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Perspective

# Biocompatible Synthetic Polymers for Tissue Engineering Purposes

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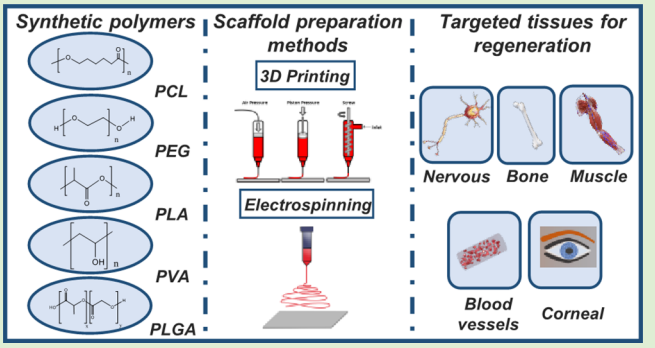
**ABSTRACT:** Synthetic polymers have been an integral part of modern society since the early 1960s. Besides their most well-known applications to the public, such as packaging, construction, textiles and electronics, synthetic polymers have also revolutionized the field of medicine. Starting with the first plastic syringe developed in 1955 to the complex polymeric materials used in the regeneration of tissues, their contributions have never been more prominent. Decades of research on polymeric materials, stem cells, and three-dimensional printing contributed to the rapid progress of tissue engineering and regenerative medicine that envisages the potential future of organ transplantations. This perspective discusses the role of synthetic polymers in tissue engineering, their design and properties in relation to each type of application. Additionally, selected recent achievements of tissue engineering using synthetic polymers are outlined to provide insight into how they will contribute to the advancement of the field in the near future. In this way, we aim to provide a guide that will help scientists with synthetic polymer design and selection for different tissue engineering applications.






## 1. INTRODUCTION

From the ancient myths of Prometheus and Osiris to modern-day Pedro Almodóvar's "The Skin I Live In", the regeneration of organs and life has fuelled the imagination of artists since the beginning of times. In medicine, tissue engineering (TE) is a relatively new, interdisciplinary field that has grown since the early 1990s. TE opened a new avenue of substituting human tissues and organs that propelled the field of regenerative medicine. The ultimate goal of TE is to develop fully functional substitutes for either damaged tissues or organs. To achieve this, living cells are usually associated with a scaffold.[1]

As most tissue-derived cells need to be attached on a solid surface to ensure their viability and growth, the role of a scaffold in TE is crucial, as it guides the development of neotissue. The scaffold aims to temporarily replace the native extracellular matrix (ECM) of the tissue of interest.[2] The materials used to fabricate such a scaffold can be metals, polymers, ceramics, or combinations thereof, depending on the requirements of each application. These materials interact with living cells to produce tissue engineered constructs.

The key requirements of any material destined for a TE scaffold are biocompatibility, biodegradability, appropriate mechanical characteristics, tunable porosity, adhesion, proliferation and differentiation of cells on their surfaces, possibility to be integrated with surrounding tissue, sterilizability, and nontoxicity.[3] These materials must also allow for minimally invasive procedures and be available at a reasonable cost. The extensive variety of materials available today provides a broad range of mechanical properties that determine which types of materials are more suitable for each tissue (Figure 1).

Polymers have gained a prominent role in TE because of a number of beneficial characteristics; they have various and tunable biodegradation rates, mechanical properties, high porosity with various pore sizes, and a high surface-to-volume ratio.[4] As seen in Figure 1, the mechanical properties of polymers (including polymer foams, elastomers, and thermosets) span a wide range, which in turn mimic many types of tissues. Mimicking these native mechanical properties is essential since cells can detect the mechanical microenvironment and adapt accordingly.

This perspective is focused on the use of synthetic polymers in TE applications. In comparison with naturally derived polymers, which are also used in TE, synthetic biodegradable polymers have many advantages, namely (i) versatile mechanical properties, from soft elastomers to stiff thermoplastics, (ii) tunable properties depending on the chemical

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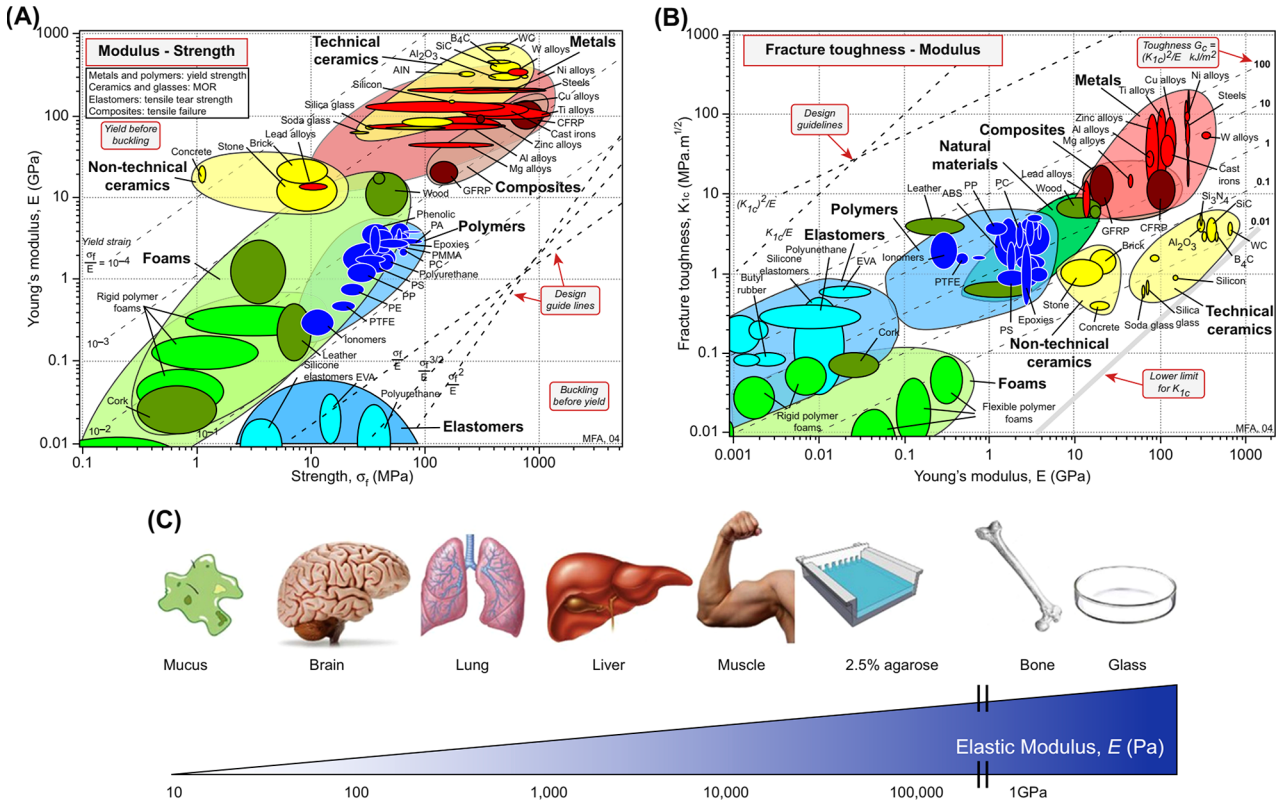


**Figure 1.** (A, B) Ashby chart of strength versus modulus of materials. (C) Young's, or elastic, modulus of tissues. Reprinted with permission from ref 5. Copyright 2008 Elsevier.

structure, (iii) can be molded with several techniques to fabricate scaffolds of different shapes, (iv) reproducible and easy manufacturing, (v) commercially available at reasonable costs, and (vi) allow the release of drugs or other bioactive molecules. In contrast, natural polymers are mostly weak and brittle, can be processed with fewer techniques because they do not melt, show differences from batch to batch, isolation methods can be time-consuming and costly raising their final cost, and suffer from immunogenicity. Since their chemical structure cannot be tuned as easily as synthetic polymers, the control of their overall fast degradation rate is more difficult in comparison with synthetic polymers.

Of course, no single material is perfect; synthetic polymers often lack cell adhesion sites, thus their chemical modifications or combinations with natural polymers are common approaches to overcome this issue. There are many publications in which a seemingly random polymeric composition or combination of polymers has been selected; its *in vitro* efficacy as cell seeding materials evaluated and their suitability for TE applications concluded. While these studies are valuable in clarifying whether certain polymers display any promise at all, there is a lack of in-depth analyses of the effect of each polymer type on tissue regeneration.

This perspective will provide insights on the relationship between the physicochemical properties of synthetic polymers and their application in TE of different tissues. The requirements for a synthetic polymer to be used as a TE scaffold will be presented, focusing on how the properties of a polymer affect its suitability. Next, the main synthetic polymers that are being explored will be discussed, along with the most common scaffold preparation methods. Then, the tissue-dependent characteristics that a polymeric scaffold must possess and selected latest advances in the preclinical studies per tissue type will be reviewed. Furthermore, examples of TE products with clinical applications that contain synthetic polymers will be presented. Finally, based on what we consider the most important findings, the views of the authors about the future role of synthetic polymers in TE will be pointed out and our suggestions to help scientists with choosing synthetic polymer scaffolds for specific applications will be presented.

## 2. REQUIREMENTS OF SYNTHETIC BIODEGRADABLE POLYMERS

Biodegradable polymers, that is, polymers susceptible to degradation by biological activity, are suitable to be used as scaffolds in TE products that are designed for tissue repair or remodeling. Often, biodegradable polymers are subcategorized depending on their fate in living organisms.[6] The most referred to subcategory are bioresorbable polymers, which are completely eliminated *in vivo*, avoiding a persistent inflammatory response, thus making them very attractive for any TE application.

There is a plethora of commercially available and lab-scale produced biodegradable synthetic polymers that were commercialized starting with the first synthetic poly(glycolic acid) (PGA) suture in 1971.[7] So, depending on the goal, polymer selection can be optimized. The suitability of any polymer for TE depends on the target tissue, especially its mechanical characteristics and biodegradation rate, which must be in line with the replacement of the scaffold by the neotissue produced by the cells.

