Anthony Atala, Robert Lanza, Antonios G. Mikos, and Robert Nerem, Eds.

CHAPTER

30

Design Principles in Biomaterials and Scaffolds

Yang Zhu, William R. Wagner
University of Pittsburgh, Pittsburgh, PA, United States

When tissue deficiencies occur as a result of trauma, disease, or congenital conditions, there is a desire to provide functional replacement tissues to the patient. The use of autografts is ideal when this option is available and is often applied for both soft and hard tissue defects with a broad variety of approaches, although donor site morbidity is a problematic consideration. In many cases, such donor tissue is not available and allotransplantation is favored, albeit with the frequently accompanying disadvantages of a limited donor supply and immunosuppressive therapy. In tissue engineering, a central concept is the application of a temporary biomaterial scaffold at the defect site to facilitate healing that will provide some restoration of functionality. If this scaffold is used to carry precursor cells or other features that may induce a functional healing, the outcome potential may be further improved. In designing such solutions for tissue repair and replacement, the parameters that define the scaffold must be selected and optimized to provide the best possible outcome. If cells are to be used, this adds further design (and regulatory) complexity. This chapter focuses on the design principles affecting degradable biomaterial scaffolds used in tissue engineering. Although acellular scaffold approaches are considered, the cellular component of seeded scaffolds will not be explicitly addressed; relevant considerations are covered elsewhere in this text.

FUNCTION AND APPLICATION-ORIENTED DESIGN OF BIOMATERIAL SCAFFOLDS

The objective for a given scaffold design is to meet the clinical needs for a specific application or set of applications. The better the understanding of the clinical need, including the underlying tissue physiology, disease pathology, and other impactful environmental parameters, the more appropriately the design parameters can be defined. As cellular and molecular biology knowledge have rapidly advanced and pathological processes are better defined, the ability to harness this knowledge in designing more advanced scaffolds has grown. The early use of temporary scaffolds in medicine was for simple mechanical support (e.g., sutures), whereas research efforts in recent decades have expanded the potential functional role that the scaffold can have, including the designed modulation of cell behavior and the incorporation of controlled release for bioactive agents.

Mechanical Support

Tissue loss and mechanical failure can be caused by various reasons, including disease processes, trauma, burn, surgical resection, and chronic inflammation. Biomaterial scaffold implantation may provide permanent or temporary mechanical support, hence maintaining the structural and functional integrity of the host tissue. In some reconstructive or cosmetic applications, the implanted scaffold role may be to improve aesthetics in addition to providing appropriate tactile or load-bearing behavior.

Mechanical support structures comprise a major part of the implantable biomedical device industry. Most of these devices are permanent and made from nondegradable metals and polymers. For instance, vascular stents are commonly nondegradable metallics such as nitinol, stainless steel, and cobalt-chromium [1]. Vascular grafts and abdominal wall meshes for hernia repair are often made from polyethylene terephthalate, polytetrafluoroethylene, polyurethane, and polypropylene [2,3]. In the orthopedic field, orthopedic screws and plates, staples, and other fixation devices are commonly stable metals [4,5]. However, each case, there has been substantial research and clinical

https://doi.org/10.1016/B978-0-12-809880-6.00030-8

investigation of degradable scaffolds [6–8]. The general cited advantages of using degradable scaffolds are (1) the potential for new tissue regeneration, (2) the reduced chronic stimulus for inflammation and ongoing foreign body response, (3) elimination of a nidus for infection risk once the material has degraded, and (4) the potential for reduced thrombotic risk and the elimination of anticoagulant therapy for blood-contacting scaffold applications. Despite these advantages, degradable scaffolds have not effectively displaced permanent scaffolds for a variety of reasons. Common factors limiting broader adoption include a higher risk for mechanical failure [9,10], increased early inflammatory response, and concerns with local tissue effects from degradation products and by-products [11].

It is common in the tissue engineering literature to find a hypothetical graph in which a hypothetical mechanical parameter is plotted versus time with three curves: scaffold, new tissue, and net construct (or combined). The scaffold curve slopes downward with time whereas the new tissue formation curve increases. Usually these curves are matched so that the net level of the mechanical parameter is maintained during the healing process. Of course, in reality this is often not the case; scaffolds remain longer than needed and potentially stress shield the tissue. Of greater concern is scaffold mechanical failure when the new tissue is insufficiently strong to take on the required load (Fig. 30.1). This is a serious concern in that such mechanical failures lead to morbidity and mortality that have limited the broader adoption of many degradable scaffold approaches, as indicated earlier. Also, such mechanical failure may be related to the underlying disease process in the treated population that may not be apparent in preclinical testing or in the application of such an approach in other populations. Therefore, in addition to selecting biomaterial scaffold designs with appropriate initial mechanical parameters approximating the host tissue, matching the degradation rate of temporary scaffolds to tissue integration and maturation is greatly important. In fact, sophisticated models seeking to capture the underlying physics and biology are under development [12].

At a cellular scale, a great deal of research in has examined how the microscale mechanical properties of biomaterial scaffolds can modulate cell behavior. Biomaterial substrate stiffness affects stem cell differentiation, including mesenchymal stem cells, induced pluripotent stem cells, and embryonic stem cells [13–15]. Many molecular pathways involved in this process have been described [16,17]. In addition to stem cell effects, substrate stiffness has been shown to affect primary cell phenotypes, including the macrophage and its polarization [18,19]. Macrophages are important cells involved in the foreign body response; thus, substrate stiffness also relates to the host tissue response to scaffolds. Researchers have shown that biomaterial stiffness modulates the adhesion, migration, and proliferation for other types of cells, as well [20].

Given the mechanical support functions that are defined for a specific clinical application of a scaffold, together with the increasingly appreciated effect that mechanical parameters can have on host response and cell behavior, selecting materials with suitable mechanical parameters is usually the first step in scaffold design. Generally, metals and ceramics have high stiffness and strength (Fig. 30.2A and B), as do many composite materials containing these two major categories of biomaterials for scaffolding. Between the two, ceramics have the disadvantage of the risk for brittle fracture. In comparison, synthetic polymeric materials and naturally derived materials are usually weaker in all major aspects. However, polymers and naturally derived materials have lower densities; thus, the differences in specific modulus and specific strength between them and metals and ceramics are not as large. Because most human tissues have stiffness values below the gigapascal range (Fig. 30.2C) [21], metals and ceramics are commonly used in hard tissue replacements (bone and teeth) and applications in which smaller scaffold dimensions are desired (e.g., coronary stents), whereas polymers and naturally derived materials are more often used for soft tissue substitutes.

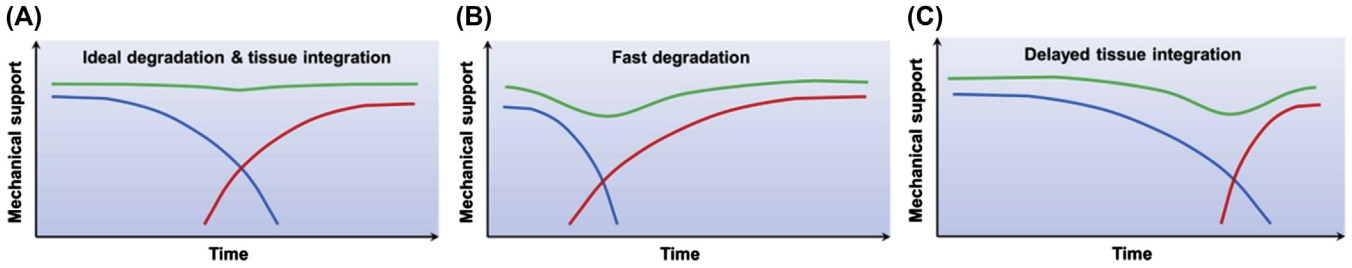

FIGURE 30.1 Mechanical support by scaffold–integrated tissue. The *blue line* indicates mechanical support by degrading scaffold; the *red line*, mechanical support by integrated tissue; and the *green line*, combined mechanical support by the scaffold–tissue combination. (A) Ideal matching between scaffold degradation and tissue integration. (B) The scaffold degrades too quickly and tissue generation is unable to compensate for some interim period, presenting a failure risk. (C) Slower scaffold degradation stress shields new tissue or prevents adequate cell migration and extracellular matrix (ECM) elaboration, leading to inadequate mechanical properties at a later time point.

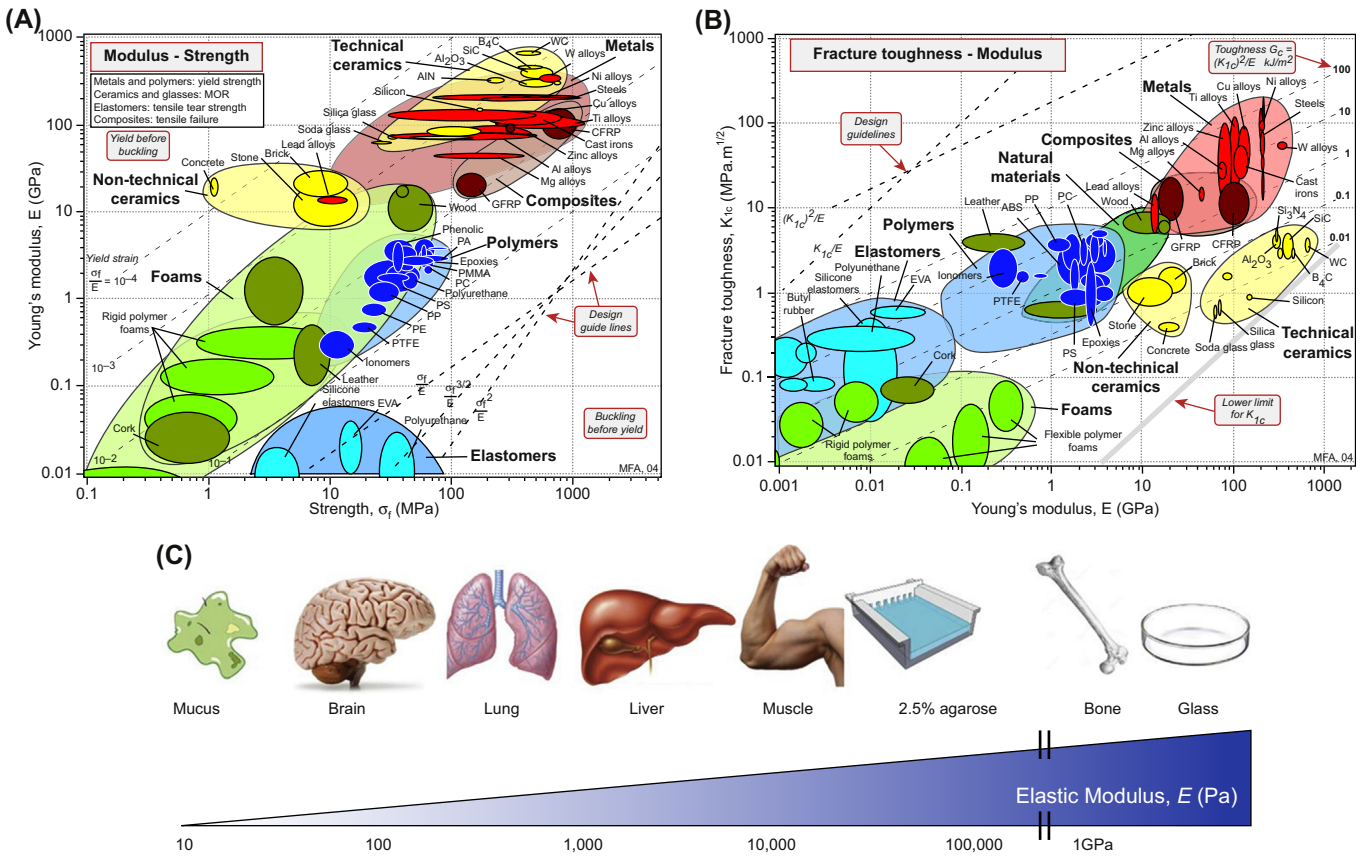

FIGURE 30.2 (A, B) Ashby chart of strength versus modulus. The "strength" for metals is the 0.2% offset yield strength. For polymers, it is the 1% yield strength. For ceramics and glasses, it is the compressive crushing strength, roughly 15 times larger than the tensile (fracture) strength. For composites, it is the tensile strength. For elastomers, it is the tear strength [22]. (C) Young's, or elastic, modulus of tissues [21]. *CFRP*, carbon fiber–reinforced thermoplastic; *EVA*, ethylene(vinyl acetate); *GFRP*, glass fiber–reinforced plastic; *MOR*, modulus of rupture; *PA*, phosphatidic acid; *PC*, phosphatidylcholine; *PE*, phosphatidylethanolamine; *PMMA*, poly(methyl methacrylate); *PP*, polypropylene; *PS*, phosphatidylserine; *PTFE*, polytetrafluoroethylene; *WC*, water cosolvent.

