CHAPTER

33

Synthetic Polymers

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INTRODUCTION

Regenerative medicine is an emerging interdisciplinary approach to repairing or replacing damaged or diseased tissues and organs. To reestablish tissue and organ function impaired by disease, trauma, or congenital abnormalities, regenerative medicine employs cellular therapies, tissue engineering strategies, and artificial or biohybrid organ devices. Typically, these techniques rely on combinations of cells, genes, morphogens, or other biological building blocks with bioengineered materials and technologies to address tissue or organ insufficiency.

Materials used in these approaches range from metals and ceramics to natural and synthetic polymers as well as their microcomposites and nanocomposites. When used in a three-dimensional context, these materials are processed into microporous and/or nanoporous cell carriers of various structures and properties, typically called scaffolds, a topic discussed elsewhere in this book. This chapter focuses exclusively on synthetic polymers used in regenerative medicine. Some synthetic derivatives of natural materials are briefly discussed where appropriate. In addition to the various facets of regenerative medicine, a plethora of synthetic polymers with different compositions and physicochemical properties have been developed and investigated; however, research is ongoing. Synthetic materials have an important key role in many applications of regenerative medicine, including implants, tissue engineering scaffolds, and orthopedic fixation devices. In a broader sense, sutures, drug delivery systems, nonviral gene delivery vectors, and sensors made from synthetic polymers are further examples.

This chapter provides a structural overview of these synthetic polymers and discusses their physicochemical characteristics, structure–property relationships, applications, and limitations. Synthetic polymers that are hydrolytically labile and erode (biodegradable polymers) are considered, as are as those that are bioinert and remain unchanged after implantation (nondegradable polymers). It is the authors' intention to provide a thorough overview of available classes of synthetic material. Some polymer classes are briefly mentioned and their chemical structures are provided; other more relevant materials are discussed in greater detail. For most polymer classes and properties, reviews are referenced for guidance to further reading.

In general, the history of biomaterials can best be organized into four eras: prehistory, the era of the surgeon hero (first-generation biomaterials), designed biomaterials and engineered devices (second-generation biomaterials), and the contemporary era leading into the new millennium (third-generation biomaterials) [1,2]. As far back as AD 600, the use of dental implants made from materials such as seashells or iron was reported. Also, there is evidence that sutures have been used to close large wounds for as long as 32,000 years. The word "biomaterials," however, was introduced within the half century. Almost at the same time, aided by rapid advancements in industrial polymer development and synthesis, the exploration of synthetic polymers for biomedical applications began. The development of plastic contact lenses, using primarily poly(methyl methacrylate) (PMMA), started around 1936, and the first data on the implantation of nylon as a suture were reported in 1941. This development was accompanied by studies on the biocompatibility of the new materials. From the beginning, differences in foreign body reactions to the materials became apparent. Additives such as plasticizers, unreacted monomers, and degradation products were discussed as possible causes leading to an awareness of polymer's quality for biomedical applications and biocompatibility testing.

At the end of World War II, a wide variety of durable, high-performance metal, ceramic, and especially polymeric materials was available, inspiring surgeons to break new ground in replacing diseased or damaged body parts.

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Materials including silicones, polyurethanes (PUs), Teflon, nylon, methacrylates, titanium, and stainless steel were available "off the shelf" for surgeons to apply to medical problems [2]. Primarily medical and dental practitioners, driven by the vision to replace lost organ or tissue functionality, used minimal regulatory constraints to develop and improvise replacements, bridges, conduits, and even organ systems based on such materials. Those pioneering approaches laid the foundation for novel procedures and engineered biomaterials. Such early implants made from industrial materials available "off the shelf" were often poorly biocompatible, in many cases owing to insufficient purity. With a developing understanding of the immune system and foreign body reactions, the first generation of materials was developed during the 1960s and 1970s by engineers and scientists for use inside the human body. The primary goal of early biomaterial development was to achieve a suitable combination of physical properties to match those of the replaced tissue with a minimal toxic response in the host [3]. After this paradigm, more than 50 implanted devices made from 40 different materials were in clinical use in 1980. In the early 1980s, research began to shift from materials that exclusively exhibited a bioinert tissue response to materials that interacted actively with their environment. Another advance in this second generation was the development of biodegradable materials that exhibited controllable chemical breakdown into nontoxic degradation products that were either metabolized or directly eliminated. Biodegradable synthetic polymers were designed to resolve the interface problem, because the foreign material is ultimately replaced by regenerating tissues and eventually the regeneration site is histologically indistinguishable from the host tissue. By 1984, resorbable polymers were routinely used clinically as sutures. Other applications in fracture fixation aids or drug delivery devices quickly emerged. Despite the considerable clinical success of bioinert, bioactive, and resorbable implants, there is still a high long-term prosthesis failure rate and the need for revision surgery [2].

Improvements in first- and second-generation biomaterials have been limited for one main reason: unlike living tissue, artificial biomaterials cannot respond to changing physiological loads or biochemical stimuli. This limits the lifetime of artificial body parts. To overcome these limitations, a third generation of biomaterials is being developed that involves the molecular tailoring of resorbable polymers for specific cellular responses. By immobilizing specific biomolecules such as signaling molecules or cell-specific adhesion peptides or proteins onto a material, it is possible to mimic the extracellular matrix (ECM) environment and provide a cell-adhesive surface [1,4–6]. Biomimetic surfaces are promising tools for controlling cell adhesion, integrating implants, differentiating cells, and developing tissues. Synthetic polymer matrices can also be tailored to deliver drugs, signaling molecules, and genetic code and thus provide versatile technologies for regenerative medicine [7–9]. Constantly expanding knowledge of the basic biology of stem cell differentiation and the corresponding signaling pathways as well as tissue development provides the basis for the molecular design of scaffolds. In attempts at tissue engineering, which aim to regenerate lost or defective tissue by transplanting in vitro engineered tissue constructs based on a patient's own cells, one no longer strives to match scaffold mechanical properties closely to those of the replaced tissue. Instead, it is considered important for the engineered transplanted construct to be steadily remodeled in vivo to resemble the histological and mechanical properties of the surrounding tissue [10]. Owing to this paradigm shift, mechanically labile hydrogels, especially injectable systems that can be used to encapsulate cells directly, have gained great importance as the basis for biomimetic cell carriers. Hydrogels are characterized by a high content of water that allows encapsulated cells to survive and enables the sufficient passive transport of nutrients, oxygen, and waste. Hydrogel-forming materials typically offer functional groups for chemical modifications, and their degradation can be controlled by chemical composition and cross-linking content.

After a brief overview on synthesis techniques, inert and biodegradable synthetic polymers representative of all three generations will be presented in subsequent sections. Their structure, synthesis, physicochemical properties, and applications will be described.

POLYMER SYNTHESIS

Polymerization reactions for the synthesis of organic polymers are often categorized into chain-growth polymerizations and step-growth polymerizations, depending on how the chemical process of chain formation proceeds. The synthesis of polymers with a carbon–carbon backbone such as polyolefins and polyacrylates typically follows a chain-growth mechanism [11]. Chain-growth polymerizations involve the steps of chain initiation, chain propagation, and termination. Characteristics of this type of polymerization are that chain growth occurs only by the addition of monomers to the active chain end, generally at a high speed, and that only the monomer and polymer are present during the reaction. Depending on the nature of the reactive center of the propagation chains, chain-growth reactions are subdivided into radical, ionic (anionic or cationic), or transition-metal mediated (coordinative

or insertion) polymerizations. Suitable monomers contain an unsaturated carbon–carbon bond (double or triple) or are cyclic molecules with a sufficiently high ring strain. For the industrial synthesis of polyolefins, for example, free radical and transition-metal mediated polymerizations are commonly employed. Unlike radical polymerization, transition-metal coordinated mechanisms, such as with Ziegler–Natta catalysts, allow for the control of polymer tacticity [12]. A milestone in chain-growth polymerization history was the development of controlled or living radical polymerization techniques that allow for the precise control of polymer composition and architecture and yield polymeric products with low polydispersity [13].

Polymers that contain heteroatoms in the main chain are typically synthesized by a step-growth mechanism. During step-growth, the polymer molecular weight increases through the reaction of any two molecular species, i.e., monomers, oligomers, and polymer chains. In contrast to chain-growth, monomers disappear early on during the reaction and the polymer molecular weight slowly increases over the course of the reaction, which can last for days. Typical polymerization types that follow a step-growth mechanism are polycondensation and polyaddition reactions. In condensation reactions, small molecules such as water, alcohols, or hydrochloric acid are eliminated during step-growth. Polyethylene terephthalate and polyamides such as nylon and poly(propylene fumarate) [14] are examples of polymers that are synthesized by condensation reactions between carboxylic acid derivatives and diols or diamines (nylon). Most polyanhydrides are also synthesized by polycondensation reactions [15]. Polyaddition reactions follow a similar mechanism because nucleophilic groups react with electrophilic moieties during polymer chain buildup. In contrast to condensation reactions, addition reactions combine monomers without eliminating a small molecule. During PU synthesis, for example, diisocyanate monomers are reacted with diamines or dihydroxy-terminated molecules in the presence of catalysts under the formation of urethane and urea groups, respectively, to build up polymer chains [16].

Ring-opening polymerizations (ROPs) also yield polymers with heteroatoms in the main chain and are used to synthesize polyamines, polyethers such as poly(ethylene glycol)s (PEGs), and most biodegradable polyesters including polylactides, polyglycolides, and copolymers [17]. ROPs can follow chain-growth and step-growth kinetics and are executed in melts or solutions in the presence of catalysts and heat.

Driven by advances in drug design through combinatorial approaches in small-molecule chemistry, similar techniques have been adapted to polymerization chemistry [18]. Through the systematic screening of libraries of polymeric materials that have similar chemistries but are synthesized from a series of different monomers and comonomers in various combinations, structure–property relations can be identified and polymer properties can be fine-tuned for specific applications. Polymer properties that are screened using such approaches include the material's glass transition temperature, degradative properties, air–water contact angle, mechanical properties, cytocompatibility and cell proliferation.

NONDEGRADABLE SYNTHETIC POLYMERS

A common characteristic of most nondegradable synthetic polymers is their biological inertness [1]. These materials were developed to reduce the host response to the biomaterial to a minimum. Nondegradable synthetic polymers provide the basis for a plethora of medical devices as diverse as suture materials, orthopedic implants, fracture fixation devices, and catheters and dialysis tubing. These materials are also applied as implantable carriers for the long-term delivery of drugs, e.g., contraceptive hormones. Despite their excellent biological inertness and well-adjustable mechanical properties, orthopedic implants made from nondegradable synthetic polymers and nondegradable bone cements ultimately fail at a high rate from problems at the interface arising from a lack of integration with the surrounding tissue, infections, or bone resorption caused by stress shielding [19,20].

Major groups of nondegradable synthetic polymers are highlighted in the following section.

Polymers With a –C–C– Backbone

Polyethylene and Derivatives

Poly(ethylene), Poly(propylene), and Poly(styrene)

Poly(ethylene) (PE) (Fig. 33.1A), poly(propylene) (PP) (Fig. 33.1B), and poly(styrene) (PS) (Fig. 33.1C) are ubiquitous industrial polymers that have been applied as biomaterials. All three thermoplastic polymers are pure hydrocarbons and are synthesized by the direct polymerization of their corresponding monomers. Whereas PE can be synthesized by the radical or ionic polymerization of ethylene, special organometallic catalysts are required to

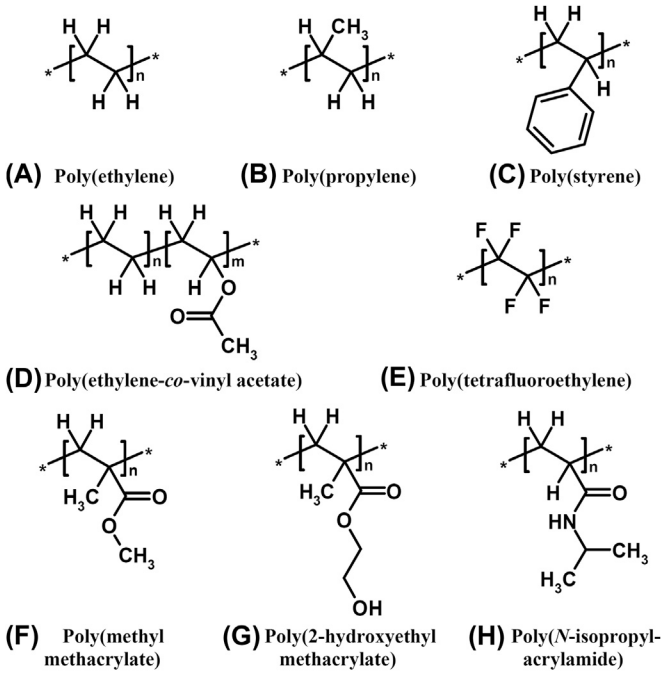

FIGURE 33.1 Chemical structures of nondegradable synthetic polymers (I).

polymerize propylene into useful PP. PE and PP are classified into several different categories based on their density, branching, and molecular weight. These parameters significantly influence the crystallinity and mechanical properties of the polymers. PE has been used to produce catheters. High-density PE, which is characterized by a low degree of branching and thus strong intermolecular forces and tensile strength, has been processed into highly durable hip prostheses. A three-dimensional fabric composed of PE fibers and coated with hydroxyapatite was used to regenerate hyaline cartilage in osteochondral defects in rabbit knees and showed successful biocompatibility [21]. The best-known application for PP is its use in syringe bodies. Copolymers of PE and vinyl acetate (poly[ethylene-*co*-vinyl acetate] [PEVAc]) (Fig. 33.1D) are widely used in nondegradable drug delivery devices [22]. PEVAc is one of the most biocompatible implant materials [23]; it has been approved by the US Food and Drug Administration (FDA) for use in implanted and topically applied devices.