The chemical structure of polymeric scaffolds ultimately determines a range of properties. Among them, surface properties have a profound impact, because they determine


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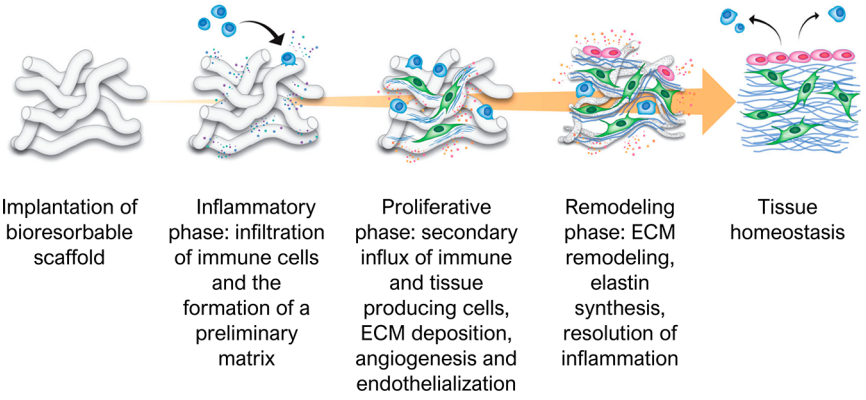


**Figure 2.** Different stages of *in situ* tissue regeneration initiated by a synthetic biodegradable polymeric scaffold. Reproduced with permission from ref 18. Copyright 2017 Nature, licensed under CC BY 4.0.

how polymers interact with cells and proteins. These properties include wettability,[8] swelling ability, electrostatic effects, hydrolytic degradation, elasticity and morphology, and affect the adjacent interfacial environment that allows the interactions of proteins on its surface.[9] Therefore, when a polymeric material interacts with cells, initially it absorbs proteins, followed by cellular attachment, adhesion, migration, proliferation, and ultimately differentiation. Cell−polymer interactions are directly related to the composition of the adsorbed protein layer, and nonspecific attachment of proteins must be avoided as this can trigger an immune response.[8]

The definition of biocompatibility changes as the field of TE is progressing. Initially, a material was considered to be biocompatible if it was inert.[10] Recently, Crawford et al. stated that the definition of biocompatibility is "the ability of a material to locally trigger and guide the proteins and cells of the host toward a nonfibrotic, vascularized reconstruction, and functional tissue integration",[11] therefore elevating the definition of biocompatibility from merely a host response to a complete regeneration of fully functional tissues. In this perspective, the term biocompatibility is used according to the latest definition of Crawford et al.

To better understand how a material triggers tissue regeneration, the host response after the implantation of scaffolds must be considered. Host response starts with protein absorption, followed by acute inflammation and chronic inflammation, and finalizes with fibrous encapsulation.[11] This fibrotic tissue consists of cross-linked connected collagen fibers that prevent vascularization and can cause thrombosis. The immune response influences regeneration[12] as immune cells secrete growth factors,[11] and via the use of immunomodulating biomaterials, fibrous encapsulation can be prevented and tissue regeneration promoted, a process known as *in situ* TE (Figure 2).[13,14] This delicate process depends on the duration of chronic inflammation that normally leads to the formation of fibrous encapsulation,[12] while a shorter duration of chronic inflammation usually results in tissue regeneration.[15] The material−immune system interaction, which is an important aspect of the biocompatibility of polymeric materials, is affected by their bulk physicochemical properties and their morphologies,[13,16] and for the latter, the immune response to a scaffold can be modulated by setting its porosity.[17] Stiff porous synthetic polymer scaffolds enable the response of macrophages toward anti-inflammatory cues, whereas soft porous synthetic polymer scaffolds cause chronic inflammation after 6 weeks *in vivo*. In this light, to tune macrophage adhesion, the combination of specific mechanical properties and porosity must be balanced.[17]

In summary, biocompatibility is a property that includes various types of biological responses that are affected by the physicochemical properties of polymers which are defined by their chemical structures (Figure 3). Therefore, since different

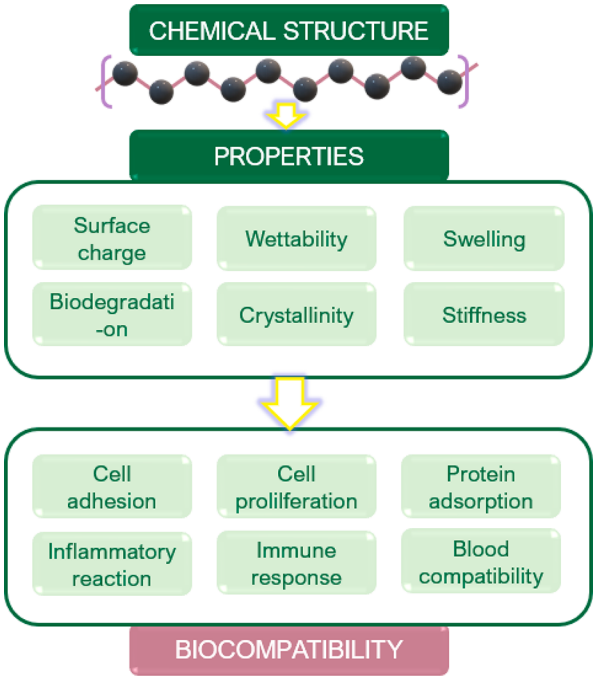


**Figure 3.** Physicochemical properties of synthetic polymers that are controlled by their chemical structure and affect biocompatibility.

biological responses occur at different target tissues, different polymers are to be used for TE.[19] Wettability and swelling are directly affected by the chemical structure and the presence of polar groups (e.g., −COOH, −OH, $-NH_2$) increases them both. Linear polymers with stereoregularity tend to be semicrystalline, while atactic, branched, or cross-linked chains give amorphous polymers. Long methylene sequences also enable polymer crystallization. The larger the crystallinity, the stronger and stiffer a polymer will be. Hydrolytic degradation rate is influenced by wettability and crystallinity, with hydrophilic amorphous polymers degrading much faster.



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## 3. CATEGORIES OF SYNTHETIC POLYMERS FOR TISSUE ENGINEERING

In this section, we analyze the basic categories of synthetic polymers used in TE and elaborate on examples from each category that we believe are the most prominent and will in our opinion dominate clinical applications in the future.

**3.1. Thermoplastic Polyesters.** Among synthetic polyesters, poly(ε-caprolactone) (PCL)[20] is by far the most frequently used one in TE, followed by poly(lactic acid) (PLA)[21] and poly(glycolic-*co*-lactic acid) (PLGA). These polymers are most often synthesized by ring opening polymerization of the corresponding cyclic monomers (ε-caprolactone, lactide, and glycolide)[22] and are commercially available at a reasonable cost and in a variety of molecular weights, with FDA approval for use in several biomedical products. Their success in TE is due to their cytocompatibility and biodegradability that occurs mainly through bulk hydrolytic degradation.[10,23,24] This degradation depends on a number of factors, but overall, PCL has the lowest degradation rate (2−3 years *in vivo*) because of the 5 methylene groups on its repeating unit, which can limit its applications.[25] PLGA has the fastest degradation rate, which can be tuned by the PLA/PGA ratio. For instance, 50:50 PLGA, 75:25 PLGA, and 85:15 PLGA degrade *in vitro* in 1−2 months, 4−5 months, and 5−6 months, respectively.[26] Acidic products are formed during hydrolytic degradation, and although being biocompatible, they can cause a decrease of pH in the microenvironment of the implant that can affect tissue regeneration.[22] This effect on tissue regeneration is under debate as blood normally functions as a buffer and thus should prevent most changes in pH. A major drawback of synthetic polyesters is their hydrophobicity, arising from the methyl and/or methylene groups of their repeating units, which results in poor wettability and cell attachment. As described in Section 2, surface properties are crucial since they affect the interactions of the implant with proteins and cells, and intermediate hydrophilicities are generally preferred to achieve such interactions.[27] Some easy and efficient methods to improve the biocompatibility and tailor the hydrolytic degradation rates of PCL, PLA, and PLGA, are to increase their hydrophilicity by coating[28] or blending with natural polymers, such as decellularized ECM,[29−33] collagen,[34−41] gelatin,[35,38,42,43] elastin,[40,44] other proteins,[40,45,46] and polysaccharides.[35,47−50] Grafting and coating with hydrophilic synthetic polymers, such as poly(glycerol sebacate) (PGS),[48,51] polyacrylamide,[52] poly(vinyl alcohol) (PVA),[53,54] poly(ethylene oxide),[55] polydopamine,[39] polyurethane (PU)[56] have also been performed, as well as plasma treatment.[49,52,57] Copolymerization and blending also help modulate the mechanical properties of these polymers.[56,58−65] Overall, PCL and PLA have been used in the TE of a wide variety of tissues, including cornea, skin, cartilage, and bone.[66] The commercial availability and processability of such thermoplastic polyesters, combined with their established applications in products that have received FDA approval, are major factors that will, in our opinion, keep these polymers in the spotlight of the optimization of TE scaffolds.

**3.2. Elastomers.** Elastic stretchability is a major mechanical property of biological tissues. Elastomeric materials are essential for the engineering of soft and flexible tissues that are subjected to dynamic loading.[67] However, despite intensive research, elastomers with adequate elasticity and biodegradability have not yet been synthesized. The following elastomers have exhibited the best combinations of properties and we believe are the most suitable for TE scaffolds.

Thermoplastic polyurethanes (TPUs) are block copolymers with alternating hard and soft segments, tunable elasticity, and mechanical properties that depend on the ratio between the two segments.[68] The soft segment is normally a long-chain diol, whereas a diisocyanate and a chain extender make up the hard segment. PCL diols and PCL-copolymer diols are often used as the soft segment in PUs, due to their flexibility and cytocompatibility.[69,70]

Recently, self-healing PUs based on dynamic covalent dimethylglyoxime-urethane groups have been reported.[71] These PUs were readily synthesized, by a one-pot reaction without the need for a catalyst. Small amounts of glycerol allowed the formation of covalent cross-links between the PU chains, and their mechanical properties could be fine-tuned by glycerol content to mimic either hard (large number of cross-links) or soft tissue (small number of cross-links). Overall, these self-healing PUs demonstrated exceptional autonomous self-healing, good cytocompatibility, and biodegradability *in vivo*; these self-healing PUs were further investigated for aortic aneurysm, nerve coaptation, and bone immobilization in animal models.

Glycerol polyesters have been extensively used in TE,[72] especially PGS and, to a lesser extent, other polyol sebacates. These polyesters are obtained in two steps: (i) a polycondensation reaction yielding mainly linear oligomers and (ii) thermal cross-linking. Curing temperature and time allow control over the cross-linking density and thus the mechanical behavior and hydrolytic degradation. PGS is highly hydrophilic and cytocompatible,[15,73−75] and to reduce the hydrolytic degradation and increase its lifetime, its numerous hydroxyl groups can be modified with hydrophobic alkyl chains.[74,76] In the same vein, poly(diol citrates) have also attracted interest in TE.[77] The most studied polymer of this family is poly(1,8-octanediol citrate) (POC).

Poly(trimethylene carbonate) (PTMC) is an amorphous polymer with a rubber-like nature[60] that degrades by enzymatic surface erosion, without releasing acidic products.[78] Weems et al. have designed a series of inks based on poly(carbonate urethane)s with pendant double bonds, allowing for cross-linking and three-dimensional (3D) printing via a radical thiol−ene addition.[79] The mechanical properties can be customized by modifying the ratio of the two monomers in the co-oligocarbonates.

Last but not least, supramolecular polymers are worth mentioning. 2-Ureido-4[1H]-pyrimidone (UPy), one of the numerous patterns used in supramolecular assemblies, allows for quadruple hydrogen bonding.[80] Functionalizing thermoplastic oligomers/polymers, such as PCL or polycarbonate (PC), with UPy groups enhances their elasticity, due to the formation of reversible intermolecular hydrogen bonds. Additionally, the UPy moieties can act as convenient anchorage points for Upy-modified bioactive molecules, conferring additional properties to the scaffolds.