Degradation Profile

As noted previously, scaffold degradation is important for tissue integration and should be well-synchronized with the latter to maintain mechanical support in implantation sites. Aside from tissue integration, degradation can have a critical role in providing pathways for metabolite diffusion and angiogenesis, as well as the release of agents loaded into the material.

Degradation Mechanisms

The mechanisms at work in biomaterial scaffold degradation vary by material type. For polymeric biomaterials, the most commonly seen mechanism is hydrolytic cleavage of backbone bonds (ester, amide, urethane, and carbonate) in polymer chains by water molecules, producing oligomers and monomers with lower molecular weights and higher solubility (Fig. 30.3A) [23]. Enzymatic facilitation of such cleavage reactions can be an important factor in accelerating degradation in vivo, and the use of enzymes in degradation buffer solutions to study degradation in vitro is common. Polymer chains can also be cleaved by free radicals, irradiation, reduction reactions, and other reagents or stimulus, depending on the bonding mechanism [24–26]. Newer concepts in polymeric biomaterial degradation include increased solubility induced by side chain cleavage [27], self-immolating depolymerization [28], and the dissociation of supramolecular assemblies [29]. Metallic biomaterials are almost exclusively selected for their degradation (corrosion) resistance. However, a great deal of research has been focused on degradable metals such as magnesium and zinc alloys for use as temporary scaffolds in a broad variety of applications [30–32]. The corrosion process proceeds by coupled electrochemical reactions with electrolytes to produce oxides, hydrogen gas, hydroxides, or other compounds (Fig. 30.3B) [33]. A high concentration of Cl^- ions significantly accelerates

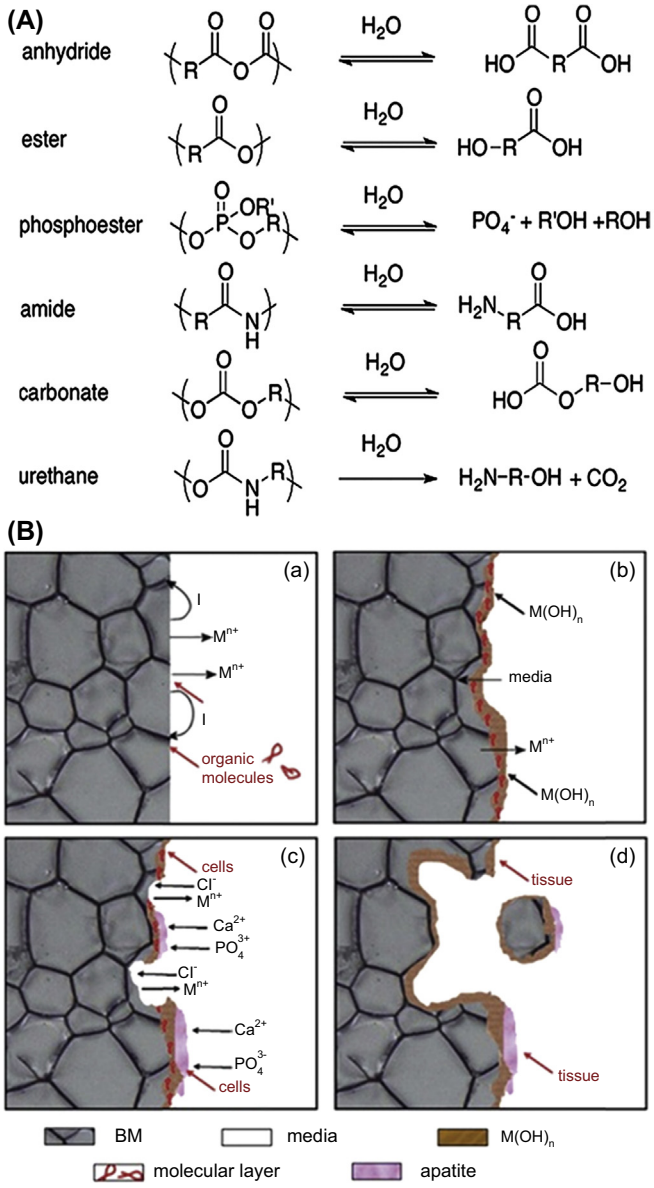

FIGURE 30.3 (A) Hydrolytically degradable linkages used in biomaterials. (B) Schematic diagram of biocorrosion at the biodegradable metal (BM)—medium interface [33].

the corrosion of metals. Cells are also subsequently involved in breaking down the metal substrate from the surface (Fig. 30.3B) [33]. The degradation of commonly used ceramic scaffolds (tricalcium phosphate, hydroxyapatite, and dicalcium phosphate) starts with the dissolution of CaP components, which is heavily affected by the solubility of the specific material. Various cell types (monocytes/macrophages, fibroblasts, and osteoblasts) are then involved in the degradation process by phagocytic mechanisms or via an acidic mechanism to reduce the microenvironmental pH that results in demineralization of the ceramic matrix and resorption [34]. For biologically sourced materials, specific enzymatic degradation has an essential role in degradation, and resistance to such degradation varies with the material composition, processing history and local tissue conditions.

Factors That Affect Degradation Rates

Several factors affect the degradation rates of biomaterial scaffolds, and these factors can be leveraged to modulate the degradation profiles of corresponding scaffolds. Most obviously, the molecular composition of the scaffold will dictate the degradation profile. For polymers with hydrolytically cleavable backbone bonds as introduced earlier, the bond type will heavily influence the degradation rate. For example, hydrolysis of anhydride bonds is

generally faster than ester bonds, which in turn is faster than amide and urethane bonds. Based on this effect, copolymerizing monomers that will result in different backbone bonds have been used to fine-tune the degradation rate of polyesters and other polymers [35]. The molecular environment around the labile bond and the relative density of labile bonds along the backbone are also important factors that can fine-tune the rate of degradation dramatically, despite maintenance of the same labile group. As a result, polyesters can vary as a class of polymer from very rapidly degrading to effectively nondegradable (e.g., polyethylene terephthalate). The hydrolytic cleavage of many of these susceptible bonds is acid catalytic and autocatalytic (degradation products of these bonds are acids); basic salts have been mixed with polyester substrates to slow down degradation whereas acidic monomers have been copolymerized purposefully to accelerate the degradation of polyesters [27,36]. Another obvious option in controlling polymeric scaffold degradation is to choose the initial molecular weight of polymer building blocks so that a greater or lesser number of cleavage events need to occur before solubility of the residual polymer is achieved.

For metallic scaffolds, innate factors affecting oxidation include the activity of the metal, phase organization (of alloys), impurities, the processing history, and the stability of the formed oxide layers [33,37]. For ceramics, the crystal type and degree of crystallinity are important parameters.

Enzymatic Degradation

Degradation on demand, or triggered degradation, is a concept receiving attention in the literature. For polymers, such triggers can include electromagnetic radiation, ultrasound, heating/cooling, or the delivery of a triggering molecule such as an enzyme. For metals, control of the oxidation/reduction reaction by the delivery of current is a ready means of control.

Looking at enzymatically triggered degradation, numerous examples of scaffolds employing this technique have been reported in which enzymes produced by the host tissue or delivered to the biomaterial scaffold accelerate degradation, particularly for naturally derived biomaterials and polymers. Matrix metalloproteinases, elastase, and other enzymes have been employed to cleave protein components in naturally derived biomaterials with high specificity, whereas enzymes such as hyaluronidase and glucanases cleave polysaccharides including hyaluronic acid, alginate, and chitosan. Some of these enzymes accelerate the degradation of synthetic polymers as well [38–42]. Segments of polypeptide, DNA, and other biomolecules have been deliberately covalently combined with synthetic materials at the molecular level or by physical mixing to provide cleavage sites for the composite scaffolds [43–45]. Because enzyme expression levels vary among tissues and some are specifically and temporally elevated in wound beds or sites of inflammation, they provide convenient local factors to be included and targeted in designing scaffold degradation profiles [46–48].

Surface to Volume Ratio

Scaffold morphology, particularly the ratio of the surface area to the volume, has a significant effect on the degradation of biomaterial scaffolds. Higher surface area ratios commonly lead to higher degradation rates of the scaffolds as a result of the greater access of backbone bonds to the surrounding aqueous environment and cofactors present in this environment. For example, electrospun nanofiber meshes made from certain polymers degrade faster than cast films with the same component [49,50]. However, in some important cases, porous structures can be associated with slower degradation [51]. This counterintuitive effect is postulated to result from the diffusion of catalytic reactants out of the scaffolds more readily in the porous case. Rapid transport facilitated by pores also serves to stabilize the pH in some Mg scaffolds, leading to a similar effect as that seen in some polymeric biomaterials [52,53]. Therefore, both opposing effects need to be considered when designing the porous structure in scaffolds. Methods of fabricating porous scaffolds are discussed in subsequent sections.

Surface Modification for Degradation Control

Another method for modulating scaffold degradation is to modify the surfaces. One mechanism is to change the surface hydrophilicity/hydrophobicity, thereby increasing or reducing water uptake that would affect the hydrolysis process. Generally, hydrophilic coatings increase degradation rates whereas hydrophobic coatings do the opposite [54–56]. For degradable metals, increasing corrosion resistance is usually the aim for surface modification, particularly when a given alloy is attractive for its processability, mechanical properties, or other considerations. Methods include simple polymeric coatings, molecular coatings that react with the surface oxide layer, plasma ion implantation, physical vapor deposition, thermal oxidation, and various electrochemical oxidation methods that have been widely applied to metallic biomaterials [56–60].

In considering scaffold degradation in general, many external factors such as mechanical load or irradiation can have a major impact on scaffold degradation rates. However, because the operational environment or processing requirements are often fixed, no further discussion of these factors will be made here.

Controlled Release of Bioactive Agents

Scaffolds may also serve as a reservoir for bioactive agent delivery including small molecule drugs, proteins, genes, cells and nanoparticles. Compared with the inherent physical and chemical features of scaffolds, the effects of released bioactive agents can extend beyond implantation sites to recruit or control circulating cells that are beneficial for tissue repair, and higher specificity can be achieved [61]. When two or more cargoes are loaded, corresponding release profiles may be programmable, which provides flexibility and can yield more desirable effects when orchestrated properly [62]. Logically, seeking synergy by combining the largely local benefits provided by the degrading scaffold with the diffusing effects from controlled-release agents has been a consistent direction explored in the effort to improve scaffold performance.

