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Elastomeric polyesters in cardiovascular tissue engineering and organs-on-a-chip

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Abstract

Cardiovascular tissue constructs provide unique design requirements due to their functional responses to the substrate mechanical properties and cyclic stretching behavior of the tissue that requires the use of durable yet elastic materials. Given the diversity in polyester synthesis approaches, an opportunity exists to develop a new class of biocompatible, elastic, and immunomodulatory cardiovascular polymers. Furthermore, the elastomeric polyester materials have the capability to provide tailored biomechanical synergy with native tissue and hence reduce inflammatory response *in vivo* and better support tissue maturation *in vitro*. In this review, we highlight underlying chemistry and design strategies of polyester elastomers optimized for cardiac tissue scaffolds. Major advantages of these materials such as their tunable elasticity, desirable biodegradation, and potential for incorporation of bioactive compounds are further expanded. Their unique fabrication methods such as micromolding, 3D stamping, electrospinning, laser ablation and 3D printing are discussed. Moreover, application of these biomaterials in cardiovascular organ-on-a-chip devices and patches are analyzed. Finally, we outline unaddressed challenges in the field that need further study to enable impactful translation of soft polyesters to clinical applications.

Keywords

Tissue Engineering; Polyester; Biomaterials; Organ-on-a-chip; Microfabrication

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1. Introduction

Biomaterial based technologies have played an indispensable role in the development of cardiovascular devices, tissue regeneration, acellular therapies, drug delivery, and *in vitro* scaffolds for tissue engineering. [1] The evolution of biomaterials has been a journey of continuous learning and innovation, marked by significant milestones that have shaped the field. In the early days, biomedical devices faced poor patient integration due to the lack of sterilization techniques and unadvanced knowledge of human biology. [2] Observations of healing of foreign bodies upon injuries during World War II inspired surgeons such as Sir Harold Ridley[3], Sir John Charnley[4], Dr. Charles Stent[5] and many other surgeons to implant biomaterials into human body in many forms such as contact lenses, hip replacements, vascular stents and grafts. At the time, materials were deemed to be "biocompatible" if they did not provoke significant immune rejection within the host body. [6] Some of the commonly utilized materials at this era were silk, silicones, metals, poly(methyl methacrylates) and Teflon. [7]

In 1960's and 1970's, biodegradability, the ability of the material to be broken down and removed from implant site became the major criteria for biocompatibility. [7] Polymers such as poly (lactic acid) (PLA), poly(glycolic) acid (PGA) or poly (lactic-co-glycolic) acid (PLGA) were developed. [8] Recent advances in understanding of concepts such as cell-surface receptors, cellular phenotypes, and cell-biomaterial crosstalk, the field has evolved to develop biomaterials that enhance the polymer-host tissue crosstalk. Novel techniques involving host immune response modulation, increased porosity to enhance vascularization, controlled drug release, biomaterials modified with bioactive molecules, nonfouling materials, thermoresponsive compounds and materials enhancing healing process have been realized. [9]

Cardiovascular tissue engineering and biomaterials has recently focused on new approaches for regeneration of cardiac muscle, the myocardium, given promise to provide solutions for the failing heart. Given the low elasticity range of human myocardium during the diastole and systole cycles (10-300 kPa), an ideal biomaterial for cardiac tissue engineering should possess a low Young's modulus to match the physiological range, as well as high elongation and tensile strength to support cyclic contractile behavior of cardiac tissue.[40-43] Polyesters have drawn great attention toward this goal due to their notable potential to mimic physiological and biochemical properties of native tissues, and match the elasticity of cardiac tissue. [10]

Polyesters are typically synthesized through esterification, which involves a reaction between an alcohol (or diol) and a carboxylic acid or (or diacid) group forming an ester linkages. [11] The ester linkage and control over crosslinking extent offers flexibility and mobility to the polymeric structure. Biodegradable polyesters are structurally and chemically stable for short- and medium-term applications and can provid mechanical cues to drive cellular behaviour[12]. They can also degrade over time via several mechanisms including hydrolysis, oxidation or enzymaticly. [13] The mechanical properties, degradation rate and biocompatibility of polyesters can be tuned by the choice of monomers and their molecular weights as well as the processing conditions (e.g., temperature, pressure, and reaction

time). [14] Elastomeric polyesters have been frequently used in cardiovascular applications as artificial heart valves[15], vascular prosthesis[16], conduits[17-18], and patches for repair of damaged myocardium or congenital malformations[18]. Biofunctionalization of these scaffold materials with natural materials such as laminin, fibronectin, collagen, and alginate can further promote cell attachment by modifying surface elasticity or hydrophobicity. [19-20]

Mechanical properties, cytocompatibility, immunomodulation and fabrication of precise micron-scale structures are some of the major challenges that should be addressed during biomaterial design process. Building on the previous successes with polyester elastomers and given the diversity in polyester synthesis approaches, it is possible to develop a new class of biocompatible, elastic, and immunomodulatory cardiovascular polymers. This review compares the biological and mechanical properties of currently developed polyesters and evaluates their advantages and shortcomings in cardiac tissue engineering and organ-on-a-chip applications. We describe the challenges associated with fabricating scaffolds from polyesters, as well as innovative approaches that have been developed to overcome some of these limitations. This review also provides a comprehensive explanation of various *in vitro* and *in vivo* applications of polyesters in the field of cardiovascular research and foresees the clinical transition of such applications. Commonly used polyesters for soft tissue engineering developed in the last 20 years are highlighted in Figure 1.