**3.3. Hydrogels.** Hydrogels are porous 3D polymeric networks that can absorb large amounts of water due to their highly hydrophilic character and can be either physically or chemically cross-linked. Cross-linking density impacts the properties of hydrogels as with increased cross-linking density, both the swelling degree and flexibility are decreased, while the tensile strength is increased. Hydrogels containing poly(ethylene glycol) (PEG), PVA, and poly(acrylamides) bear


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similarities to the ECM and are thus suitable for the growth and proliferation of cells.[81,82]

PEG is mainly used in pharmaceutical and biomedical applications, notably due to its "stealth" properties, and because of its high hydrophilicity it is used for the preparation of hydrogels. However, PEG must be first functionalized to obtain hydrogels with suitable mechanical properties. This functionalization can be done by modification either with photopolymerizable groups (acrylates, methacrylates), or with groups susceptible to chemical cross-linking (e.g., norbornene).[83,84] Furthermore, PEG lacks bioactivity and thus is often additionally functionalized by cell-adhesive peptides or combined with natural polymers.[85−88]

Besides mechanical properties, cross-linking affects swelling as well; lower cross-linking generally allows for a higher swelling. Swelling is another important factor that should be taken into account in the design of scaffolds. For example, although low cross-linking density is more favorable to endothelial network formation,[83,84] large swelling has a negative impact on network formation. However, cross-linking density is inversely proportional to swelling, and a low cross-linking density results in large swelling. In contrast, an enhanced network formation was observed in a hybrid hydrogel with no swelling. Poly(2-alkyl-2-oxazoline)s are another class of polymers that have similar properties to PEG, although poly(2-oxazoline)s are superior to PEG in terms of synthetic versatility.

PVA is another synthetic polymer with a strong hydrophilic character that is able to form hydrogels.[82,89,90] PVA is obtained by hydrolysis of poly(vinyl acetate) and is commercially available in various hydrolysis degrees and molecular weights. Decreasing the hydrolysis degree grants a higher aqueous solubility, and like PEG, the numerous hydroxyl groups prevent protein adsorption. PVA is however a mechanically weak polymer. The mechanical properties of PVA can be strengthened with the addition of nanocellulose,[91,92] while its bioactivity can be improved by the incorporation of natural polymers or bioceramics.[93−96]

Poly(amino acids) are synthetic polyamides composed of a single amino acid and poly(glutamic acid) has been studied the most.[97,98] Poly(L-lysine) has been shown to upregulate mesenchymal condensation during developmental skeletogenesis *in vitro*. A random polypeptide composed of α-L-glutamic acid and lysine was prepared by ring opening polymerization and further cross-linked to obtain a cryogel with large interconnected pores (≥100 μm).[99] The structure of this cryogel and thus its mechanical properties could be tuned by the ratio of the two amino acids. In a similar approach, poly(α-L-glutamic acid) was cross-linked with lysine in the presence of sodium alginate and bacterial cellulose.[100] Sodium alginate was further cross-linked with $Ca^{2+}$ ions to create a double interpenetrating network. The resulting hydrogel was applicable to osteochondral TE, with a compression modulus similar to natural articular cartilage.

Apart from poly(2-hydroxylethyl methacrylate), acrylates are not used much in hydrogels.[82] Nevertheless, a parallel screening of 380 polymers showed that poly(methyl methacrylate-*co*-methacrylic acid) with a 9:1 ratio has the best potential for use in a chondrocyte culture.[101] Cross-linked hydrogels were prepared with poly(methyl methacrylate-*co*-methacrylic acid), PEG-diacrylate as a cross-linker and PEG as a porogen. After lyophilization, the hydrogel supported the maintenance of a differentiated chondrocyte phenotype, stimulating cell proliferation, and secretion of a cartilage-like ECM, demonstrating its potential for use in osteoarthritis treatment.

## 4. DESIGN ASPECTS, POLYMER SELECTION, AND LATEST ADVANCES

When designing a scaffold, the chemical structure of the chosen polymer is of crucial importance, as it directly affects its biocompatibility. As described in Section 2, a multitude of surface properties and the morphology affect the interactions of the scaffold with tissues, determining the choice of the "ideal" polymeric material, provided that the effect of each property on the biocompatibility is known. This is not an easy task; the complexity of living tissues makes the design of artificial ones with the same features a real challenge. However, extraordinary progress has been made toward better understanding polymer−protein interactions and therefore their biocompatibility.[102] When designing scaffolds for TE, it is important to aim at an architecture that can mimic biologically, structurally, and functionally the native tissue.[94,103] Engineered scaffolds which contain components and possess microstructures similar to native tissues are more effective in tissue repair.[104]

Properties that arise from the chemical structures and are known to significantly influence biological response have been reviewed already in depth.[19] Control of the materials' properties is a known approach to design better biomaterials, for instance hydrophobic surfaces absorb more proteins but in an non-native conformation,[105] so moderate wettability is preferred to retain the function of proteins and maximize cell adhesion.[106] Likewise, high surface charge decreases protein adhesion but improves blood compatibility. Also, since cell membranes are usually negatively charged, scaffolds with positively charged surfaces show enhanced cell adhesion. Mechanical properties, which are controlled by the chemical structure and crystallinity, are crucial because cells are susceptible to the stiffness of the scaffold and their phenotype can be altered by it. Finally, a more obvious effect is that of certain groups that improve the adhesion of biological compounds and those are −OH, $-CH_3$, $-OSO_3H$, −COOH, and $-NH_2$ groups.[19,107] Of course, different target tissues require variable scaffold properties. Below, we explore the specific requirements of each TE application in relation to the polymers used as scaffolds and we discuss selected recent findings.

### 4.1. Synthetic Polymers for Soft Tissue Regeneration.

Soft tissues include cardiovascular tissue such as valves, aorta and heart muscle, dense connective tissue such as ligaments and tendons, loose connective tissue such as cartilage, and epithelial tissue like lining organs and intestines. Each target tissue requires scaffolds with suitable mechanical properties and structures.[108]

*4.4.1. Adipose Tissue.* There are two types of adipose tissue in the human body: white adipose tissue and brown adipose tissue, with the former being the predominant form. Mechanical properties of adipose tissue depend on the anatomical site where it is located and its specific function. Adipose tissue is exposed to large deformations; thus, the fabricated scaffolds should be flexible and withstand physiologically induced deformations. Furthermore, the scaffold must have interconnected pores with openings >100 μm to provide effective oxygen levels that promote angiogenesis and nutrient diffusion.[109,110]


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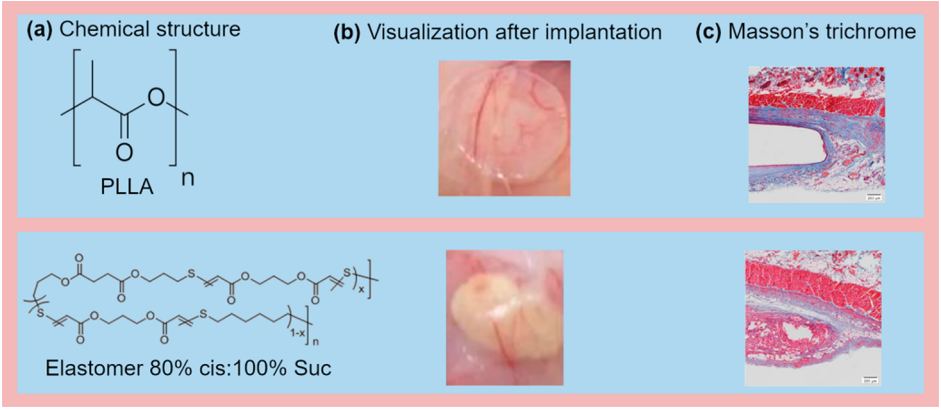


**Figure 4.** Subcutaneous *in vivo* biodegradation of PLLA (top) and 80% cis/100% succinate elastomer (bottom) after 4 months. (a) Chemical structures, (b) visualization, and (c) Masson's trichrome staining. The images are reproduced under the terms of the Creative Commons CC BY with permission from ref 111. Copyright 2021 Nature.

PLA, PCL, PTMC, and TPU-based polymers have widely been explored in adipose tissue regeneration. PLA scaffolds are characterized by brittleness and relatively high strength which makes it unsuitable in our opinion, while TPU scaffolds present high elongation, an attractive Young's modulus, as well as excellent abrasion and tear resistance.[56] PTMC has an excellent potential in adipose tissue regeneration because of its flexibility, derived from its linear macromolecular chain, amorphous character, and very low glass transition temperature. Likewise, P(CL-*co*-LA) and P(LA-*co*-TMC) show better adipogenic differentiation when compared to the stiffer PLA and PLGA, as the aliphatic units of PCL and PTMC comonomers make them more elastic.[66]

To customize the biodegradation rate while retaining the elastic properties, new elastomers with varying ratios of cis:trans double bonds based on succinic acid were developed.[111] In contrast with neat PLLA, after 4 months of subcutaneous implantation in rats (Figure 4), the new elastomer accelerated cellular infiltration degraded almost completely and small vessels were formed, with minimal inflammation and granuloma formation. The faster degradation rate that matched tissue regeneration rates better and the flexibility of the new polymer are the main factors that facilitated its success. However, PLLA is a brittle, nonelastic polymer, not suitable for soft TE and we believe comparisons of the new elastomer with other synthetic polymers, established as suitable for adipose TE (P(CL-*co*-LA) and P(LA-*co*-TMC)) must be performed to determine if their performance is improved enough to compensate for the complexity of the synthetic procedure and the cost that comes with it. Regardless, such elastomers with controlled properties inspire the development of polymers suitable for the regeneration of a range of tissues.

*4.4.2. Muscle Tissue.* 40% of the human body consists of muscle tissues which are highly adapted to their function, but with limited ability to restore themselves after damage.[38] Myoblasts are precursor muscle cells, while the differentiated muscle cells in postnatal muscle are the muscle fibers. Muscle fibers are highly specialized, long, cylindrical cells that can range from 10 to 100 mm in diameter and from mm up to many cm in length.

Skeletal muscle TE scaffolds need to have additional properties, that is, the ability to induce myoblast alignment, direct myogenic differentiation, restore the contractile function, and promote vascularization and innervation.[112] Scaffolds with fibrillar structure similar to that of native muscle promote myoblast attachment, alignment, and proliferation as well as vascularization, because they allow topographical contact guidance. Such scaffolds can be used for *in situ* skeletal muscle TE, acting as cell-free guides to enable endogenous regeneration. Because the cell-free approach is always faster and more economical, we believe that this route should be the dominant one in future research aiming to introduce muscle TE in clinical practice. As an example, Kim et al. produced 3D printed scaffolds that comprised of a micropatterned PCL strut, obtained using PVA fibrillation, to mimic the microfibrils of muscles that help myoblasts to align.[41] These struts consisted of microfibrils that were subsequently coated with collagen and induced myotube formation because they could imitate skeletal muscle cell alignment and fusion *in vitro*.

Thus, the polymers used must be processable with techniques that can create topographical features (e.g., soluble for electrospinning, thermoplastics for melt electrowriting, 3D printing). Cells attach to and organize well around such fibers with a diameter smaller than the diameter of the cells,[113] and although different microfiber diameters have been investigated,[38,114,115] the ideal diameter has not been determined. Electrospinning is a widely employed technique for the fabrication of muscle TE scaffolds, with a variety of synthetic polymers including the polyesters PCL and PLGA (because they are processable and biodegradable), and conductive polymers like polyacrylonitrile (PANI), polypyrrole (PPy), and poly(3,4-ethylene dioxythiophene) (PEDOT).[112,116,117] These conductive polymers are used as an alternative or complementary approach to topographical contact guidance, to facilitate the restoration of the contracting function of muscles which is a response to electrical signals, reduce scar tissue, and enhance myotube formation.[117] Because of the insolubility, brittleness, and difficulty in processing that arise from aromatic units in their structure, they are often combined with other processable, softer polymers like PCL.[118] Conductive polymer oligomers also improve their proccesability, but the conductivity is reduced.

