers are macromolecules that consist of covalently bonded repeating units, which can be of the same (homopolymers) or different (co-polymers) molecule type [27]. A variety of natural and synthetic polymers are used as soft tissue transplants, facial prostheses, denture, hip and joint replacements as well as medical adhesives, sealants and coatings [14].

Polymers are commonly selected based on their physical characteristics, composition, and mechanical properties; how easily they can be modified and moulded; their heat and electric conductivity as well as their ability to integrate into and attach to native tissue [47].

2.2.1 Natural polymers

Natural polymers possess similar properties to native tissues. They are non-toxic and exhibit protein binding-sites and biochemical moieties that are important for tissue regeneration. However, natural polymers are often associated with immunological reactions, low mechanical strength and degradation at body temperature limiting their usability [14].

One of the most commonly used natural polymers is collagen. More than twenty different collagens are known in connective tissues such as bone, tendon, skin, cartilage and ligaments of the ECM of different species. Collagen type I is the main component in bone, skin and tendon, whereas type II is found in articular cartilage. Because of its abundance in nature, its importance for tissue homeostasis and growth, collagen has been investigated as material for bone, cartilage, tendon, skin and blood vessel regeneration [11]. In the clinic, collagen is used for the generation of dermal tissue, neo-tissue formation and wound healing [14]. Further natural polymers are chitosan, hyaluronic acid, fibrin and silk.

Silk, or silk fibroin, is a naturally occurring polymeric protein produced by insects and worms. The protein content gives rise to silk's biocompatibility and its high tensile strength making it an ideal biomaterial for biomedical applications as gels, sponges and films [11, 48–53]. Silk composites fabricated from silk-chitosan and silk-hydroxyapatite have been used to improve silk's elasticity, degradation and porosity [54, 55].

Hyaluronic acid (HA), a non-adhesive glycosaminoglycan (GAG), occurs mostly in connective, epithelial, and neural tissue [56]. HA is commonly used as hydrogel for the regeneration of bone, cartilage and the vascular system and for drug delivery [11].

Chitosan is a biodegradable polysaccharide produced through partial deacetylation of chitin. Chitosan scaffolds exhibit similar properties to naturally occurring GAGs, leading to their bioactivity, and support cellular adhesion [11, 57]. It has been investigated as scaffold material in combination with collagen and HA, as well as PCL for bone, cartilage and nerve regeneration [11].

2.2.2 Synthetic polymers

Synthetic polymers were developed with tailored physical and chemical properties depending on the desired application to overcome limitations of natural polymers. Synthetic polymers are linear, branched or cross-linked depending on their molecular arrangement [58] and possess amorphous or crystalline structures [27]. In addition, synthetic polymers are cheaper in production and enable improved functionality [11]. Commonly used synthetic polymers are poly(lactic acid-co-glycolic acid) (PLGA), polyglycolic acid (PGA), polylactic acid (PLA), polycaprolactone (PCL) and poly-hydroxybutyrate (PHB) [11, 27, 59, 60].

PGA, PLA and PCL are used for sutures, interference screws, fixation plates for meniscal repair and craniomaxillofacial fixtures and 3D scaffolds. However, they are known to induce inflammatory responses and are limited in mechanical integrity and controlled degradation. Hence, metal/polymer composites such as Mg/PCL have been developed [27]. Biodegradable synthetic polymers

Synthetic polymer	Application	References
Poly(L-lactic acid) (PLLA); poly (D-lactic acid) (PDLA)	Sutures, drug delivery, vascular grafts, bone screws, fixation pins, dermal filler for facial atrophy (Scultra™)	[11, 61]
Poly(lactic-co-glycolic acid) (PLGA)	Drug delivery	[11, 62]
Polycaprolactone (PCL)	Long-term implant, maxillo-cranial facial implant; drug release	[11, 63]
PCL-gelatin, PCL-chitosan, PCL-collagen	Tissue regeneration	[60, 64, 65]
Poly-para-dioxanone (PPD)	Internal fracture fixation, medical implant as films, foams and moulded scaffolds	[47, 66, 67]
Low-density polyethylene (LDPE), high-density polyethylene (HDPE)	Total hip arthroplasty and treatment of osteolysis as polymer-ceramic composites; rhinoplasty surgery	[68–71]
Poly(methyl methacrylate) (PMMA)	Orbital medical implants, rhinoplasty, cranioplasty, bone cement in hip joint replacement, dental implant for restoration and aesthetics	[72–76]
Polydimethylsiloxane (PDMS)	Enclosing implantable electronic devices and sensors, medical implants, oesophagus substitutes, catheters, shunts, blood pumps and peacemakers	[77–80]
Polyamides (PA), e.g., nylon and nylon-composites	Sutures, fabrication of dentures; scaffold materials and nanofillers for bone regeneration	[81, 82]
Carbon nanotubes (CNT) and composites	Metal coatings for load-bearing musculoskeletal implants to improve surface porosity, reduce metal ionisation and promote the formation of hydroxyapatite	[83]

Table 2.
Synthetic polymers commonly used for the fabrication of biomedical implants.

are chosen based on the required physical, chemical and mechanical material characteristics (**Table 2**).

2.3 Metals and alloys

Due to their mechanical properties, the ease of their processing and the possibility to sterilise them, metals and alloys are ideal materials for biomedical implants [34].

Metals are commonly used as load-bearing orthopaedic implants such as wires, screws, fixation plates, artificial joints for hips, knees, shoulders and ankles, as well as for dental, cardiovascular and craniofacial applications [14].

Novel magnesium alloys have been investigated for orthopaedic and cardiovascular applications [84, 85]. Combining magnesium alloys with aluminium or rare earth metals improves their mechanical properties [86, 87]. However, the accumulation of these elements is associated with neurotoxicity and hepatotoxicity [88]; hence, these alloys are not suitable for biomedical applications. Instead, extensive research is carried out to develop nontoxic magnesium alloys [89], such as Mg-Si and Mg-Sr alloys [90].