Many physical and chemical parameters of a scaffold affect the release profile experienced by the loaded cargo. Several of these factors overlap with factors regulating scaffold degradation, as degrading scaffolds open new channels for cargo diffusion. Some of the more important scaffold design parameters that influence the release of water-soluble agents are discussed subsequently.

Effect of Porous Structures

In diffusion-controlled delivery systems, porous structures provide an easier path for the molecules detaching from the material substrate to exit from the scaffolds and enter surrounding tissues, compared with diffusing through relatively dense material substrates. Therefore, easier access to pores and higher connectivity between pores facilitate faster soluble molecule release from a scaffold [63]. However, this theory does not always strictly apply because higher porosities may decrease the degradation rates of some polymer scaffolds, which would slow the accelerated delivery owing to the degradation effects.

At the molecular level, free volume will affect the diffusion rate. Taking hydrated hydrogel systems, for example, for gels with mesh sizes comparable to the size of the loaded agent, diffusion coefficients are decreased owing to steric hindrance provided by the cross-linked polymer chains [64]. Mesh sizes comparable to the size of the loaded agent increase the molecule diffusion path length compared with hydrogels with mesh sizes much larger than the releasing agent [64].

Affinity-Based Release

Affinity between the bioactive agent and the scaffold substrate affects the tendency of loaded molecules to permeate the material volume and approach the interface of the material−pore and materia−/tissue. Through transient interactions between the loaded cargo and the delivery scaffold, affinity-based systems (e.g., heparin-binding proteins for heparin, aptamers for nucleic acids, cyclodextrins for hydrophobic antibiotics) can minimize burst release while providing fine-tunable release profiles by attenuating diffusional release [65]. Related studies about affinity systems have shown that the addition of an affinity group to the therapeutic may be done so as not to affect the bioactivity of interest detrimentally, which supports the practicality of this strategy [66,67]. In addition, mathematical simulations have been developed to predict release profiles, which could be useful in predicting desired release profiles and designing release systems [65].

An alternative method to fabricate affinity-based release systems is to recognize a specific molecule selectively by the scaffold substrate known as molecular imprinting (Fig. 30.4) [68]. In molecular imprinting, the bioactive agents work as template molecules to create imprints in the polymer networks, which subsequently function as affinity binding domains [69]. Compared with nonaffinity systems, release retention was observed in imprinted systems [70]. Molecular imprinting systems would be advantageous for drug delivery because of their ability to sustain the release of a therapeutic agent, enhance the loading capacity, release the bioactive agents by in response to the stimuli intelligently, and enantioselectively load and release the eutomer (isomer of interest) [71].

On-Demand Release

The strategies mentioned earlier are effective passive methods to obtain sustained, prolonged release. However, it is often desirable to have a designed response to changing conditions as tissue healing or remodeling proceeds or to provide a more optimal delivery of an agent dependent on externally determined factors. More active, on-demand

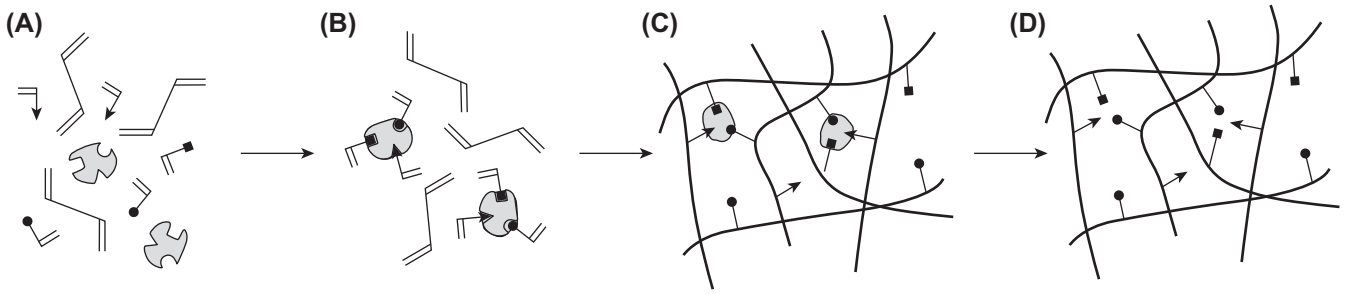

FIGURE 30.4 Molecular imprinting. (A) Solution mixture of template, cross-linking monomer, and functional monomers (triangles, squares, and circles). (B) Complex formation between functional monomers and template via covalent or noncovalent chemistry. (C) The formation of the polymer network typically via free radical polymerization. (D) Template removal step that leaves binding sites specific to the original template [68].

modulation of bioactive agent release can be achieved with on-and-off triggers. The most commonly used triggering mechanisms include (1) pH or temperature, (2) enzymes that cleave cross-linkers used to immobilize bioactive agents, or (3) drugs or ions that trigger the cleavage of an engineered substrate, resulting in the release of encapsulated cargoes [72–78]. Externally applied stimuli including light, electric or magnetic fields, and ultrasound can also modify scaffold structures or bioactive agent immobilization and regulate release [72,79]. The strategies introduced in this section can be applied to control the release of single bioactive agents and to program the delivery of two or more factors to obtain synergic effects [72,80,81].

Scaffold Morphology

As noted previously, scaffold morphology can greatly influence scaffold degradation, mechanical properties, and bioactive agent release. In this section, morphology is considered in terms of microscale pores and surface features, and progress in modulating scaffold morphological parameters is discussed.

Methods for Fabricating Porous Scaffolds

Conventional fabrication methods to generate porous scaffolds commonly used in tissue engineering include temperature-induced phase separation, salt leaching, gas foaming, electrospinning (for polymers and natural products); gas injection through the melt, gas foaming, plasma spraying, sintering, space holder methods (for metallic scaffolds); and dry-pressing, extrusion, and slip-casting (for ceramic scaffolds). The literature provides many excellent reviews covering these approaches and applications with materials processed in this manner [82–86]. Beyond these methods, newer technologies allow more design control over the scaffold geometry.

Solid free-form fabrication (SFF) technologies are the most important advances made in scaffold fabrication [87]. Among SFF, three-dimensional (3D) printing fabricates 3D structures by inkjet printing liquid binder solution onto a powder bed (Fig. 30.5A). Fused deposition modeling deposits molten thermoplastic materials through two heated extrusion heads with a small orifice in a specific lay-down pattern. The basic concept of stereolithography is to control the polymerization spatially of photocurable resin in a 2D pattern and to extend it to 3D by repeating in-plane polymerization in a layer-by-layer fashion (Fig. 30.5C). Selective laser sintering and melting employs a laser to scan the surface of powdered polymer or metal particles in a specific 2D pattern to sinter by heating them above the melting temperature. 3D plotting or direct-write bioprinting extrudes a viscous liquid material from a pressurized syringe into a liquid medium with matching density and deposits the materials in one long continuous strand or in individual dots to create desired 3D shapes (Fig. 30.5B) [87–91].

Anisotropic and Gradient Scaffolds

Anisotropy and gradient features are widely found in human tissues and organs, including the interfaces between tissues, such as the bone–cartilage interface. This morphology has important implications for the mechanical and biological behavior of these tissues. Therefore, it is interesting to fabricate anisotropic and gradient biomaterials as scaffolds to guide regeneration in a manner that provides greater biomimicry of the native state. Anisotropic and gradient cues include composition, pore structure, stiffness, and fiber orientation. A variety of scaffold processing methods have been developed. Listed here are several representative examples for both methodologic and therapeutic effects.

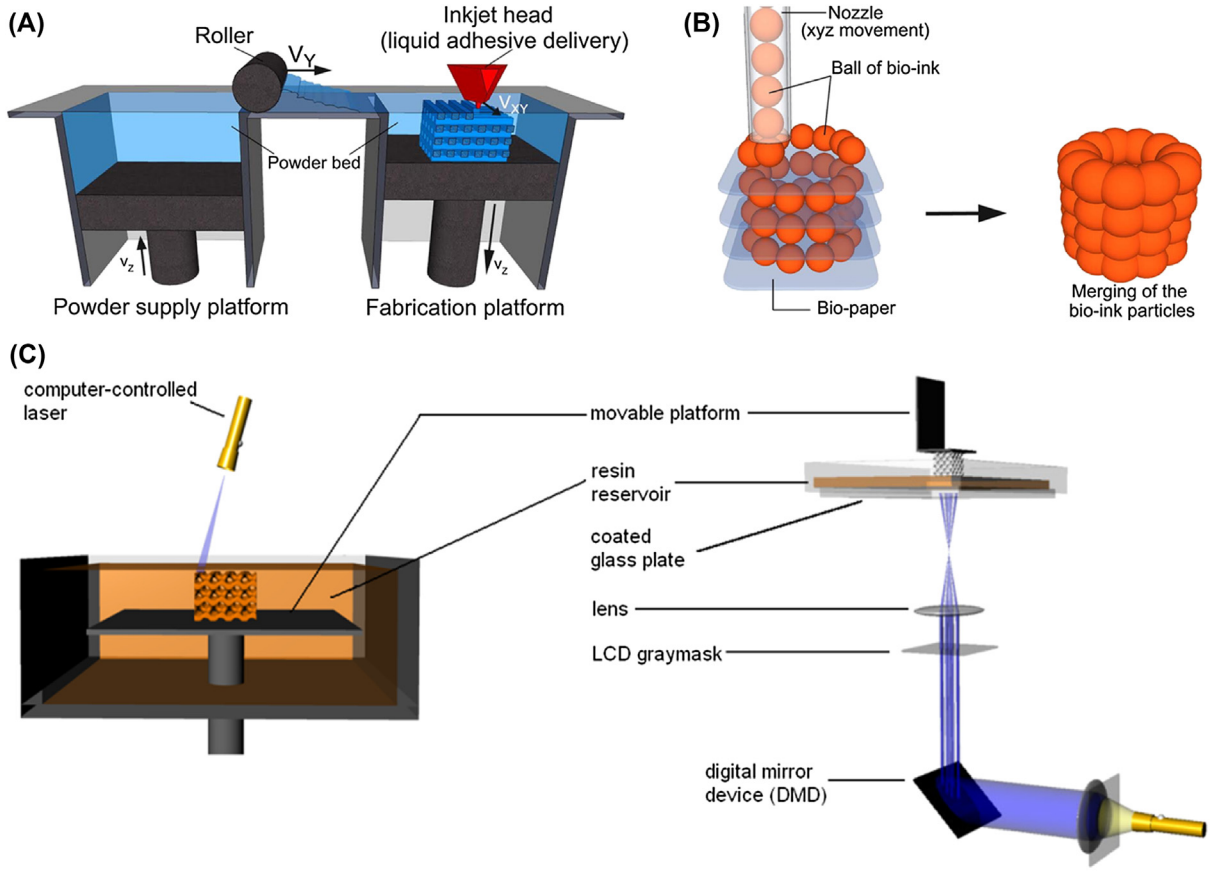

FIGURE 30.5 Schematic illustration of (A) three-dimensional (3D) printing, (B) 3D plotting/direct-write bioprinting, (C) stereolithography [88–90]. LCD, *liquid* crystal display.

Concentration gradients of bioactive molecules such as growth factors are often desired to drive spatially distinct biological responses to a scaffold. Such gradients have been created using microfluidic platforms or allowing a limited period of diffusion from a reservoir connected to one edge of a scaffold. In a case where platelet-derived growth factor was differentially loaded, tissue invasion depth and blood vessel density increased with the magnitude of the gradient, whereas cortical neurites showed sensitivity to the magnitude of an insulin-like growth factor-1 concentration gradient [92,93]. By controlling the cross-linking density, a gradient modulus was achieved in a polyethylene glycol (PEG) hydrogel. The human osteoarthritic chondrocyte number and phenotype were maintained in regions with a lower storage modulus compared with stiffer regions [94]. A modified one-step gravity sintering method was used to distribute pores with gradient sizes in calcium polyphosphate scaffolds, which induced greater osteoblast differentiation and mineralization in gradient calcium polyphosphate scaffolds in contrast to homogenous calcium polyphosphate scaffolds [95].