Vitrasert , Implanon, and NuvaRing are examples of PEVAc-based drug delivery platforms [24–26] for ocular applications and long-term contraception. For the latter application, PE-based implants have also been developed.

PS is a hard, brittle polymer used to fabricate tissue culture flasks and dishes. By copolymerization with butadiene, copolymers with improved elasticity are synthesized that are used to make catheters and medical devices for perfusion and dialysis.

Poly(tetrafluoroethylene)

Poly(tetrafluoroethylene) (PTFE) (Fig. 33.1E), well-known as Teflon (DuPont), can be synthesized from liquid tetrafluoroethylene by radical polymerization and through the fluorination of PE. Among the known polymers, PTFE has the lowest coefficient of friction and excellent resistance to chemicals, and it is hemocompatible. Porous PTFE fiber meshes (Gore-Tex) have become a popular synthetic vascular graft material [27].

Poly(meth)acrylates and Polyacrylamides

Poly(meth)acrylate hydrogels are used in medical devices, especially for ocular applications (e.g., contact lenses and intraocular lenses), as drug delivery systems, and as cell delivery systems [28–30]. Three major types, PMMA, poly(2-hydroxyethyl methacrylate) (PHEMA), and poly(*N*-isopropylacrylamide), are discussed in more detail subsequently.

A variety of (meth)acrylate and acrylamide monomers with different functional groups are available; thus, poly(-meth)acrylates and polyacrylamides of different chemical compositions can be synthesized. Together with the free carboxylic acid moieties of (meth)acrylic acid, the presentation of different functional groups and charges along copolymer chains or within cross-linked hydrogels is possible. Using an imprinting technique, these moieties can

be oriented so that pouches are created that interact noncovalently with molecules, e.g., drugs or therapeutic peptides and proteins, via ionic interactions, hydrogen bonds, $\pi-\pi$ interactions, and hydrophobic interactions [31,32]. Besides intelligent hydrogels for controlled drug release, this technology has an impact on microfluidic devices, biomimetic sensors, intelligent polymeric membranes [33], and analyte-sensitive materials [34].

Poly(methyl Methacrylate)

PMMA (Fig. 33.1F) is a nondegradable polyacrylate and is the most commonly applied nonmetallic implant material in orthopedics. It was used as an essential ingredient to make dentures and then in the mid-1950s, PMMA was introduced for use in orthopedic surgery [35]. PMMA tissue biocompatibility became further apparent when Plexiglas fragments were accidentally implanted in the eyes and other body tissues of World War II fighter pilots during aircraft crashes.

PMMA can be polymerized in situ and cross-linked from a slurry containing PMMA and methyl (meth)acrylate monomers; thus, it is used as a common bone grafting material, mainly in the fixation of orthopedic prosthetic materials for hips, knees, and shoulders [36]. PMMA-based bone cements can be mixed with inorganic ceramics or bioactive glass to modulate curing kinetics and enforce mechanical properties. Antibiotics can be loaded within the cement to reduce the risk for prosthesis-related infection. Significant drawbacks of self-curing PMMA cements are that they are not degraded, that their high curing temperatures and toxic monomers can cause necrosis of the surrounding tissue, and that the cements have limited interactions with surrounding bone [37,38]. Therefore, the development of alternative injectable bone cements is directed toward biodegradable materials with improved curing properties and osteoconductive interfaces.

Because of its excellent biocompatibility and hemocompatibility and ease of manipulation, PMMA is used in many medical devices, including blood pumps and dialyzers. Its optical properties make it a candidate material for implantable ocular lenses and hard contact lenses [29]. PMMA also offers physical and coloring properties that are beneficial for denture fabrication [37].

Poly(2-hydroxyethyl Methacrylate)

PHEMA (Fig. 33.1G) was the first hydrogel to be successfully employed for biological use [39]. PHEMA has become the major component of most soft contact lenses and is also part of intraocular lenses [29]. Owing to their free hydroxyl groups, PHEMA gels contain relatively high amounts of water, which facilitates the diffusion of solutes and oxygen. PHEMA has excellent biocompatibility, which initiates the development of a plethora of hydroxyethyl methacrylate–containing copolymers. Hydrogels fabricated from PHEMA and copolymers have been intensively characterized for controlled drug delivery applications [40,41] and employed for biomedical uses. PHEMA gels, which have limited mechanical properties, have been used in attempts to reconstruct female breasts and nasal cartilages, and as artificial corneas as well as wound dressings [42].

In a subcutaneous rabbit model, porous PHEMA sponges promoted significant cellular ingrowth and neovascularization combined with good cytocompatibility [43]. A mineralization technique was demonstrated that exposed carboxylate groups on cross-linked PHEMA hydrogel scaffolds, promoting calcification [44].

Poly(*N*-isopropylacrylamide)

Poly(*N*-isopropylacrylamide) (PNiPAAm) (Fig. 33.1H) is important for injectable applications in drug and cell delivery using minimally invasive techniques because of its unique physicochemical properties [45]. PNiPAAm undergoes (lower critical) phase separation, resulting in the formation of an opaque hydrogel in response to a temperature above 32°C, the material's lower critical solution temperature (LCST). This thermoresponsive behavior is the result of strong hydrogen bonds between the polymer and water molecules and the specific molecular orientations of these bonds caused by the molecular structure of the polymer. The formation of hydrogen bonds between the polymer and the solvent lowers the free energy of the solution. Because of the hydrophobic *N*-isopropyl residues in PNiPAAm, the hydrogen bonds between water and the amide functionality require specific molecular orientation. Such ordered structures lead to negative entropy changes and positive contributions to the free energy. Because the enthalpic contribution to the free energy is temperature-dependent, the formation of strong but specifically oriented hydrogen bonds is no longer thermodynamically favored above a certain temperature. Consequently, PNiPAAm dissolves in water below the LCST. At and above the LCST, the polymer chains partially desolvate and undergo a coil-to-globule transition resulting in colloidal aggregation that may lead to gel formation or polymer precipitation [46,47]. Hydrogels formed by linear PNiPAAm at 32°C are instable and collapse substantially as the temperature is increased above the LCST. The synthesis of cross-linked networks and copolymers, typically with hydrophilic building blocks, has resulted in materials that demonstrate reversible thermogelation and form hydrogels with no

significant syneresis at body temperature. Different PNiPAAm-containing copolymers for cell delivery have been synthesized with acrylic acid, PEG, hyaluronic acid, and gelatin [45,48–50]. Detailed information is available for the in vitro and in vivo use of gelatin–PNiPAAm conjugates for the regeneration of articular cartilage [51,52]. A series of multifunctional *N*-isopropylacrylamide (NiPAAm)-based copolymers has also been developed [53]. One example is the injectable, thermosensitive macromer poly(NiPAAm-*co*-polylactide–hydroxyethyl methacrylate (HEMAPLA)–*co*-acrylic acid-*co*-*N*-acryloxysuccinimide) [54] that is composed of HEMAPLA for increased biodegradability via elevated backbone solubility upon PLA hydrolysis and reactive succinimide esters for the cross-linking of, e.g., type I collagen. Further examples of such advanced copolymers include a series of amphiphilic NiPAAm-based macromers with dual gelation properties [55,56], calcium ion–sensitive macromers of a similar design with vinylphosphonic acid as comonomer [57], and a series of anhydride group–containing oligomers synthesized with maleic anhydride and a key copolymer [58]. The latter have been used to formulate dual-component hydrogels with gelatin [59], cross-linked gelatin microparticles, as well as tubular conduits [60]. NiPAAm-based copolymers with at least dual functionality have also been synthesized with glycidyl methacrylate as comonomer [61]. The introduction of epoxides allowed for effective cross-linking and dual-component hydrogel engineering with polyamidoamine-based diamines [62]. Syneresis in NiPPAm-based hydrogels could be suppressed and their degradation improved by the integration of dimethyl-γ-butyrolactone acrylate as comonomer with a hydrolysable lactone structure [63,64]. The chemical incorporation of the comonomer monoacryloxyethyl phosphate and subsequent ester formation with glycidyl methacrylate allowed for the introduction of phosphatase degradable linkages in injectable hydrogels for bone regeneration [65,66].

Polyethers

PEG (Fig. 33.2A), often also called poly(ethylene oxide) (PEO), is a nondegradable polyether of the monomer ethylene glycol. Technically, PEG and PEO should not be used as synonyms because PEO is synthesized from the monomer ethylene oxide and typically is terminated by only one hydroxyl group and an initiator fragment [67]. Commonly, PEG is often used to refer to the polymer with a molecular weight less than 30,000–50,000 Da whereas PEO is used for higher molecular weights. PEG is water soluble and solutions of its high–molecular weight form can be categorized as a hydrogel. PEG hydrogels for biomedical applications are typically composed of polymer chains that are cross-linked. These cross-linked networks frequently contain chemical bonds between the PEG chains and the cross-linkable moieties, which are prone to aqueous hydrolysis and therefore are characterized as biodegradable systems. The molecular weight of the PEG chains cross-linked in such hydrogels is below a threshold molecular weight to allow for complete resorption by renal elimination of the individual chains. Consequently, these materials are discussed as biodegradable polymers in the Cross-linked Polyesters section.

Favorable characteristics of PEG and PEO include their high hydrophilicity, bioinertness, and outstanding biocompatibility, which make them candidate biomaterials [68]. PEG and PEO are frequently used as hydrophilic polymeric building blocks in copolymers with more hydrophobic degradable or nondegradable polymers for drug delivery [69], gene delivery, tissue engineering scaffolds, medical devices, and implants. PEG has also been immobilized on polymeric biomaterial surfaces to make them resistant to protein absorption and cell adhesion. These effects are attributed to highly hydrated PEG chains on the polymer surfaces that exhibit steric repulsion based on an osmotic or entropic mechanism [70]. Attempts to benefit from this phenomenon include the design of long-circulating nanoparticles or liposomes [71–74] and PEGylated enzymes or proteins with a prolonged functional residence time in vivo compared with unmodified biomolecules [75,76].

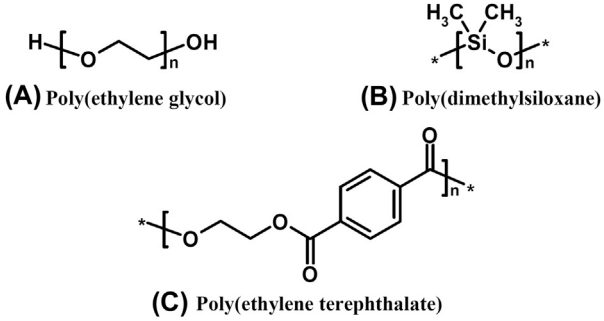

FIGURE 33.2 Chemical structures of nondegradable synthetic polymers (II).

A variety of PEG-containing block copolymers for injectable drug delivery have been developed [77]. The most prominent class is triblock copolymers composed of two hydrophilic PEO blocks and one hydrophobic poly(propylene oxide) (PPO) block, also known as Pluronics or poloxamers. These materials are designed to have phase transition behavior similar to thermogelling PNiPAAm-containing materials (see Poly(*N*-isopropylacrylamide) section). Poloxamers have been intensively investigated for the delivery of drugs and proteins [78]. Because Poloxamers are nondegradable, biodegradable structural analogues have been synthesized. They are described within the next section, Block Copolymers of Polyesters or Polyamides With Poly(ethylene glycol).