Titanium alloys are among the most commonly used metal alloys [91] due to their biocompatibility [92] and corrosion resistance [93]. Their composition

and microstructure vary depending on their elemental composition [94]. The mechanical properties of B-titanium alloys have a Young's modulus like bone but possess a low fatigue strength. Their mechanical properties can be enhanced through the addition of silicon dioxide, zirconium dioxide and Yttrium oxide. Furthermore, to increase their wear resistance, titanium alloys are surface treated. Pure titanium alloys are used in pacemaker cases, ventricular devices, implantable drug pumps, screws and staples in spinal surgery, dental implants and craniofacial implants. Ti-6Al-4V alloys are used in hip and knee replacements and dental implants. Due to the release of aluminium and vanadium ions, which can cause neurological conditions such as Alzheimer's, Ti-6Al-4V alloys are not considered safe for long-term use. β-Titanium alloys substituted with stabilising elements like zirconium, tantalum and molybdenum are safer compared to Ti-6Al-4V [27], and alternative titanium alloys, vanadium free Ti-6Al-7Nb and Ti-5Al-2.5Fe, are being developed [95].

Titanium has become the material of choice for implants; however, components of prosthetics are still manufactured from gold alloys, stainless steel, nickel-chromium alloys and cobalt-chromium alloys [35]. Cobalt chromium alloys enable the fabrication of customised grafts including subperiosteal implants. They are mainly composed of cobalt, chromium and molybdenum, which give rise to corrosion resistance and mechanical properties [96, 97]. Stainless steel alloys such as iron-chromium-nickel-based alloys are used as orthopaedic implants such as ramus blade, ramus frame, stabiliser pins and some mucosal inserts. Due to its nickel content, these alloys possess a low corrosion resistance and induce immunological reactions in patients with nickel allergies [34, 38].

3. Implant properties

Implant materials should possess adequate chemical and physical properties to allow for host tissue infiltration and nutrient transport; biocompatibility to avoid immunological responses; and corrosion resistance, degradation and bioresorbability to enable normal cellular activity and controlled implant degradation [14, 27, 98]. In addition, temporary implants should possess a highly interconnected porous structure to allow cell migration and nutrient and waste transport, provide suitable surface topography to support cell adhesion and growth, as well as allow for the release of bioactive molecules if applicable [5, 11, 12].

Mechanical properties like Young's Modulus, tensile, compressive and shear strength, yield strength and fatigue strength are required to ensure uniform stress distribution, to minimise the movement or fracture of the implant [34].

3.1 Surface properties

Surface properties influence cell adhesion and cellular and tissue responses. Surface tension determines the wettability by a wetting fluid, such as blood or water [11, 34]. Implant surfaces are also categorised by roughness, texture and the orientation of irregularities [38, 99]. The surface textures can vary from concave or convex. Concave surface textures occur due to additive treatments such as hydroxyapatite coatings, whereas convex surfaces are created through etching and blasting. Furthermore, implant surfaces can either be isotropic, meaning that implant properties are independent from the measurement direction, or anisotropic, which means properties are directionally dependent [12, 34].

3.2 Corrosion and degradation of implants

3.2.1 Metal corrosion

Corrosion is the involuntary breakdown of metals by an electrochemical reaction and through the loss of ions from the metal surface in an acidic, an alkaline or a neutral environment. It is one of the most common reasons for implant failure [98]. **Table 3** summarises the types of corrosions that have been observed in metal implants [98–100].

Magnesium for example corrodes faster with an increase of impurities such as nickel, copper and iron [101]. The higher the purity of magnesium, the slower its corrosion rate. However, pure magnesium is not suitable for medical implants due to its mechanical characteristics. Instead, calcium is used for the grain refinement in magnesium alloys [102]. Orthopaedic implants fabricated from Mg-Ca alloys were observed to corrode over a 3-month period after bone formation [103]. Magnesium's mechanical properties can also be enhanced through Mg-Zn with calcium, manganese, yttrium or zirconium [104, 105]. Mg-Zn alloys withstand galvanic corrosion and biocorrosion *in vitro*; however, biocorrosion *in vivo* resulted in a 2 mm/year reduction of a Mg-Zn alloy used as rods in femur shafts [106].

3.2.2 Polymer degradation

Polymer degradation, or biodegradation, occurs through a process called hydrolysis. The polymer surface is attacked by organisms, which secrete enzymes breaking down ester bonds in macromolecules. The resulting smaller polymer molecules are further converted into carbon dioxide and water. The process of biodegradation varies for each polymer [27, 107, 108]; however, all polymers lose their mechanical integrity. To date, PGA, PLA and PLGA among others have been explored for biomedical implants [27]. Their degradation into non-toxic by-products made them favourable materials for temporary biomedical implants [109]. Poly(L-lactic) acid

Corrosion type	Explanation	Biomedical implants
Crevice corrosion	• Occurs in narrow regions • Metal ions create localised positive charge in the crevice	• Interfaces between screws/plates and bone
Pitting corrosion	• Occurs in implants with small surface pit • Metal ions react with chloride ions resulting in rough surfaces	• Orthopaedic and dental implants
Galvanic corrosion	• Occurs due to electrical gradient between Co-Cr alloys, Ni-Cr, Ag-Pd, Au-ternary Ti	• Oral/dental implants • Screws and nuts
Corrosion fatigue and fretting	• Occurs due to cyclic stress	• Bone cement • Femoral implants • Bone plates and screws at the bone-stem interface • Stem-cement interfaces of modular hip implant

Table 3.
Types of corrosions observed in metallic biomedical implants.

(PLLA) has been shown to induce inflammatory responses *in vivo* upon degradation due to its high crystallinity; hence, poly(D, L-lactic acid) (PDLA) was synthesised [110, 111].

PLGA degrades into acidic moieties, which in higher concentrations can affect the microenvironment of the implant's surrounding tissue. This can be especially important for drug delivery applications, where pH-sensitive drugs are used [11]. By increasing the amount of poly(glycolic acid) (PGA) compared to poly(lactic acid) (PLA) in PLGA, the degradation rate is reduced; hence, less acidic by-products are formed [11].