Creating thermal gradients when fabricating temperature-induced phase separation scaffolds was effective in arranging unidirectional porous structures and induced anisotropic cell attachment, proliferation, and migration [96,97]. Aligned fibrous scaffolds could be prepared by 3D printing and electrospinning. These unidirectional features have been employed in organizing new tissues including nerve, cornea, tendon, and muscle [98–100]. Applying similar processing methods on both x and y directions could mimic alternating orientating cells and ECM such as that in laminar cardiac tissues [101,102].

Surface Feature Manipulation

It is widely known that surface features and patterns can have a significant influence on cell attachment, locomotion, survival, and differentiation [103,104]. However, discrete patterns can be challenging to fabricate across the surfaces of 3D scaffolds using many of the most common fabrication techniques. Less discrete control of the surface is

more readily achieved, effectively varying the roughness, to affect responses of adhering cells [105,106]. Appropriate creation of microsurface or nanosurface structures can either promote or reduce cell adhesion [107,108]. In addition, cell migration can be guided by micrometer-scale roughness and hydrophilicity gradients [109,110]. Using specific interactions with adsorbed proteins and cell surface receptors, cell migration can be modulated [111].

Injectable Scaffolds/Controlling Morphology In Situ

Traditionally, biomaterial scaffolds are formed in vitro before implantation. Technologies have allowed the minimally invasive delivery of scaffolds and the formation in situ of desired microstructures, which reduce the risk for invasive surgical procedures [112]. In addition, in situ–formed pores would allow cell infiltration before significant scaffold degradation, which may promote tissue integration.

Metallic scaffolds including coils and stents can be compressed with large deformation ratios to allow packaging on catheters for guided delivery. After deployment in targeted regions, these scaffolds can either revert to their original shape with high elasticity or be shaped by catheter-associated mechanisms such as inflatable balloons. Porous ceramic and polymeric scaffolds can be delivered by injection as solution precursors mixed with porogens [113,114]. As the biocompatible solvents absorb and the porogens dissolve in vivo, the result is porous structures. An alternative method to forming porous hydrogels in situ is to bind micrometer building blocks covalently via self-assembly in the tissue [115]. Elastic, high water–content hydrogels are squeezed through syringe needles and partially regain their porous structure in vivo [116,117].

Traceability and Imaging

Common to preclinical biomaterial and medical device evaluations is the recovery at different time points of implanted scaffolds from experimental animals or patients for subsequent histological, proteomic, and genetic assessments. Valuable information has been extracted by employing this paradigm. However, real-time monitoring options for the scaffold or tissue environment are limited and constrain the capacity of researchers and clinicians to monitor scaffold performance and sense potential negative events such as mechanical failure and detailed aspects of the biological response. Furthermore, as the tools to manipulate the status of smart, responsive biomaterials continue to expand, the desire is increasing for parameters that reflect scaffold status at given postimplantation time points.

Tracking scaffold material with noninvasive imaging techniques including magnetic resonance imaging, ultrasound, and computed tomography scanning is favored. Essential to scaffold tracking is the ability to differentiate the biomaterial signal from the tissue background. Different signal generation mechanisms are involved in these imaging techniques, with contrast originating from differences in parameters such as water content, radio opacity, stiffness, density, and magnetism. Contrast can be specifically created by adding contrast agents during scaffold formation [118–121]. However, the potential toxicity of contrast agents needs to be considered [122]. Greater contrast properties for the scaffold provide for improved resolution in the imaging techniques to reveal greater structural detail. Although not considered in this chapter, the labeling of loaded cells is commonly pursued in the context of tissue constructs [123].

SAFETY AND BIOCOMPATIBILITY REQUIREMENTS FOR BIOMATERIAL SCAFFOLDS

Achieving the desired level of functionality for a given medical application is obviously central to assembling the design objectives for a biomaterial scaffold system. However, the safety of such a system must explicitly be demonstrated as the pathway to clinical application is traversed. Several general concerns will apply to all scaffolds, whereas other considerations will be specific to the given application. The governing regulatory body (e.g., the U.S. Food and Drug Administration) will ultimately dictate the specific testing required for progression to early-stage clinical evaluation. Biomaterial scaffolds are medical devices by definition, and as the World Health Organization has pointed out in its guidelines: (1) absolute safety cannot be guaranteed, (2) the consideration of a given device's safety is a risk management issue, (3) safety is closely aligned with device effectiveness and performance, (4) safety must be considered throughout the life span of the device, and (5) the assurance of safety requires shared responsibility among the stakeholders [124]. As specifically addressed in International Standards Organization Document 10993, some of the principal considerations in demonstrating device safety include local and systemic

toxicity, carcinogenicity, pyrogenicity, sensitization, potential for infection, hemocompatibility, and adverse foreign body responses. Furthermore, because the scaffold system is biodegradable, the evaluation of biodegradation products both in vitro and in vivo must be explicitly addressed.

Infection and Sterilization

Bacteria can adhere to biomaterial scaffolds before, during, and after the implantation procedure. Although completely eliminating the possibility of bacterial contamination before implantation is impossible, major sterilization protocols including radiation, ethylene oxide (EtO), hydrogen peroxide, or steam can be designed to achieve a recommended sterility assurance level (SAL) (usually a risk of one nonsterile device in a million) [125]. The scaffold thus needs to be compatible with at least one of the sterilization methods and the design processes should reflect consideration for sterilization step. The various methods each have trade-offs in terms of their impact on the underlying material, expense, and integration with the manufacturing process. Specifically, the sterilization procedure may affect material performance by the same mechanisms used to kill bacteria, e.g., each of these sterilization methods can decrease the molecular weight of PEG-based polymers [126]. For scaffolds made from natural products (such as proteins or polysaccharides) and those containing naturally derived bioactive ingredients, EtO, heating, and radiation may denature and alter the structural or functional components of the scaffold. Although metals and ceramics are more stable compared with polymer and naturally derived materials, the labile versions of these materials can be more sensitive to some of the sterilization methods. For all of the scaffold types, because degradability is a feature, considerations must be given to packaging and storage methods, including the determination of shelf-life under prescribed conditions.

Across all implanted medical devices, the incidence of device-centered infections is much higher than the SAL, which has led to the conclusion that most infections occur as a result of exposure to bacteria during the implantation procedure or after device placement (Fig. 30.6). An attractive feature of biodegradable scaffold systems is the limited implant period, because the scaffold is replaced by native tissue, which removes the nidus for infection that remains with nondegradable devices. Current strategies that have been explored to reduce the potential for infection in nondegradable devices generally apply to scaffolds as well. These approaches fall into three general categories: (1) surface modification to impart resistance to bacterial adhesion [127,128], (2) loading of antibiotic agents into the biomaterial for controlled release [129,130], and (3) modifying or otherwise designing the surface to encourage

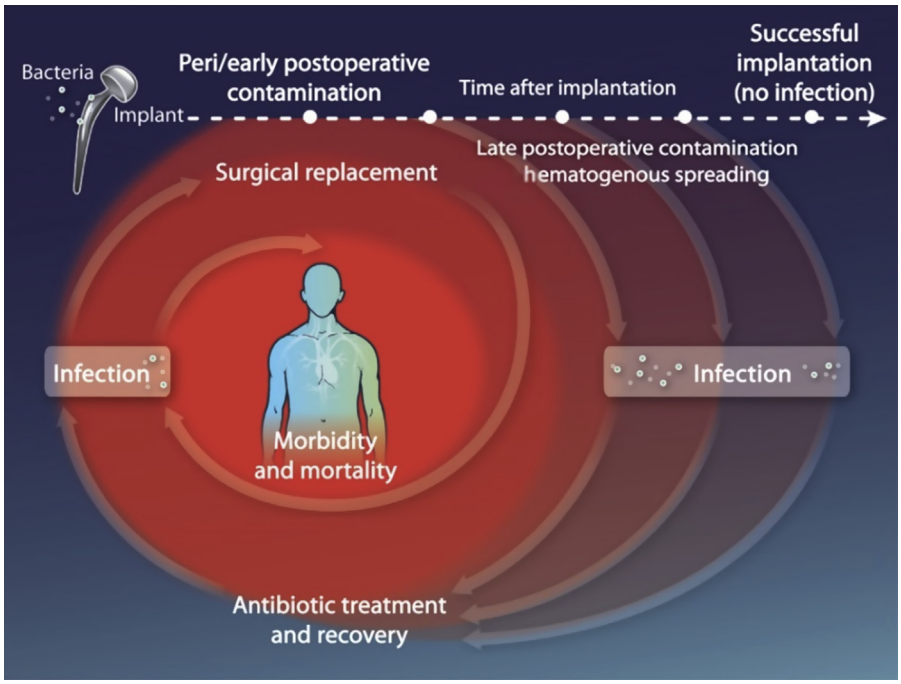

FIGURE 30.6 Patient risk factors for developing a biomaterial-associated infection. Revision surgery patients are at greater risk than primary surgery implant patients, whereas the risk of an implant or device becoming infected hematogenously decreases with time after implant placement due to more extensive host tissue integration [132].

rapid coverage and integration with host tissue, thus minimizing the likelihood of further exposure to and colonization by planktonic bacteria [131]. Because the scaffold design generally seeks to integrate and be replaced with native tissue, the latter approach is particularly attractive, although controlled antibiotic release in the early period may also be attractive.

Toxicity

Major components of scaffolds are not present in the human body (e.g., polycaprolactone) or at unnaturally high concentrations (e.g., high dosage of magnesium in magnesium scaffolds). These components and corresponding degradation products may induce acute, subacute, or chronic toxicities, especially with allo- and xeno-sourced products [133]. Pyrogenicity, genotoxicity, carcinogenicity, reproductive, and developmental toxicity are the main risks of scaffold toxicity.

Endotoxins are abundant in the environment and have high affinity to various biomaterials; they are the major factors that cause pyrogenicity [134]. In addition, endotoxins have strong proinflammatory effects. Different methods have been developed to lower the endotoxin level in scaffolds [135,136]. Resin monomers, glass ionomers, graphene oxide nanosheets, and other substances have been shown to be genotoxic [137–139]. On the other hand, much research has been focused on testing carcinogenicity in chemicals and small particles and has identified a variety of risky species that are dissolved components or wear debris of biomaterial scaffolds [140,141]. Improvements in scaffold design could mitigate the carcinogenic potentials, e.g., lower the possibility of generating debris production [142]. Organ-on-a-chip and laboratory-on-a-chip technologies have been employed to fabricate medical-device-on-a-chips as in vitro models for medical device toxicity tests [143].

Hemocompatibility

Scaffold hemocompatibility is a concern in the acute period when the device placement procedure involves some level of blood contact, and more chronically for scaffolds that will experience ongoing exposure to blood, such as with stents, cardiac valve scaffolds, or vascular grafts and patches. For all concerns regarding blood-contacting materials, the potential exists for the material to induce hemolysis, complement activation, and the formation of thrombus or embolus. Hemolysis can result from the material properties or the induced flow path created by a scaffold, such as high–fluid shear regions. The characterization of hemolysis for materials and devices is well-described in standards and in the literature [144,145]. Complement activation is generally related to surface properties; guidance exists to assess the activation of this immune system pathway [146–148]. Like hemolysis, thrombogenicity depends on both the material properties and the blood flow pathway near the scaffold surfaces. The status of the patient's blood is also a consideration, because anticoagulant and antiplatelet medications can be prescribed to reduce the safety risks associated with thrombosis.