Polyglycerols (also called polyglycidols) have gained recognition as an alternative to PEG and PPO. The main distinguishing feature of this polymer is the presence of an additional hydroxyl group on the monomer. As a result, polyglycerols can have a linear structure with a free hydroxyl group per repeat unit or a hyperbranched structure, in which all three hydroxyl groups contribute to the formation of the polyether [79,80]. Linear polyglycerol was found to possess properties similar to PEG with regard to biocompatibility and protein absorption resistance. In addition, the materials exhibit thermoresponsive behavior [81].

Polysiloxanes

Polysiloxanes, or silicones, are a general category of polymers consisting of a silicon-oxygen backbone with organic groups, typically methyl groups, attached to the silicon atoms [82]. Certain organic side groups can be used to link two or more chains. By varying the silicon-oxygen chain length, side groups, and extent of cross-linking, silicones with properties ranging from liquids to hard plastics can be synthesized. Silicone synthesis typically involves the hydrolysis of chlorosilanes into linear or cyclic siloxane oligomers, which are then polymerized into polysiloxanes by polycondensation or polymerization, respectively. The most common polysiloxane is linear poly(dimethylsiloxane) (Fig. 33.2B).

Polysiloxanes, which are characterized by unique material properties combining biocompatibility and biodurability, have found widespread application in health care [82]. The materials' high biodurability is a result of other material properties such as hydrophobicity, low surface tension, and chemical and thermal stability. Silicone surfaces have been found to inhibit blood from clogging for many hours and thus have been used to fabricate silicone-coated needles, syringes, and other blood-collecting instruments. Silicone materials have also been employed as heart valves and components in kidney dialysis, blood oxygenators, and heart bypass machines owing to their hemocompatibility. Silicone elastomers have been used in numerous catheters, shunts, drains, and tubular implants such as artificial urethra. Significant orthopedic applications of silicones are joint implants in hands and feet. The most prominent application of silicones is their extensive use as cosmetic implants in aesthetic and reconstructive plastic surgery. Prosthetic silicone implants are available for the breast, scrotum, chin, nose, cheek, calf, and buttocks. Different silicone materials, including slightly cross-linked silicone gels, are combined to achieve a natural feel. Controversy arose regarding the safety of popular silicone gel-filled breast implants in the early 1990s. These discussions initially involved an increased risk for breast cancer; it then progressed to autoimmune connective tissue disease and evolved to the frequency of local or surgical complications such as rupture, infection, and capsular contracture. To date, no epidemiology study has indicated that the rate of breast cancer has significantly increased in women with silicone breast implants [83]. However, a slight increase in anaplastic large cell lymphoma, a rare cancer of the immune system, is being discussed as connected with breast implants [84]. Studies on autoimmune or connective tissue disease agreed regarding the lack of causal association between breast implants and these diseases [85,86]. A safety concern that was discussed involves the amount of platinum (the part of catalysts used during silicone synthesis) that is released from silicone implants and accumulated in the host organism [87,88]. Other complications, especially implant rupture, are persisting problems; in 1992, the FDA restricted the use of silicone gel-filled implants. Since then, the implants may be used only under certain controlled conditions [89]. In 2016, the FDA approved three types of saline-filled breast implants and five types of silicone gel-filled ones, and required the manufacturers of silicone gel-filled implants to conduct postapproval studies to characterize the safety and effectiveness of their implants.

Polysiloxane gels, which combine the high oxygen permeability of silicone and the comfort and clinical performance of conventional polyacrylate hydrogels, enable the fabrication of soft, gas-permeable contact lenses for extended wear. In contrast to conventional hydrogels, silicone gels render the surface of the lens highly hydrophobic and less "wettable," which frequently results in discomfort and dryness during lens wear. Surface modifications of the silicones or the addition of conventional hydrogels are suitable strategies to compensate for the hydrophobicity.

Overall, polysiloxanes have been increasingly applied in medicine since the 1960s; today, they are one of the most thoroughly tested and important biomaterials.

Other Nondegradable Polymers

Poly(ethylene Terephthalate)

Poly(ethylene terephthalate) (Fig. 33.2C), a linear polyester synthesized by polycondensation of terephthalic acid and ethylene glycol, is typically processed into fiber meshes. These meshes are applied as vascular grafts [27] or used to reinforce prostheses.

Hydrolytically Stable Polyurethanes

PUs are a heterogeneous class of polymers that consist of organic units joined by urethane links (Fig. 33.3). Generally, PUs can be synthesized from a bischloroformate and a diamine or by reacting a diisocyanate with a dihydroxy component. PUs used in biomedical applications typically have a segmented structure that results in useful physicochemical properties [90]. Such segmented PUs or PU copolymers are elastomers composed of alternating polydispersed "soft" and "hard" segments. These two segments are thermodynamically incompatible and phase-segregate, resulting in discrete, crystalline domains of the associated "hard" segments surrounded by a continuous, amorphous phase of "soft" segments. The segregated domains are stabilized by interchain hydrogen bonds and are responsible for the materials' mechanical properties [91]. Segmented PUs are synthesized in a two-step process that provides control over polymer architecture (Fig. 33.3A). The first step involves the synthesis of an isocyanate-terminated prepolymer from a diisocyanate (D in Fig. 33.3) and a hydroxyl group terminated polyether or polyester (P in Fig. 33.3). The prepolymer and excess diisocyanate are then reacted with a hydroxy or amine group-terminated chain extender (C in Fig. 33.3) to generate the final PU (Fig. 33.3A).

A chain extender terminated with hydroxy groups yields segmented PUs, whereas a diamine extender yields PU-urea (Fig. 33.3B). The "hard" segment of the PU copolymer is composed of the diisocyanate and the chain extender, whereas the "soft" segment contains the polymeric segment introduced during the first step. The extent of phase separation depends on the molecular weights, chemistry, and relative percentages of the building blocks [92].

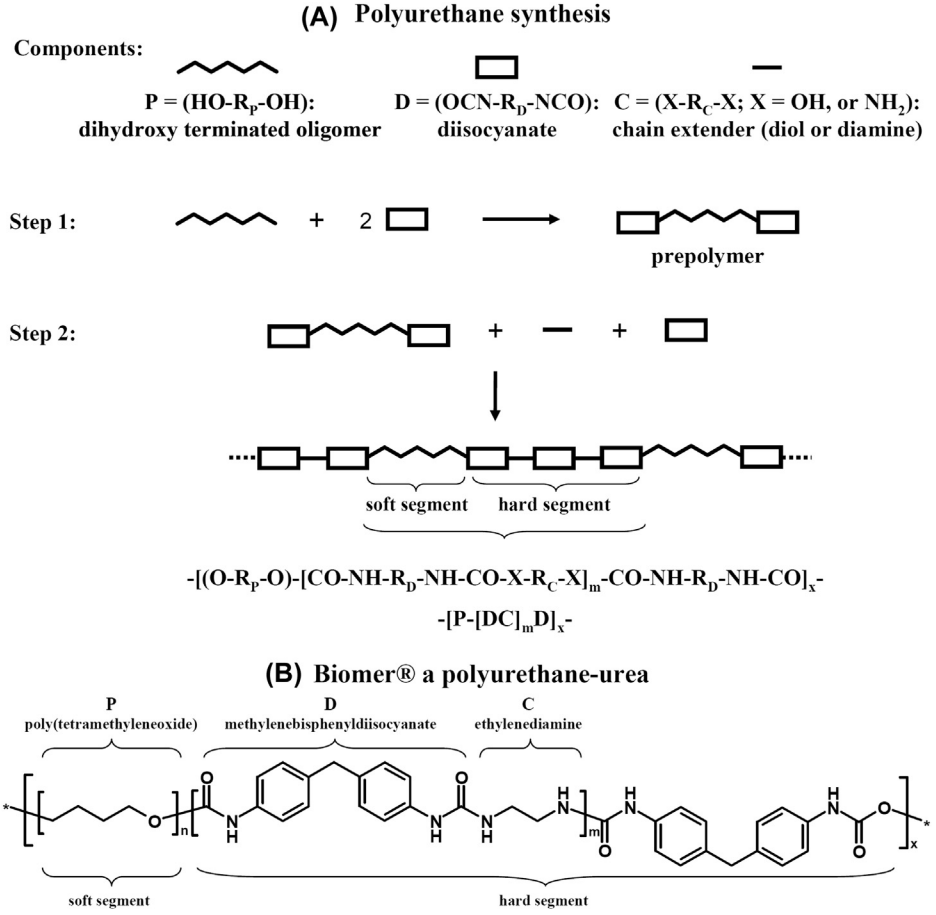

FIGURE 33.3 General synthesis scheme (A) and an example structure (B) for polyurethanes.

After almost 50 years of use in biomedical applications, PUs remain one of the most popular groups of biomaterials for the fabrication of medical devices. Their popularity results from a wide range of versatility with regard to tailoring their physicochemical and mechanical properties, blood and tissue compatibility, and degradative properties by altering block copolymer composition. Biomedical PUs are used in numerous medical devices such as breast implants, catheters, vascular and aortic grafts, pacemaker leads, artificial heart valves, and artificial hearts; they perform well in a variety of in vivo applications. PUs often have better blood and tissue compatibilities compare with numerous other synthetic polymers. The efficient removal of impurities from the polymer synthesis, such as catalyst residues and low−molecular weight oligomers, has critically determined PU biocompatibility [93].

Traditional PUs such as Biomer (in which the dihydroxy-terminated oligomer (P) is polytetramethylenen oxide, the diisocyanate (D) is methylene bisphenylenediisocyante and ethylenediamine is the chain extender (C)) (Fig. 33.2D), were materials of first choice. However, the assumption of polyetherurethane nondegradability had to be revised in response to the well-documented failures of pacemaker leads and breast implant coatings containing PUs in the late 1980s. Although PUs can be designed to be stable against hydrolysis, these materials have been shown to degrade in the biological environment by mechanisms including oxidation and enzyme and cell-mediated degradation [92,94,95]. Oxidation of PUs can be initiated by peroxides, free radicals, and enzymes. Metal-catalyzed oxidation was found to be most frequently associated with pacemaker lead failure. Another important oxidation-driven problem with long-term PU implants is environmental stress cracking. PU surfaces become coated with a protein layer that enhances the adhesion of macrophages. The macrophages, activated by proteins of the complement family, release oxidative factors that accelerate the degradation of the polymer [96].

Chemical design criteria have been identified for biostable PUs. To increase the degree of interchain hydrogen bonding, on which biostability partially depends, low−molecular weight oligomeric diols (P) are preferred as building blocks. To avoid oligomer hydrolysis, oligoethers are favored over oligoesters. Aromatic diisocyanates (D) have been found to yield more biostable PUs than aliphatic diisocyanates. The use of a diamine chain extender (C) instead of a dihydroxy-terminated one typically results in stronger PU-urea, but polymer fabrication is often hampered because of solubility problems. The use of soft segment building blocks with high crystallinity, such as polycaprolactone, or silicone-based oligomers is also assumed to improve polymer biostability [92].

PUs can be surface modified to reduce the risk of thrombosis or improve interactions with cells and tissues. Different strategies, including adsorption, covalent grafting, and the use of self-assembled monolayers, have been applied to distribute proteins such as fibronectin, or adhesion peptides, which contain the integrin-binding peptide motif RGD, across the PU surface [92,97].

BIODEGRADABLE SYNTHETIC POLYMERS FOR REGENERATIVE MEDICINE

Biodegradable synthetic polymers offer a number of advantages over nondegradable materials for applications in regenerative medicine. Like all synthetic polymers, they can be synthesized at reproducible quality and purity and fabricated into various shapes with desired bulk and surface properties. Specific advantages include the ability to tailor mechanical properties and degradation kinetics to suit various applications. Clinical applications for biodegradable synthetic polymers are manifold and traditionally include resorbable sutures, drug delivery systems, and orthopedic fixation devices such as pins, rods, and screws [98]. Synthetic biodegradables were widely explored as artificial matrices for tissue engineering applications [99−103]. For such applications, the mechanical properties of the scaffolds, which are determined by the constitutive polymer, should functionally mimic the properties of the tissue to be regenerated. Ultimately, the polymeric support is designed to degrade while transplanted or invading cells proliferate, lay down ECM, and form coherent tissue that ideally is functionally, histologically, and mechanically indistinguishable from the surrounding tissue. To engineer scaffolds suitable for different applications, a wide variety of biodegradable polymers are required ranging from pliable, elastic materials for soft tissue regeneration to stiff materials that can be used in load-bearing tissues such as bone. In addition to the mechanical properties, the degradation kinetics of polymer and ultimately scaffold also have to be tailored to suit various applications.

The major classes of synthetic, biodegradable polymers are briefly reviewed and their potential in regenerative medicine is discussed subsequently.