3.3 Biocompatibility

Biocompatibility indicates a desired response of the implant to its biological surrounding [34] and depends on biodegradability and corrosion. The ISO 10993 standard series is used to assess biocompatibility of medical grade materials and medical devices [112]. Test categories investigate the materials' cytotoxicity, sensitization, irritation, toxicity, implantation and biodegradation [71]. Materials that meet these criteria include noble metals and titanium, their alloys, cobalt-based alloys, but also alumina, zirconia, quartz, fused silica, bioglass, silicon, biocompatible polymers like epoxies, silicones, polyurethanes, polyimides, silicon-polyimides, polycyclic-olefins, silicon-carbons, and liquid crystal polymers [113].
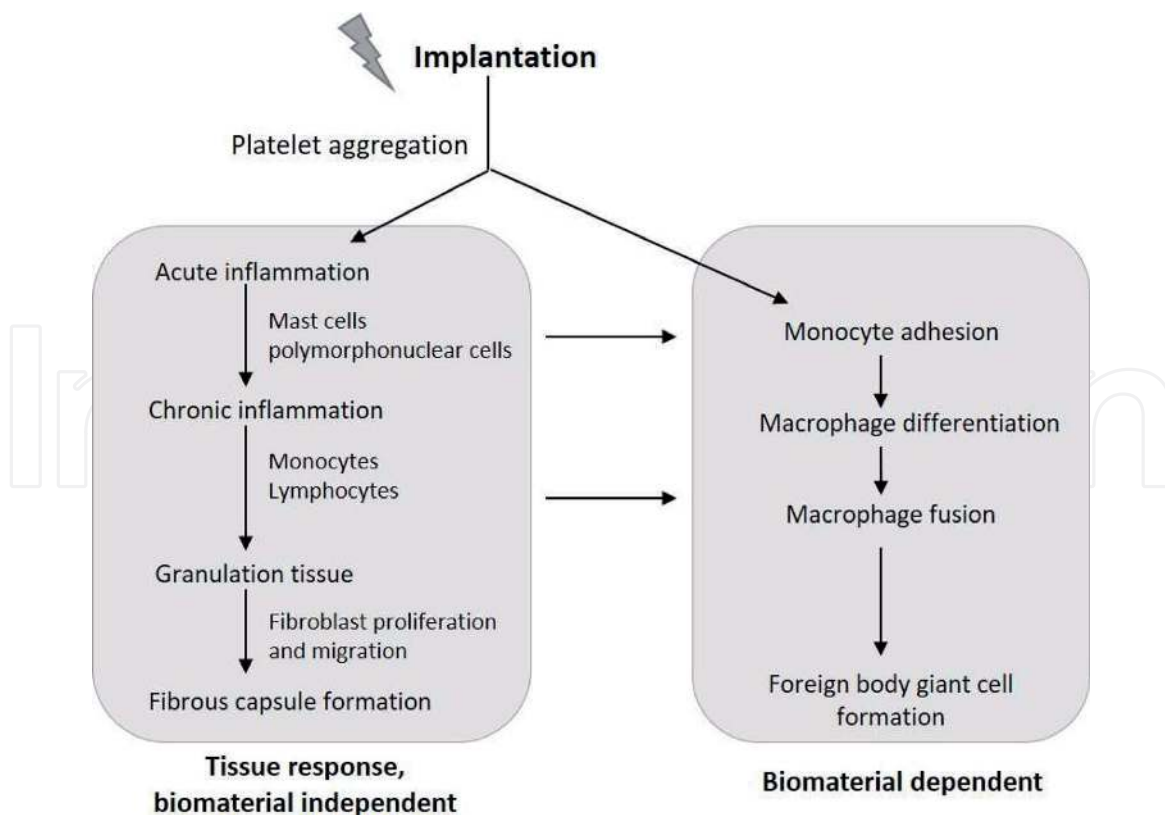
3.4 Foreign body response

Foreign body response (FBR) is a non-specific immune reaction of the body to implanted materials. This inflammatory reaction can happen in response to surgical implantation of biodegradable or non-biodegradable materials present in medical devices or implants [114, 115]. FBR can modulate the safety and/or function of the implanted material. FBR is characterised by distinct phases, namely onset, progression and resolution [116] (**Figure 1**). The onset starts with the surgical implantation of the biomaterial, for example, subcutaneously, which causes local tissue damage [117]. Upon tissue damage, vessel permeation to cells and proteins increases and coagulation occurs where inflammatory mediators like vascular endothelial growth factor (VEGF) plays an important role along with neutrophils and macrophages to initiate the wound healing process. In parallel, angiogenic factors stimulate local vasculature.

FBR comprises of a biomaterial-dependent and biomaterial-independent reaction (**Figure 1**). If biodegradable materials are present, the FBR will persist until the material is fully degraded. With non-degradable or long-term implants, a fibrotic capsule creating a barrier between the material and the body will form.

Progression of FBR depends on the material's surface chemistry and wettability [118], where protein, antibody and macrophage adsorption can vary due to the material's intrinsic properties. Additionally, fibrinogen can be adsorbed by the implant altering its structure. During FBR's progression, leukocyte extraversion occurs from the blood vessels. These migrate towards the foreign body. Consequently, polymorphonuclear neutrophils (PMNs) are activated, which recruit cells including macrophages to the site. Macrophage activation leads to the recruitment of fibroblasts, monocytes and more PMNs [116], which ultimately increases production of extracellular matrix and hence implant encapsulation and fibrosis.

Phagocytosis occurs from the onset when antibodies are non-specifically adsorbed by the biomaterials, thus recruiting phagocytes. During progression,

Figure 1.
Foreign body response to implant materials. Sequence of events and responses leading to the fibrous capsule formation and foreign body giant cell formation (adapted from [117]).

phagocytosis by macrophages is continuously promoted through the degradation of the material through biodegradation.

Material particles too large to be phagocyted cause the formation of larger multinucleated cells by fusion of macrophages. These so-called foreign body giant cells possess an irregular shape with more than 20 nuclei dispersed randomly. Giant cells will usually disappear once the foreign body is fully degraded. Surface roughness and surface/volume ratio of the implant can influence the adhesion of macrophages or prevalence of fibrosis [114].

As part of FBR, fibrosis is critical in tissue engineering, since capsule formation can prevent the diffusion of molecules (e.g., drugs) and continuous fibrosis formation can lead to capsule shrinkage thus affecting the implant structure [119]. It has been shown that inhibition of TGF-β can reduce capsule formation [120].

Finally, resolution of the foreign body response involves the degradation of the biomaterial or removal of the non-degradable material.

3.4.1 Immunomodulation for circumventing the foreign body response

Biomaterials' characteristics partly determine the body's immune response to the implant. Implant pore size and morphology are critical since they can allow immune cells and macromolecules to interact with the implant. In addition, degradation products derived from implants like scaffolds and medical devices, as well as their constantly changing surfaces, can trigger the immune response [121]. Recent implants can carry therapeutic cells. These cellular implants provoke an immune response due to encapsulated cells, posing further challenges besides biomaterial compatibility and design [122–124].

Polymers such as collagen, alginate, chitosan, polyethylene glycol, polyvinyl alcohol and polyurethane are used in several implantable products that may have an inherent biocompatibility. Understanding how these polymer's chemical and physical properties can be used to either avoid immune response or modulate it, while improving their functionality, is crucial for the advancement of these systems [121].