Thrombogenicity remains a major cause of scaffold failure for blood-contacting biomaterial scaffolds, including vascular grafts and stents [149,150]. Thrombi formed on scaffolds may occlude vessels or embolize and lead to life-threatening ischemia in distal tissues (e.g., pulmonary emboli or embolic stroke) [151]. Because the coagulation pathway and platelet adhesion are initiated on artificial surfaces by protein adsorption, the design of scaffold surface properties to alter this adhesion process to reduce thrombogenicity has long been a focus of research in the biomaterials community. Common approaches include those that seek to reduce overall protein adsorption by increasing surface hydrophilicity, presenting zwitterionic groups, attaching specific bioactive molecules, or manipulating surface roughness. Surface attachment of the anticoagulant heparin or heparin analogs is one of the most widely employed strategies [152,153]. Surface modification with zwitterionic polymers such as phosphoryl choline or sulfobetaine derivatives can effectively reduce protein adsorption; it has been shown to reduce thrombogenesis for a variety of underlying surfaces [154–156]. Layer-by-layer assembly has also used to create antifouling surfaces [157]. Rough surfaces generally increase the potential for platelet deposition [158]. Therefore, smooth and even lubricious scaffold surfaces have been employed to reduce thrombogenesis [159,160], although an alternative approach of presenting rough surfaces to encourage rapid tissue integration has been used in chronically placed nondegradable devices [161,162]. With the theme of tissue integration central to scaffold placement, the development of an endothelial layer over the blood-contacting surfaces is an attractive way to reduce the ongoing risk for thrombosis and thromboembolism. This is a common vision for blood vessel, cardiac valve, and stent scaffold design. Such endothelialization may be encouraged by specific surface ligands or the controlled release of bioactive agents, as well as endothelial cell or endothelial progenitor cell seeding or recruitment from the circulation or nearby tissue [163–165].

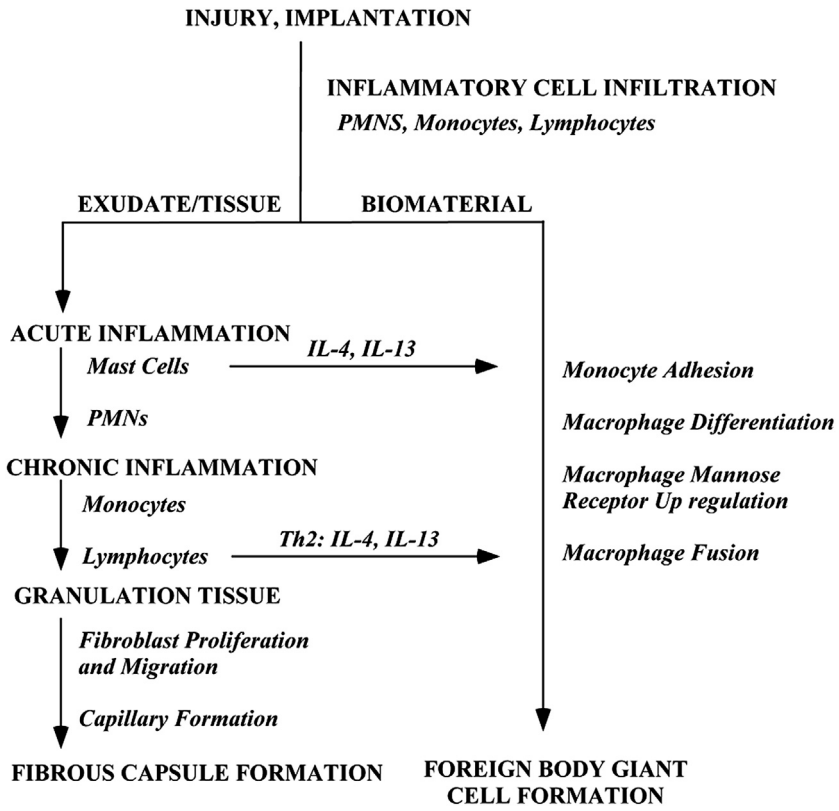

FIGURE 30.7 Sequence of events involved in inflammatory and wound healing responses leading to foreign body giant cell formation. This shows the potential importance of mast cells in the acute inflammatory phase and T helper 2 (Th2) lymphocytes in the transient chronic inflammatory phase with the production of interleukin (IL)-4 and IL-13, which can induce monocyte and macrophage fusion to form foreign body giant cells. *PMN*, polymorphonuclear leukocytes [167].

Foreign Body Response

Implantation of biomaterial scaffolds induces inflammatory and wound healing pathways, which result in a common response if the material is synthetic and nondegradable. Similarities of the response across materials and implant locations has led to the designation of these sequelae as the "foreign body response" (Fig. 30.7). Degradable scaffolds will ultimately remove a central feature of the chronic foreign body response (the implant immediately surrounded by encapsulating fibrous tissue), but during the degradation period of the scaffold, the response is roughly equivalent, although ultimately with more active phagocytosis by macrophages in the surrounding tissue. Of note, with materials based on decellularized tissue, this response outcome may follow a different pathway that has been termed "constructive remodeling," with important differences in the cellular and molecular components [166]. From a safety perspective, the extent of inflammation and fibrosis in the area of scaffold placement is a concern in terms of how this response may lead to failure of the device or inhibition of the device's function. Also of concern is the variability that may occur with this response such that in some patients a more vigorous inflammatory response may lead to accelerated scaffold degradation and early mechanical failure or other morbidity such as local pain and swelling. Readers are encouraged to refer to reviews for the latest concepts regarding foreign body responses [167–170].

Because macrophage behavior is a critical determinant in the direction of the foreign body response, there has been attention to examining how macrophage behavior can be influenced by scaffold topography, stiffness, surface chemistry, and naturally derived bioactive components [19,167,171,172]. Of interest to the biomaterial community are strategies that may serve to influence the foreign body response by modulating macrophage behavior. One approach is to passivate scaffold surfaces in an attempt to render the material substrate "invisible" or neutral to macrophages. Ultralow-fouling zwitterionic hydrogels resisted macrophage adhesion and capsule formation for at least 3 months in a mouse subcutaneous model [173]. In another study, triazole derivatives of alginate were identified to modulate immune cell populations at the surface of hydrogels made from these molecules, specifically

macrophages, in a manner that inhibited their activation and disrupted fibrotic processes, leading to the mitigation of foreign body response in nonhuman primate models [174]. A second strategy has been to polarize local macrophages actively toward an M2 phenotype (a phenotype associated with the promotion of tissue repair and regeneration in contrast to the proinflammatory M1 phenotype [168]). It was widely reported that a decellularized tissue-based material alternative referred to as ECM-based products can induce M2 polarization of macrophages. Thus, aside from fabricating scaffolds directly from ECM products, efforts have been made to produce composites of scaffolding material, usually synthetic polymers, and ECM-derived components as additives [168,175,176].

MANUFACTURABILITY

Even at the earliest stages of the design process for biomaterial scaffolds, it is worth considering how scaffold production ultimately might be scaled up in a manner consistent with good manufacturing practice to ensure stable quality. More broadly, translational and regulatory challenges from the manufacturing perspective will need to be addressed if the scaffold is to move toward a clinical impact, and early identification of design limitations in this area may allow the implementation of an approach with a greater likelihood of success.

As introduced earlier, selecting the scaffold material is often the first step in scaffold development. Regulatory agencies focus on application-oriented pathways in which a specific type or composition of material is approved for one application (device) at a time and reevaluation is needed for a different application. The selection of widely used materials in approved devices such as poly(lactic-co-glycolic acid), stainless steel, and hydroxyl apatite can be attractive because their safety as components in existing products has been demonstrated and general sterilization and biocompatibility protocols have been addressed in a manner that may greatly reduce the material-associated risk for the new application. Furthermore, supplier and manufacturing considerations, from raw material sourcing to material synthesis, and even scaffold formation may have been addressed successfully. Taking polymeric biomaterials as an example, despite the exploding diversity of material designs reported in the literature and the great advancement with controlled polymerization, a limited set of degradable polymers is still commonly implemented owing to practical considerations regarding regulatory approval, costs, and manufacturability. Although newer designs for degradable polymers may possess a better-controlled structure and molecular weight, enabling the integration of powerful biological and imaging functions, the synthesis and processing steps may be markedly more complex, require more strictly monitored controls and systems, and require a more extensive approval pathway compared with a less effective but still functional material. Some of these obstacles may be overcome by modifying laboratory fabrication protocols and considering trade-offs in complexity or benefit early in the design and evaluation process.

With rapid advances in SFF and the attractiveness of combining such technology with patient-specific imaging and even personalized medicine, the promise is presented of better designs suited for individual patient needs. One could imagine controlling the material, morphology, and bioactivity in a patient-specific manner. This will be an area of substantial investment in coming years, and if the patient benefits are great enough compared with nonindividualized solutions with simpler materials, the cost of implementing such technologies in a regulatory-compatible and economically attractive manner would be justified.

SUMMARY

The use of temporary biomaterial scaffolds for regenerative medicine approaches to tissue failure provides a means to support the transition from a synthetic, externally generated “bandage” to an autologous, functional tissue outcome. The potential to mediate a complete and effective transition remains elusive for many tissues and disease states. For the team designing such regenerative medicine solutions, the considerations for the scaffold are many, and there is much more potential for the scaffold than to serve as a well-designed physical support that appropriately transfers load to ingrowing tissue. As noted in this chapter, the team has an increasing array of tools to control the degradation process, design for tissue integration, deliver bioactive agents in an appropriate temporal fashion, and use these design options to meet specific hypothesized needs for the tissue and patient group in question. Ultimately, scaffold design considerations must fit within a much broader array of considerations that will touch upon many other topics covered in this text. As with many of those other topics, the field is dynamic, challenging, and ripe with the opportunity for new investigators to have an impact on the future of regenerative medicine.