Polyesters

Polyesters have been attractive for biomedical applications because of their ease of degradation by the primarily nonenzymatic hydrolysis of ester linkages along the backbone. In addition, degradation products can be

resorbed through the metabolic pathways in most cases, and there is the potential to tailor the structure to alter degradation rates [104].

A vast majority of biodegradable polymers studied belong to the polyester family [105]. Polyester fibers, which also became popular in the textile industry, were used as resorbable sutures [106]. Promising observations regarding the biocompatibility of the materials led to applications in drug delivery, orthopedic implants, and tissue engineering scaffolds, particularly for orthopedic applications [98,102,107–110].

Polyesters of α-Hydroxy Acids

The family of polyesters can be subdivided according to the structure of the monomers. In poly(α-hydroxy acids), each monomer has two functionalities, a carboxylic acid and a hydroxyl group, located at the carbon atom next to the carboxylic acid (α-position), that form ester bonds. Poly(α-hydroxy acids) are linear thermoplastic elastomers that typically are synthesized by ROP of cyclic dimers of the building blocks [111,112]. Poly(lactic acid) (PLA) (Fig. 33.4A), poly(glycolic acid) (PGA) (Fig. 33.4B), and a range of their copolymers, including poly(lactic-*co*-glycolic acid) (PLGA) (Fig. 33.4C) are prominent representatives not only of biodegradable polyesters but of biodegradables in general. The cyclic dimers that are polymerized during PLA and PGA synthesis are called lactide and glycolide, respectively. Therefore, the polymers are often named polylactides or polyglycolides. For reasons of consistency with the general term poly(α-hydroxy acids), the terms PLA and PGA will be used here. Poly(α-hydroxy acids) have a long history of use as synthetic biodegradable materials in a number of clinical applications. Initially, resorbable sutures were made from these materials [113]. Later, poly(α-hydroxy acids) were the basis for controlled release systems for drugs, proteins and vaccines [114–118], and orthopedic fixation devices [119]. Langer and coworkers pioneered the development of these polymers in the form of porous scaffolds for tissue engineering [120].

Because of the chiral nature of lactic acid, several forms of PLA exist: poly(L-lactic acid) (P_LLA), for example, is synthesized from L-lactide. The polymerization of racemic lactide leads to poly(D,L-lactic acid) ($P_{D,L}LA$), which is an amorphous polymer. P_LLA, in contrast, is a semicrystalline polymer with a crystallinity of around 37%. P_LLA is characterized by a glass transition temperature between 50°C and 80°C and a melting temperature between 173°C and 178°C. Amorphous $P_{D,L}LA$ is typically used in drug delivery applications, whereas semicrystalline P_LLA is preferred in applications in which high mechanical strength and toughness are required, e.g., for sutures and orthopedic devices. PGA is also a semicrystalline polymer with a higher crystallinity of 46–52%. Thermal characteristics of PGA are glass transition and melting temperatures of 36°C and 225°C, respectively. Because of its high crystallinity, unlike PLA, PGA is not soluble in most organic solvents; the exceptions are highly fluorinated organic solvents such as hexafluoroisopropanol. Consequently, common processing techniques for PGA include melt extrusion, injection, and compression molding.

PLA, PGA, and PLGA undergo homogeneous erosion via ester linkage hydrolysis into the degradation products lactic acid and glycolic acid, which are both natural metabolites that are fully metabolized and excreted as carbon dioxide and water. Degradation of poly(α-hydroxy acid)s showed characteristics typical of bulk erosion. Bulk erosion occurs when water penetrates the entire structure and the device degrades simultaneously [121]. During the initial stages of degradation, almost no mass loss can be detected. Analysis of the average molecular weight of the polymer bulk over the same period, however, reveals a steady decrease in molecular weight. Once the polymer chains throughout the bulk are degraded below a certain threshold, the water-soluble degradation products are washed out and the system collapses, accompanied by significant mass loss. Because of its well-accessible ester group, PGA degrades rapidly in aqueous media. PGA sutures typically lose their mechanical strength over 2–4 weeks postoperatively [122]. To adapt these properties to a wider range of applications, copolymers with more hydrophobic PLA were synthesized and investigated. The two main series are those of P_LLGA (Fig. 33.4C) and $P_{D,L}LGA$. It was shown that the range of compositions from 25% to 70% glycolic acid (GA) for L-lactic acid (L-LA)/GA and from 0% to 70% GA for D,L-LA/GA are amorphous [104,105,123–126]. For the P_LLGA copolymers, the rate of hydrolysis was slower at either extreme of the copolymer composition range. It is generally accepted that intermediate PLGA copolymers have a shorter half-life in vivo than either homopolymer. Besides the polymer composition, the rate of degradation is affected by factors such as the configurational structure, copolymer ratio, crystallinity, molecular weight, morphology, stresses, the amount of residual monomer, bulk porosity, and the site of implantation [104].

Multiple in vitro and in vivo studies that were conducted on the biocompatibility of PLA, PLGA, and PGA have generally revealed satisfying results [127]. Consequently, PLA, PLGA copolymers, and PGA are among the few biodegradable polymers with FDA approval for human clinical use.

Concerns with poly(α-hydroxy esters) typically focus on the accumulation of acidic degradation products within the polymer bulk that can have detrimental effects on encapsulated drugs in delivery applications [128–130] or can cause late noninfectious inflammatory responses when released in a sudden burst upon structure breakdown

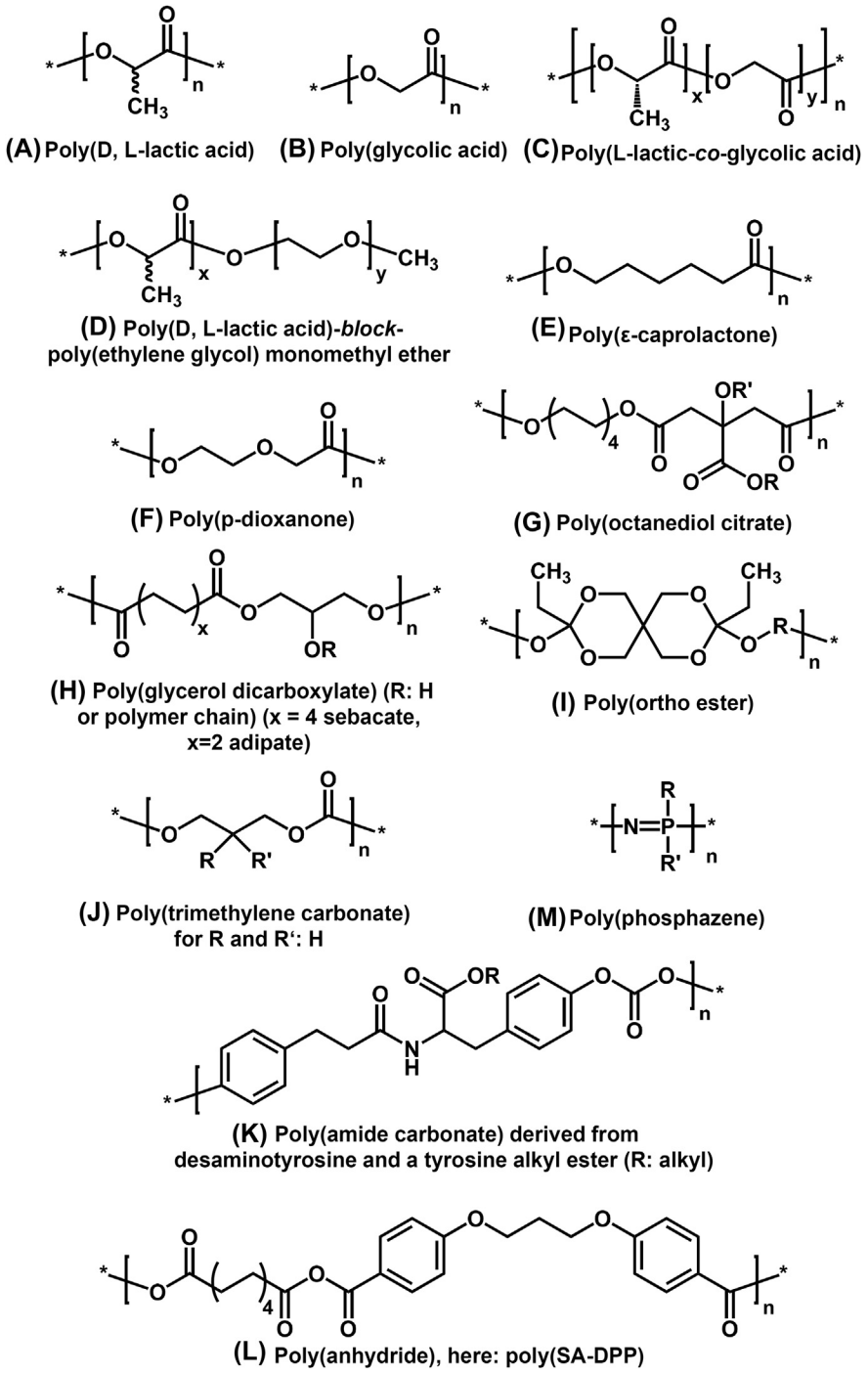

FIGURE 33.4 Chemical structures of biodegradable synthetic polymers.

[131–133]. This adverse reaction can occur weeks and months postoperatively and might need surgical drainage. This is a major concern in orthopedic applications, in which implants of considerable size would be required and which may result in the release of degradation products with high local acid concentrations. Inflammatory response to poly(α-hydroxy acids) were also found to be triggered by the release of small particles during degradation that were phagocytosed by macrophages and multinucleated giant cells [117,134]. In general, implant size as well as surface properties appear to be critical factors with regard to biocompatibility. Fewer concerns seem to exist regarding the application of poly(α-hydroxy acids) in soft tissues compared with hard tissue applications [127]. Injectable P_LLA has been employed for skin volume restoration by using its stimulating effect on collagen production [135].

Poly(α-hydroxy acids) were the materials of choice when one of the key concepts of tissue engineering, the de novo engineering of tissue by combining isolated cells and three-dimensional macroporous cell carriers in vitro, was first realized and developed [120,136,137]. Polymers based on lactic acid and GA are still popular scaffold materials, especially for orthopedic applications such as bone, cartilage, and meniscus, as outlined in several reviews [101,138–140]. Limitations of this class of materials include insufficient mechanical properties with regard to load-bearing applications [110] and inflammatory or cytotoxic events caused by the accumulation of acidic products during degradation.

To cover a broader range of mechanical and physicochemical properties, such as water absorption, polymer degradation, and polymer–drug interactions, block copolymers containing PLA and hydrophilic PEO or PEG were synthesized for drug delivery applications [141,142]. Solid particulate systems from these block copolymers were almost invisible to the immune system owing to the hydrophilic PEG chains that swell on the surface [71,143] (see Polyethers section) (Fig. 33.4D). The stealthiness of such surfaces is mainly caused by the suppression of protein adsorption, which also inhibits cell adhesion. Investigations into cell adhesion to PEG–PLA diblock copolymer surfaces revealed that cell adhesion can be controlled and cell differentiation can be modulated by the PEG content [144]. With the objective of specifically controlling cell–polymer interactions, PEG–PLA copolymers were further developed to allow for the covalent attachment of signaling molecules [145,146]. Because these polymers were insoluble in water, they could be processed into macroporous scaffolds for tissue engineering applications [147]. Furthermore, diblock and triblock copolymers of PLA with PEG were investigated as microscale and nanoscale vehicles for drug delivery [148,149], as well as for tissue engineering applications [150].

Another direction in which to broaden the range of mechanical and chemical properties of PLA centers on the use of α-hydroxy acids that possess longer alkyl or aryl side chains [151] or feature a side chain with an additional double or triple bond or a functional group [152]. An important effect of such an incorporation is the modulation of the glass transition temperature of the resulting polymer [153]. For example, a viscous copolymer of lactic acid and 2-hydroxy-octanoic acid was investigated as a delayed intravitreal release system for vasodilatory substances or as an excipient for sustained-release drug formulations [154–156].