Instead of using inherently conductive polymers, conductive carbon or metal nanomaterials can be added in nonconductive polymers.[112,119] In this vein, Pluronic-CHO, a PEG-*block*-poly(propylene glycol) copolymer with aldehyde end groups, was used as the synthetic polymer in the formulation of


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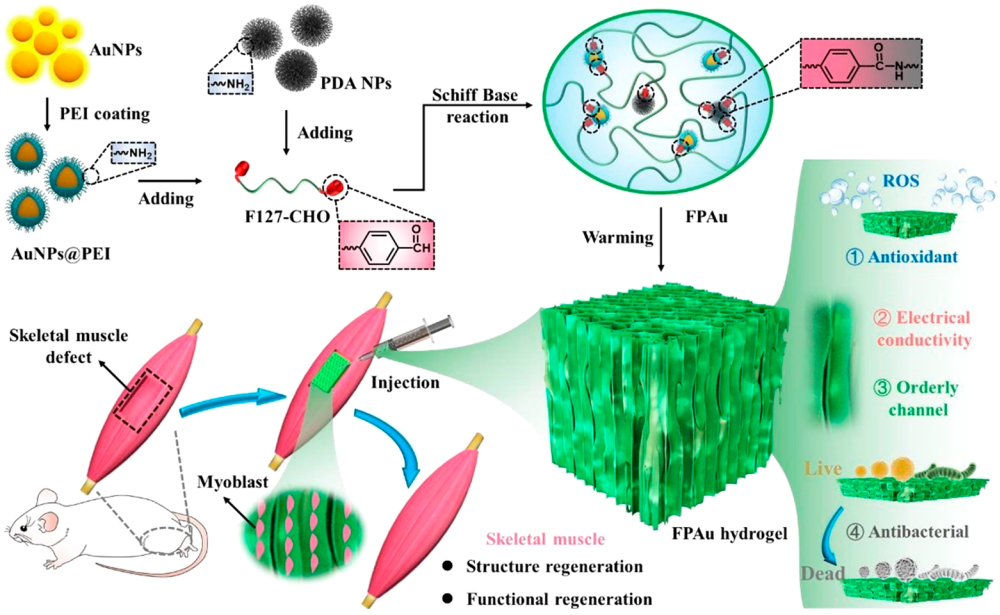


**Figure 5.** Injectable conductive antioxidant antibacterial nanocomposite hydrogel scaffold based on Pluronic micelles cross-linked with PDA nanoparticles and PEI-decorated gold nanoparticles. The scaffold was able to regenerate full-thickness skeletal tissue in a rat model. Reprinted with permission from ref 120. Copyright 2021 Elsevier.

antioxidant, antibacterial, and electroconductive injectable hydrogels for skeletal muscle TE (Figure 5).[120] Polydopamine (PDA) nanoparticles were added for their antioxidant activity, while gold nanoparticles provided electroconductivity. To cross-link the hydrogels, the gold nanoparticles were decorated with polyethylenimine (PEI) that reacted with the aldehyde groups of Pluronic. The combination of injectability, antioxidant activity, and conductive and antibacterial ability along with the porosity facilitated structure−functional regeneration *in vitro* and *in vivo*. Use of nanomaterials always adds another hurdle in the assesement of the safety of scaffolds because they can cause cytotoxicity and accumulate *in vivo*. Thus, we believe that their use must be limited to niche applications.

Advanced synthetic polymer-based scaffolds for skeletal TE include electroconductive polymers in various forms, such as hydrogels or 3D porous scaffolds, but always have specific topographical features and high elasticity.[117,121] To match the stiffness of muscle and promote myotube differentiation, ideally the scaffolds used must have a Young's modulus of ~10 ± 4 kPa,[122] which falls under elastomers, and be able to withstand high contractile forces. Therefore, we suggest that the polymers of choice for skeletal muscle TE are electroactive polymers combined with a soft processable and biodegradable polymer, such as PCL, capable of being molded into an anisotropic structure that mimics native muscle. For example, PEDOT-*g*-PCL copolymers are conductive, processable, 3D printable, and capable of inducing cell alignment and myotube differentiation.[116] Still, the "perfect" synthetic polymer for muscle TE has not been developed, and it requires the combination of good processability, conductivity, and biodegradability.

*4.4.3. Blood Vessels.* Blood vessels are classified into three types: arteries, veins, and capillaries.[123] The ECM of a blood vessel varies in composition, thickness, and overall architecture, and there are large-diameter (inner diameter >6 mm) and small-diameter (inner diameter <6 mm) vessels.[124,125] The blood vessel walls are made of three layers with different composition, mechanical properties, and structure, and because the elastic modulus of vascular walls is not constant,[123] researchers have fabricated polymer scaffolds with different elastic moduli (4−130 MPa).[123] However, it is also crucial that scaffolds are hemocompatible and provide the initial requisite mechanical strength to withstand *in vivo* hemodynamic forces until vascular muscle cells and fibroblasts secrete the vessel wall ECM, and this feature has not been thoroughly investigated to determine the ideal strength values.[126] Since blood vessels are 3D fibrous structures with fiber sizes in the range of 50−500 nm, fibrous and especially nanofibrous scaffolds are highly in demand.[123] Various polymers have been used to fabricate fibrous scaffolds by electrospinning, including PCL, P(LA-*co*-CL), PLA, and PU, resulting in fiber diameters in the range from 50 nm to 3 μm. In a study that compared scaffolds with fibers of increasing diameters, it was concluded that cells adhered on single fibers with diameter ~4.45 μm, elongating along the axes. In contrast, cells adhered and spread over multiple fibers in the scaffolds with thinner fibers (0.27 μm−2.4 μm), likely due to the contact guidance of these smaller fibers. The cells on the scaffolds with thinner fibers presented numerous actin fibers and formed strong focal adhesion over time, while in the scaffolds with the larger fibers, the cells collapsed into a spindle-shaped morphology with no distinct actin fibers and very few focal adhesion points.[127]

PCL is the dominating polymer among the newer scaffolds that are explored for the regeneration of vessels[15,52,74,92,128−134] and is preferred because of its mechanical properties (ductility), suturability, and absence of graft dilation. To compensate for its slow degradation rate, it is combined with other polymers. Multilayer scaffolds are preferred for small vessels to avoid re-occlusion.[135] To impart the scaffold with the desired elasticity and promote the synthesis of elastin, PGS can be used as the internal layer of vascular grafts.[15] Additionally, fast degrading materials like PGS or PLGA promote better cell infiltration and prevent


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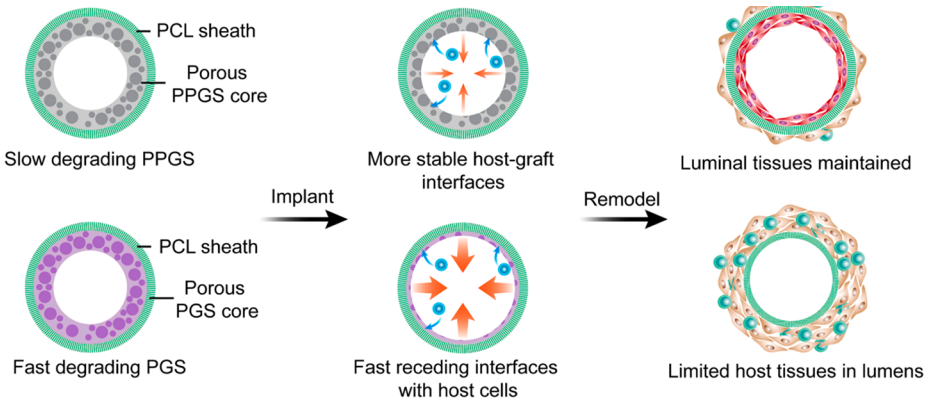


**Figure 6.** Impact of biodegradation rate of PGS and its derivative with palmitate (PPGS) on host remodeling of vascular grafts. PGS is less hydrophobic and degrades fast *in vivo*. The PGS graft presents a less stable and relatively fast receding interface with host cells. This could explain why the graft dilates. PPGS is more hydrophobic and degrades slower *in vivo*. The more stable interface leads to the maintenance of the luminal tissues. Reprinted with permission from ref 74. Copyright 2021 Elsevier.

calcification.[136] Cells are not added in tissue-engineered vascular grafts (TEVGs), as vessel remodelling is initiated by the host's immunoregenerative response. The combination of a porous PCL sheath with a PGS core afforded synthetic grafts comparable to autologous vein grafts in rat carotid artery models.[15] When modified with palmitic acid, the biodegradation rate of PGS was decelerated and the performance of the grafts was improved (Figure 6).[74] Antithrombogenic polymers or biological molecules have also been tested *in vivo* with success, namely as an inner layer of POC[137] or functionalization with heparin.[92,133]

Cutting-edge research is being conducted on the development of *in situ* heart valve TE. Modern days efforts involve cell free scaffolds made from synthetic biodegradable polymers that replace malfunctioning heart valves.[18] Such a bioresorbable heart valve made from a supramolecular thermoplastic elastomer based on bis-urea-modified polycarbonate (PC-BU) was implanted in sheep and was still functional 1 year after implantation.[138] In contrast with TEVGs, tissue-engineered heart valve (TEHV) scaffolds must degrade more slowly to allow the regeneration of a fully functioning valve, and PC-BU has a segmented molecular definition that provides it with well-defined thermal and mechanical properties, and only a small variety of hydrolytic degradation products.

*4.4.4. Nervous Tissue.* The nervous system consists of the central nervous system (CNS), which includes the brain and the spinal cord, and the peripheral nervous system (PNS), which consists of the cranial and spinal nerves. The nervous tissue includes two types of cells: neurons, which are the electrically excitable cells, and neuroglia, which are supporting cells that in contrast with neurons, have the ability to divide.[139] In the PNS, the regeneration of more than 10 mm nerve lesions is poor. Nerve injuries with a gap smaller than 1 cm can be regenerated by reconnecting the two nerve ends. In the more anatomically complex CNS, the regeneration of axons is inhibited by a number of factors, resulting in limited axonal bundle regeneration.[140]

Nerve conduits are used as alternatives to autografts or allografts for peripheral or central nerve regeneration. These conduits must protect the nerve, direct the regeneration of the axons, reduce scar tissue formation, and overall improve the quality of the regenerated nerve.[140,141] While FDA-approved conduits do exist, these are only recommended for the restoration of small injuries (≤3 cm), and their performance is inferior to those of autografts. Among these, Nerbridge, Neurolac, Salutunnel and Neurotube contain synthetic polymers (PLGA, PVA, PGA, and P(DLLA-*co*-CL).[142] As a result, neural TE is not only an established but also an evolving procedure for restoring nerve and track function.