References

[1] Garg S, Bourantas C, Serruys PW. New concepts in the design of drug-eluting coronary stents. Nat Rev Cardiol 2013:248–60.
[2] Hiob MA, She S, Muiznieks LD, Weiss AS. Biomaterials and modifications in the development of small-diameter vascular grafts. ACS Biomater Sci Eng 2016:712–23.
[3] Ibrahim AM, Vargas CR, Colakoglu S, Nguyen JT, Lin SJ, Lee BT. Properties of meshes used in hernia repair: a comprehensive review of synthetic and biologic meshes. J Reconstr Microsurg 2015:83–94.
[4] Smith TO, Sexton D, Mann C, Donell S. Sutures versus staples for skin closure in orthopaedic surgery: meta-analysis. BMJ 2010:c1199.
[5] Goodman SB, Yao Z, Keeney M, Yang F. The future of biologic coatings for orthopaedic implants. Biomaterials 2013:3174–83.
[6] Mattesini A, Secco GG, Dall'Ara G, Ghione M, Rama-Merchan JC, Lupi A, Viceconte N, Lindsay AC, De Silva R, Foin N, Naganuma T, Valente S, Colombo A, Di Mario C. ABSORB biodegradable stents versus second-generation metal stents: a comparison study of 100 complex lesions treated under OCT guidance. JACC Cardiovasc Interv 2014:741–50.
[7] Williams Simon F, Rizk S, Martin David P. Poly-4-hydroxybutyrate (P4HB): a new generation of resorbable medical devices for tissue repair and regeneration. Biomed Tech Biomed Eng 2013:439.
[8] Middleton JC, Tipton AJ. Synthetic biodegradable polymers as orthopedic devices. Biomaterials 2000:2335–46.
[9] Teo AJT, Mishra A, Park I, Kim Y-J, Park W-T, Yoon Y-J. Polymeric biomaterials for medical implants and devices. ACS Biomater Sci Eng 2016:454–72.
[10] Brannigan RP, Dove AP. Synthesis, properties and biomedical applications of hydrolytically degradable materials based on aliphatic polyesters and polycarbonates. Biomater Sci 2016:9–21.
[11] Williams DF. On the mechanisms of biocompatibility. Biomaterials 2008:2941–53.
[12] Hollister SJ. Scaffold design and manufacturing: from concept to clinic. Adv Mater 2009:3330–42.
[13] Engler AJ, Sen S, Sweeney HL, Discher DE. Matrix elasticity directs stem cell lineage specification. Cell 2006:677–89.
[14] Macri-Pellizzeri L, Pelacho B, Sancho A, Iglesias-Garcia O, Simon-Yarza AM, Soriano-Navarro M, Gonzalez-Granero S, Garcia-Verdugo JM, De-Juan-Pardo EM, Prosper F. Substrate stiffness and composition specifically direct differentiation of induced pluripotent stem cells. Tissue Eng Part A 2015:1633–41.
[15] Evans ND, Minelli C, Gentleman E, LaPointe V, Patankar SN, Kallivretaki M, Chen X, Roberts CJ, Stevens MM. Substrate stiffness affects early differentiation events in embryonic stem cells. Eur Cell Mater 2009:1–14.
[16] Park JS, Chu JS, Tsou AD, Diop R, Tang Z, Wang A, Li S. The effect of matrix stiffness on the differentiation of mesenchymal stem cells in response to TGF-beta. Biomaterials 2011:3921–30.
[17] Lv H, Li L, Sun M, Zhang Y, Chen L, Rong Y, Li Y. Mechanism of regulation of stem cell differentiation by matrix stiffness. Stem Cell Res Ther 2015:103.
[18] McWhorter FY, Davis CT, Liu WF. Physical and mechanical regulation of macrophage phenotype and function. Cell Mol Life Sci 2015: 1303–16.
[19] Sridharan R, Cameron AR, Kelly DJ, Kearney CJ, O'Brien FJ. Biomaterial based modulation of macrophage polarization: a review and suggested design principles. Mater Today 2015:313–25.
[20] Mason BN, Califano JP, Reinhart-King CA. Matrix stiffness: a regulator of cellular behavior and tissue formation. Eng Biomater Regen Med 2012:19–37.
[21] Barnes JM, Przybyla L, Weaver VM. Tissue mechanics regulate brain development, homeostasis and disease. J Cell Sci 2017:71–82.
[22] Ashby MF. Chapter 4-material property charts, materials selection in mechanical design. 4th ed. Oxford: Butterworth-Heinemann; 2011. p. 57–96.
[23] Deshayes S, Kasko AM. Polymeric biomaterials with engineered degradation. J Polym Sci Part A: Polym Chem 2013:3531–66.
[24] Ali SAM, Doherty PJ, Williams DF. The mechanisms of oxidative-degradation of biomedical polymers by free-radicals. J Appl Polym Sci 1994:1389–98.
[25] Simpson M, Gilmore BF, Miller A, Helt-Hansen J, Buchanan FJ. Irradiation of bioresorbable biomaterials for controlled surface degradation. Radiat Phys Chem 2014:211–6.
[26] Phillips DJ, Gibson MI. Biodegradable poly(disulfide)s derived from RAFT polymerization: monomer scope, glutathione degradation, and tunable thermal responses. Biomacromolecules 2012:3200–8.
[27] Zhu Y, Jiang H, Ye S-H, Yoshizumi T, Wagner WR. Tailoring the degradation rates of thermally responsive hydrogels designed for soft tissue injection by varying the autocatalytic potential. Biomaterials 2015:484–93.
[28] Peterson GI, Larsen MB, Boydston AJ. Controlled depolymerization: stimuli-responsive self-immolative polymers. Macromolecules 2012: 7317–28.
[29] Webber MJ, Appel EA, Meijer EW, Langer R. Supramolecular biomaterials. Nat Mater 2015:13–26.
[30] Staiger MP, Pietak AM, Huadmai J, Dias G. Magnesium and its alloys as orthopedic biomaterials: a review. Biomaterials 2006:1728–34.
[31] Ma J, Zhao N, Zhu D. Endothelial cellular responses to biodegradable metal zinc. ACS Biomater Sci Eng 2015:1174–82.
[32] Kirkland NT. Magnesium biomaterials: past, present and future. Corr Eng Sci Technol 2012:322–8.
[33] Zheng YF, Gu XN, Witte F. Biodegradable metals. Mater Sci Eng R Rep 2014:1–34.
[34] Sheikh Z, Abdallah M-N, Hanafi A, Misbahuddin S, Rashid H, Glogauer M. Mechanisms of in vivo degradation and resorption of calcium phosphate based biomaterials. Materials 2015:7913–25.
[35] Hakkarainen M, Albertsson AC, Karlsson S. Weight losses and molecular weight changes correlated with the evolution of hydroxyacids in simulated in vivo degradation of homo- and copolymers of PLA and PGA. Polym Degradation Stab 1996:283–91.
[36] Ara M, Watanabe M, Imai Y. Effect of blending calcium compounds on hydrolytic degradation of poly(DL-lactic acid-co-glycolic acid). Biomaterials 2002:2479–83.
[37] Zhao D, Witte F, Lu F, Wang J, Li J, Qin L. Current status on clinical applications of magnesium-based orthopaedic implants: a review from clinical translational perspective. Biomaterials 2017:287–302.
[38] Patterson J, Siew R, Herring SW, Lin AS, Guldberg R, Stayton PS. Hyaluronic acid hydrogels with controlled degradation properties for oriented bone regeneration. Biomaterials 2010:6772–81.

[39] Kong HJ, Kaigler D, Kim K, Mooney DJ. Controlling rigidity and degradation of alginate hydrogels via molecular weight distribution. Biomacromolecules 2004:1720–7.
[40] Banerjee A, Chatterjee K, Madras G. Enzymatic degradation of polymers: a brief review. Mater Sci Technol 2014:567–73.
[41] Helling AL, Tsekoura EK, Biggs M, Bayon Y, Pandit A, Zeugolis DI. In vitro enzymatic degradation of tissue grafts and collagen biomaterials by matrix metalloproteinases: improving the collagenase assay. ACS Biomater Sci Eng 2017:1922–32.
[42] Yahyouche A, Zhidao X, Czernuszka JT, Clover AJ. Macrophage-mediated degradation of crosslinked collagen scaffolds. Acta Biomater 2011:278–86.
[43] Yang J, Jacobsen MT, Pan H, Kopecek J. Synthesis and characterization of enzymatically degradable PEG-based peptide-containing hydrogels. Macromol Biosci 2010:445–54.
[44] Um SH, Lee JB, Park N, Kwon SY, Umbach CC, Luo D. Enzyme-catalysed assembly of DNA hydrogel. Nat Mater 2006:797–801.
[45] Nicodemus GD, Bryant SJ. Cell encapsulation in biodegradable hydrogels for tissue engineering applications. Tissue Eng Part B Rev 2008: 149–65.
[46] Tondera C, Hauser S, Kruger-Genge A, Jung F, Neffe AT, Lendlein A, Klopfleisch R, Steinbach J, Neuber C, Pietzsch J. Gelatin-based hydrogel degradation and tissue interaction in vivo: insights from multimodal preclinical imaging in immunocompetent nude mice. Theranostics 2016:2114–28.
[47] West JL, Hubbell JA. Polymeric biomaterials with degradation sites for proteases involved in cell migration. Macromolecules 1999:241–4.
[48] Lopresti ST, Brown BN. Chapter 4-host response to naturally derived biomaterials A2-badylak, Stephen F, host response to biomaterials. Oxford: Academic Press; 2015. p. 53–79.
[49] Cui W, Li X, Zhu X, Yu G, Zhou S, Weng J. Investigation of drug release and matrix degradation of electrospun poly(DL-lactide) fibers with paracetanol inoculation. Biomacromolecules 2006:1623–9.
[50] Yixiang D, Yong T, Liao S, Chan CK, Ramakrishna S. Degradation of electrospun nanofiber scaffold by short wave length ultraviolet radiation treatment and its potential applications in tissue engineering. Tissue Eng Part A 2008:1321–9.
[51] Pan Z, Ding J. Poly(lactide-co-glycolide) porous scaffolds for tissue engineering and regenerative medicine. Interface Focus 2012:366–77.
[52] Gu XN, Zhou WR, Zheng YF, Liu Y, Li YX. Degradation and cytotoxicity of lotus-type porous pure magnesium as potential tissue engineering scaffold material. Mater Lett 2010:1871–4.
[53] Lam KH, Nieuwenhuis P, Molenaar I, Esselbrugge H, Feijen J, Dijkstra PJ, Schakenraad JM. Biodegradation of porous versus non-porous poly(L-lactic acid) films. J Mater Sci Mater Med 1994:181–9.
[54] Zhang H, Zhou L, Zhang W. Control of scaffold degradation in tissue engineering: a review. Tissue Eng Part B Rev 2014:492–502.
[55] Bakry A, Martinelli A, Bizzarri M, Cucina A, D'Ilario L, Francolini I, Piozzi A, Proietti S. A new approach for the preparation of hydrophilic poly(L-lactide) porous scaffold for tissue engineering by using lamellar single crystals. Polym Int 2012:1177–85.
[56] Tang YW, Santerre JP, Labow RS, Taylor DG. Application of macromolecular additives to reduce the hydrolytic degradation of polyurethanes by lysosomal enzymes. Biomaterials 1997:37–45.
[57] Singh R, Dahotre NB. Corrosion degradation and prevention by surface modification of biometallic materials. J Mater Sci Mater Med 2007: 725–51.
[58] Leitao E, Silva RA, Barbosa MA. Electrochemical and surface modifications on N+-ion-implanted 316 L stainless steel. J Mater Sci Mater Med 1997:365–8.
[59] Villermaux F, Tabrizian M, Yahia LH, Meunier M, Piron DL. Excimer laser treatment of NiTi shape memory alloy biomaterials. Appl Surf Sci 1997:62–6.
[60] Wang CX, Wang M, Zhou X. Nucleation and growth of apatite on chemically treated titanium alloy: an electrochemical impedance spectroscopy study. Biomaterials 2003:3069–77.
[61] Tasso R, Fais F, Reverberi D, Tortelli F, Cancedda R. The recruitment of two consecutive and different waves of host stem/progenitor cells during the development of tissue-engineered bone in a murine model. Biomaterials 2010:2121–9.
[62] Browne S, Pandit A. Multi-modal delivery of therapeutics using biomaterial scaffolds. J Mater Chem B 2014:6692–707.
[63] Al-Sokanee ZN, Toabi AA, Al-Assadi MJ, Alassadi EA. The drug release study of ceftriaxone from porous hydroxyapatite scaffolds. AAPS PharmSciTech 2009:772–9.
[64] Lin CC, Metters AT. Hydrogels in controlled release formulations: network design and mathematical modeling. Adv Drug Deliv Rev 2006: 1379–408.
[65] Vulic K, Shoichet MS. Affinity-based drug delivery systems for tissue repair and regeneration. Biomacromolecules 2014:3867–80.
[66] Vulic K, Shoichet MS. Tunable growth factor delivery from injectable hydrogels for tissue engineering. J Am Chem Soc 2012:882–5.
[67] Vulic K, Pakulska MM, Sonthalia R, Ramachandran A, Shoichet MS. Mathematical model accurately predicts protein release from an affinity-based delivery system. J Control Release 2015:69–77.
[68] Kryscio DR, Peppas NA. Mimicking biological delivery through feedback-controlled drug release systems based on molecular imprinting. AIChE J 2009:1311–24.
[69] Mohtaram NK, Montgomery A, Willerth SM. Biomaterial-based drug delivery systems for the controlled release of neurotrophic factors. Biomed Mater 2013:022001.
[70] Wang NX, von Recum HA. Affinity-based drug delivery. Macromol Biosci 2011:321–32.
[71] Cunliffe D, Kirby A, Alexander C. Molecularly imprinted drug delivery systems. Adv Drug Del Rev 2005:1836–53.
[72] Lee K, Silva EA, Mooney DJ. Growth factor delivery-based tissue engineering: general approaches and a review of recent developments. J R Soc Interface 2011:153–70.
[73] Shim WS, Kim SW, Lee DS. Sulfonamide-based pH- and temperature-sensitive biodegradable block copolymer hydrogels. Biomacromolecules 2006:1935–41.
[74] Klouda L, Mikos AG. Thermoresponsive hydrogels in biomedical applications. Eur J Pharm Biopharm 2008:34–45.
[75] Lutolf MP, Weber FE, Schmoekel HG, Schense JC, Kohler T, Muller R, Hubbell JA. Repair of bone defects using synthetic mimetics of collagenous extracellular matrices. Nat Biotechnol 2003:513–8.
[76] Miyata T, Asami N, Uragami T. A reversibly antigen-responsive hydrogel. Nature 1999:766–9.