Polyesters of Lactones

The most prominent and thoroughly investigated polylactone is poly(ε-caprolactone) (PCL) (Fig. 33.4E), an aliphatic, semicrystalline polyester with an interestingly low glass transition temperature (−60°C) and melting temperature (59-64°C) [105,157]. PCL is considered to be biocompatible [158]. PCL is prepared by the ROP of the cyclic monomer ε-caprolactone and is compatible with a range of other polymers. Catalysts such as stannous octoate are used to catalyze the polymerization and low–molecular weight alcohols can be used as the initiator and to control the molecular weight of the polymer [159]. ε-Caprolactone can be copolymerized with numerous other monomers. Copolymers with PLA and PEG are probably the most noteworthy and have been investigated extensively [160–163]. PCL degrades at a much slower rate than PLA and therefore is most suitable for the development of long-term implantable drug delivery systems. These copolymers of caprolactone with lactide were synthesized to accelerate degradation rates [105]. Tubular, highly permeable poly(L-lactide-*co*-ε-caprolactone) guides were found to be suitable for the regeneration and functional reinnervation of large gaps in injured nerves [164]. Although this study focused on tissue regeneration, the application of PCL in drug delivery devices is still far more common [165]. With the increasing popularity of electrospinning, a laboratory-scale technique that allows for the fabrication of nonwoven meshes composed of nanofibers and/or microfibers [166], PCL might find its way into cell-based therapies because slowly degrading polymers are preferred for this technique to ensure sufficient stability of the fibers [167].

Poly(p-dioxanone) (Fig. 33.4F), another polylactone, and its copolymers with lactide, glycolide, and/or trimethylene carbonate, are synthesized by catalyzed ROP and have been used in a number of clinical applications ranging from suture materials to bone fixation devices [168,169]. The use of analogues of p-dioxanone bearing methyl or more complex groups for homopolymerization or copolymerization allows for the fine-tuning of degradation properties of the polymer [170].

Another class of polymer that is accessible via the polymerization of lactones is poly(hydroxy-alkanoates) (PHAs), which are composed of hydroxy acids with the hydroxyl group located at least in the β-position relative to the carboxylic acid group [171]. PHAs are mostly produced biosynthetically; the resulting polymer is perfectly isotactic and highly crystalline. Synthesis via ROP of lactones, on the other hand, enables the production of syndiotactic and atactic PHAs with altered physicochemical and mechanical properties [172].

Polyesters of Polyols and Carboxylic Acids

In addition to using monomers bearing a hydroxyl and a carboxyl group on the same molecule, elastomeric polyester networks have been synthesized by combining two kinds of building blocks, one bearing two or more hydroxyl groups (a polyol), such as glycerol [173], and one bearing two or three carboxyl groups (a dicarboxylic acid or tricarboxylic acid), such as citric acid [174]. Polymers are synthesized from the two building blocks by polycondensation either by organometallic, metal-oxide [175], enzyme-based catalysis [176] or without using exogenous catalysts [177,178], depending on the employed building blocks.

Poly(diol citrates) are synthesized from citric acid and various low− or high−molecular weight diols [174]. Poly(1,8-octanediol-*co*-citrate) (POC) (Fig. 33.4G; R, R′: −H), one of the first poly(diol citrates), demonstrated mechanical properties such as tensile strength, Young's modulus, and elongation at break that justify applications in ligament reconstruction and vascular engineering [178]. Variations in chemical composition, especially diol chemistry, allowed for the synthesis of a variety of biodegradable elastomers covering a range of mechanical and degradative properties [179]. With regard to vascular tissue engineering, POC showed good hemocompatibility and exhibited decreased platelet adhesion and clotting relative to P_LLGA and expanded poly(tetrafluoro ethylene) [180]. Endothelial cell attachment and differentiation were supported with no modification of the surface. To improve the mechanical properties of the POC elastomer, unsaturated acrylate and fumarate diols were added during the condensation reaction and moieties for secondary cross-linking were introduced [181]. Further modification of the employed diols and functionalization of the pendant carboxyl and hydroxyl groups of citric acid led to citrate-based biomaterials with potential applications ranging from regeneration of hard and soft tissue to drug delivery, bioadhesive, and imaging functions [174].

Poly(glycerol sebacate) (Fig. 33.4H; $x = 4$) is an elastomeric polymer network made from the triol glycerol and sebacic acid (decanedioic acid) [182]. It is developed for use in the regeneration of soft tissues such as cardiac [183], vascular, retinal, and neural tissue. A similar polymer, poly(glycerol adipate) (Fig. 33.4H; $x = 2$), made from glycerol and adipic acid (hexanedioic acid), is being examined for use as a nanoparticulate drug delivery system after esterification with fatty acids [184].

Linear polymers of this type are synthesized from a diol and a dicarboxylic acid [185]. An example is poly(butylene succinate), which is synthesized from 1,4-butanediole and succinic acid [186] and which has been evaluated for use in the regeneration of cartilage [187] and bone tissue [188].

Polyorthoesters

Polyorthoesters (POEs) (Fig. 33.4I) were developed by Alza Corporation and SRI International in 1970 in the search for a new biodegradable polymer for drug delivery applications [189]. Since then, polymer synthesis has improved. POEs are synthesized by condensation or addition reactions typically involving dialcohols and monomeric orthoesters or diketene acetals, respectively. The use of triethylene glycol as the diol component produced predominantly hydrophilic polymers, whereas hydrophobic materials could be obtained by using 1,10-decanediol. Orthoester is a functional group containing three alkoxy groups attached to one carbon atom. In POEs, two of the three alkoxy groups are typically part of a cyclic acetal (Fig. 33.4G).

POEs were synthesized that degrade by surface erosion, which is characterized by a constant decrease in bulk mass while the polymer molecular weight within the polymer bulk is preserved [190]. It is known that materials built from functional groups with short hydrolysis half-lives and low water diffusivity tend to be surface eroding. Polymers that exhibit surface erosion can be used to fabricate drug delivery systems that release loaded drugs at a constant rate at a high aspect to volume ratio (e.g., as for wafers).

The addition of lactide segments to the POE structure resulted in self-catalyzed erosion and allowed for fine-tunable degradation times ranging from weeks to months [191]. POEs provide the material platform for a variety of drug delivery applications including the treatment of postsurgical pain, osteoarthritis and ophthalmic diseases, and the delivery of proteins and DNA. Block copolymers of POE and PEG have been prepared and their use as drug delivery matrices or as colloidal structures for tumor targeting are being explored [189].

Initial biocompatibility studies revealed that POEs provoked little inflammation and were largely absorbed by 4 weeks. In contrast, $P_{D,L}LA$ degraded more slowly and provoked chronic inflammation with multinuclear giant cells, macrophages with engulfed material, and proliferating fibroblasts within the same model. Ossicles with bone marrow had formed in the implants of POE combined with demineralized bone. In PLA/demineralized bone implants, bone formation was inhibited [192,193].

Polycarbonates

Polycarbonates have become interesting biomaterials because of their excellent mechanical strength and good processability. The degradation of most polycarbonates is controlled by hydrolysis of the carbonate group, which yields two alcohols and carbon dioxide, which alleviates the problem of acid bursting seen in polyesters [104,194]. The structural variation in the pendant side groups allows polymers to be prepared with different mechanical properties, degradation rates, and cellular responses.

The most prototypical polycarbonate is poly(trimethylene carbonate) (Fig. 33.4J), generated by ROP of the monomer 1,3-dioxan-2-one (trimethylene carbonate [TMC]). By using substituted analogues of this monomer, it is possible to introduce additional functionalities into the material [195]. Altered material properties resulting from these functionalities widen the prospect for the use of polycarbonates in tissue and bone regeneration [196,197] as well as in drug delivery [198,199] and as polymer-based antibiotics [200,201].

Because TMC-based polycarbonates degrade extremely slowly under physiological conditions [195], polyiminocarbonates [202] and tyrosine-based polycarbonates [203] (Fig. 33.4K) have been engineered to yield biodegradable polymers with good mechanical strength [204] for use in drug delivery and orthopedic applications. Tyrosine-based polycarbonates that contain a pendant ethyl ester group have been shown to be osteoconductive and to possess mechanical properties sufficient for load-bearing bone fixation. Long-term (48-week) in vivo degradation kinetics and host bone response to tyrosine-derived polycarbonates were investigated using a canine bone chamber model [205]. Histological sections revealed intimate contact between bone and the polymer. It was concluded that from a degradation-biocompatibility perspective, the tyrosine-derived polycarbonates appear to be comparable to PLA, if not superior, in this model. The incorporation of desaminotyrosyltyrosine units without a pendant ester and low–molecular weight PEG allows for the development of tyrosine-based polycarbonates with faster degradation without affecting the osteoconductive properties [206], which are further improved upon by combining the polymer scaffolds with calcium phosphate minerals and bone morphogenetic protein 2 (BMP-2) [207]. Variations in the composition of these terpolymers can be used to engineer ultrafast degrading and resorbing polymers that may be suitable for the coating of implants in brain tissue to minimalize adverse effects [208].

Block Copolymers of Polyesters or Polyamides With Poly(ethylene Glycol)

Amphiphilic block copolymers of biodegradable polymers with PEG have become popular materials for injectable drug delivery applications [78]. Inspired by the thermoresponsive behavior observed for nondegradable A-B-A–type triblock copolymers composed of hydrophilic PEO (block A) and hydrophobic PPO (block B), polymer development focused on synthesizing biodegradable analogs of these poloxamers (or Pluronics) that were water soluble at ambient temperature and formed stable hydrogels at body temperature. Biodegradable block copolymers were synthesized by substituting the hydrophobic PPO block with a biodegradable polymer block such as PLA or PCL [69,77,209].

Biodegradable, physically cross-linkable block copolymers of inverse structure (that is, B-A-B triblock copolymers with two biodegradable hydrophobic polymer blocks [block B] and a hydrophilic PEO block) were also investigated as protein delivery systems [148,210].

Polyurethanes

PUs represent a major class of synthetic elastomers that have excellent mechanical properties and good biocompatibility. PUs have been evaluated for a variety of medical devices and implants, particularly for long-term implants.

Knowledge gained about the mechanisms of PU biodegradation in response to implant failures throughout the 1990s has been translated to form a new class of bioresorbable materials [95]. Research has employed the flexible chemistry and diverse mechanical properties of PUs to design degradable polymers for a variety of regenerative applications. Segmented PUs with varied molecular structure have been synthesized to control the rates of hydrolysis [95,211]. To obtain biodegradable, segmented PUs, significant changes were required to the structural components historically used for their synthesis. Traditional aromatic diisocyanates (D; compare with Fig. 33.3) can yield toxic or carcinogenic degradation products when they are part of a degradable PU; therefore, linear diisocyanates are preferred, such as lysine-diisocyanate, which yields the nontoxic degradation product lysine. The soft segment, which is typically composed of an oligomeric diol (P; compare with Fig. 33.3), is typically the block of the PU used to modify the degradation rate. Biodegradable PUs have been synthesized with a variety of soft segments including PEO, degradable polyesters such as PLA, PGA, or PCL, and their combinations. Other strategies focus on the copolymers' hard segments. PUs were synthesized that contain enzyme-sensitive linkages introduced with

the chain extender (C; compare with Fig. 33.3). For example, the use of a phenylalanine diester chain extender yielded a PU that showed susceptibility to enzyme-mediated degradation upon exposure to chymotrypsin and trypsin.

Saad et al. investigated cell and tissue interactions with a series of degradable polyesterurethanes. In vivo investigations showed that all test polymers exhibited favorable tissue compatibility and degraded significantly over 1 year [212]. Polyurethane-urea matrices were shown to allow vascularization and tissue infiltration in vivo [213]. The flexible chemistry and diverse mechanical properties of PU materials allowed researchers to design degradable polymers to regenerate diverse tissues including neurons, vasculature, smooth muscle, cartilage, and bone [27,95,214].

To accelerate the degradation behavior of polyesterurethanes, polyester segments in the polymer backbone were partially substituted with polycarbonate, yielding poly(ester carbonate)urethane-ureas [215]. Flexible, low-moduli biodegradable PU, or poly(ether carbonate urethane)-ureas, were synthesized with polyether-based domains containing biodegradable sections as soft segments [216]. Examples of such soft segments include poly(trimethylene carbonate) (PTMC)-based triblock copolymers such as PTMC−PEO−PTMC and thermoresponsive pentablock copolymers such as PTMC−PEO−PPO−PEO−PTMC. For controlling the response of a biological system to materials, surface and bulk modifications are a common strategy. To this end, a series of biodegradable polyesterurethane-urea elastomers with variable amino content were developed. Via the amine groups, carboxylated phosphorylcholine was conjugated to polymer for bulk functionalization [217]. This modification significantly reduced platelet adhesion to the material and inhibited rat vascular smooth muscle cell proliferation. Such materials may find use as coatings in cardiovascular devices or as scaffolds for cardiovascular tissue regeneration. Enzyme-degradable PU was synthesized by using a collagenase-sensitive peptide as a chain extender [218].