2. Novel polyesters utilized in tissue engineering and organs-on-a-chip

Polyesters have been widely used as the material of choice for fabrication of tissue engineering scaffolds due to their degradation properties *in vivo,* cytocompatibility and ease of fabrication. [11, 26-28] Clinically used polyesters such as poly-L-lactic acid (PLLA) or polycaprolactone (PCL) often have a significantly higher elasticity compared to soft tissues. [29-30] Mechanical mismatch with the properties of native tissues can trigger a variety of adverse response including fibrosis[31], and inflammation[32] and reduce the fidelity and impaired cell maturation of *in vitro* models. [33] To address these shortcomings, polyesters with lower Young moduli (i.e. less than 1 MPa) have been of great interest in cardiac scaffold applications. [34] Several variations of polyester chemistries have been explored for scaffold development, including polyhydroxyalkanoates (PHAs), poly(ε-caprolactones) (PCL), poly(poly sebacate)s and poly(diol citrate)s (Figure 2). In this review, our emphasis is on soft polyesters suitable for engineering cardiac and vascular tissues, while a comprehensive overview of polyester biomaterials has been addressed elsewhere. [26]

2.1. Polyhydroxyalkanoate (PHA)

PHAs are biodegradable polyesters, naturally produced by both gram-positive[35] and gram-negative bacteria[36], in the presence of excess carbon sources and lack of alternative resources such as nitrogen, phosphorous, potassium and magnesium. They are often classified into short- (4 to 5 carbons), medium- (6 to 14 carbons), and long-chained (14 or more carbons) PHAs. [37] (Figure 2a) These polyesters provide multiple opportunities to adjust their utility by functionalization of unsaturated side chains. [38] For example, their hydrophobicity can be adjusted to control cell attachment and drug absorption to the scaffold. [39-40] Another advantage of PHA is their non-toxicity and hydrolytic degradation to

carbon dioxide and water. [41] Commonly used PHAs are: poly(3-hydroxybutyrate) (PHB) [42], poly(4-hydroxybutyrate) (P4HB) [43], poly(3-hydroxybutyrate-co-4-hydroxybutyrate) (P34HB) [44] and poly(3-hydroxybutyrate-co-3-hydroxyvalerate) (PHBV) [45]. Their organic origins and biodegradability make them a great candidate for drug delivery[46], biomedical device fabrication[47] and tissue engineering[48]. Degradation of PHAs results in R-3HA groups which can be transformed to 2-alkylated 3HB or β-lactones, giving rise to antibiotic compounds such as carbapenem or macrolide. [49] Hemoembolizing agents such as rifampicin have also been encapsulated in PHB or PHVB microspheres for controlled drug delivery. [50] Tepha FLEX®, a PHB-based suture, has recently been approved by FDA for transplantation. [51] Non-porous PHAs exhibit a significantly higher elasticity (i.e., 3.7 MPa to 739.7 MPa) than myocardium; hence, highly porous cardiac patches from PHAs have been created to mimic properties of the native tissue. [42] Control over degradation[52] , elasticity[53] and batch-to-batch variability[54] are the main challenges to be addressed when using this family of materials. Moreover, challenges with purification of PHAs should be considered for its application in tissue engineered platforms. [55]

2.2. Poly (ε-caprolactone) (PCL)

PCL is widely used to its cytocompatibility[56], ease of processing[57] and viscoelastic properties[58]. This polyester, can be either derived directly from cyclic ester, ε-caprolactone or indirectly through decomposition of ε-caprolactone to 6-hydroxyhexanoic acid and its polycondensation[59] or ring opening of ε-caprolactone[60]. (Figure 2b, 2c) PCL is soluble in various organic solvents such as chloroform, toluene, benzene, and dichloromethane and immiscible with alcohol and water. [61] As a result, PCL is one of the most common materials used within electrospinning or solvent casting methods. [62] Despite the fact that elasticity of pure PCL is high (i.e., 210-440 MPa) [61], by using different fabrication techniques and manipulating its molecular weight, its mechanical properties can be tuned. [63] PCL has been the frequent material of choice for construction of 3D cardiac[64-65] or vascular[66] scaffolds. PCL monomers have been frequently combined with other polymers to generate co-polymers, such as poly (lactic-co– ε-caprolactone) (PLCL) [67] or poly(glycolide-co- ε-caprolactone) (PGCL) [68], with modified properties. PCL is highly hydrophobic[69], limiting cell adhesion and proliferation on its surface. As a result, the methodologies for fabrication of PCL-based cardiac substrates should overcome their high elastic modulus and surface hydrophobicity.

2.3. Poly (glycerol sebacate) (PGS)

PGS is developed by polycondensation of glycerol, the natural building block of lipids, and sebacic acid, a metabolic intermediate of fatty acid synthesis. [70] (Figure 1a, Figure 2d) Physical properties of PGS can be altered by manipulating monomer feed ratio or degree of esterification. [71] PGS spontaneously crosslinks after exposure to 120°C for a minimum duration of 72 hours; however, crosslinking agents such as methylene diphenyl diisocyanate (DMI) or hexamethylene diisocyanate (HDI) can be added to accelerate this synthesis process. [72-73] Acylating prepolymer to poly (glycerol sebacate) acrylate (PGSA) can provide a UV cross-linkable elastomer for uses such as an on-site surgical sealant. [74] Co-polymers of PGS family have also demonstrated great potential in soft tissue engineering. For instance, bonding of PGSA with hydroxyethyl methacrylate (HEMA) resulted in polyesters with

tunable characteristics and shape-memory properties. [75] Although PGS has not yet been approved by FDA in a specific device, both of its monomers as well as similar polyester surgical sealants such as SETALUM™ (Gecko) have received FDA and CE Mark approvals. PGS and its composites were also used in fabrication of cardiac patches to enhance the cardiac function *in vivo*. [76-78]

2.4. Poly (diol citrates)

Poly(diol citrates) are formed from a reaction of a diol- group and citrate group. Depending on the degree of crosslinking, these polyesters can have more physiological relevant mechanical properties for cardiac utility. Poly (1,8-octanediol citrate) (POC), poly (octanediol citrate-co-sebacate) (POCS), poly (octamethylene maleate anhydride) (POMaC), poly (octamethylene maleate anhydride 1,2,4-butanetricarboxylate) (1,2,4 polymer), poly (itaconate-co-citrate-co-octanediol) (PICO) and adhesive polyesters are some of the poly(diol citrates) currently utilized for cardiac or vascular tissue engineering.