[77] Ehrbar M, Schoenmakers R, Christen EH, Fussenegger M, Weber W. Drug-sensing hydrogels for the inducible release of biopharmaceuticals. Nat Mater 2008:800–4.
[78] Ehrick JD, Deo SK, Browning TW, Bachas LG, Madou MJ, Daunert S. Genetically engineered protein in hydrogels tailors stimuli-responsive characteristics. Nat Mater 2005:298–302.
[79] Jager EW, Smela E, Inganas O. Microfabricating conjugated polymer actuators. Science 2000:1540–5.
[80] Yilgor P, Tuzlakoglu K, Reis RL, Hasirci N, Hasirci V. Incorporation of a sequential BMP-2/BMP-7 delivery system into chitosan-based scaffolds for bone tissue engineering. Biomaterials 2009:3551–9.
[81] Awada HK, Johnson NR, Wang Y. Sequential delivery of angiogenic growth factors improves revascularization and heart function after myocardial infarction. J Control Release 2015:7–17.
[82] Hollister SJ. Porous scaffold design for tissue engineering. Nat Mater 2005:518–24.
[83] Yazdimamaghani M, Razavi M, Vashaee D, Moharamzadeh K, Boccaccini AR, Tayebi L. Porous magnesium-based scaffolds for tissue engineering. Mater Sci Eng C Mater Biol Appl 2017:1253–66.
[84] Ryan G, Pandit A, Apatsidis DP. Fabrication methods of porous metals for use in orthopaedic applications. Biomaterials 2006:2651–70.
[85] Jones JR. Reprint of: review of bioactive glass: from Hench to hybrids. Acta Biomater 2015:S53–82.
[86] Liu X, Ma PX. Polymeric scaffolds for bone tissue engineering. Ann Biomed Eng 2004:477–86.
[87] Chia HN, Wu BM. Recent advances in 3D printing of biomaterials. J Biol Eng 2015:4.
[88] Billiet T, Vandenhaute M, Schelfhout J, Van Vlierberghe S, Dubruel P. A review of trends and limitations in hydrogel-rapid prototyping for tissue engineering. Biomaterials 2012:6020–41.
[89] van Noort R. The future of dental devices is digital. Mater: Dent; 2012. p. 3–12.
[90] Melchels FP, Feijen J, Grijpma DW. A review on stereolithography and its applications in biomedical engineering. Biomaterials 2010: 6121–30.
[91] Pattanayak DK, Fukuda A, Matsushita T, Takemoto M, Fujibayashi S, Sasaki K, Nishida N, Nakamura T, Kokubo T. Bioactive Ti metal analogous to human cancellous bone: fabrication by selective laser melting and chemical treatments. Acta Biomater 2011:1398–406.
[92] Akar B, Jiang B, Somo SI, Appel AA, Larson JC, Tichauer KM, Brey EM. Biomaterials with persistent growth factor gradients in vivo accelerate vascularized tissue formation. Biomaterials 2015:61–73.
[93] Kothapalli CR, Honarmandi P. Theoretical and experimental quantification of the role of diffusive chemogradients on neuritogenesis within three-dimensional collagen scaffolds. Acta Biomater 2014:3664–74.
[94] Callahan LA, Ganios AM, Childers EP, Weiner SD, Becker ML. Primary human chondrocyte extracellular matrix formation and phenotype maintenance using RGD-derivatized PEGDM hydrogels possessing a continuous Young's modulus gradient. Acta Biomater 2013:6095–104.
[95] Chen L, Song W, Markel DC, Shi T, Muzik O, Matthew H, Ren W. Flow perfusion culture of MC3T3-E1 osteogenic cells on gradient calcium polyphosphate scaffolds with different pore sizes. J Biomater Appl 2016:908–18.
[96] de Mulder ELW, Buma P, Hannink G. Anisotropic porous biodegradable scaffolds for musculoskeletal tissue engineering. Materials 2009: 1674–96.
[97] Guan J, Fujimoto KL, Wagner WR. Elastase-sensitive elastomeric scaffolds with variable anisotropy for soft tissue engineering. Pharm Res (N Y) 2008:2400–12.
[98] McCullen SD, Autefage H, Callanan A, Gentleman E, Stevens MM. Anisotropic fibrous scaffolds for articular cartilage regeneration. Tissue Eng Part A 2012:2073–83.
[99] Fierz FC, Beckmann F, Huser M, Irsen SH, Leukers B, Witte F, Degistirici O, Andronache A, Thie M, Muller B. The morphology of anisotropic 3D-printed hydroxyapatite scaffolds. Biomaterials 2008:3799–806.
[100] Wu J, Du YQ, Watkins SC, Funderburgh JL, Wagner WR. The engineering of organized human corneal tissue through the spatial guidance of corneal stromal stem cells. Biomaterials 2012:1343–52.
[101] Hinton TJ, Jallerat Q, Palchesko RN, Park JH, Grodzicki MS, Shue HJ, Ramadan MH, Hudson AR, Feinberg AW. Three-dimensional printing of complex biological structures by freeform reversible embedding of suspended hydrogels. Sci Adv 2015:e1500758.
[102] Lind JU, Busbee TA, Valentine AD, Pasqualini FS, Yuan H, Yadid M, Park SJ, Kotikian A, Nesmith AP, Campbell PH, Vlassak JJ, Lewis JA, Parker KK. Instrumented cardiac microphysiological devices via multimaterial three-dimensional printing. Nat Mater 2017:303–8.
[103] Chen CS, Mrksich M, Huang S, Whitesides GM, Ingber DE. Geometric control of cell life and death. Science 1997:1425.
[104] Kilian KA, Bugarija B, Lahn BT, Mrksich M. Geometric cues for directing the differentiation of mesenchymal stem cells. Proc Natl Acad Sci USA 2010:4872–7.
[105] Deligianni DD, Katsala ND, Koutsoukos PG, Missirlis YF. Effect of surface roughness of hydroxyapatite on human bone marrow cell adhesion, proliferation, differentiation and detachment strength. Biomaterials 2001:87–96.
[106] Huang HH, Ho CT, Lee TH, Lee TL, Liao KK, Chen FL. Effect of surface roughness of ground titanium on initial cell adhesion. Biomol Eng 2004:93–7.
[107] Gittens RA, McLachlan T, Olivares-Navarrete R, Cai Y, Berner S, Tannenbaum R, Schwartz Z, Sandhage KH, Boyan BD. The effects of combined micron-/submicron-scale surface roughness and nanoscale features on cell proliferation and differentiation. Biomaterials 2011: 3395–403.
[108] Ishizaki T, Saito N, Takai O. Correlation of cell adhesive behaviors on superhydrophobic, superhydrophilic, and micropatterned superhydrophobic/superhydrophilic surfaces to their surface chemistry. Langmuir 2010:8147–54.
[109] Ren T, Mao Z, Guo J, Gao C. Directional migration of vascular smooth muscle cells guided by a molecule weight gradient of poly(2-hydroxyethyl methacrylate) brushes. Langmuir 2013:6386–95.
[110] Mao Z, Yu S, Ren T, Gao C. Gradient biomaterials and their impact on cell migration. In: Gao C, editor. Polymeric biomaterials for tissue regeneration: from surface/interface design to 3D constructs. Singapore: Springer Singapore; 2016. p. 151–85.
[111] Ren T, Yu S, Mao Z, Gao C. A complementary density gradient of zwitterionic polymer brushes and NCAM peptides for selectively controlling directional migration of schwann cells. Biomaterials 2015:58–67.
[112] Antonios GM, Johnna ST. Formation of highly porous biodegradable scaffolds for tissue engineering. Electron J Biotechnol 2000;3(2).
[113] Xu HH, Weir MD, Burguera EF, Fraser AM. Injectable and macroporous calcium phosphate cement scaffold. Biomaterials 2006:4279–87.