Amino Acid−Derived Polymers, Poly(amino Acids), and Peptides

Amino acids are an interesting building block for polymers because of the biocompatibility of the degradation products and the degradability of the amide or ester bonds by which amino acids are typically polymerized or integrated in copolymers. Early studies on pure poly(amino acids)s revealed significant concerns regarding the materials' immunogenicity and mechanical properties [219]. To improve those unfavorable properties, amino acids have been used as monomeric building blocks in polymers that have a backbone structure different from that of natural peptides. Based on polymer structure and chemistry, four major groups have been used to classify such "nonpeptide amino acid−based polymers": (1) synthetic polymers with amino acid side chains, (2) copolymers of natural amino acids and non−amino acid monomers, (3) block copolymers containing peptide or poly(amino acid) blocks, and (4) pseudopoly(amino acids) such as α-peptoids [220].

As in tyrosine-derived polycarbonates (discussed in the Polycarbonates section), L-tyrosine is the predominantly employed amino acid in the synthesis of tyrosine-derived polyarylates and polyesters. These copolymers exhibit excellent engineering properties and polymer systems can be designed whose members have exceptional strength (polycarbonates), flexibility and elastomeric behavior (polyarylates), or water solubility and self-assembly properties (copolymers with PEG). Poly(DTE carbonate) (Fig. 33.4K; R: $-CH_2CH_3$) exhibits a high degree of tissue compatibility and is being evaluated by the FDA for possible clinical use [219].

A combinatorial library of degradable tyrosine-derived polyarylates was synthesized by copolymerizing 14 different tyrosine-derived diphenols and eight different aliphatic diacids in all possible combinations, resulting in 112 distinct polymers [221]. Significant differences were observed in the mechanical properties of the polymers and fibroblast proliferation assays with these materials. This illustrates that such combinatorial approaches provide a library of related polymers that encompasses a broad range of properties and permits the systematic study of material-dependent biological responses in order to choose a suitable material for a specific application.

Another amino acid that has received interest as a component in synthetic polymers for biomedical purposes is L-lysine. Lysine has been investigated as a component in urethane/urea esters, both as a linear block with a free carboxyl group for functionalization [222] and as a three-armed branching point in which the carboxyl group bears an ester with another amino functionality. Degradation studies of the latter material pointed to oxidative processes having an important role in the degradation of such a material in vivo [223]. Lysine was also employed in block copolymers with PEG and PLA that showed no cytotoxic effect [224], in an allylamine-initiated homopolymer copolymerized with PEG-diacrylate as a hydrogel for nerve regeneration [225] or in a genipin-cross-linked poly(L-lysine) hydrogel for drug delivery, and as a cell culture substrate [226].

In a more general context, the polymerization of amino acids with side chain functionalities yields polymer chains with pendent functional groups that can be used for further functionalization. In addition to lysine and tyrosine, other amino acids have been selected for their side chain functionalities [227], including glutamic acid [228] and

L- dihydroxyphenylalanine [229] to influence calcium phosphate mineralization and L-arginine for the synthesis of urethane/urea polymers as biodegradable gene therapy vector [230].

The most common route to generate homopolymers of amino acids or a poly(amino acid) segment in block copolymers uses the ROP of N-carboxy-anhydrides (NCAs) [231,232]. This process yields polymers that are composed of a single amino acid or a random sequence of amino acids when multiple NCAs are reacted simultaneously. Block copolymers can be obtained when NCAs of different amino acids are polymerized in a stepwise manner. An important issue of long chains of these synthetic poly(amino acids) is high immunogenicity [219]. In contrast, solid-phase peptide synthesis, pioneered by Merrifield, and genetic engineering allow for the automated and highly efficient synthesis of peptides of a predefined sequence. Synthetic peptides have become an important polymer class for biomedical applications. Specifically, peptides and peptide-amphiphiles that undergo self-assembly—driven in situ gelation in response to temperature, pH, or chemical stimuli are interesting because these materials can be minimally invasively implanted starting from aqueous solutions [233–235].

Genetically engineered elastin-like polypeptides, which are composed of a pentapeptide repeat and undergo inverse temperature phase transition, have been used to encapsulate chondrocytes. Cell culture studies showed that cartilaginous tissue formation was supported, characterized by the biosynthesis of sulfated glycosaminoglycans and collagen [236].

Self-assembled peptide-amphiphiles form hydrogels composed of nanofibers resembling the native ECM components, with the amphiphiles composed of a peptide with hydrophilic and hydrophobic domains, a hydrophilic peptide attached to a hydrophobic lipid chains, or copolymers composed of the peptide and a hydrophobic component [237]. These hydrogels have been demonstrated to be cytocompatible in cell encapsulation studies [238]. Peptide nanostructures designed through self-assembly strategies and supramolecular chemistry have the potential to combine bioactivity with biocompatibility [239]. In addition, such structures can be used to deliver proteins, nucleic acids, drugs, and cells.

Peptide-amphiphile nanofibers were shown to promote the in vitro proliferation and osteogenic differentiation of marrow stromal cells [240]. For dental tissue engineering, dental stem cells were encapsulated in peptide-amphiphile hydrogels containing adhesion peptides and enzyme-cleavable sites. The cells proliferated and differentiated within the gels and remodeled the matrices [241].

Polyanhydrides

Drug delivery technologies rely on engineered polymers that degrade in a well-controllable and adjustable fashion [22]. An increased understanding of erosion mechanisms led to a demand for synthetic polymers that contain a hydrolytically labile backbone while limiting water diffusion within the polymer bulk significantly to confine erosion to the polymer—water interface. Such surface-eroding polymers allow for the fabrication of drug delivery devices that erode at constant velocity at any time during erosion, thus releasing incorporated drugs at constant rates [242]. Polyanhydrides were engineered following this paradigm by selecting the anhydride linkage, one of the least hydrolytically stable chemical bonds available, to connect the building hydrophobic monomers.

Polyanhydrides (Fig. 33.4L) have been synthesized by various techniques, including melt condensation, ROP, interfacial condensation, dehydrochlorination, and dehydrative coupling agents [243]. Solution polymerization traditionally yielded low—molecular weight polymers. Different dicarboxylic acid monomers have been polymerized to yield polyanhydrides with various physicochemical properties. Examples are linear, aromatic, or fatty acid—based dicarboxylic acid monomers, and fatty acid—terminated polyanhydrides. Polyanhydrides made from linear sebacic acid (SA) and aromatic 1,3-*bis*(*p*-carboxyphenoxy)propane (CPP) (Fig. 33.4L) have been engineered to deliver carmustine (BNCU), an anticancer drug, to sites in the brain after primary resection of a malignant glioma [244]. Poly(SA-CPP) hydrolyzes into nontoxic degradation products and local chemotherapy with BCNU wafers was shown to be tolerated and to offer a survival benefit to patients with newly diagnosed malignant glioma, although this therapy revealed potentially problematic side effects [245,246].

The chemical composition of a polyanhydride can be used to custom-design its degradation properties. Whereas polyanhydrides from linear monomers such as poly(SA) degrade within a few days, polymerized aromatic dicarboxylic acids such as poly(1,6-*bis*[*p*-carboxyphenoxy]hexane) degrade much more slowly (up to a year) [247,248]. Combined with their unique degradation and erosion properties, the structural versatility of polyanhydrides make them precious materials for numerous medical, biomedical, and pharmaceutical applications in which degradable polymers that allow for perfect erosion control are needed [242]. With regard to tissue engineering applications, polyanhydrides have also been interesting polymers owing to their degradative properties and their good biocompatibility [249]. The use of polyanhydrides in load-bearing orthopedic applications, however, is restricted because of their limited mechanical properties. Poly(anhydrides-*co*-imides), which were developed to combine

the good mechanical properties of polyimides with the degradative properties of polyanhydrides, were shown to have compressive strengths comparable to human bone [250] and displayed good osteocompatibility [251].

Photopolymerizable polyanhydrides have been synthesized with the objective of combining high strength, controlled degradation, and minimal invasive techniques for orthopedic applications and were shown to be osteocompatible [252]. Depending on the chemical composition, these materials reached compressive and tensile strengths similar to those of cancellous bone [253].

An interesting strategy for the controlled release of bioactive substances has been explored with poly(anhydride-esters). Bioactive substances such as antiinflammatory drugs [254], analgesics [255], and antiseptics [256] have been used as monomers or comonomers for polyanhydrides. Upon polymer degradation, the active substances were released from the polymer bulk in a controlled manner. To guide bone regeneration, salicylic acid–containing, poly(anhydride-ester)-based flexible sheets were investigated as barriers to prevent excessive BMP-2–induced bone formation [257].

Polyphosphazenes

Polyphosphazenes (Fig. 33.4M), which are polymers containing a high–molecular weight backbone of alternating phosphorus and nitrogen atoms with two organic side groups attached to each phosphorus atom, are a relatively new heterogenic class of biomaterials. Because different synthetic pathways allow for a tremendous variety of derivatives, phosphazene polymers exhibit a diverse spectrum of chemical and physical properties. As a result of this variety, these polymers are suitable for many biomedical applications ranging from templates for nerve regeneration to cardiovascular and dental uses as implantable and controlled-release devices [258–261].

The best-studied and most important route to polyphosphazenes, whose synthesis is generally more involved than that for most petrochemical biomaterials but offers unique flexibility, is macromolecular substitution. A reactive polymeric intermediate, poly(dichlorophosphazene), is typically synthesized by a thermal ring opening cationic polymerization of hexachlorocyclotriphosphazene in bulk at 250°C, which yields a polydisperse high–molecular weight product. The intermediate is reacted with low–molecular weight organic nucleophiles, resulting in stable, substituted polyphosphazenes, which in this case are also addressed as poly(organo)phosphazenes. Depending on the substituent chemistry, the polyphosphazene is more or less susceptible to hydrolysis. Biodegradable hydrophobic polyphosphazenes have been synthesized using imidazolyl, ethylamino, oligopeptides, amino acid esters, and depsipeptide groups (dimers composed of an amino acid and a glycolic or lactic ester) as hydrolysis-sensitive side groups. Hydrolytic degradation products include the free side group units phosphate and ammonia as a result of backbone degradation [258]. Hydrogel-forming, hydrophilic polyphosphazenes can by synthesized by introducing small, hydrophilic side groups such as glucosyl, glyceryl, or methylamino. Ionic side groups yield polymers that form hydrogels upon ionic complexation with multivalent ions [262]. Hydrophilic, water-soluble polyphosphazenes with amphiphilic side groups such as poly(*bis*[methoxyethoxyethoxy]phosphazene) (Fig. 33.4M, R,R′: $-OCH_2CH_2OCH_2CH_2OCH_3$) display an LCST (see the Poly(*N*-isopropylacrylamide) section) and are responsive to changes in temperature and ionic strength [263]. Both hydrophilic and hydrophobic polyphosphazenes have demonstrated potential as biocompatible materials for controlled protein delivery. Ionic polyphosphazenes have been explored as vaccine delivery systems and poly(*di*[carboxylatophenoxy]phosphazene) has demonstrated remarkable adjuvant activity in the immunogenicity of inactivated influenza virions and commercial trivalent influenza vaccine in the soluble state [258].

Porous scaffolds from biodegradable polyphosphazenes have been shown to be good substrates for osteoblast-like cell attachment and growth with regard to skeletal tissue regeneration [264]. It was also shown that hydroxyapatite deposition was supported by polyphosphazenes with side groups containing antioxidative properties [265]. Tubular polyphosphazene nerve guides were investigated in a rat sciatic nerve defect. After 45 days, a regenerated nerve fiber bundle was found to bridge the nerve stumps in all cases [259].

Biodegradable Cross-linked Polymer Networks

The chemical cross-linking of individual linear polymer chains results in networks of increased stability. This concept has been extensively explored for applications in regenerative medicine and most likely represents the concept of choice for modern biomaterial research, especially if polymer cross-linking can be conducted inside a tissue defect [266]. The cross-linking of hydrophobic polymers or monomers results in tough polymer networks that can be used for orthopedic fixation. PMMA (Fig. 33.1F), the main component in injectable bone cements, is the most prominent example. Because of their hydrophobicity, the precursors are typically injected as a moldable liquid or paste free of additional solvents. In situ cross-linking can be initiated thermally or photochemically by UV-rich light. Both ways of initiation are also applicable to hydrophilic injectable systems that form highly swollen

gels (hydrogels) as a result of precursor cross-linking. In contrast to hydrophobic networks that scarcely swell in the presence of water, injectable hydrogels are characterized by a high water content and diffusivity, which allow for the direct encapsulation of cells and sufficient transport of oxygen, nutrients, and waste. Hydrophobic networks, however, often require the addition of a leachable porogen, such as salt particles, to facilitate cell migration and tissue ingrowth. Generally, injectable polymer systems have considerable advantages over prefabricated implants or tissue engineering scaffolds, which include the ability to fill irregularly shaped defects with minimal surgical intervention [267].