Synthetic polymers must be chosen for the fabrication of nerve guidance conduits because their properties can be easily tailored to match the requirements for efficient conduit performance. PNS conduits must be flexible, biodegradable, permeable, porous, conductive and with minimal swelling, properties that synthetic biodegradable polyesters possess but can also be easily tuned.[141] Soft substrates allow for attachment and growth of neurons,[143] whereas surfaces with low wettability stimulate 3D neuronal growth and differentiation.[144] Regarding conductivity, the scaffolds must have the ability to temporarily change the voltage over the cell membrane to create an action potential, releasing neurotransmitters to excite the next neuron.[145] The use of electroconductive biomaterials such as PPy and PANI has thus recently gained a lot of interest, as these can stimulate cells electrochemically and electromechanically,[146] but they are not biodegradable nor processable, as explained in Section 4.4.2.

Different designs of conduits have been reported, including hollow tubes, multichannel, porous, filled, and grooved conduits.[147] In comparison with hollow conduits, more complex designs yield improved nerve repair.[142] Among the synthetic polymers used, PCL is one of the best picks for nerve TE because it is flexible and can be 3D printed to give such complex structures[141,148,149] In our opinion, the combination of these properties with the availability in the market at a relatively good price as well as the previous regulatory approval in medical devices make PCL-based materials such as copolymers (P(DLLA-*co*-CL)) the most reasonable synthetic polymers of choice for nerve TE. Copolymerization with D,L-lactide helps accelerate the otherwise slow hydrolytic degradation of PCL. The 3D printed nerve conduits from PCL that contained adipose derived mesenchymal stem cells promoted improved nerve regeneration in comparison with cell-free PCL, and the resulting functional motor and electrophysiological recovery in sciatic nerve injuries in rats were comparable to autografts.[150]

**4.2. Synthetic Polymers for Skin Regeneration.** The fabrication of a skin scaffold that will exhibit the features of


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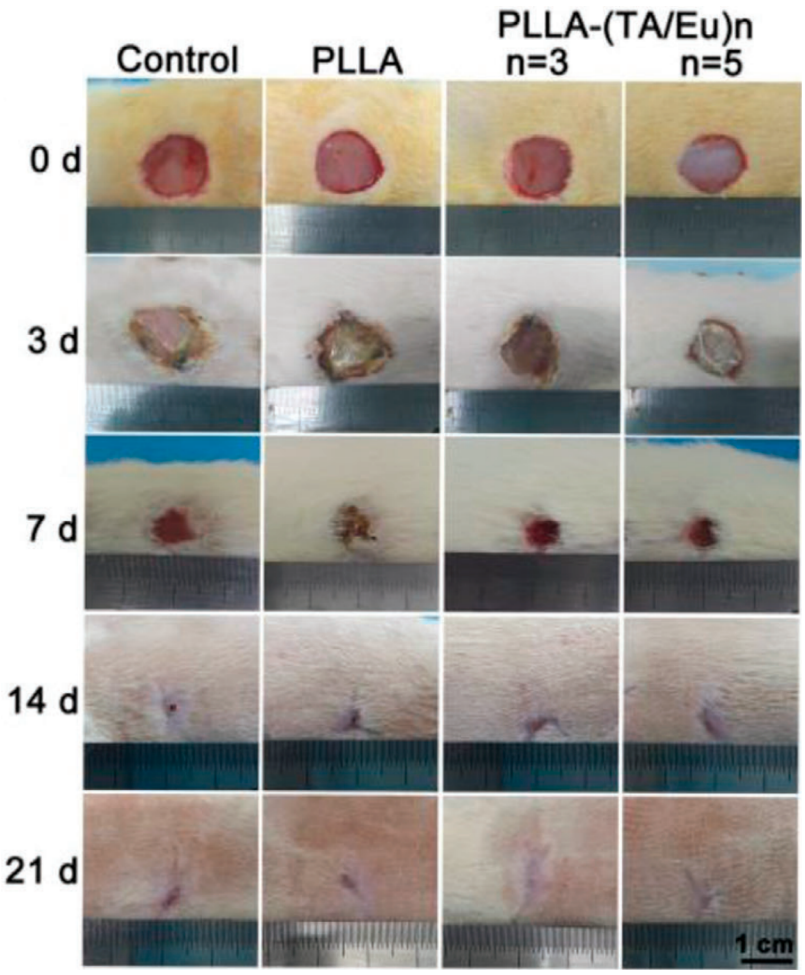


**Figure 7.** PLLA-based nanofibrous mats with tannic acid and europium promote wound closure and angiogenesis in rats. Reproduced with permission from ref 162. Copyright 2021 Wiley-VCH GmbH.

normal skin has been the topic of intense research. Human skin is very thin (1−4 mm) and has elastomer-like properties,[104] and therefore engineered scaffolds must exhibit high elasticity and durability to allow suturing and handling.[151−153] The porosity, pore diameter, and wall thickness are also important parameters for fabricating scaffolds, as these influence the biological behavior of cells. Scaffolds with high porosity are suitable for cell seeding and nutrient exchange, and the pore diameter of human acellular dermal matrix is 131.2−96.8 $\mu$m with a median value of 95 $\mu$m.[104] When the pore size is >10 $\mu$m, the migration of cells in the scaffolds is possible.[153] To match the normal healing time of a skin incision, a skin regeneration scaffold must degrade in about 25 days.[153]

To obtain the preferred biological responses that lead to skin regeneration, adequate wettability is required to enable the formation of bonds between the wound and the scaffold.[42,153] The surface of the scaffolds must present high hydrophilicity and large water absorption capacity, for example, it was found that small water contact angle values of PCL/natural polymer (gelatin and collagen) scaffolds ($\theta$ = 25−49.5°) and large swelling ratios (up to 2000%) enhanced cell adhesion, proliferation, and differentiation.[154] Additionally, scaffolds must offer an adequate surface for cell residence and must retain structural integrity and dimensional stability when physicians handle and implant scaffolds onto the damaged site of the host.

PLGA, PLA, and PCL are being investigated for skin regeneration due to their good mechanical stability and processability.[34,42,45,49] PLA and PLGA have been used to fabricate a plethora of skin regeneration scaffolds with various techniques (3D printing, electrospinning,[34,42,155] gas foaming,[156] porogen leaching,[157] phase separation,[158] fiber bonding[159]), and of these techniques, electrospinning is the best known for skin TE. However, due to the PLA's innate hydrophobicity, the cell's attachment, viability, and proliferation are delayed. PCL has also been extensively studied for skin TE due to its elastic properties, arising from its chain's flexibility and its ability to support the engineering of dermal substitute tissue,[26,160] but due to its hydrophobicity it inhibits skin formation.[45] PLGA electrospun fiber diameters in the range of 350−1100 nm are the most suitable among synthetic aliphatic polyesters for the optimum growth and proliferation of skin fibroblasts.[161] Overall, the role of the nonhydrogel forming synthetic polymer is that of providing structural integrity and processability. PVA and PVP have been studied for skin regeneration due to their ability to form hydrogels that can also be loaded with active ingredients such as growth factors.[93] PVA hydrogels have a similar structure and mechanical properties to the native skin tissue, manifesting good adherence of fibroblasts. In addition, both PVP and PVA


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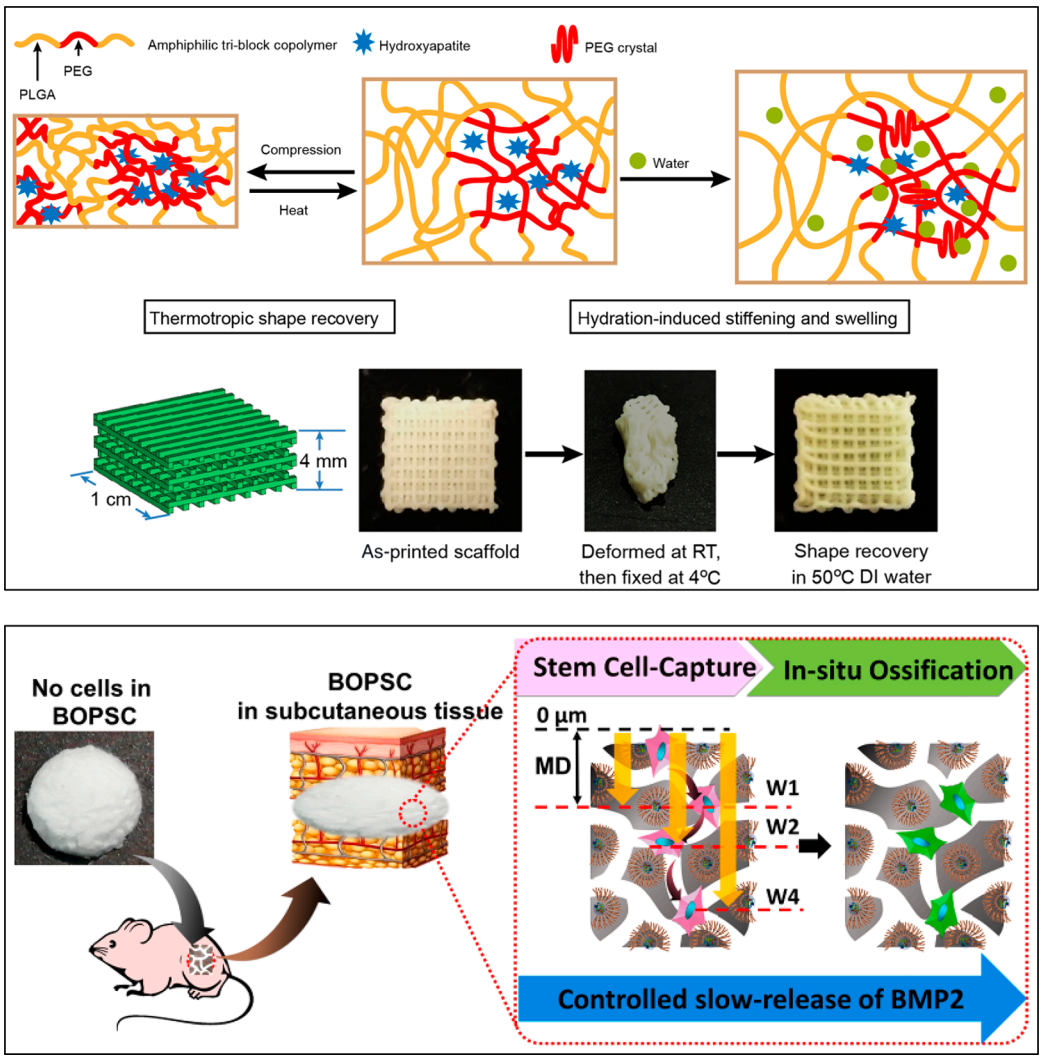


**Figure 8.** (top) Thermal-responsive shape memory and hydration-induced stiffening and swelling behaviors of a representative amphiphilic 25% HA PLGA-PCL-PLGA composite. Reprinted with permission from ref 166. Copyright 2019 AAAS. (bottom) *In vivo* cells capture and *in situ* osteogenic induction of bioactive PLGA-*co*-poly(ether imide) osteo-polyester scaffold (BOPSC) accompanied by BMP2-release in mice. Reproduced with permission from ref 170. Copyright 2021 Elsevier; licensed under CC BY 4.0.

are highly hydrophilic, which makes them good adsorbents of wound fluid and can resist external environmental stresses from pathogens or other origins, contributing to the wound healing process.[26]

Synthetic polymer scaffolds for skin TE are almost always combined with a natural polymer, most often collagen or gelatin to ameliorate their low cell adhesion. The role of collagen and glycosaminoglycans on the regeneration of full thickness skin was recognized early on, before the growth of TE as an autonomous field.[151−153] Recently, an antioxidant and angiogenetic wound dressing that was based on PLLA and contained tanic acid and europium was developed. The dressing was in the form of electrospun nanofiber mats that were able to scavenge excessive reactive oxygen species in wound sites on rats, promote angiogenesis, and accelerate wound healing (Figure 7).[162] Besides its antioxidant activity, tannic acid increased the hydrophilicity of PLA, which was crucial in the successful demonstration of the scaffolds.