Strategies to circumvent the FBR include changing the biomaterial's surface properties like wettability, its chemical moieties, and surface charge, because they affect protein adhesion to the biomaterial [121, 125].

To create more hydrophilic surfaces, monolayers of hydrophilic polymers such as polyethylene glycol (PEG) and polyethylene oxide (PEO) are added, thus preventing protein adsorption altogether [126]. The deposition of chemical moieties like amino ($-NH_2$), carboxyl ($-COOH$), hydroxyl ($-OH$), and methyl ($-CH_3$) groups allows the modulation of cellular adhesion influencing inflammatory cell infiltration and macrophage response affecting the fibrotic capsule thickness around the implant [121]. Surface charge is important for the FBR immunomodulation. There have been contradicting reports on how exactly neutral, positive or negative charges reduce the inflammatory response connected to the FBR. Generally, negatively charged surfaces tend to inhibit the immune response through reduced cell adhesion [127].

Moreover, implant topography including texture, shape and size has shown to trigger an FBR [121]. Therefore, several manufacturing techniques like particles, assembled monolayers and photolithography are used to create variety of shapes, sizes and surface topographies [128, 129]. Surface roughness at the nanoscale can modulate protein adsorption [130], while variations in surface roughness at microscale affect cells directly [131]. For example, the inflammatory response of titanium used for dental or orthopaedic applications can be decreased by altering its surface nano-and microstructures via physical or chemical procedures [121].

Macrophage interaction with differently shaped biomaterials demonstrated preferred internalisation of nanorods via pinocytosis compared to nanospheres. Additionally, sharper cornered surfaces led to more acute immune responses than smoother surfaces [121, 132]. Moreover, spherical alginate capsules of 1.5 mm or greater were reported to be more biocompatible than their smaller, non-spherical comparators, demonstrating that larger, rounder, smoother capsules could diminish the FBR [133].

The use of decellularised ECM as scaffolds by removing immunogenic components to avoid an acute response but keeping the original structure has been studied. While decellularised ECMs contribute to a pro-regenerative environment [134], it has been discussed that the immune response modulation still depends on the original tissue from which the ECMs have been obtained. Therefore, this option still presents a potential solution with more research needed to advance its understanding, manufacturing and impact [134].

The incorporation of bioactive molecules such as adhesion molecules, drugs and growth factors to promote immunological interaction with the host attenuating its response has been investigated. Bioactive molecules bound to the biomaterial for controlled release aiding tissue regeneration [125] include proinflammatory molecules like prostaglandins [135] and anti-inflammatory molecules like cytokines [136]. Combining their delivery with glucocorticoids improved tissue regeneration and attenuation of inflammation [137]. In recent years, the encapsulation of immune cells that act as producers or inducers of specific biological responses to reduce inflammation and/or induce repair has been investigated as immunomodulation strategy [125]. Examples include the encapsulation of MSCs to decrease the fibrosis in FBR [138] or the encapsulation of macrophages to mediate pro-angiogenic activation [139].

Overall, understanding the fundamental biological systems associated with FBR and the structural, physical and chemical properties of biomaterials will lead to new designs and strategies allowing to circumvent or work together with the natural body's response towards implants.

4. Bioactive implants

Implants can be bioactive, inducing an alteration to the surrounding tissue, by their own biomaterials imparting this alteration to the surrounding tissue, by releasing a drug (or drugs) inducing bioactivity, or by containing cells that can produce bioactive molecules. In the following sub-sections, we discuss the implant bioactivity induced by drugs and cells implicating in drug delivery and in tissue regeneration.

4.1 Bioactive implantable and injectable drug delivery systems

Bioactive implants may incorporate active substances including small chemicals, peptides, proteins, hormones and even cells, which will have a therapeutic function in the human body. For drug delivery, these systems are commonly administered via parenteral route by injection or implantation. There are also implantable drug delivery systems that can be administered via ocular administration or via surgical procedures such as brain implants (e.g., Gliadel®). Implantable drug delivery systems are designed to slowly release the active substance(s) that they carry, thus avoiding repetitive injection. The active substance is delivered at a consistent predictable rate creating a drug release profile. This avoids peaks and troughs in the drug-blood level, which is common for non-long acting injectable products (e.g., intravenous solutions). Implantable drug delivery systems can be also injected subcutaneously, intramuscular or via other sites including intra-articular. They include implants and suspensions of micro- or nano-particles. Typically, these systems are preferred when the active substance has a poor absorption by other means of administration or a short half-life. The major advantages of such systems are improved pharmacokinetics, control of the drug release rate, and enhanced patient acceptability due to the reduction of side effects by maintaining the drug-blood level constant and by decreasing administration frequency [140, 141].

Sustained drug release is obtained via diffusion of the active substance through a biomaterial matrix, or released through biomaterial biodegradation, or a combination of both mechanisms. To date, commonly used biomaterials for drug delivery are either biodegradable like PCL and PLA or non-biodegradable like polydimethylsiloxane, polyethyl vinyl acetate, or titanium alloy [141]. Several approaches have been developed to produce implantable drug delivery systems [142] and to control the drug release. These include (i) using diffusion via membrane permeation, either porous or semi-porous membranes; (ii) controlling drug release by matrix diffusion using porous polymers; (iii) reservoir systems, where the drug is encapsulated in an inner reservoir; and (iv) actively releasing the drug from the implant via osmotic pressure, electric current, vapour pressure, hydrolysis or ultrasound activation.