2.4.1. Poly (1,8-octanediol citrate) (POC)—POC is a biodegradable and antimicrobial polyester for soft tissue engineering applications. [79] (Figure 1b, Figure 2e) POC has gained significant attention due to its high tensile strength and low elastic modulus. [80-81] POC has been shown to support growth of endothelial cells[82] and differentiation of bone-marrow derived mesenchymal stem cells[83]. This polymer was also used to make composites with PCL, and electrospun to create aligned fibrous sheets for cardiac tissue culture. [84-85] POC/PCL composite is soluble in non-toxic solvents such as acetic acid and formic acid, reducing potential solvent toxicity issues in electrospinning process. [85] Furthermore, therapeutic agents such as lidocaine have been incorporated within the microstructure of POC to obtain tunable drug release kinetics. [86] Under physiological conditions, POC degrades into non-toxic products, citric acid and 1,8-octanediol, which can both be metabolized and eliminated by the body. [87-88] The two POC-based bone implants of CITRESPLINE® and CITRELOCK® (Accutive technologies) have been recently FDA-approved for surgical implantation.

2.4.2. Poly (octanediol citrate-co-sebacate) (POCS)—POCS is a tunable polymer formed from one-pot polycondensation of 1,8-octanediol, citric acid and sebacic acid. [89] (Figure 2f) Viscoelastic properties and degradation kinetics of POCS could be manipulated by changing the monomer ratio of citric acid to sebacate ratio. [89-90] Other groups have created conductive POCS by incorporating up to 5% carbon nanotubes using a novel screw-coating of the material with carbon nanotubes. [91] Pendant carboxyl groups on the surface of crosslinked POCS can regulate cellular attachment[95] and covalently bond with extracellular matrix (ECM) molecules to enhance cell attachment. [92] POCS has been electrospun along with fibrinogen to enhance cell attachment and proliferation. [93]

2.4.3. Poly (octamethylene maleate (anhydride) (POMaC)—POMaC is a biodegradable elastomer, synthesized through one-pot polycondensation reaction of citric acid, maleic anhydride and 1,8-octanediol. [94](Figure 1c, Figure 2g) Liquid pre-polymer generated through this synthesis, contains several vinyl and ester groups. Vinyl groups enable free radical polymerization with the addition of a photoinitiator and use of an

appropriate wavelength of light. [94] In addition to the vinyl groups, POMaC structure is comprised of pendant carboxylic acid and alcohol groups undergoing esterification reactions, a post-polymerization process that is accelerated at higher temperatures. [94] Vinyl groups formed from UV crosslinking are non-polar and hence contribute to hydrophobic behaviour of the products, while ester bonds are highly susceptible to hydrolytic degradation. [95-96] The unique dual-crosslinking mechanism of POMaC creates an opportunity to tune degradation of the final biomaterial by altering monomer feed ratios. [94, 97] Moreover, pendant functional groups of POMaC are binding sites for bioactive molecules such as peptides or protein conjugates. [98]

POMaC is a soft elastomer, with tunable properties that can match physiological properties of native myocardium and negligible changes upon cyclic stretching. This makes POMaC a good material for support of contractile behaviour of cardiac tissue both *in vivo* and *in vitro.* [18, 23, 99-102] Additionality, the ability to perfuse POMaC within polydimethylsiloxane (PDMS)-based microchannels facilitates microfabrication of a wide variety of micro-scaled geometries. [18, 23, 99] The anisotropic properties of POMaC-based micropatterned scaffolds are used to control cardiac tissue compaction, resulting in better cardiomyocyte elongation and maturation. [18, 23] Anisotropic patches fabricated with POMaC are not only well functional *in vitro*, but they have shown to significantly improve cardiac functional properties post myocardial infarction (MI) compared to other polymers such as poly(ethyl glycol) (PEG). [18] Other favorable properties of POMaC such as the ability to be partially UV-crosslinked and 3D stamped have resulted in AngioChip, a thick perfusable structure with the capability of forming 3D vascular networks. [99]

2.4.4. Poly (octamethylene maleate (anhydride) 1,2,4-butanetricarboxylate) (1,2,4 polymer)—To further increase the elasticity of polymers for cardiovascular applications, we previously synthesized 1,2,4 polymer using a similar polycondensation reaction. [12] (Figure 1d, Figure 2h) One of the major advantages of 1,2,4 polymer is its elasticity variation with monomer composition, porosity and the degree of crosslinking. [12] The relatively lower Young's modulus of 1,2,4 polymer (44 ± 7 kPa[12]) falls within the lower limits of mechanical properties of myocardium, while still enabling a reasonable ultimate tensile strength, thereby making this material a great candidate for cardiac tissue engineering. The polymer also degrades both hydrolytically and enzymatically under aqueous conditions and upon culture with cells, suitable for *in vitro* and *in vivo* applications. Finally, when compared to POMaC and the FDA approved PLLA, 1,2,4 polymer has demonstrated higher T cell recruitment and similar inflammatory response (with less overall macrophage response compared to POMaC). [12]

2.4.5. Poly(itaconate-co-citrate-co-octanediol) (PICO)—PICO is a recently developed biodegradable elastomer, synthesized by a multi-step polycondensation reaction of triethyl citrate (TEC), 1,8-octanediol and dimethyl itaconate. [12] (Figure 1e, Figure 2i) Like POMaC, liquid PICO prepolymer can be injected into PDMS molds with small microchannels to create customizable scaffold designs. [12] Another recent design has looked into modification of patterns and porosity to obtain desirable elasticity matching that of the cardiac tissue. [25] Due to its tunable mechanical properties, ability to be micromolded to

various 3D patterns and degradation into immunomodulatory monomers (i.e., citric acid[103] and itaconate[104]), PICO has a great potential for application in scaffolds for various soft tissues and *in vivo* implantation. PICO degradation releases itaconate (ITA), which has demonstrated capacity as a small molecule to regulate inflammation[105] but has been limited in efficacy through oral delivery due to rapid removal from circulation. [106] Synthesis of polyester materials containing itaconate, and subsequent degradation enables slower release of ITA. While yet to be investigated, PICO materials may offer intrinsic capacity to regulate inflammation upon implantation, providing utility in graft adoption of a tissue engineered construct.