**4.3. Synthetic Polymers for Bone and Cartilage Regeneration.** Bone is a complex tissue that contains compositional and structural gradients.[163] The specific requirements for materials applied in bone regeneration are mechanical stability, controllable degradation kinetics, osteoinductivity, osteoconductivity, osteointegration, and antibacterial properties.[33,164] The compressive modulus values of bone are 18−22 GPa and 0.1−0.9 GPa for cortical bone and trabecular bone, respectively.[165] Ceramic bone substitutes have stiff or brittle structure and lack mechanical endurance; therefore, polymers in the form of meshes, hydrogels, and sponges/foams are looked upon as replacements.[166] Scaffold hydrophilicity is crucial concerning their osteoconductive ability, as moderate hydrophilic surfaces lead to high cell adhesion[55] with an optimum surface water contact angle reported in the range 55°−75°.[94] Since synthetic polymers are not able to promote osteogenesis on their own, scaffolds for bone TE made of synthetic polymers always contain other types of compounds, like natural polymers, inorganic fillers, and/or growth factors. The ECM of bone is ceramic, so most scaffolds also contain synthetic ceramics like bioglass, hydroxyapatite, and tricalcium phosphate.[94,163,167] Coatings[33,168] and surface modification[39,65] of neat materials are often employed to enhance their bioactivity, antimicrobial and mechanical properties.


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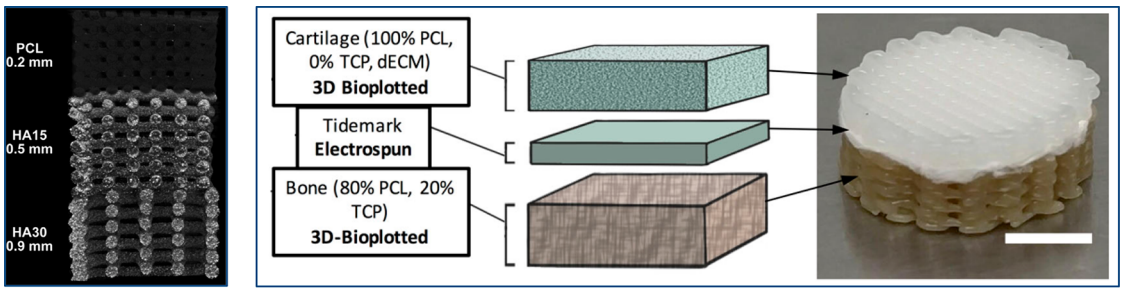


**Figure 9.** Design of multilayer scaffolds based on PCL for osteochondral TE applications. (a) Micro-CT image of the side view of gradient porosity of a scaffold with PCL and different concentrations of HA. Reprinted with permission from ref 180. Copyright 2021 Elsevier. (b) Scaffold design for full-osteochondral TE with PCL, dECM, and TCP. Reproduced with permission from ref 30. Copyright 2020 John Wiley & Sons, Inc.; licensed under CC BY 4.0.

Many polymers possess the required mechanical stability, however when aiming for properties' optimization, copolymerization or blending with other polymers is performed. Block copolymers[58,103,166] usually with an ABA-structure (hard A blocks and a soft B portion),[58] are good options because hard blocks provide mechanical strength and soft blocks enhance the hydrophilicity of the scaffold, promoting cell attachment. The polymers used most often recently in bone TE are PCL,[32,33,167,169−173] PLGA,[29,39,163,170,172,174,175] PUs,[54,176] followed by PLGA-*b*-PEG-*b*-PLGA,[166] polymethacrylate derivatives,[101] poly(propylene fumarate),[163] polyphosphazenes,[175] polyhydroxyalkanoates,[172] and combinations thereof.

Osteointegration in early stages is affected by the scaffold's macroscopical 3D structure and its inner 3D microstructure. Interconnected pores promote tissue growth,[103] but affect their mechanical properties since larger pore sizes lead to inferior mechanical properties.[47] However, interconnected macroporosity (>300 $\mu$m) provides roughness on the surface of the scaffolds,[32] promoting vascularization and attachment of osteoprogenitor cells, facilitating direct reparative osteogenesis,[166,176] and the applicable porosity can be designed using synthetic polymers through lyophilization, electrospinning, 3D printing, or vacuum-aided solvent casting.

Composite materials based on thermoplastic polymers combine the advantages of each category to give rise to improved bone substitutes, and along with their ability to be 3D printed, more and more research is dedicated on fabricating bone TE scaffolds using composite materials.[177] Novel cell-free approaches in combination with cutting edge fabrication techniques such as 3D printing have showed promising preclinical results. The decoration of synthetic polymer scaffolds with *in vitro* generated bone ECM by stem cells was proven a suitable method for improving bioactivity, controlling the immune response, and inducing angiogenesis.[29,32] Furthermore, a scaffold that can be surgically inserted with unprecedented ease was prepared using a PLGA-PEG-PLGA amphiphilic triblock copolymer combined with 25% hydroxyapatite.[166] The copolymer imparted the scaffold with thermotropic shape recovery (Figure 8a) and stiffening and swelling after contact with water that stabilized it following insertion in rat femoral segmental defects. This unique property is only achievable by using synthetic polymers. In addition, scaffolds from PCL and PLGA-PEI loaded with bone morphogenic protein (BMP) were able to capture stem cells *in vivo* (Figure 8b), as a cell free approach to repair nonload-bearing bone.[170] As in other tissues, bone TE is also looking for ways to avoid the introduction of cells in the scaffolds before implantation. Thus, we believe that polymer-based 3D printed composites are currently a great choice for bone TE.

Cartilage is a soft tissue directly in contact with bones and defined by changes in the biochemical composition, structure, and mechanical properties from its surface to the subchondral bone. Cartilage is mainly composed of water (60%−80%), ECM components (mainly collagen II fibers), proteoglycans, chondrocytes, and a progressively decreasing gradient concentration of calcium ions from the subchondral bone area to its surface.[165] The collagen fibers and the proteoglycans give cartilage its large water uptake capability, tensile strength, and compressive resilience. Cartilage differs from other soft tissues, as it is avascular, aneural, and alymphatic, with a low cell to ECM ratio that makes its regeneration in the human body difficult. Therefore, developing effective cartilage TE products is of great significance from a clinical point of view.

Cartilage is much softer and elastic than bone, and as a result, soft substrates can induce chondrogenesis.[101,165] Compressive strength in the range 0.5−3 MPa is adequate for cartilage regeneration, while the ideal scaffold pore sizes for chondrogenesis are 90−120 $\mu$m.[165] Because of their high water content and injectability, polymeric hydrogels are a good option to mimic its structure,[88,101,178,179] while multilayered scaffolds with gradient can mimic the continuous compositions of native cartilage and osteochondral bone.[30,163,165,169,180,181]

As in osteogenesis, the optimization of the materials applied in cartilage regeneration is conducted by blending and coating of the materials. Coatings can lead to higher gene expression,[50] whereas blends are formed to combine the optimum properties of the materials, that is, enhanced biocompatibility and mechanical strength, like for example, chitosan and PEG diacrylate blends.[88] PEG-based hydrogels have suitable mechanical properties for cartilage TE.[182,183] Polyacrylates with surface amine groups and poly(methyl methacrylate-*co*-methacrylic acid-*co*-PEG-diacrylate) hydrogel scaffolds have been shown to induce chondrogenesis of mesenchymal stem cells even in the absence of chondrogenic induction factors.[101,184] These polyacrylates with surface amine groups could have promoted induction factor production arising from direct cell-scaffold interactions.[101] The presence of a polypeptide as poly(L-lysine) on oligo[poly(ethylene glycol) fumarate] hydrogels resulted in enhancement of chondro-


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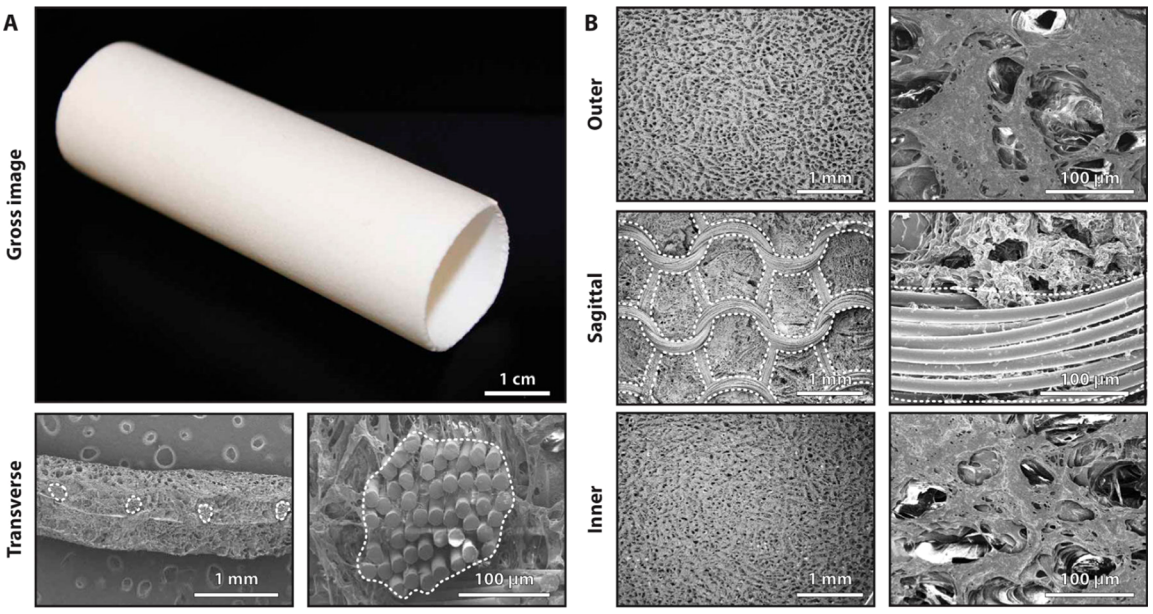


**Figure 10.** Scaffold made from synthetic biodegradable polyesters for the development of TEVGs. (A) Gross image of a tubular scaffold. Low- and high-magnification transverse SEM images of the scaffold show the PGA fiber bundles, outlined in white. (B) Low-magnification (left) and high-magnification (right) SEM images of the scaffold showing the porous inner and outer surfaces, the middle layer, and the PGA fibers. Reprinted with permission from ref 202. Copyright 2020 AAAS.

genesis of MSCs,[179] since poly(L-lysine) promotes chondrogenesis via the upregulation of functional N-cadherin expression. In general, the available amine groups on the surface of scaffolds play an important role in enhancing chondroinduction.