Typically, simple rod-like solid implants, produced by hot melt extrusion processes using biodegradable polymers like PLA, PCL, PLGA and PEVA, often display a biphasic drug release kinetics showing a burst release due to the drug being deposited on the surface or near the surface of the implant, followed by a zero-order kinetics reflected by drug diffusion, matrix erosion, or a combination of both depending on the polymeric biomaterial used. **Table 4** summarises drug release systems that are currently commercially available or

System	Product	Drug	Manufacturer	Indication	Clinical status
Implants [143–148]	Zoladex® (PLGA solid rod, 1 × 10 mm)	Goserelin (up to 3 month release)	AstraZeneca	Prostate cancer	Approved by FDA
	Nexplanon® (radiopaque PEVA solid rod)	Etonogestrel (release up to 3 years)	Merck	Contraception	Approved by FDA
	ITCA 650 (Medici technology, former Duros®)	Exenatide (release up to 2 years)	Ipsen	Type 2 diabetes	Clinical Phase III/ NDA
	MK-8591 (PCL solid implant)	EFdA (long-term release)	Merck	HIV treatment and prevention	Pre-clinical/Phase I
Microparticles [149–151]	Risperdal Consta® (PLGA microspheres)	Risperidone	Janssen	Antipsychotic	Approved by FDA
	Decapeptyl SR® (PLGA microspheres)	Triptorelin	Debiopharm/Ferring/ Ipsen	Prostate cancer	Approved by FDA
	Sandostatin LAR® (PLGA microspheres)	Octreotide	Novartis	Acromegaly	Approved by FDA
	Bydureon® (PLGA microspheres)	Exenatide	Amylin/AstraZeneca	Type 2 diabetes	Approved by FDA
	Vivitrol® (PLGA microspheres)	Naltrexone	Alkermes	Opioid/alcohol dependence	Approved by FDA
In situ hydrogels [152, 153]	Eligard® (Atrigel® technology)	Leuprolide acetate	Sanofi-Aventis	Prostate cancer	Approved by FDA
	Posidin® (Sabre® technology)	Bupivacaine	Durect/Sandoz	Postoperative pain	Clinical Phase III/ NDA
	Relday® (Sabre® technology)	Risperidone	Durect/Zogenix	Schizophrenia/bipolar disorder	Phase I
	Sublocade® (Atrigel® technology)	Buprenorphine	Indivior	Severe opioid use disorder	Approved by FDA

Summarised are current systems that are commercially available or under development. Table was adapted from [140, 141, 148, 151, 153].

Table 4.
Drug delivery systems as implantable and injectable depots.

under development. There are numerous advantages to using implants in drug delivery such as the possibility of removal after treatment, the consistent and predictable drug release, and versatility in manufacture using various biomaterials. However, there are potential disadvantages of this dosage form, where often a specialised device (e.g., trocar) and technique are needed for implantation and removal requires minor surgical procedures. Additionally, there may be complications in locating the implant for removal since it can migrate from its original location. From a commercialisation point of view, this type of bioactive implant may require complex regulatory and commercial strategies for market approval [154].

Injectable drug delivery systems, such as particulate suspensions or hydrogels like *in situ* forming gel depots, are designed from biodegradable biomaterials, injected (e.g., subcutaneous, intramuscular), form a depot, erode when in contact with body fluids, and release the drug by diffusion and erosion [149]. Injectable depots are not designed to be retrieved. Examples of injectable depots are micro- or nano-scale particles, where the drug is encapsulated within the polymer matrix. The polymeric particles are commonly prepared from biodegradable materials (e.g., PLGA, PCL, or silica) since the intent is to deliver the depot system once by injection, let it erode and release the drug with time.

Choosing the polymer grade, type and combining polymer types can help tune the drug release as necessary [149, 154]. Key points in preparing these bioactive depots are the choice of the biomaterial (biodegradable/erodible), the physico-chemical properties of drug to be encapsulated (i.e., hydrophobic or hydrophilic), the drug loading needed to deliver the therapeutic dose, and the inherent pharmacokinetics of the drug. This will inform the choice of manufacturing methods, often by emulsification. Common polymers used in these preparations are PLGA and PLA, where their long safety records deem these polymers as preferred, even though some minor inflammatory responses can still be reported [150].

Hydrogels, prepared from different types of biomaterials (e.g., hyaluronic acid, polyesters and chitosan) have been extensively investigated as carriers for sustained drug release [152, 155]. *In situ* forming hydrogels as injectable depots pose major advantages over other drug release systems since they allow for rapid, painless and easier administration through smaller needle sizes. These biodegradable *in situ* depots are of low viscosity prior injection and solidify into a gel or solid depot after injection, typically due to a specific trigger depending on the chemistry of the chosen biomaterial [153].

4.2 Bioactive cell-based implants as drug delivery systems

Before commercialising a cellular implant, it needs to be approved by FDA's Cellular, Tissue and Gene Therapies Advisory Committee. The Committee evaluates the safety and effectiveness of cellular implants for the reconstruction, repair or replacement of damaged tissues [156].

Cell-based drug delivery systems can be defined as technologies capable of treating diseases using living cells to deliver the therapeutic bioactive molecules in the body, as either transport system or as production units [157]. Some examples of commercially available or under development cell-based implants are shown in **Table 5**. These cell-based drug delivery systems are used as constant producers of bioactive molecules in the form of implant devices. Judging by the current developments in this technology, a major driving force behind this type of delivery is the improvement in treatment of insulin-dependent diabetes mellitus. The biggest challenge in cell-based drug delivery systems is avoiding immune response.

Company	Product	Application	Method of action	Manufacture
Neurotech	Encapsulated cell therapy (ECT)	Ophthalmology	Ciliary neurotrophic factor (CNTF) has neuroprotective effects on photoreceptors.	Encapsulated human cells producing CNTF into the back of the eye.
VIaCyte	Encaptra®	Stem cell delivery for treatment of diabetes mellitus	Human stem cells are isolated and differentiated into β islet cells contained into a pouch, which is implanted.	PTFE porous membrane device filled with cells.
Sernova	Cell Pouch™ with Sertolin™	Diabetes/haemophilia/thyroid disease	Therapeutic cells are inserted into a pouch made of medical-grade materials inserted subcutaneously; Sertolin® is a patented immune protection system.	Pouch made of medical-grade materials.
PharmaCyte	Cell-in-a-box®	Pancreatic cancer/breast cancer/diabetes	Uses cotton cellulose to encapsulate cells.	Single cell encapsulation in proprietary polymer, freeze-drying process to keep cells viable in the long term.
Beta-O2	βAir® bioartificial pancreas	Diabetes, adrenal insufficiency	Device using alginate—high guluronic acid and high mannuronic acid—to encapsulate cells and impregnate a PTFE porous membrane, respectively. Also comprises an oxygen-providing chamber, which needs refilling.	Single cell encapsulation in proprietary polymer, freeze-drying process to keep cells viable in the long term.
Sigilon	Afibromer™	Diabetes	Human stem cells differentiated to β islets encapsulated in modified alginate spheres, which suppress immune system response and FBR.	
Encapsulife	Encapsulation system for the immunoisolation of living cells	Diabetes	Cellulose-based polymer encapsulation of cells.	Pancreatic islets encapsulated are stimulated to produce insulin.
Organogenesis incorporated	GINTUIT	Mucogingival conditions	Keratinocytes and fibroblasts produce cytokines and growth factors that promote healing and regeneration of the tissue.	Allogeneic keratinocytes and fibroblast in bovine collagen.