2.4.6. Adhesive polyesters—Traditionally, sutures[107], bioabsorbable wires[108] and staples[109-111] were used in surgical applications for holding tissues together, stopping body fluids and enabling healing mechanisms. These methods, not only require an expert surgeon to apply them, but they also promote chronic inflammation[112], involve a risk of infection[113], and are hard to apply depending on the mechanics of the tissue of interest. [114-115] Inspired by adhesion mechanistic of mussels, dopamine, a protein member of catecholamine family, has been of interest to scientists for creation of novel adhesive biomaterials as a surgical glue. [116-117] Dopamine undergoes a self-polymerization reaction and creates a thin layer of polydopamine which can enhance protein attachment and cell adhesion. [118] Embedding dopamine within the microstructure of many polymers have been shown to increase the adhesion properties of the polymer in the short term. [119-121] Injectable citrate-based mussel-inspired bioadhesives (iCMBAs) were developed by reaction of PEG, citric acid and catechol-containing molecules such as dopamine. [122] This material was applied as a wound dressing *in vivo* and resulted in the reduction of pro-inflammatory and the promotion of anti-inflammatory response within rodent models. It also led to a more physiological relevant mechanical properties of the skin compared to conventional suturing methods. [122] Later on, they developed an enhanced iCMBA, with reacting 10-undecylenic acid (UA), conjugated to citric acid, dopamine and PEG. [122-123] UA is a natural fatty acid with antimicrobial properties against several strands of bacteria, fungi and viruses, that acts by disrupting membrane integrity within these microbial cultures. [124-125] More recently, we created an adhesive material by one-pot synthesis of citric acid, PEG, maleic anhydride and dopamine for 28 to 72 hours. [126] (Figure 2j) The adhesive patch was demonstrated to have a superior adhesion to the heart tissue *in vivo* compared to POMaC or fibrin glue. [126] Further research is warranted to explore other adhesive molecules and optimize their properties for potential therapeutic applications such as minimization of inflammatory response and use of 3D human *in vitro* models for material evaluation.

3. Interplay between polyester chemistry and cardiovascular tissue physiology

Enhanced cell-biomaterial crosstalk[25], cytocompatibility [130] and ease of chemical modification make polyesters an optimal choice for designing cellular microenvironments and deriving the desired cell response. In this section, we describe these unique advantages of polyester elastomers and highlight opportunities they provide to the engineered tissues.

Table 1 summarizes some of the most important properties of commonly used soft polyesters in comparison to *in vivo* tissue properties.

3.1. Cell adhesion mechanisms and surface modification

Cellular adhesion and tissue formation can be affected by surface chemistry or bulk material properties. Cell adhesion is a complex process involving surface receptors and their ligands. Integrin receptors are the key receptors for cell adhesion to ECM or scaffold materials and are heterodimers composed of two subunits: α and β. [131] In the extracellular domain, integrin receptors bind to the binding sites of ECM proteins derived from fibronectin (RGD, REDV, KQAGDV, and PHSRN),laminin (LRE, IKLLI, PDGSR, IKVAV, LRGDN, LGTIPG, and YIGSR), collagen (DGEA and GFOGER) (from collagen) or elastin (VAPG). [132] Upon binding of the extracellular domain, cytoplasmic protein talin binds to the β subunit of integrin and links it to actin cytoskeleton, initiating cytoskeletal remodeling. [133] Various surface modification techniques have been leveraged to enhance cell binding to the surface using reactions such as 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide/N-hydroxysuccinimide (EDC/NHS). [134] Many of the polyesters contain carboxylic group (-COOH) can be functionalized using EDC/NHS chemistry to immobilize biomolecules and crosslink integrin binding domains in order to improve cell adhesion. [135] For instance, PCL/poly(m-anthranilic acid) (P3ANA) copolymer was functionalized by RGD-group to enhance cell attachment and proliferation on the scaffold. [136] Other groups have incorporated bioactive components within POC polyester and observed an enhanced vascularization of the *in vivo* model. [137]

Given the wide choice of these building monomers, polyesters also have a unique ability to incorporate bioactive molecules like lidocaine[86], itaconate[138] or dopamine[123, 126] within their backbone structure. These bioactive components will drive application-specific mechanical and physical properties. For instance, dopamine-embedded polymers had an enhanced ability to attach to surfaces[123, 126] and consequently could be used as a surgical glue to hold cardiac patches in place. [77] Furthermore, highly polar groups in polyesters and their entanglement allow the physical incorporation of nano-scaled materials within polyester lattice. For example, Ahadian *et al.* incorporated carbon nanotubes (CNT) within 1,2,4 polymer and showed electrical conduction within the resultant polyester composite. [139] This nanocomposite was later used as a substrate for cardiac tissue engineering to enhance excitation threshold and induce cardiac fiber alignment. As soft polyesters are further explored in tissue engineering applications, modification of these materials with bioactive components would provide researchers a greater ability to model native tissue environment.