A number of demanding requirements have to be fulfilled by synthetic materials for applications in regenerative medicine. In addition to physicochemical properties that fit the application site, the polymer and any adjuvant component that is required to formulate an in situ cross-linkable system have to be biocompatible. Ideally, the resulting network should also have the ability to support cell growth and proliferation early in the tissue regeneration process [53,266].

The cross-linkable synthetic polymers that will be discussed in the following sections are reactive polyesters. The main chemical functionality involved in the chemical cross-linking mechanisms is the polarized, electron-poor double bond, such as in vinylsulfones and in esters of acrylic acid, methacrylic acid, and fumaric acid. Other chemically or thermally cross-linkable macromonomer functional groups are styryl, coumarin, and phenylazide; these will not be discussed here [268].

Cross-linked Polyesters

Fumarate-based polymers: The development of fumarate-based polyesters for biomedical applications began several decades ago. Fumaric acid is a naturally occurring metabolite found in the tricarboxylate cycle (Krebs cycle); it is composed of a reactive double bond available for chemically cross-linking reactions. These characteristics make fumaric acid a candidate building block for cross-linkable polymers. The first and most comprehensively investigated fumarate-based copolymer is the biodegradable copolyester poly(propylene fumarate) (PPF) (Fig. 33.5A). PPF was first polymerized from fumaric acid and propylene oxide [269]. Mikos and coworkers optimized the synthesis of PPF and broadly investigated the tissue compatibility and applications of PPF both in vitro and in vivo [14]. Synthesis progressed to the copolymerization of fumaryl chloride and 1,2-propanediol (propylene glycol) [270]. It

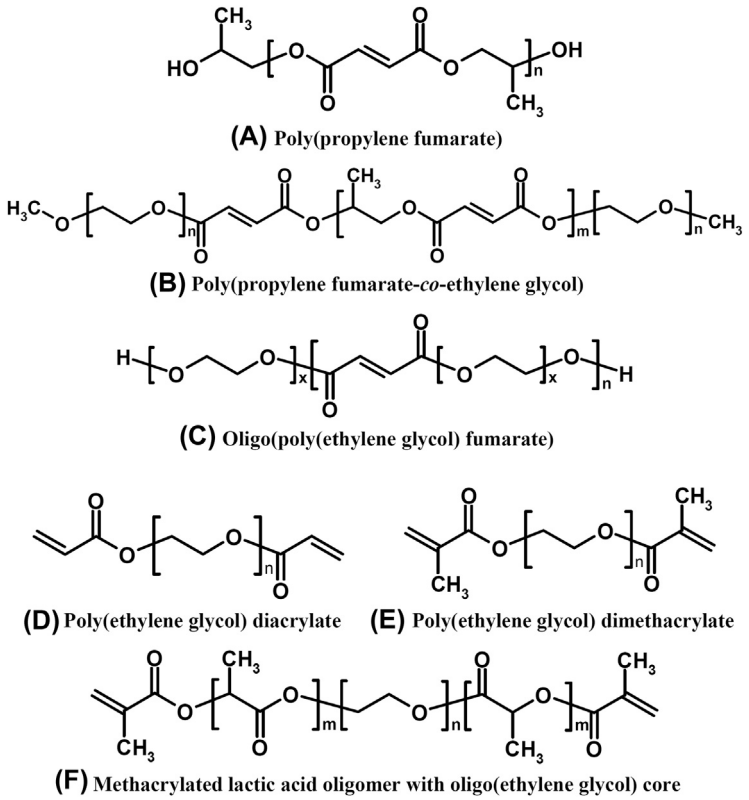

FIGURE 33.5 Chemical structures of synthetic polymers for the fabrication of cross-linked biodegradable networks.

now involves the transesterification of diethylfumarate with propylene glycol and subsequent polycondensation of the diester intermediate *bis*(2-hydroxypropyl) fumarate (PF) [271]. A variety of methods to synthesize PPF have been explored; each results in different polymer molecular weights and properties [272]. PPF has been developed as an alternative to PMMA bone cements. PPF can be injected as a viscous liquid and thermally cross-linked in vivo, eliminating the need for direct exposure of the defect site to light. Typically, PPF is cross-linked with either methyl methacrylate or *N*-vinyl pyrrolidone (NVP) monomers and benzoyl peroxide as a radical initiator [273,274]. Depending on the ratio of initiator, monomer, and PPF, the curing time can be controlled between 1 and 121 min. Compared with PMMA, which is not resorbable and is limited because its high curing temperatures (94°C) can cause necrosis of the surrounding tissue, the curing temperature of PPF has been shown not to exceed 48°C [275,276]. PPF can also be photocross-linked via the electron-poor double bonds along the backbone. Typical formulations include NVP, diethylfumarate, or PF-diacrylate (PF-DA) as comonomers together with a photoinitiator such as *bis*(2,4,6-trimethylbenzoyl) phenylphosphine oxide [277–279]. The mechanical properties of PPF, which depend on the composition, synthesis condition, and cross-linking density, are promising. However, these materials are probably not sufficient for load-bearing applications, especially when used as macroporous scaffolds [267,278,280]. One strategy to strengthen PPF scaffolds further includes the incorporation of nanoparticulate fillers. Reinforced PPF composites have been synthesized using aluminum oxide–based ceramic nanoparticles and chemically modified single-walled carbon nanotubes (SWNT). For just 0.05 wt% loading with the latter, a 74% increase was recorded for the compressive modulus and a 69% increase for the flexural modulus compared with plain PPF/PF-DA [281]. The chemical integration of alumoxane nanoparticles in cross-linked PPF/PF-DA networks resulted in a significantly increased flexural modulus [282]. Both the PPF/alumoxane nanocomposites and the PPF/SWNT nanocomposites were processed into macroporous tissue engineering scaffolds [283,284] and showed good biocompatibility in vitro [285,286] and in vivo [287,288].

Microparticulate ceramic materials such as β-tricalcium phosphate (β-TCP) were also employed as an inorganic filler to improve the mechanical properties of composite scaffolds and improve the material's osteoconductivity [289]. The composite scaffolds exhibited increased compressive strengths in the range of 2–30 MPa, and β-TCP reinforcement delayed scaffold disintegration significantly in vivo [290]. Rabbit in vivo studies also revealed the biocompatibility of photocross-linked PPF scaffolds in both soft and hard tissues [291].

PPF hydrolytically degrades at the ester bonds along its backbone. The degradation time depended on the polymer structure as well as other components such as fillers. In vitro studies identified the time needed to reach 20% original mass ranging from around 84 days (PPF/β-TCP composite) to over 200 days (PPF–$CaSO_4$ composite) [266]. Slow-degrading, porous antibiotic-releasing PPF exhibited properties suitable for craniofacial degradable space maintenance applications [292].

To broaden the application spectrum for in situ cross-linkable PPF, block copolymers with hydrophilic PEG of different compositions were synthesized. Poly(propylene fumarate-*co*-ethylene glycol) (P[PF-*co*-EG]) (Fig. 33.5B) was synthesized from PPF and PEG in a transesterification reaction catalyzed by antimony trioxide; propylene glycol was removed by condensation [293]. Behravesh et al. modified the synthesis to yield well-defined ABA-type triblock copolymers from 2 mol monomethoxy-PEG and 1 mol PPF [294]. Generally, P(PF-*co*-EG) copolymers are hydrophilic polymers with specific properties including crystallinity and mechanical characteristics that depend on the molecular weights of the individual blocks and the copolymer. As a result, platelet attachment to P(PF-*co*-EG) hydrogels was significantly reduced compared with the PPF homopolymer, which makes these copolymers candidate materials when direct biomaterial–blood contact is inevitable, such as for vascular grafts [295]. Most P(PF-*co*-EG) copolymers are amphiphiles and soluble in water; this makes them candidate materials for injectable applications. ABA-type copolymers showed thermoreversible properties comparable to other PEG-containing triblock copolymers discussed earlier. The thermogelling properties of P(PF-*co*-EG) depended on the PEG's molecular weight and salt concentration and the physical gelation temperature could be adjusted to values below body temperature [294]. In addition, the hydrophobic PPF block is highly unsaturated and available for additional chemical cross-linking, which could result in stiff cross-linked networks suitable for fabricating prefabricated cell carriers. In vitro degradation studies of macroporous, cross-linked P(PF-*co*-EG) scaffolds revealed considerable mass loss and swelling over 12 weeks. In these studies, the degradation rate depended mainly on the content of the PEG-DA cross-linker and was almost unaffected by the construct porosity. Overall, the results indicated a bulk degradation mechanism of the macroporous constructs [296]. In a subcutaneous rat model, P(PF-*co*-EG) hydrogels demonstrated good initial biocompatibility followed by the development and maturation of a fibrous capsule, which is often seen for polymeric implants [270]. Overall, the reported in vitro cytotoxicity and in vivo biocompatibility assays suggest that P(PF-*co*-EG) hydrogels have potential for use as injectable biomaterials. Fisher et al. demonstrated the suitability of thermoresponsive P(PF-*co*-EG) hydrogels for chondrocyte delivery in regenerating articular cartilage defects [297].

As previously discussed for stealthy PEG-containing biodegradables, PEG content and the hydrophilicity of cross-linked P(PF-*co*-EG) hydrogels are critical factors affecting cell adhesion [298]. Low-adhesive hydrogels enable a controlled surface or bulk modification with adhesion molecules specifically to enhance cell adhesion. P(PF-*co*-EG) hydrogels have been modified by the covalent integration of agmatine [299] and the adhesion peptide GRGDS [300]. Significantly increased numbers of smooth muscle cells and marrow stromal cells adhered compared with the unmodified networks.

An exclusively hydrophilic fumarate-based macromer is oligo(poly[ethylene glycol] fumarate) (OPF) (Fig. 33.5C). OPF macromers have been synthesized from PEG and fumaryl chloride by a simple condensation reaction in the presence of triethylamine. OPF cross-linking with or without the addition of a cross-linker such as PEG-DA can be initiated photochemically [301] or thermally [302]. In contrast to chemically cross-linked PPF and P(PF-*co*-EG), both of which form rigid polymer networks with a low water content, cross-linked OPF networks exhibit properties typical of hydrogels. Gel characteristics mainly depended on the molecular weight of PEG and the reactant ratio [301]. Cross-linked OPF hydrogels degrade hydrolytically along the ester bonds between fumaric acid and PEG, resulting in increased polymer swelling and a decreased dry weight. The weight loss of OPF hydrogels depended on their cross-linking density [303]. Studies investigating the mechanical properties revealed that cross-linked OPF hydrogels made from low−molecular weight PEG (1000 Da) swelled less, were stiffer, and elongated less before fracture compared with hydrogels composed of longer PEG chains. OPF hydrogels can also be combined in layers to form biphasic gels, with each phase having different material properties [302]. An in vitro investigation was conducted of the cytotoxicity of each component of OPF hydrogel formulation and the resulting cross-linked network employing marrow stromal cells (MSCs). After 24 h, the MSCs maintained more than 75% viability for OPF concentrations below 25% (w/v). A high−molecular weight (3400 Da) PEG-DA cross-linker demonstrated significantly higher viability compared with lower−molecular weight (575 Da) PEG-DA. Leachable products from cross-linked OPF hydrogels were found to have minimal adverse effects on MSC viability [304]. The in vivo bone and soft tissue compatibility of OPF hydrogels was demonstrated using a rabbit model [303]. Based on these promising biocompatibility data, OPF-based hydrogels were investigated as injectable drug, DNA, and cell delivery devices. Cross-linked OPF hydrogels that encapsulated gelatin microparticles were developed as a means of simultaneously delivering two chondrogenic proteins, insulin-like growth factor-1 and transforming growth factor-β1 [305], a strategy that promoted cartilage regeneration [306]. In a more complex approach involving a bilayered OPF hydrogel and the release of a chondrogenic and an osteogenic growth factor, the materials demonstrated the potential for osteochondral tissue repair [307].

Kasper et al. developed and characterized composites of OPF and cationized gelatin microspheres that released plasmid DNA in a sustained, controlled manner in vivo [308]. To control cell adhesion to the hydrophilic hydrogels, RGD adhesion peptide-modified OPF hydrogels were developed [309]. OPF hydrogels have also been shown to be useful as injectable cell delivery vehicles for bone regeneration. MSCs were directly combined with the OPF hydrogel precursors and encapsulated during thermal cross-linking. In the presence of osteogenic supplements, MSC differentiation in these hydrogels was apparent by day 21. By day 28, mineralized matrix could be seen throughout the hydrogels [310]. Hydrogel properties have been identified as affecting osteogenic differentiation within these systems [311]. Studies focused on combining cell and growth factor delivery using injectable OPF formulations [312].