Table 5.
Examples of commercially available cell-based implants for drug delivery.

4.3 Bioactive cellular implants as tissue replacements

When damages due to disease, injury or trauma lead to the degeneration of tissues, it is necessary to provide support for their repair, replacement or regeneration. Common approaches include tissue transplantation, both from the patient's own body (autograft) and from a donor (allograft). However, harvesting autografts is expensive and invasive and the patient may experience infections and hematomas. While for the allografts, there are risks of rejection along with the infections due to the surgery or the transplanted tissue [158]. With tissue engineering, biological implants are developed that restore, maintain and improve the tissue function [159]. Implants provide the environment for cell adhesion and proliferation to grow new tissues. They can also include active substances like growth factors and drugs as well as cells to aid tissue regeneration [11]. Cell-based scaffolds are either cultured *in vitro* with the aim of synthetizing tissues that can be implanted, or to be implanted directly in the damaged region [158]. **Table 6** summarises some of the recent studies about cell-based implants tested on *in vivo* models.

4.3.1 Primary cells versus stem cells

The advantage of using cell-based scaffolds is the possibility to customise the construct using cells derived from the patient (primary cells). In this way, there is no risk of rejection due to immunological incompatibility. Cells can be isolated from biopsies and then seeded on the scaffold (**Figure 2**). However, primary cells are differentiated, post-mitotic cells. This leads to a limited lifespan, where after a limited number of cell doubling, they will enter in senescence and stop dividing, but are still viable [166, 167]. Moreover, primary cell types are difficult to culture, because they have difficulties adhering and proliferating *in vitro* [168].

To overcome problems associated with primary cells, stem cells have been be used. Stem cells are present in most if not all tissues and, according to their origin, they can be classified into embryonic and adult stem cells. Stem cells are able to both duplicate (self-renew) and differentiate in one or more cell types [167].

Embryonic stem cells (ESCs) are isolated from inner cell mass of embryo at the blastocyst stage. They can differentiate in any cell type (pluripotency) and have a high rate of self-renewal. Unfortunately, they can cause an immune response, as they are derived from a different body, so immunosuppression is necessary to avoid rejection. Moreover, the injection of undifferentiated ESC can lead to the formation of teratoma [169].

Adult stem cells (ASCs) are multipotent cells that can differentiate in a limited number of cell types, which reside in a specific microenvironment, the stem cell niche. Their role is to replace damaged and dead cells in the tissue to maintain homeostasis [170].

ASCs can be isolated from bone marrow, blood, adipose tissue, liver and skin [169]. Compared to ESCs, ASCs proliferate more slowly and have limited expansion capacity *in vitro*. Like primary cells, they can enter in senescence [171]. With age, their regenerative potential, growth and divisions are affected [172]. The most commonly used type of ASCs is mesenchymal stem cells (MSCs). These cells can differentiate into musculoskeletal cells, marrow and other cells of connective tissue, and they can provide trophic support and modulate the immune response [173]. They can migrate to a damaged region and promote healing by secreting molecules involved in angiogenesis and cell proliferation and inhibit oxidative stress and apoptosis [174, 175].

Application	Cell type	Implant	Outcome	Reference
Tendon regeneration	Rat tendon stem/progenitor cells	Asymmetric chitosan-based sponges	• Tenogenic specific genes expression and protein production *in vitro* and *in vivo*. • Formation of aligned collagen fibres *in vivo*.	[160]
Neural tissue engineering	Schwann cells, human bone marrow mesenchymal stem cells (BMSCs)	Polyvinyl alcohol (PVA)/sulphate alginate nanofibers	• Metabolic active cells adhered to scaffold. • Mesenchymal stem cells differentiate in neuronal cells.	[161]
Wound healing and skin regeneration	Wharton's jelly mesenchymal stem cells (MSCs)	Poly(ε-caprolactone) (PCL)/gelatin nanofibers	• Nanofibrous biodegradable scaffolds. • Cells were metabolic active and proliferative after 21 days in culture. • MSCs on the scaffolds reduced the presence of denaturised proteins *in vitro,* possible anti-inflammatory response.	[162]
Mandible defects repair	Endothelial progenitor cells (EPCs), BMSCs	Biodegradable bioactive glass ceramic scaffold	• Expression of osteogenesis and angiogenesis markers *in vitro*. • After 9 months post-implantation *in vivo*, the defects were nearly completely recovered, and angiogenesis was promoted.	[163]
Acute kidney injury	Human placenta-derived mesenchymal stem cells (hP-MSCs)	Self-assembling peptide hydrogel	• hP-MSCs niche, cell survival and angiogenesis were promoted in *in vivo*. • Renal functions were ameliorated.	[164]
Spinal cord regeneration	Neural stem cells (NSCs)	Elastic poly(sebacoyl diglyceride) (PSeD) scaffolds coated with poly(sebacoyl diglyceride)-isoleucine-lysinevaline-alanine-valine-serine (PSeD-IKVAVS)	• Graft-host integration in spinal cord *in vivo*. • NSCs exhibited neuronal differentiation. • Inflammatory cells infiltrated the lesion site, functional recovery after 4 weeks. • Degradation products of PSeD-IKVAVS promoted NSCs differentiation, inhibited neuronal apoptosis and alleviated inflammation.	[165]

Table 6.
Examples of recent studies on cell-based implants.