Bulk material properties such as porosity, hydrophobicity, surface energy, topography and elasticity can affect cellular attachment. [135] Porosity is another important factor as it can influence tissue integration and vascularization. [102, 140] Highly porous materials are generally less stiff compared to their pure solid counterparts, thus facilitating cell infiltration, neovascularization, and improved transport of nutrients and waste removal. [141] As an example, AngioChip platform, a POMaC-based blood vessel network on a chip, has incorporated both macro- and micro- porosity to enable cell extravasation and small

molecule infiltration from the engineered micron-sized vessels. [99] Creation of patterned superhydrophilic and superhydrophobic surfaces can also engineer cellular attachment into desired shaped[142]. Cardiomyocytes attachment can also be achieved through topographical patterning of the surface. For instance, Au et al. have unidirectionally abraded surfaces to achieve parallel microgrooves and induce cellular alignment in cardiomyocytes. [143]

3.2. Mechanotransduction and polyester mechanical properties

Engineered scaffolds provide a unique ability to design 3D mechanical cues and hence drive cellular responses resembling the native tissue. [144] Material elasticity[145], porosity[146] and topography[147-148] are often optimized in tissue engineering to match the mechanical properties of the targeted tissue or the disease microenvironment. Mechanical properties of the cellular environment can activate different pathways related to cell migration [149], differentiation[150], ECM deposition and degradation[151-152], cytoskeletal arrangement[149], muscle contraction[153-154] and cellular maturity[155] could be affected. For *in vivo* applications, implantation of stiffer materials has demonstrated impact on macrophage driven inflammation, ultimately leading to fibrosis. [156]

In general cells can sense and respond to mechanical properties of their surrounding materials via intracellular factors such as talin and vinculin in processes known as mechanotransduction. [157] In the case of cardiac tissue, activation of these pathways causes rearrangement of actin and myosin fibers in cardiomyocytes, and hence affects cardiac contraction, alignment, and maturation. Mechanosensing is not limited to cardiomyocytes; cell subpopulations in cardiac tissue such as stromal cells, e.g. fibroblasts, undergo phenotypical changes when subjected to stiff substrates. [158] Topography or surface features, can be another driver of cellular behaviour. It has been shown that both micrometer[25] and nanometer[159] scaled topography can drive cardiac alignment and assist in formation of highly organized functional cardiac tissues. [143] Thus, when designing a biomaterial for cardiac tissue engineering, it is critical to biomimetically design these factors to minimize the impact on functionality of the cardiac tissue.

Polylactide and polylactone family (such as PCL, poly(D-lactide) (PDLA) and PLLA), despite their FDA approval in several medical devices, have a considerably high elasticity (~0.65-2.7 GPa[160-161]) compared to the cardiac tissue, which hinders their ability to recapitulate native tissue properties. [94, 162-163] Despite the fact that stiffer tissues such as trabecular and cortical bone (elasticity of ~10.4-20.7 GPa) [164] or human articular hip cartilage (elastic modulus of ~0.67-1.8 MPa) [165], have relatively similar mechanical properties, elasticity of many soft tissues are considerably lower. For instance, the elastic modulus is ~40-180 kPa for skin [166], ~280-300 for thoracic and abdominal aortas[167], ~64-112 kPa for the bovine spinal cord [168] and ~200-500 kPa for the human myocardium in diastolic and systolic state. [169-172] Matched elasticity with the target tissue could prevent tissue deformation and significant irritation within the microenvironment. [173-174]

Several biodegradable polyester materials such as POMaC and PICO offer the flexibility to tune their mechanical properties to closely resemble the native tissue. This can be achieved by adjusting the nano- and micro-scaled porosity of the materials as well as modifying the synthesis conditions and monomer ratios. [18, 94, 99, 129]

3.3. Biodegradation

Depending on the chemical structure and surface area of polyester scaffolds, water can penetrate the scaffolds to different degrees, leading to hydrolysis of the polymers over time. [13] Controlled polymer degradation during integration with host is a critical factor for cardiovascular patches. Polyesters have attracted a lot of attention due to their moderate biodegradation enabling temporary implants[175] and drug delivery systems[176]. Polyester degradation involves the breakage of ester bond to carboxylic acid and alcohol groups. [177-178] The increase of solution acidity will further autocatalyze degradation with raising the nucleophilic properties of water. [179] Degradation studies have been also conducted in basic conditions to accelerate hydrolysis process and predict long-time degradation capacity of polymers. [94, 129, 180] In other attempts, cells have been cultured adjacent to the material to capture crosstalk between the polymer and a specific cell type. Porous polyester structures have shown enhanced water absorption and hence an accelerated biodegradation. [12] Davenport Huyer *et al.* showed a greater mass loss in 1,2,4 polymer and POMaC in porous structures compared to the non-porous conditions. [12] The degradation process was further accelerated when scaffolds were further cultured with neonatal rat cardiomyocytes. [12] Degradation dynamics differs *in vivo* according to specific body conditions such as the local acidity of host tissue, mechanical loads[181] and the cellular response to the implant[182]. The ideal kinetics of polymer degradation is also both species- and tissue- dependant. For instance, an ideal degradation of polymers for myocardial regeneration applications would happen between 1 week to 6 months in rodent cardiac patches aiming to restore tissue functionality post-MI. [183] This will allow sufficient time for cell remodelling whilst minimizing immune response to invasive materials, and matches the period needed for a complete remodelling post infarction. This timeframe would be at least 3 months in humans given the slower pace of remodelling and the larger surface area of human heart. [184]

Polyesters degradation would ideally result in monomers that are naturally occurring in the body like citric acid[94], glycolic acid[76], and sebacate[90]. Citric acid, for instance is a crucial compound in the citric acid cycle (Kerb cycle), a fundamental cellular respiratory pathway. [185] Similarly, glycolic acid is part of glycolysis pathway, a metabolic pathway for glucose uptake. [186] Other polyesters, also degrade into molecules that can be easily metabolized by the body. For instance, sebacic acid and octanediol can be enzymatically digested in the body. [187] PCL can also degrade into caprolactones, further hydrolyzed into 6-hydroxyhexanoic acid, a naturally occurring carboxylic acid. [188] In conclusion, ideally the degradation of polyesters would result in chemicals that are recognized and metabolized by the body, hence reducing the risk of adverse reactions and improving biomaterial-host tissue integration. Polymer degradation also increases the porosity of the scaffold and hence promote the crosstalk between the tissue and biomaterial. For instance, several groups have attempted to drive tissue remodelling in situ after myocardial infarction (MI). Further work is needed to study the effect of monomer ratios on degradation properties, enabling engineers to fine-tune degradation kinetics upon translation into clinical applications.