A novel 1,4-butanediol thermoplastic polyurethane elastomer managed to mimic the tribological performance of cartilage better than PCL and PLA.[185] The elastomer was 3D printed with FDM, and pore geometry heavily influenced cell integration. A triangular geometry was superior in terms of cell adhesion and proliferation of infrapatellar fat pad adipose MSCs.[186] Besides those tailor-made polymers, commercially available thermoplastics are still studied, and scaffolds for cartilage TE with complex structures are prepared, especially with the contribution of 3D printing.[30,180,187] The ease of reproduction of porous scaffolds made from PCL or PLGA with a controlled, organized porous structure gives a unique feature to these polymers, as such organized structures are essential in mimicking the inherent complexity of osteochondral tissues. Finally, gradient multilayer scaffolds containing other compounds that improve osteogenesis, such as HA[180] (Figure 9a), tricalcium phosphate (TCP) and decellularized ECM (dECM)[30] (Figure 9b) or PCL conjugates with hyaluronic acid binding peptides derived from aggrecan,[187] were prepared with 3D printing and could provide a valuable and reproducible solution to combat cartilage morbidity.

**4.4. Corneal Regeneration.** The human cornea is a mechanically strong and transparent multilayer tissue that resembles a fibril-reinforced laminate biocomposite as it contains collagen lamellae.[188] These layers of the cornea are the epithelium, Bowman's layer, Descemets membrane, endothelium, and the stroma which occupies 90% of the cornea and contains the collagen lamellae. The unique properties of the cornea that must be reproduced in the scaffolds designed for cornea TE are (i) transparency, (ii) nonangiogenetic, (iii) absent or minimal inflammatory reaction, (iv) mechanical properties that allow suturing without tearing, and (v) adequate nutrient permeability ($\sim 2.2 \times 10^{-18}$ $m^4$ $N^{-1}$ $s^{-1}$).[189]

While collagen-based or decellularized scaffolds are the most common ones in corneal TE, collagen is a rather expensive and fragile natural polymer. The mechanical properties, biocompatibility, and easy processability of synthetic polymers have yielded numerous preclinical studies and some clinical trials[190] that used these polymers as scaffolds for corneal TE.[191−195] Synthetic polymers play the role of limbal stem cell carriers, especially in the form of contact lenses, for the repair of ocular surface impairments or limbal stem cell deficiency.[193]

The transparency of the cornea is attributed to the small, aligned collagen fibrils with regular spacing of its ECM. The alignment of the scaffold also facilitates the alignment, cell migration, and promotion of the keratocyte phenotype of corneal stromal cells. Therefore, the polymer used must be processable with techniques that allow the fabrication of fibrous, aligned surfaces with curvature (e.g., electrospinning, 3D printing), and most synthetic polymers are like so. However, achieving small enough fiber diameters to mimic the stroma (≈36 nm) and accurate spacing control is a challenge in the manufacturing of scaffolds. The curvature of the scaffolds is also proven to have an effect on orientation and phenotype of both stromal and epithelial corneal cells.[196] However, the semicrystalline character of many synthetic polymers makes them hazy, and therefore, spacing between the fibers and/or use of amorphous polymers is recommended. Additionally, when manufacturing scaffolds in the form of contact lenses, lubricity and softness are necessary to ensure comfortable wear. Synthetic polymers with long aliphatic sequences and polar end groups tend to be soft and pliable, moderately hydrophilic, and soluble, making them suitable for corneal TE.

During the past few years, synthetic polymers stand out in the research for corneal TE, and the one, in our opinion, that stands out the most is PCL.[192] Usually combined with other polymers to accelerate its degradation rate, such as PGS,[48,51]


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collagen,[35,37,197] gelatin,[35] chitosan,[35,48] or modified with ECM,[31] PCL has been used to prepare and evaluate scaffolds, using mostly electrospinning. While the use of natural polymers and especially collagen has been proved to better mimic the structure of the cornea, issues with price and weak mechanical properties resulted in limited applicability and the combination of a natural with a synthetic polymer currently appears to be the prevailing choice for the development of artificial, tissue engineered corneas. These new constructs are expected to not only minimize the need for donor corneas but also replace amniotic membranes that are often used for corneal stem cell transplantation.[198] Because of the precedent in FDA approval of PCL for biomedical applications and its flexibility that allows it to withstand suturing, many preclinical studies use this polymer. Sun et al. fabricated corneal grafts with collagen and PCL with improved tension stress.[197] A novel electrospinning method was also developed in order to prepare hemispherical scaffolds from PCL and collagen that resemble the shape and the radial alignment of nanofibers of the native cornea. The alignment significantly improved the proliferation of corneal stem cells *in vitro* and the expression of the relevant gene markers.[37] A viable synthetic stroma substitute was developed *in vitro* using PCL and melt electrowriting.[199] Due to its chemical structure with cross-links and long aliphatic chains, PGS is an amorphous and elastic polymer, both being very attractive properties for corneal TE. When combined with PCL, aligned nanofibers can closely mimic the native cornea and are more hydrophilic and therefore improve cell proliferation when compared with PCL alone.[48,51]

As the cornea is a relatively simple tissue, with no blood vessels and only a few cell types, the impact of TE on the treatment of ocular diseases is expected to be invaluable, and relatively soon, as the main goal of corneal TE is to minimize the need for corneal tissue from end-of-life donors, the availability of which is inadequate for the number of patients awaiting transplantation.[200]

## 5. SYNTHETIC POLYMER TE SCAFFOLDS WITH CLINICAL APPLICATIONS

Tissue-engineered products based on synthetic polymer scaffolds have been used for selected patients, where following standard routes was no longer a viable option. Currently, a tubular scaffold made from electrospun PGA fibers and P(CL-*co*-LA) and seeded with autologous bone marrow-derived mononuclear cells is undergoing a Phase II clinical trial as a TEVG for the treatment of complex congenital heart disease in children (Figure 10).[201,202] Another ongoing TEVG trial demonstrated that a valved conduit made from an electrospun scaffold that comprised of PCL, PC, and 2-ureido-4[1H]-pyrimidone (UPy) had promising preliminary outcomes in a small group of patients, as an alternative to allograft conduits which typically fail in young children.[203] In this case, no cells or other bioactive factors were added on the scaffold, but the scaffold itself was designed to attract the patient's own cells. The role of the polymer in these TEVGs is to cause a foreign body response that triggers the regenerative process. As the polymer degrades, neotissue is formed and inflammation reduces, showing the crucial role of the polymer's biodegradation rate and controllable inflammation in the restoration of the tissue.[134,204] More specifically, if the scaffold is resorbed too quickly, mechanical failure will occur. If it is resorbed too slowly, a persistent foreign body response will occur that will cause fibrotic tissue accumulation and finally valve malfunction. TEVG scaffolds must be resorbed relatively slowly to allow tissue maturation before they are fully resorbed. Besides tailoring the chemical structure of the polymer used, the microstructure of the scaffold can help maintain the balance between resorption and tissue formation.

Commercially available tissue engineered cellular dermal substitutes where the skin is grown on synthetic polymers include Dermagraft and Trancyte.[205,206] The structure of the skin, the easy growth of skin cells and the in-depth knowledge of skin biology contributed to the early introduction of engineered skin in the clinical practice. In Dermagraft, fibroblasts are cultured in a bioreactor on a PLA/PGA knitted scaffold and in Trancyte on nylon. In contrast with collagen-based scaffolds, fibroblasts proliferate very fast on synthetic polymers and deposit large amounts of ECM, and the scaffolding polymer is a commercial product that has been regulatory approved. These products are being used in the treatment of chronic wounds, such as diabetic ulcers and third degree burns as alternatives to skin from cadavers.

BioSeed-C is a commercially available product for TE of autologous cartilage.[207] It is comprised of a PLGA and polydioxane scaffold where autologous chondrocytes are expanded and retransplanted into the defective cartilage and is significantly better in regenerating cartilage when compared with the traditional autologous chondrocyte implantation approach.[208]

A clinical trial on the restoration of corneal epithelium is using silicon hydrogel contact lenses as carriers for autologous epithelial stem cells. This contact lens approach was shown to be a successful alternative for the treatment of limbal stem cell deficiency, with 63% of the patients showing a healthy ocular surface at the short to midterm follow up.[190]

The small number of available products might initially discourage us from envisioning more TE applications for synthetic polymers. However, we must keep in mind that first and foremost, this field is a novel one. The few, but seemingly quite successful, products that exist will help to establish regulations and promote the development, approval, and marketing of others. Additionally, these products inspire the continuation of research that will contribute toward discoveries in different fields, which are essential for planning better TE strategies.

## 6. CONCLUSIONS AND OUTLOOK

The quest for biocompatible synthetic biomaterials is still ongoing; the use of new techniques and polymers with optimized compositions and properties will be instrumental in broadening the range of TE products that are safe and efficient for clinical use.

Currently, the main challenges concerning the use of synthetic polymers, besides the general hurdles that TE faces (such as regulatory matters, difficulties in scaling up cell cultures, setting up clinical trials, and the potential big risks on human health, suboptimal vascularization), are the difficulty in defining standards for biocompatibility testing[9] and optimizing the choice of biomaterial, which results from a lack of sufficient knowledge of the human body, tissues, and immune responses.

Therefore, obtaining an in-depth knowledge of the effect of polymer chemistry on the regeneration of tissues via their interactions with the host's cells, but also the immune system,[16] will allow us to fully exploit the potential of these versatile materials. Gathering such specialized knowledge will


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Biomacromolecules 2022, 23, 1841−1863

require collaborative contributions from a multidisciplinary pool of scientists, including polymer scientists, bioengineers, biologists, and medical doctors. Ultimately, we believe an important milestone TE will achieve in the future is to allow specialized, personalized treatment options to patients where traditional approaches fail, with a significant contribution from the rapid development of 3D printing. Reaching the ultimate goal of an effective tissue formation with minimal risks, safe clinical translation, and at a reasonable cost might still sound like a dream, but we are already harvesting the fruits of all the research that has been conducted in the last few decades. Faster translation to the clinic might be achieved for cell-free scaffolds, due to the cost, difficult logistics, and regulatory and ethical issues that the use of cells raises. Thus, the role of polymers will remain in the spotlight.

Regarding synthetic polymers, we saw an increase in the number of biodegradable polymers that have been designed specifically as scaffolds, synthesized and characterized, offering many choices for new TE formulations. TE scaffolds are fabricated and will, in our opinion, keep being fabricated mostly with additive manufacturing and electrospinning or combinations of different techniques.[209] Regardless of the recognized significance of the latest research, there is a lack of consistency in their evaluation that requires a need for the establishment of protocols that compare results obtained in different preclinical studies, especially those of biocompatibility.[11]

We envision the development of versatile materials that will be effective on the regeneration of multiple tissues and of cell free scaffolds that are not strictly regulated, and are stored and transported with relative ease. Connection of the polymers' properties with the regeneration and immune responses is more necessary than the development of new polymers toward the development of such materials. In fact, we believe that the constant designing and synthesis of new synthetic polymers might hinder clinical translation, as these polymers demand extensive testing and significantly increase the time and investment mandatory for regulatory approval. To balance the risk, the cost, and the potential benefits of new synthetic polymers in TE, niche applications where no established polymers are suitable for should be targeted.