Induced pluripotent stem cells (iPSCs) originate from fully differentiated somatic cells, which are dedifferentiated to form iPSCs by a process called reprogramming. The methodology was developed in 2006 [176] and involves the stimulation of genes that are active during the embryogenesis. Thanks to the cell derivation, the implantation of these cells does not lead to rejection. However, as with ESCs, iPSCs can form teratoma. Moreover, some of the genes that are activated are also associated with tumour development [177].
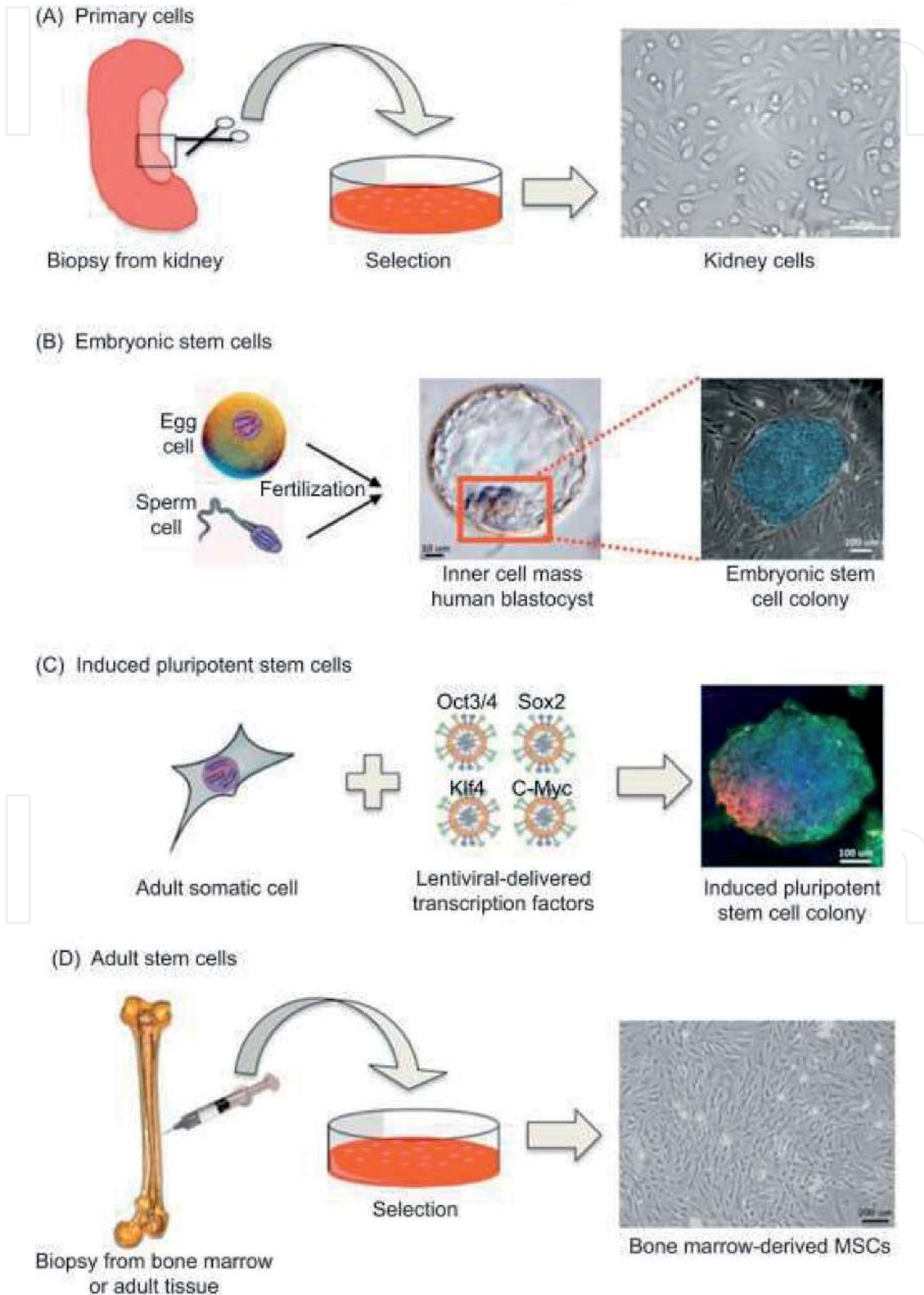
Figure 2.
Source of cells used for cell-based implants. Image adapted from [168].

5. Implant manufacture

To generate tissue replacements, it is essential to resemble the native extra-cellular matrix (ECM). Therefore, the matrix composition, shape and physical properties are crucial. Nanofibers, sponges or gels have been fabricated using numerous different techniques or combinations of techniques to mimic the native ECMs. Some of these techniques and their biomedical applications are presented in **Table 7**.

5.1 Solvent casting particulate leaching

Solvent casting particulate leaching is a technique developed in 1993 by Mikos et al., where a polymer is dissolved in an organic solvent and the polymer solution is mixed with an insoluble porogen. The solvent is evaporated by solvent casting or freeze-drying techniques. The evaporation leads to a porogen-polymer compound, which is washed to remove the porogen leaving a porous polymer matrix behind [187, 188]. This method is relatively easy to use and inexpensive [189]. Pore size, porosity and interconnectivity can be controlled selecting the right polymer, porogen and their concentration [190].

5.2 Phase separation

Phase separation employs temperature changes that separate the polymeric solution in two phases: the lean phase (low polymer concentration) and the rich phase (high polymer concentration). Briefly, the polymer is dissolved in a solvent, then, the temperature is rapidly decreased to have a liquid-liquid separation and two-phase solid is formed [191]. Finally, the liquid is removed by extraction, evaporation or sublimation [192].

5.3 Freeze-drying

Freeze-drying technique or lyophilisation [193] is based on a sublimation process that will produce a porous scaffold. A polymer is added to a mixture of water and organic solvent and moved into a mould. The mixture is quickly frozen and, by lowering the pressure to few millibars, the water and the organic solvent sublimate. The complete removal of the liquid phase takes place under vacuum [189, 194, 195]. To control porosity and pore size, polymer/water ratio, ionic concentration, viscosity and pH, together with freezing rate and temperature, can be changed [194, 195].

5.4 Electrospinning

Electrospinning is used to produce micro- and nanofibers. It is widely used as it can produce matrix that can resemble the native ECMs. Nanofiber scaffolds offer mechanical support and a nanoscale environment for the cells [196, 197]. A polymer solution is added to a syringe. Then, high voltage is applied, and the solution accelerates to a collector of opposite charge. The solution-air inter-face changes from rounded to conical, due to the repulsive electrostatic forces between the polymer molecules in solution and the attractive force between the polymer solution and the collector. The polymer solution is ejected from the syringe when the electrostatic forces are higher than the surface tension of the solution. Then, the solvent evaporates, and the solid polymer is deposited