3.4. Inflammation, proliferation, and tissue remodeling

The response of host tissue to implanted biomaterial has three main stages: inflammatory, proliferative, and remodelling phase. During the inflammatory phase, monocytes are

activated to pro-inflammatory macrophages (M1 macrophages) after exposure to growth factors such as transforming growth factor beta (TGF-β) or monocyte chemoattractant protein (MCP)-1 and preliminary matrix layer is deposited on the biomaterial. [189] This is followed by the proliferative phase, in which anti-inflammatory macrophages (M2 macrophages) are activated by exposure to cytokines such as interleukin (IL)-4, IL-10, IL-14. [190] In this stage, other cell types such as fibroblasts, mesenchymal stem cells, smooth muscle progenitor cells and endothelial progenitor cells are summoned to the surface to deposit ECM proteins such as collagen and laminin and promote vascularization. [191] In the tissue remodelling phase, proteins from matrix metalloproteinase (MMP) family are secreted to facilitate ECM remodelling and rearrangement and resolution of inflammatory response. [192]

Polyesters can be designed to modulate the regenerative capacity of the host tissue. [193] These materials also provide a unique opportunity for surface modification by incorporating different biologically active components such as peptides or growth factors, creating a selective environment for cell attachment. [194] For instance, ITA is a well-established molecule that plays a critical role in metabolic reprogramming of macrophages. [195] Metabolism of M1 macrophages is characterized by a broken tricarboxylic acid (TCA) cycle (Kerb cycle). [196] This leads to an accumulation of citrate and succinate through inhibition of isocitrate dehydrogenase (IDH). [196] Upon accumulation of citrate over time, citrate is metabolized to ITA, inhibiting succinate dehydrogenase (SDH) and activating anti-inflammatory pathways by engagement with cysteine-reactive protein residues to reduce macrophage inflammation. [197] Incorporation of ITA in the polyester backbone allows controlled release of the molecule and anti-inflammatory activity within the host. [138]

Degradation of citrate-based polyesters provides similar bioactivity; the released citric acid can be absorbed by the adjacent cells as a metabolic fuel thereby creating better tissue integration and enhanced angiogenesis. [198] While there have been limited attempts as using polyesters as regenerative therapy, further work can be done on incorporation of the compounds targeting different phases of inflammatory cascade to drive tissue regeneration. Additionally, current polyesters need to be further studied for long-term safety and other regulatory requirement approvals.

4. Tailoring structure of polyester elastomers via microfabrication and 3D printing

Elastomeric polyesters discussed above can be crosslinked through different mechanisms such as UV[23, 99, 102, 227-228] or heat[17, 229-230] treatment, laying the foundation of several innovative techniques for fabrication of soft polyester-based scaffolds. [231-232] Methods such as electrospinning, laser ablation, micro-molding, 3D stamping and 3D printing have have emerged as effective approaches for achieving such scaffolds with high-resolution and accuracy at the microscale.

Electrospinning is a process where electrically charged streams of dissolved polymers are subjected to a high-voltage electric field, resulting in the production of elongated nanofibers as the solvents evaporate. Various polymers have been electrospun to create

scaffolds with tunable mechanical properties and high porosity. [233-239] However, for soft tissue engineering, only a few candidates such as PGS, have been shown to be adaptable to the electrospinning process. [17, 238-241] The fabrication of PGS via electrospinning is challenging due to its low molecular weight and limited number of organic solvents that can dissolve cured PGS. [238] The addition of spinnable polymers such as PCL[239-240], poly(methyl methacrylate) (PMMA) [241], polyvinyl chloride (PVA) [17, 242], or PLLA[238] have been explored to overcome these challenges. (Figure 3a) Electrospinning of POC/PLCL[84] or POC/PCL[85] composites as well as soft polyester-urethane[236-237] have also shown a potential in the fabrication of soft scaffolds. Laser ablation involves using brief laser bursts in the ultraviolet spectrum to rupture polymer chains, creating photo-ablated cavities. [243] This technique is commonly used for processing hard polyesters. [16, 244-246] Nevertheless, researchers have implemented laser ablation in the fabrication of PGS-based scaffolds with diamond-shaped holes for soft tissue engineering. [15, 21, 247] Laser ablation can also be used to create microholes on PICO or POMaC microtubes to enhance permeability and cell communication. [232] (Figure 3b) While laser ablation is a rapid and flexible approach, the surface finish quality, however, is poor and bulge formation along the scan route is a common problem in this technique.

Molding via microfabricated PDMS structures allows the development of injectable scaffolds with micron-scaled features. [18, 25, 129, 139] The process involves creating a mold using photolithography, adding PDMS to the mold to create the required indentations, and placing the PDMS mold onto a substrate to create microchannels/cavities. [97, 248] The polyester of interest is then added to the PDMS channels, and UV light or heat is used to crosslink the polymer. (Figure 3c) This technique has been used to create scaffolds with various lattice designs and pore sizes. [12, 18, 25, 126, 129, 139] 3D stamping integrates soft polyesters into the fabrication of vascularized myocardium and multi-organs connected through endothelialized vasculature. [24, 99, 227, 249-250] The fabrication process involves creating polyester layers using PDMS molds followed by aligning and bonding the individual layers through UV or heat crosslinking.