[114] Krebs MD, Sutter KA, Lin AS, Guldberg RE, Alsberg E. Injectable poly(lactic-co-glycolic) acid scaffolds with in situ pore formation for tissue engineering. Acta Biomater 2009:2847–59.
[115] Griffin DR, Weaver WM, Scumpia PO, Di Carlo D, Segura T. Accelerated wound healing by injectable microporous gel scaffolds assembled from annealed building blocks. Nat Mater 2015:737–44.
[116] Verbeke CS, Mooney DJ. Injectable, pore-forming hydrogels for in vivo enrichment of immature dendritic cells. Adv Healthc Mater 2015: 2677–87.
[117] Bencherif SA, Sands RW, Bhatta D, Arany P, Verbeke CS, Edwards DA, Mooney DJ. Injectable preformed scaffolds with shape-memory properties. Proc Natl Acad Sci USA 2012:19590–5.
[118] Lusic H, Grinstaff MW. X-ray-computed tomography contrast agents. Chem Rev 2013:1641–66.
[119] Tang J, Sheng Y, Hu H, Shen Y. Macromolecular MRI contrast agents: structures, properties and applications. Prog Polym Sci 2012:462–502.
[120] Zhang Z, Nair SA, McMurry TJ. Gadolinium meets medicinal chemistry: MRI contrast agent development. Curr Med Chem 2005:751–78.
[121] Kim K, Wagner WR. Non-invasive and non-destructive characterization of tissue engineered constructs using ultrasound imaging technologies: a review. Ann Biomed Eng 2016:621–35.
[122] Hasebroock KM, Serkova NJ. Toxicity of MRI and CT contrast agents. Expert Opin Drug Metab Toxicol 2009:403–16.
[123] Terrovitis JV, Bulte JW, Sarvananthan S, Crowe LA, Sarathchandra P, Batten P, Sachlos E, Chester AH, Czernuszka JT, Firmin DN, Taylor PM, Yacoub MH. Magnetic resonance imaging of ferumoxide-labeled mesenchymal stem cells seeded on collagen scaffolds-relevance to tissue engineering. Tissue Eng 2006:2765–75.
[124] WHO. Medical device regulations: global overview and guiding principles. 2003.
[125] von Woedtke T, Kramer A. The limits of sterility assurance. GMS Krankenhhyg Interdiszip 2008;3(3): Doc19.
[126] Bhatnagar D, Dube K, Damodaran VB, Subramanian G, Aston K, Halperin F, Mao M, Pricer K, Murthy NS, Kohn J. Effects of terminal sterilization on PEG-based bioresorbable polymers used in biomedical applications. Macromol Mater Eng 2016:1211–24.
[127] Desai NP, Hossainy SFA, Hubbell JA. Surface-immobilized polyethylene oxide for bacterial repellence. Biomaterials 1992:417–20.
[128] Kingshott P, Griesser HJ. Surfaces that resist bioadhesion. Curr Opin Solid State Mater Sci 1999:403–12.
[129] Dave RN, Joshi HM, Venugopalan VP. Novel biocatalytic polymer-based antimicrobial coatings as potential ureteral biomaterial: preparation and in vitro performance evaluation. Antimicrob Agents Chemother 2011:845–53.
[130] Sileika TS, Kim H-D, Maniak P, Messersmith PB. Antibacterial performance of polydopamine-modified polymer surfaces containing passive and active components. ACS Appl Mater Interfaces 2011:4602–10.
[131] Gristina AG, Naylor P, Myrvik Q. Infections from biomaterials and implants: a race for the surface. Med Prog Technol 1988:205–24.
[132] Busscher HJ, van der Mei HC, Subbiahdoss G, Jutte PC, van den Dungen JJ, Zaat SA, Schultz MJ, Grainger DW. Biomaterial-associated infection: locating the finish line in the race for the surface. Sci Transl Med 2012:153rv110.
[133] Anderson JM. Biological responses to materials. Annu Rev Mater Res 2001:81–110.
[134] Lieder R, Petersen PH. Ó.E. Sigurjónsson, endotoxins—the invisible companion in biomaterials research. Tissue Eng B Rev 2013:391–402.
[135] Zhang H, Fan D, Deng J, Zhu C, Hui J, Ma X. Effect of Tris-acetate buffer on endotoxin removal from human-like collagen used biomaterials. Mater Sci Eng C 2014:124–9.
[136] Tarafa PJ, Williams E, Panvelker S, Zhang J, Matthews MA. Removing endotoxin from metallic biomaterials with compressed carbon dioxide-based mixtures. J Supercrit Fluids 2011:1052–8.
[137] Müller BP, Eisenträger A, Jahnen-Dechent W, Dott W, Hollender J. Effect of sample preparation on the in vitro genotoxicity of a light curable glass ionomer cement. Biomaterials 2003:611–7.
[138] El-Yamany NA, Mohamed FF, Salaheldin TA, Tohamy AA, Abd El-Mohsen WN, Amin AS. Graphene oxide nanosheets induced genotoxicity and pulmonary injury in mice. Exp Toxicol Pathol 2017:383–92.
[139] Kleinsasser NH, Schmid K, Sassen AW, Harréus UA, Staudenmaier R, Folwaczny M, Glas J, Reichl F-X. Cytotoxic and genotoxic effects of resin monomers in human salivary gland tissue and lymphocytes as assessed by the single cell microgel electrophoresis (Comet) assay. Biomaterials 2006:1762–70.
[140] Kirkpatrick CJ, Alves A, Köhler H, Kriegsmann J, Bittinger F, Otto M, Williams DF, Eloy R. Biomaterial-induced sarcoma : a novel model to study preneoplastic change. Am J Pathol 2000:1455–67.
[141] Klosterhalfen B, Klinge U, Schumpelick V. Carcinogenicity of implantable biomaterials. In: Bendavid R, Abrahamson J, Arregui ME, Flament JB, Phillips EH, editors. Abdominal wall hernias: principles and management. New York, NY: Springer New York; 2001. p. 235–6.
[142] Hallab NJ. A review of the biologic effects of spine implant debris: fact from fiction. SAS J 2009:143–60.
[143] Guan A, Hamilton P, Wang Y, Gorbet M, Li Z, Phillips KS. Medical devices on chips. 2017. p. 0045.
[144] Seyfert UT, Biehl V, Schenk J. In vitro hemocompatibility testing of biomaterials according to the ISO 10993-4. Biomol Eng 2002:91–6.
[145] Říhová B. Biocompatibility of biomaterials: hemocompatibility, immunocompatiblity and biocompatibility of solid polymeric materials and soluble targetable polymeric carriers. Adv Drug Del Rev 1996:157–76.
[146] Ekdahl KN, Lambris JD, Elwing H, Ricklin D, Nilsson PH, Teramura Y, Nicholls IA, Nilsson B. Innate immunity activation on biomaterial surfaces: a mechanistic model and coping strategies. Adv Drug Deliv Rev 2011:1042–50.
[147] Lyle DB, Bushar GS, Langone JJ. Screening biomaterials for functional complement activation in serum. J Biomed Mater Res A 2010:205–13.
[148] Hakim RM. Chapter 18 Complement activation by biomaterials. Cardiovasc Pathol 1993:187–97.
[149] Brewster LP, Bufallino D, Ucuzian A, Greisler HP. Growing a living blood vessel: insights for the second hundred years. Biomaterials 2007: 5028–32.
[150] Joner M, Finn AV, Farb A, Mont EK, Kolodgie FD, Ladich E, Kutys R, Skorija K, Gold HK, Virmani R. Pathology of drug-eluting stents in humans: delayed healing and late thrombotic risk. J Am Coll Cardiol 2006:193–202.
[151] Jung F, Braune S. Thrombogenicity and hemocompatibility of biomaterials. Biointerphases 2015:029601.
[152] Dimitrievska S, Cai C, Weyers A, Balestrini JL, Lin T, Sundaram S, Hatachi G, Spiegel DA, Kyriakides TR, Miao J, Li G, Niklason LE, Linhardt RJ. Click-coated, heparinized, decellularized vascular grafts. Acta Biomater 2015:177–87.
[153] Wang LR, Qin H, Nie SQ, Sun SD, Ran F, Zhao CS. Direct synthesis of heparin-like poly(ether sulfone) polymer and its blood compatibility. Acta Biomater 2013:8851–63.

[154] Ye SH, Arazawa DT, Zhu Y, Shankarraman V, Malkin AD, Kimmel JD, Gamble LJ, Ishihara K, Federspiel WJ, Wagner WR. Hollow fiber membrane modification with functional zwitterionic macromolecules for improved thromboresistance in artificial lungs. Langmuir 2015: 2463–71.
[155] Sin M-C, Chen S-H, Chang Y. Hemocompatibility of zwitterionic interfaces and membranes. Polym J 2014:436–43.
[156] Damodaran VB, Murthy NS. Bio-inspired strategies for designing antifouling biomaterials. Biomater Res 2016:18.
[157] Manabe K, Kyung KH, Shiratori S. Biocompatible slippery fluid-infused films composed of chitosan and alginate via layer-by-layer self-assembly and their antithrombogenicity. ACS Appl Mater Interfaces 2015:4763–71.
[158] Jamiolkowski MA, Pedersen DD, Wu WT, Antaki JF, Wagner WR. Visualization and analysis of biomaterial-centered thrombus formation within a defined crevice under flow. Biomaterials 2016:72–83.
[159] Yuan S, Luan S, Yan S, Shi H, Yin J. Facile fabrication of lubricant-infused wrinkling surface for preventing thrombus formation and infection. ACS Appl Mater Interfaces 2015:19466–73.
[160] Janairo RR, Zhu Y, Chen T, Li S. Mucin covalently bonded to microfibers improves the patency of vascular grafts. Tissue Eng Part A 2014: 285–93.
[161] Woolley JR, Teuteberg JJ, Bermudez CA, Bhama JK, Lockard KL, Kormos RL, Wagner WR. Temporal leukocyte numbers and granulocyte activation in pulsatile and rotary ventricular assist device patients. Artif Organs 2014:447–55.
[162] Woolley JR, Kormos RL, Teuteberg JJ, Bermudez CA, Bhama JK, Lockard KL, Kunz NM, Wagner WR. Preoperative liver dysfunction influences blood product administration and alterations in circulating haemostatic markers following ventricular assist device implantation. Eur J Cardio Thorac Surg 2015:497–504.
[163] Chen Z, Li Q, Chen J, Luo R, Maitz MF, Huang N. Immobilization of serum albumin and peptide aptamer for EPC on polydopamine coated titanium surface for enhanced in-situ self-endothelialization. Mater Sci Eng C Mater Biol Appl 2016:219–29.
[164] Liang C, Hu Y, Wang H, Xia D, Li Q, Zhang J, Yang J, Li B, Li H, Han D, Dong M. Biomimetic cardiovascular stents for in vivo re-endothelialization. Biomaterials 2016:170–82.
[165] Punnakitikashem P, Truong D, Menon JU, Nguyen KT, Hong Y. Electrospun biodegradable elastic polyurethane scaffolds with dipyridamole release for small diameter vascular grafts. Acta Biomater 2014:4618–28.
[166] Brown BN, Londono R, Tottey S, Zhang L, Kukla KA, Wolf MT, Daly KA, Reing JE, Badylak SF. Macrophage phenotype as a predictor of constructive remodeling following the implantation of biologically derived surgical mesh materials. Acta Biomater 2012:978–87.
[167] Anderson JM, Rodriguez A, Chang DT. Foreign body reaction to biomaterials. Semin Immunol 2008:86–100.
[168] Brown BN, Ratner BD, Goodman SB, Amar S, Badylak SF. Macrophage polarization: an opportunity for improved outcomes in biomaterials and regenerative medicine. Biomaterials 2012:3792–802.
[169] Klopfleisch R. Macrophage reaction against biomaterials in the mouse model - phenotypes, functions and markers. Acta Biomater 2016: 3–13.
[170] Morris AH, Stamer DK, Kyriakides TR. The host response to naturally-derived extracellular matrix biomaterials. Semin Immunol 2017: 72–91.
[171] Sussman EM, Halpin MC, Muster J, Moon RT, Ratner BD. Porous implants modulate healing and induce shifts in local macrophage polarization in the foreign body reaction. Ann Biomed Eng 2014:1508–16.
[172] Hachim D, LoPresti ST, Yates CC, Brown BN. Shifts in macrophage phenotype at the biomaterial interface via IL-4 eluting coatings are associated with improved implant integration. Biomaterials 2017:95–107.
[173] Zhang L, Cao Z, Bai T, Carr L, Ella-Menye JR, Irvin C, Ratner BD, Jiang S. Zwitterionic hydrogels implanted in mice resist the foreign-body reaction. Nat Biotechnol 2013:553–6.
[174] Vegas AJ, Veiseh O, Doloff JC, Ma M, Tam HH, Bratlie K, Li J, Bader AR, Langan E, Olejnik K, Fenton P, Kang JW, Hollister-Locke J, Bochenek MA, Chiu A, Siebert S, Tang K, Jhunjhunwala S, Aresta-Dasilva S, Dholakia N, Thakrar R, Vietti T, Chen M, Cohen J, Siniakowicz K, Qi M, McGarrigle J, Lyle S, Harlan DM, Greiner DL, Oberholzer J, Weir GC, Langer R, Anderson DG. Combinatorial hydrogel library enables identification of materials that mitigate the foreign body response in primates. Nat Biotechnol 2016:345–52.
[175] Sicari BM, Dziki JL, Siu BF, Medberry CJ, Dearth CL, Badylak SF. The promotion of a constructive macrophage phenotype by solubilized extracellular matrix. Biomaterials 2014:8605–12.
[176] D'Amore A, Yoshizumi T, Luketich SK, Wolf MT, Gu X, Cammarata M, Hoff R, Badylak SF, Wagner WR. Bi-layered polyurethane - extracellular matrix cardiac patch improves ischemic ventricular wall remodeling in a rat model. Biomaterials 2016:1–14.