Technique	Material	Application	Outcome	References
Solvent casting—particulate leaching	Poly(L-lactic acid) (PLLA) and matrilin-3 (MATN3)	Articular cartilage regeneration	• Nanofibrous porous scaffold. • Cell hypertrophy and endochondral ossification prevented *in vivo*. • Chondrogenesis is promoted *in vivo*.	[178]
Phase separation—particulate leaching	Poly(lactic acid) (PLA)	Bone tissue engineering	• Porous scaffold. • Osteosarcoma cells (MG63) were metabolic active and viable after 14 days in culture.	[179]
Freeze-drying	Poly(ε-caprolactone) (PCL) and zein	Drug delivery	• Porous and degradable scaffold. • Degradation rate increases with the concentration of zein.	[180]
Freeze-drying and self-assembly	Collagen	Tissue engineering	• Aligned collagen scaffolds. • Rat fibroblasts and neurons elongate along aligned fibres.	[181]
Freeze-drying	Silk fibroin-chitosan	Cartilage regeneration	• Porous scaffold. • MSCs were metabolic active, viable and differentiate after 21 days in culture.	[182]
Electrospinning	Poly(ε-caprolactone) (PCL)/poly(D,L-lactide-co-glycolide) (PLGA)/gelatin	Vascular tissue engineering	• Dual-oriented/bilayer hydrophilic nanofibers. • Smooth muscle cells and endothelial cells were viable after 7 days; orientation along the fibres.	[183]
Electrospinning	SiO₂CaO	Wound healing	• Cotton wool-like, fibrous and porous scaffold. • Human fibroblast seeded on top were metabolic active and proliferative after 7 days in culture, and produced vascular endothelial growth factor.	[184]
3D printing	Copper/tetrakis (4-carboxyphenyl) porphyrin/β-tricalcium phosphate (Cu-TCPP-TCP)	Bone tumour ablation and osteogenesis	• Metal-organic photothermal nanosheets. • Promoted osteosarcoma cell death *in vitro,* ablation of subcutaneous bone tumour tissue *in vivo*. • Adhesion of bone marrow MSCs HUVEC *in vitro*. • MSCs differentiated in osteocytes. • HUVEC expressed angiogenesis markers *in vitro*. • Enhanced bone regeneration *in vivo*.	[185]
E-jet 3D printing	Poly(lactic-co-glycolic acid) and drugs (5-fluorouracil and NVP-BEZ235)	Drug delivery in orthotopic breast cancer	• Long-term drug release near the tumour site. • Less risk for normal tissue. • No need for several administrations.	[186]

Table 7.
Techniques used for the fabrication of bioactive implants.

on the collector. By changing the voltage, collector, polymer concentration and solvent, it is possible to control the size of the fibres [196, 198].

5.5 Additive manufacturing techniques

Additive manufacturing (AM) techniques, or solid freeform fabrications (SFFs), are based on the use of computer-aided design (CAD) to fabricate scaffolds. The CAD controls the layer-by-layer deposition of material. The advantage of these methods is the full control of the topography of the construct [196, 198].

Three-dimensional (3D) printing is a commonly used AM technique that was developed at the Massachusetts Institute of Technology in 1990s [198, 199]. The CAD is converted in a stereo lithography (STL) file and exported to the 3D printer to control the movement and deposition of the material.

This technique allows the inclusion of cells within the scaffold, as high temperature or solvents are not required for its production [200]. In recent years, 3D printing has been used to produce scaffolds and anatomically customised implants based on MRI and CT scans. The AM can be classified in three different approaches [201], namely laser-based (stereolithography, selective laser sintering, electron beam melting and binder jetting) [202–204], nozzle-based (fused deposition modelling and melt electrospinning writing) [204–208] and indirect 3D printing [209–211].

5.6 Injection moulding

Injection moulding is one of the most commonly used techniques for large-scale production of thermoplastic items. The plastic is melted and injected into a mould of desired shape. When the material solidifies, the mould is removed, and the finished part is extracted [212]. Metal constructs can also be fabricated with this technique. Metal injection moulding uses fine metal powders mixed with a binder and is injected with a conventional thermoplastic moulding machine. The binder is then removed, and the product is formed. This method allows the production of constructs with a sophisticate shape and higher mechanical properties [213].

5.7 Self-assembly

Self-assembly is the spontaneous formation of molecular units in supramolecular structures, without external intervention. These molecules interact through hydrogen bonding, van der Waals and electrostatic forces. Due to their biocompatibility and biodegradability, peptides are commonly used for self-assembly. Specific structure can be created by modifying the amino-acidic composition of the peptides [189, 214]. These nanostructures can be used in drug delivery and tissue engineering [215].

5.8 Manufacturing considerations

The manufacturing of bioactive implants, whether these are for tissue engineering or for drug delivery purposes, includes several common aspects. These include the manufacturing methods that are employed, the biomaterial source, use of solvents, scalability, the need for aseptic facilities or if final product sterilisation is preferred, and if a specifically designed device is needed to administer the implant.

Most importantly, the regulatory strategy for filing needs to be in place soon in product development to define all the data that are needed for submission. It is important to define if the bioactive implant will be considered a drug product, a medical device, or a combination product (drug-device), and in which markets should it be launched, as different markets have different regulations and requisites for the different categories.

Comprehensive reviews and discussions on the regulatory aspects for filing medical devices, and combination products in the biomedical field were reviewed [216–218]. Ragelle et al. provide an excellent perspective for nanoparticle-based biomaterials, its manufacture and regulatory outlook for biomedical engineering [219].

To enable the use in animals and humans, the sterilisation process is important. If the manufacturing method is simplified enough, the use of aseptic technique for manufacturing, using filters and a particulate-free environment, will be possible although costly and complex for significantly large-scale manufacturing. For devices where metals are used, sterilisation by moist or dry heat may be possible.

However, for implants that involve polymers or heat-sensitive bioactive molecules, the preferred sterilisation method is gamma-irradiation. The drawback of using this technique is the potential risk to polymer and/or bioactive molecule degradation, changing the release rate and potentially compromising the efficacy of the implant [150]. Depending on the biomaterial and bioactive molecule involved, there may be ways to avoid degradation upon gamma-irradiation, such as using an antioxidant mixed with the drug. Apart from aseptic conditions, gamma-irradiation of the final product remains the best solution but exposes one of the disadvantages of developing bioactive implants as it is still a costly technique bringing its own risks [220].

6. Summary

In this chapter, we reviewed the current literature about bioactive biomedical implants applicable to regenerative therapies and used in drug delivery. To generate new biomedical implants, biomaterials are continuously developed, either through entirely new or by combining advantageous properties of well-known and safe biomaterials to improve the application and effectiveness of implants. Thus, materials that enhance the natural response of the body and simultaneously provide support for cell adhesion and proliferation are required. Another field that has developed in recent years is cell-induced bioactivity, where cells are used in implants for tissue regeneration and disease treatment. While there are several manufacturing techniques to create application-specific bioactive implants, new technologies, such as additive manufacturing, bring advantages and versatility to the field.

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