3D stamping enables producing a perfusable and permeable tube, known as AngioTube, vascularized with endothelial cells. [249-252] (Figure 3d) Similarly, multiple polyester layers with microchannel cavities can be 3D stamped to create AngioChips, which offer branching vascular lumens for tissue engineering and organ-on-a-chip applications. [99, 248] (Figure 3e) The resulting AngioTubes or AngioChips can be incorporated into well plate-typed bioreactors, where the tubes extend over multiple wells to form an integrated vasculature for studying dynamic events (InVADE). [24] Control of lattice shape in such platforms allows matching apparent elasticity and scaffold anisotropy to those of the native tissues. (Figure 3f) Despite their potential, PDMS micro-molding and 3D stamping methods face challenges in scalability, requiring complex equipment, manual skill, and time-consuming fabrication processes. Additionally, the rectangular cross-sections of the produced tubes and channels limit their ability to mimic native vascular tissue accurately.

3D printing of polyesters is challenging due to their low elastic modulus and long gelation time. Secondary hydrogels, such as gelatin or Carbomer, are used as supporting materials during the printing process and can be removed later. [232, 253-254] Techniques like extrusion-

based 3D printing[254] and the freeform reversible embedding of suspended hydrogels (FRESH) method[232] have been employed to print polyester structures and vascular tubes. (Figure 3b) Stiffer UV crosslinkable polyesters such as poly(propylene fumarate) (PPF) [255], PCL[256-257] and POMaC/poly(ethylene glycol) diacrylate (PEGDA700) composite[258] were also printed using stereolithography (SLA) techniques.

5. In vitro and in vivo applications of soft polyesters

Soft polyesters have a great potential for fabrication of *in vitro* cardiovascular models, as well as scaffolds that can be implanted *in vivo*. In this section, we will review recent advances in using polyesters in cardiovascular tissue engineering models and their advantages. Although these models can properly recapitulate native environment, their translation into clinical use and pharmaceutical applications requires further studies on the application-specific optimizations of scaffold properties.

5.1. In vitro

In vitro models aim to recapitulate the functionality of native tissues in the format of organ-on-a-chip devices or larger-scaled 3D tissues. Cardiac-on-a-chip models should be able to produce a contraction force of 2-4mN/mm^2 in a cyclic manner and transmit electrical signals at a ~25cm/s. [259] Although natural polymers such as gelatin, fibrin, alginate, and hyaluronic acid can provide ECM-like microenvironments for different cell types, they are often lack mechanical stability and the elastic modulus of the cardiovascular tissue. [74] Synthetic polyesters, on the other hand, offer several advantages such as mechanical strengths, tunable elasticity, controllable degradation and ease of fabrication. [139, 259]

5.1.1. Organ-on -a-chip—Conventionally, organ-on-a-chip platforms are fabricated with PDMS due to its biocompatibility, optical transparency, gas permeability and high elastic modulus. [260-262] However, PDMS can non-specifically adsorb biomolecules due to the hydrophobic interactions, resulting in variations in the concentrations of culture media compounds and the introduced drugs/reagents. [263] Polyester scaffolds have been carefully designed to provide structural support, imitate native ECM, and promote cell adhesion, proliferation and differentiation[139, 263] and provide the capability of tuning their mechanical properties, degradation profile, tissue culture conditions, fabrication technique and porosity. [99]

Given the low elastic moduli of POMaC and its mechanical stability, this polymer can be cast into microscale wires and assembled into miniature cardiac tissue culture wells with two microwires spaced apart, giving rise to Biowire platform. Autofluoresent properties of POMaC allows tracking of wire displacement and correlating it to cardiac force, hence warrants a non-invasive *in situ* method for tracking cardiomyocyte contraction and electrophysiology. [264] Long term electrical stimulation of the obtained tissues would result in cardiomyocyte maturation[101-102, 264], modelling of complex diseases such as cardiac fibrosis[100, 265] and more physiological relevant drug testing results[101-102, 264]. (Figure 4a) Biowire platform, acquired by Valo Health, is currently being used in industry for drug discovery and development.

Vascularization of the engineered microtissues plays a crucial role in their functionality when studied on a chip, since the cell metabolism is highly susceptible to exchange rate of nutrients, metabolite, and oxygen in such organs. AngioChip platform, developed by our group, is capable of creating permeable vascular lumens for organ-on-a-chip engineering. [99] This technology combines two unique features: (1) a polymer-based 3D branched microchannel network with thin and permeable, yet mechanically stable walls to support the built-in vasculature coated with endothelial cells, and (2) a hydrogel embedding the cells which is cast into the polymer mesh around the network such that the parenchymal cells remodel the matrix and compact around the built-in vasculature to form a functional tissue. POMaC-based polymer lumens of AngioChip, with intricate pore structures are controlled from the nanometer to millimeter scale to model transfer of molecules and cells between vasculature and parenchymal space. [99] The lumen could be confluently endothelialized, and vessels are able to sprout in response to an angiogenic stimulus. AngioChip was utilized to recapitulate vascularized cardiac tissue and synchronized beating that could macroscopically compress the chip without damaging the vascularized network during the perfusion. Application of AngioChip with HEPG2 liver cell lines also allowed investigations of urea secretion and terfenadine metabolism *in vitro*. [99]