Reactive cyclic acetal polymers: Current synthetic polyesters and polyanhydrides possess distinctive properties and are used extensively in clinical practice. Despite their popularity, the acidic degradation products liberated from the bulk of these polymers raise concerns regarding adverse effects and inflammation of the implantation site. In an effort to develop alternative materials, extensive research is being done to synthesize polymers that biodegrade hydrolytically without releasing pH-affecting moieties. Polymers based on acetals, cyclic acetals, and ketals degrade and form degradation products with hydroxyl, carbonyl, and/or aldehyde groups, depending on the structure of the monomers [313]. These polymers can be used for both soft and hard tissue repair. An example of a cyclic acetal-based building block is 5-ethyl-5-(hydroxymethyl)-β,β-dimethyl-1, 3-dioxane-2-ethanol (EH).

Relatively simple polymeric cyclic acetal networks can be fabricated by the radical polymerization of diacrylated EH (EHD). The resulting networks are hydrophobic; they do not swell in water and they support osteoprogenitor cell adhesion [314]. Using the traditional salt leaching technique, macroporous biodegradable scaffolds were fabricated that supported myoblast adhesion and proliferation; they were investigated for muscular tissue engineering [315]. Networks with increased hydrophilicity were designed by copolymerizing hydrophilic PEG-DA [316], generating water-swellable EHD/PEG-DA hydrogels that were formulated as an injectable system that allowed cross-linking under cytocompatible conditions and sustained encapsulated osteoprogenitor cells for up to 7 days [317]. Copolymerization with methyl-terminated PEG monoacrylate, on the other hand, resulted in nonswelling biocompatible networks with increased hydrophilicity [318].

Other groups of biomaterials are based on polyacetals and polyketals and have shown potential in drug delivery applications owing to their pH-dependent degradation [313]. The development of alternative synthetic polymers such as those described here is a critical step toward the future success of many tissue engineering and drug delivery applications.

Polymers containing acrylate, methacrylate or vinylsulfone functionalities: Precursors of cross-linked biodegradable polyester networks that bear vinylsulfone, acrylate, or methacrylate functionalities include PEG-DA (Fig. 33.5D), PEG-dimethacrylate (Fig. 33.5E), PEG vinylsulfones, diacrylated PLA-PEG-PLA block copolymers, acrylic modified PVA, methacrylate-modified dextran, and acrylated chitosan [45,99,268]. Because the last two examples are synthetic derivatives of natural macromolecules, they are not discussed further here. Besides such hydrophilic, natural macromolecules, which are considered to be candidate building blocks based on their inherent biocompatibility, PEG is the most prominent synthetic component of cross-linked polymer networks owing to its biocompatibility and inertness. As described earlier, PEG is hydrophilic and does not promote cell adhesion. To improve cell adhesion to cross-linked PEG hydrogels, adhesion peptides containing the tripeptide motif RGD were incorporated [319–321]. Research on engineered hydrogels has focused on mimicking the invasive characteristics of native ECMs by including substrates for matrix metalloproteinases (MMPs) in addition to integrin-binding sites. PEG hydrogels cross-linked in part by MMP-sensitive linkers were made degradable and invasive for cells via cell-secreted MMPs [322]. Critical-sized defects in rat crania were completely infiltrated by cells and were remodeled into bony tissue within 5 weeks when these gels were loaded with recombinant human BMP-2 and implanted in the defect site. As in natural ECMs that sequester a variety of cellular growth factors and act as a local depot for them, invading cells were presented with a mitogen that, in this case, specifically promoted bone regeneration [323]. The PEG-based hydrogels used in these studies were fabricated by a "click"-type conjugate addition reaction between vinylsulfone-functionalized branched PEG and thiol-bearing peptides under almost physiological conditions.

To enhance the initial mechanical stability and biodegradability of cross-linked PEG-based hydrogels, oligomeric biodegradable lipophilic blocks such as oligo(lactic acid) [324] (Fig. 33.5F) and oligo(caprolactone) [325], were included in the cross-linkable polymeric precursors. In a critical-sized cranial defect model, porous cross-linked scaffolds made from diacrylated poly(ethylene glycol[2]-lactic acid[10]) combined with osteoinductive growth factors showed potential as an in situ–forming synthetic bone graft material [326].

Biodegradable oligomeric macromers containing biodegradable segments were synthesized for hard tissue applications and drug delivery. To enable more flexibility in materials design and the degree of cross-linking, the central hydroxyl-bearing core molecule was changed from a linear diol such as PEG to a trivalent alcohol with different degrees of ethoxylation [327]. Oligomeric biodegradable domains were incorporated by ROP of lactides or caprolactone. Macromer reactivity for cross-linking was introduced by methacrylation of the chain termini. The degree of core ethoxylation as well as the content of lactic acid or caprolactone units per arm controlled the material properties and provided a material platform for different applications. A similar material system with higher molecular weights was developed for ocular drug delivery [328,329]. These macromers contained lactide- and trimethylene carbonate–based degradable domains and were end-functionalized for cross-polymerization with methylfumarate or methacrylate moieties. Acrylated poly(glycerol sebacate) has been used as an effective tissue adhesive [330].

Photopolymerized (meth)acrylated biodegradable hydrogels have been used in a wide range of biomedical applications. As described earlier, limited interactions with proteins are characteristic of hydrophilic surfaces. Consequently, applications such as the use of cross-linked hydrogels as a barrier applied after a tissue injury to improve wound healing or as a cell encapsulation material that immunoisolates transplanted cells capitalize on this property [99,331]. Islets of Langerhans encapsulated in PEG-DA hydrogels and transplanted to develop a bioartificial endocrine pancreas are a prominent example of the latter application. The hydrogels are permeable for nutrients, oxygen, and metabolic products and enable the entrapped islets to survive and secrete insulin that is released by diffusion. Hydrophilic tissue barriers from cross-linked polyesters such as P(EG-*co*-LA) diacrylate have been used to prevent thrombosis and restenosis after vascular injury and postoperative adhesion formation after many abdominal and pelvic surgical procedures.

Cross-linked hydrophilic polyesters are also promising depots for local drug delivery because of their compatibility with hydrophilic macromolecular drugs, such as proteins or oligonucleotides. The materials' tissue compatibility and hemocompatibility even allow for intravascular applications [332]. Drug release from cross-linked hydrogels generally can be well-controlled by adjusting swelling, the cross-link density, and polymer degradation [30,333,334].

Photopolymerized methacrylated polymer networks have also been widely explored for injectable tissue engineering [45,335]. Elisseeff and coworkers employed PEG-DA scaffolds for cartilage engineering by encapsulating

chondrocytes, MSCs, and embryonic stem cells. In these studies, the cross-linked PEG-based hydrogels served as an efficient scaffold for anchorage-independent cells and promoted tissue formation. Photogelation, which offers good spatial and temporal control of hydrogel curing, was used to control the spatial organization of different cell types within a three-dimensional system for osteochondral defect regeneration by sequentially polymerizing multiple cell and hydrogel layers. In an attempt to promote hydrogel−tissue integration, a tissue-initiated polymerization technique was developed that uses in situ generated tyrosyl radicals to initiate the photogelation of an injectable macromer solution [336].

Traditionally, photopolymerization is initiated by directly exposing materials to UV or visible light in accessible cavities or during invasive surgery. For PEG-dimethacrylate hydrogels, it was shown that light, which penetrates tissue including skin, can cause photopolymerization indirectly (transdermal photopolymerization). In vivo studies revealed that gels can be polymerized in 3 min with no harm to imbedded chondrocytes and subsequent cartilaginous tissue formation, as indicated by increasing the glycosaminoglycans (GAGs) and collagen contents [337]. In deep crevices, such as may be found in larger orthopedic defects, problems are expected to arise from limited light penetration and inconsistent photopolymerization. For those applications, thermally induced cross-linking techniques appear to be advantageous [266].

Hydrogel-forming macromonomers containing other functionalities: The development of injectable hydrophilic macromonomers that can be cross-copolymerized to hydrogels under physiological conditions using cytocompatible chemistries has become a major focus in biomaterial development. The process started with the development of protocols using photo- or heat-initiated free radical polymerization of hydrophilic, typically PEG-based macromonomers in the presence of cells [266,304]. Over the years, several alternative strategies have been explored employing specific addition reactions [6], classical bioconjugation chemistry, and “click” chemistry [338,339], as well as enzymatic conjugation [340]. Specific examples include the Michael-type addition between thiol groups of designed peptides and multiarm PEG vinylsulfone [341], or the conjugation reaction between amine groups and succinimidyl esters that was used to fabricate transparent PEG-hydrogels for ocular applications from branched PEG-succinimidyl propionates and bifunctional or multifunctional PEG-amines [342]. A more complex engineering approach was presented for the direct fabrication of biologically functionalized gels with ideal structures that can be photopatterned to generate specific microenvironments in situ, all in the presence of cells [343]. In this approach, an enzymatically degradable peptide macromer was reacted with a multiarm PEG-azide through a copper-free “click” chemistry that allows for the direct encapsulation of cells. Subsequently, biological functionalities, e.g., adhesion peptides, were introduced within the gel by a thiol-ene photocoupling chemistry in real time and with micrometer-scale resolution. Another approach to the design of biodegradable and biofunctional hydrogel hybrids focuses on integrating GAGs to synthetic polymer networks. Multiarmed PEG (star-PEG) was processed to covalent hybrid networks with GAGs, mainly heparin [344,345]. In the design of hydrogels, the importance of controlling degradation properties as well as externally triggered degradation mechanisms has become clear [346,347], in addition to optimizing the base material, in situ polymerization chemistries, and cell−material interactions.

APPLICATIONS OF SYNTHETIC POLYMERS

Synthetic polymers have a vital role in biomedical applications, including nano-, micro-, and macroscopic drug and gene delivery devices [115,348−350], orthopedic fixation devices [351], and cosmetic and prosthetic implants [98], and as artificial matrices for tissue engineering applications [101]. The interested reader may be directed to the referenced reviews that provide in-depth insight into current trends and technologies. Researchers have sought to develop and clinically explore third-generation biomaterials [1] that are designed to control protein adsorption, cell adhesion and differentiation, implant integration, and foreign body reaction, and to develop biomimetic synthetic materials [4,5,352].

CONCLUSION/SUMMARY

Synthetic biomaterials have progressed from testing “off-the-shelf” plastics not developed for biomedical purposes to a field of synergistic research by engineers, scientists, and physicians dedicated to tailoring material properties for specific applications. Current trends have shifted the focus toward biology to understand and then mimic physiological interactions and signaling.

Hydrogels, especially injectable systems, have attracted increasing attention due to the ease of their application, their structural similarity to native ECM, and their good compatibility for direct cell encapsulation because of their high water content. In tissue engineering, it is no longer believed that the biomaterial itself has to provide mechanical properties comparable to the diseased tissue; instead, the polymer has to promote defect site remodeling and tissue regeneration in vivo such that the regenerated tissue is histologically and functionally indistinguishable from the surrounding tissue. Hydrogels might be superior to hydrophobic polymers in that regard, because they can degrade more quickly, which solves the problem of the formation of nonfunctional fibrous tissue on the polymer−tissue interface. Also, hydrogel breakdown can be synchronized with cell proliferation and migration by using an enzymatically cleavable cross-linker.

Besides providing tailored degradative properties, synthetic materials for regenerative medicine should allow for minimally invasive application techniques, integrate well with the surrounding tissue, and promote cell adhesion, migration, and differentiation. The development and thorough characterization of injectable biodegradables provide the foundation for injectable tissue regeneration. Nevertheless, in situ gelation or polymerization concepts will have to be developed and optimized with regard to the cytocompatibility and stability of the resulting construct. The implementation of biomimetic design strategies will enable control and custom-designed cell−biomaterial interactions to guide tissue formation from transplanted cells. Strategies based on gene delivery or gene-activating biomaterials also have great potential in regenerative medicine, but the long-term safety of such therapies remains to be proven. Developments in stem cell biology and conjugation chemistry, such as biorthogonal "click" chemistries, have allowed for the convenient biofunctionalization of the polymeric base structures presented in this chapter with small molecules, peptides, proteins, GAGs, or DNA/RNA toward implant materials with tailored properties and bioactivity. Advances in additive manufacturing provide tools to process such engineered synthetic biomaterials into customized implants with optimized outer shapes and pore structures as well as porosity.

Overall, advances in the field of biomaterial synthesis and the design of physicochemical properties in conjunction with rapidly increasing knowledge in stem cell biology regarding adhesion, migration, differentiation, and signaling will reveal design concepts for improved injectable, biomimetic, polymer-based formulations for tissue engineering applications.

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