Thus, when designing and testing newly synthesized polymers, a scientist must first answer the following questions: Do the existing, established, and commercially available polymers face significant problems that might prevent clinical applications? If so, do we understand what is causing the problems? Are the polymers designed in a way to overcome these problems? Is the performance improved enough to justify the cost, time, and regulatory hurdles that new polymers will undoubtedly face?

After studying the preclinical and clinical advances on TE applications that use synthetic polymers, the author's perspective on the directions that will advance the field and contribute toward developing better polymeric scaffolds are discussed below, separated by the type of target tissue.

**6.1. Soft Tissues.** Polymers for soft TE should keep focusing on improving the elasticity, tuning the biodegradability of already known synthetic polymers, and mimicking the mechanical properties of the native tissue as closely as possible. Elastomers as well as soft thermoplastic polyesters and their copolymers will continue to be in the forefront of developments. Cell free scaffolds for *in situ* TE will enable the introduction of more scaffolds in clinical practice.

**6.2. Vessels and Heart Valves.** Currently, biodegradable polyesters with previous FDA approval dominate the field. The benefits of immunomodulating scaffolds without cells are already established, and polymers with inherent antithrombogenic properties or functionalization with anticoagulant molecules show promise for scaffolds with improved function. To obtain better TEHVs, the understanding of the relationship between TEHV stenosis, polymer, and inflammation is crucial and, in our opinion, it must be studied in more depth.

**6.3. Muscle.** To better mimic native muscle tissue, micropatterned, electroconductive, or stimuli-responsive elastic composites based on synthetic polymers are optimal. To create the desired micropatterns, 3D printing will be utilized, as it allows easy production of aligned structures. Gaining a better understanding on how electroconductive polymers regulate muscle tissue formation will help with the choice of the polymer, which will then be used to produce cell-free scaffolds that recruit stem cells on site. From our view, such scaffolds will likely be the preferred choice over cell-laden scaffolds. Finally, we believe that new biodegradable conductive polymers must be developed, as they will help progress the field significantly.

**6.4. Nerves.** It is necessary to better understand the interactions of neural cells with topographical patterns of synthetic polymer scaffolds. So far, it has been suggested that a combination of different materials and design approaches, such as multichannel or nanostructured nerve conduits, will have improved performance. Additionally, there is a need to develop biodegradable conductive polymers and improve the potential of large-gap peripheral nerve repair.

**6.5. Skin.** In the future, more simple systems without cells that impart issues of allergenicity, cryopreservation, and distribution must be developed. Thus, the role of polymers in combination with biological molecules should be in the spotlight, and polymers with an established safety such as PVP, PCL, and PLGA, combined with natural polymers to improve cell attachment, are cheap and efficient candidates.

**6.6. Bone.** In bone TE, thermoplastic polyesters that allow 3D printing of complex designs are the synthetic polymers of interest and should be the synthetic polymers of choice. Future scaffolds must be designed to allow *in vivo* stem cell capture and *in situ* osteogenic induction. PCL is prominent for such hard tissues because of its printability and slow degradation.[25]

**6.7. Cartilage.** To mimic full osteochondral defects, reproducible multilayer or continuous gradient composition scaffolds are needed.[165] Synthetic polymer hydrogels will play an integral role in the fabrication of such scaffolds, especially when processed with 3D printing. Spatially controlled biochemical cues that make the addition of differentiation factors unnecessary are considered a state-of-the-art approach.[187]

**6.8. Cornea.** Synthetic polymer scaffolds for corneal regeneration must consist of fibers with radial alignment and a cell source is always required. Instead of testing new polymers, better knowledge on the effect of physical properties on regeneration will accelerate clinical translation. Anti-inflammatory corneal scaffolds must be developed for high-risk patients. Finally, because of the relative low risk of clinical trials, corneal TE strategies are expected to reach the bedside faster than others.

To help guide the readers on which synthetic polymer to select when targeting a specific TE application, we compiled a table (Table 1) that contains the synthetic polymers that, from


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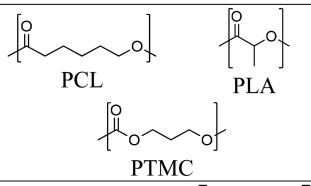
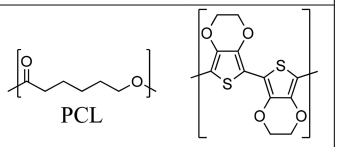
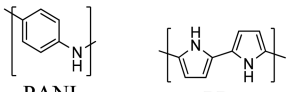
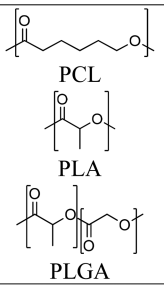
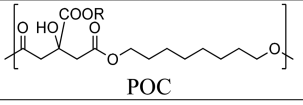
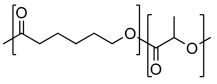
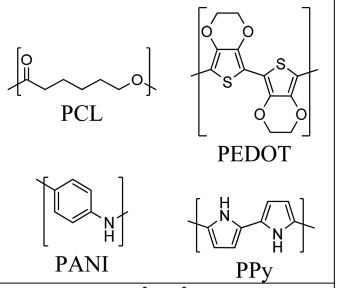
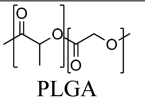
Biomacromolecules 2022, 23, 1841−1863

**Table 1. Structure−Property Guide and Suggestions on the Use of Synthetic Polymers as TE Scaffolds**

| Target tissue | Chemical structure | Derived properties | Resulting desired scaffold characteristics | Polymer suggestions | Repeating units |
|---|---|---|---|---|---|
| Adipose | Long aliphatic moieties, asymmetric monomers | Low glass transition temperature and crystallinity | Soft and pliable | P(CL-co-LA) P(LA-co-TMC) |   |
| Muscle | Non-crosslinked, aliphatic moieties | Soluble, electrospun and printable | Fibrillar, myoblast attachment and proliferation | PCL-co-conductive polymer (e.g. PEDOT, PPy, PANI, polyaniline) |   |
| | Long aliphatic moieties | Elasticity | Myotube differentiation | |   |
| | Alternating double and single bonds | Conductivity | Restoration of contractile function | | |
| Vessels | Long aliphatic moieties | Elasticity | Mimicking of native vessels | PCL-PGS, P(CL-co-LA), PLGA |   |
| | Non-crosslinked, aliphatic moieties | Soluble | Fibrillar (electrospinning) | | |
| | Asymmetric monomers | Low $T_g$ and low crystallinity, fast degradation | Cell infiltration and prevention of calcification | | |
| | Citric acid moiety | Calcium chelating anticoagulant | Anti-thrombogenic | POC inner layer |   |
| Nerves | Long aliphatic moieties | Soft | Attachment and growth of neurons | P(CL-co-DLLA) |   |
| | Long methylene moieties | Low wettability | 3D neuronal growth and differentiation | | |
| | Non-crosslinked, aliphatic moieties | Processable | Porous, permeable | | |
| | Alternating double and single bonds | Conductive | Neuron excitation | PCL-co-conductive polymer (e.g. PEDOT, PPy, PANI, polyaniline) |   |
| Skin | Polar groups | Hydrophilicity, water content | Cell adhesion, proliferation, and differentiation | PVA, PVP, PLGA |   |
| | Long aliphatic moieties | Elasticity | Mimicking of native tissue | |   |
| | Non-crosslinked, aliphatic moieties | Processable | Porous, permeable, vascularization | |   |



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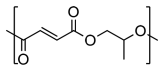
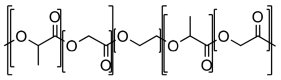
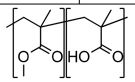
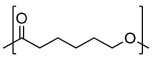
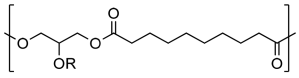
Biomacromolecules 2022, 23, 1841−1863

Table 1. continued

| Target tissue | Chemical structure | Derived properties | Resulting desired scaffold characteristics | Polymer suggestions | Repeating units |
|---|---|---|---|---|---|
| Bone | Non-crosslinked, aliphatic moieties | Processable, 3D printable | Interconnected macroporosity, facilitates bone growth, vascularization | PCL, PLGA, PLA, PLGA-PEG-PLGA, PPF based composites with bioactive additives |  PPF |
| | Stereoregularity | Semicrystalline, rigid | Provide mechanical support | |  PLGA-PEG-PLGA |
| Cartilage | Polar groups | Hydrophilicity, water content, crosslinkable | Hydrogel, mimicking native cartilage | PEG/PEO, PVA, Polyacrylates Modified with amine groups |  PEG  PVA |
| | Long aliphatic sequences | Low $T_g$ and crystallinity | Deformability | | |
| | Surface amine groups | Cell-scaffold interactions | Chondrogenesis | |  Poly(methylmethacrylate-co-methacrylic acid) |
| Cornea | Long aliphatic sequences, asymmetric monomers | Amorphous, elastic | Transparency, softness | PCL-natural polymers PCL-PGS blends |  PCL |
| | Polar groups | Hydrophilicity | High water content | | |
| | Non-crosslinked, aliphatic moieties | Soluble | Fibrillar (via electrospinning and bioprinting) | |  PGS |

our point of view, are the most appropriate per tissue. The influence of the chemical structure on the properties that control their suitability for the different TE applications is included. All of these have been reported to efficiently regenerate the target tissues, but besides that, the commercial availability and pre-existing regulatory approval were considered, which we think are crucial factors in accelerating clinical applications.

Besides the optimization of polymer of choice, safer clinical trials are necessary to ultimately be used in the clinical practice. Conducting reliable and accurate *ex vivo* studies will allow the safer evaluation of materials as future bedside products.

In summary, synthetic biocompatible polymers have played an integral role in the development of TE as a whole, and they will continue to be in the spotlight of future research. A deeper understanding of their interactions with human tissues and precise control of their properties by continuous testing is going to allow us to obtain better materials for not only TE, but also for biomedical devices and 3D printed biomedical products.

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### Notes

The authors declare no competing financial interest.

## ABBREVIATIONS

TE, tissue engineering; PGA, poly(glycolic acid); PCL, poly(ε-caprolactone); PLA, poly(lactic acid); PLGA, poly(glycolic-co-lactic acid); PGS, poly(glycerol sebacate); PVA, poly(vinyl alcohol); PU, polyurethane; TPU, thermoplastic polyurethane; POC, poly(1,8-octanediol citrate); PTMC, poly(trimethylene carbonate); PEG, poly(ethylene glycol); ECM, extracellular matrix; Ppy, polypyrrole; hMSCs, human mesenchymal stem cells; RGD, arginylglycylaspartic acid; PDLLA, poly(D,L-lactic acid); FDM, fused deposition modeling; PC, polycarbonate;



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Biomacromolecules 2022, 23, 1841−1863

PVP, poly(vinylpyrrolidone); PANI, polyacrylonitrile; PEDOT, poly(3,4-ethylene dioxythiophene); PDA, polydopamine; PEI, polyethylenimine; TEVGs, tissue-engineered vascular graft; PPGS, PGS derivative with palmitate; TEHV, tissue-engineered heart valve; PC-BU, bis-urea-modified polycarbonate; CNS, central nervous system; PNS, peripheral nervous system; BMP, bone morphogenic protein; PVP, poly(vinylpyrrolidone); TCP, tricalcium phosphate; dECM, decellularized ECM; UPy, 2-ureido-4[1H]-pyrimidone

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