As an alternative approach, a single porous microchannel, AngioTube, could be fabricated by combining micromolding and 3D stamping techniques. AngioTube was embedded in 96-well plates to create InVADE system. [24, 227, 266] A programmed rocking system facilitated fluid circulation in the wells, relying on gravity-driven flow. The channel permeability, cell migration, and vessel sprouting is enabled in AngioTubes through nano and micro scaled designed porosity. [227]. Lai et al. recapitulated liver, cardiac tissue, and cancer invasion cascade via InVADE platform. [227] The open 96-well plate concept enables ease of tissue extraction and seeding. In later studies, InVADE system was utilized to investigate the effect of CuO and SiO_2 nanoparticles on cardiovascular system under perfusion. [249] The platform demonstrated that the release of reactive oxygen species (ROS) and secretion of pro-inflammatory cytokines under the influence of nanoparticles brought about electrical and contractile dysfunction of cardiac tissue. [249] InVADE platform has also been utilized for the evaluation of chemotherapeutic medication, gemcitabine, on pancreatic ductal adenocarcinoma (PDAC) co-cultured with stromal fibroblast. [266] The result demonstrated an enhanced tumor viability and higher dose requirement for PDACs in perfused conditions, compared to stationary tissue culture. [266] In another study, InVADE was employed to assess the impact of SARS-CoV-2 on the endothelialized AngioTubes and therapeutic efficacy of an antiopoietin-1 derived QHREDGS peptide. [250, 267] By circulation of immune cells in the engineered vasculature, cytokine storm was induced, where vascular dysfunction is advanced due to the over-secretion of cytokines from activated endothelial cells and monocytes.[135] Three-dimensional printing of polyester microtubes has also been shown effective in organ-on-a-chip applications, enabling cardiomyocytes and endothelial cell attachment, upon placement of the tubes into customized 96 well plates. [232, 254] (Figure 4b)

5.1.2. *In vitro* cardiac tissue models—Three-dimensional printing of CMs embedded in polyester-based scaffolds [268-269] has resulted in successful cm-scaled heart models.

[268-269] However, many of these models are still incapable of recapitulating spatial changes and physiological phenomena such as ejection fraction and MI. Zhang et al. developed a 3D scaffold made of multiple 2D POMaC scaffold meshes assembled together through a hook and loop system, termed as Tissue-Velcro. [23] The design provided anisotropic mechanical properties and allowed for culture of multiple cell types. Moreover, the disassembly of the layers with preserved structure for further analysis of the cells was quite straightforward. [23] Other studies demonstrated that up to 0.5wt% carbon nanotubes (CNTs) could be embedded in 1,2,4 polymer to increase the electrical conductivity of the fabricated patches and hence improve cardiac electrical excitability. [139]. Similarly, in a model demonstrated by Mohammadi et al., the myocardial architecture of left ventricle and its various myofiber anisotropic angles were recapitulated *in vitro*. [25] (Figure 4c) The model comprised multi-stacked 2D CMs coated sheets assembled as a conical cardiac ventricle. The design incorporated both elastic PICO as a backbone and a collagen/Matrigel hydrogel for encapsulating CMs and enhancing cell attachment. The embedded holes in each sheet enhanced the delivery of oxygen and nutrients and promoted cellular crosstalk. [25] Despite the significant work in 3D tissue models, further work needs to be done to create better physiologically relevant cardiac models with the ability to reconstruct the complexities of native organs.

5.2. In vivo applications

Poor biological integration, low biocompatibility, and high chance of fibrosis often hinder application of engineered scaffolds *in vivo*. [270-274] Given the low elastic modulus of human myocardium during the diastole and systole cycles (10-300 kPa), an ideal elastomer for implantable patches should possess similar Young's modulus, as well as high elongation and tensile strength in order to support contractile behavior of cardiac tissue. [12, 97, 275-276] Implementation of cardiac patches with better physiological integration has raised a great interest towards restoring the functionality of the heart upon injury. [277] Patches could be made of a combination of synthetic polymers and natural hydrogels[278-279 280 259, 281-285] A landmark study by Zimmermann et al. demonstrated that the use of cardiac patches, made of heart cells incorporated in collagen I and Matrigel, on the epicardial surface of the heart can result in functional improvement post-MI. [286] One issue with the current cardiac patches is the invasiveness of open-heart surgery for placement of the patch on the cardiac surface, limiting their applicability and posing risks such as chest wound infection. Montgomery *et al.* have developed a shape-memory scaffold constructed of POMaC which could enable precise injection of fully functional tissues to the heart, noninvasively. [18] The scaffold with mechanical anisotropy could be delivered through a 1mm I.D. needle, recovering its initial shape upon injection without affecting cardiomyocyte viability or function. The patches could significantly improve the cardiac function in post-MI rats, and demonstrated similar vascularization, macrophage recruitment and cell survival compared with open heart surgery. [287] POMaC-based AngioChips, cultured with neonatal rat cardiomyocytes, were also shown to enable direct surgical anastomosis with different setups, artery-to-artery or artery-to-vein and support cardiomyocytes elongation and mural cell penetration after a week. [99] (Figure 4d)

One important issue with cardiovascular grafts and catheters is contamination and bacterial infection. [288] Integration of ITA, an anti-microbial compound, into the backbone of polyesters could potentially reduce the chance of infection in the implants made of such materials. [129, 138 289] In PICO and ITA polymer, a stable release of ITA was observed through degradation of the polyester backbone in neutral hydrolytic or slightly alkaline conditions (pH=8) mimicking the body environment. [129, 138]

6. Conclusions and Future Perspectives

Soft polyesters often exhibit desirable properties including low elastic moduli[97], versatile methods of crosslinkability [291], short term stability, long-term biodegradation[101] and ability to crosslink bioactive chemicals to the polymeric backbone[97]. These properties enable tissue engineers to design higher fidelity models using these polymers. [21, 28, 102, 264] Although many soft polyesters such as PGS[220], POC[22], POMaC[94], 124 polymer[12] and PICO[129] have been developed in the past 20 years with superior biodegradability and tissue mimicking elasticity, their long-term response in the host needs to be further studied prior to clinical translation. On the other hand, some of these materials have recently been FDA-approved in specific devices, further emphasizing the potential of these materials in implantation. They have also been incorporated into organ-on-a-chip devices such as Biowire[264], AngioChip[99] or AngioTube[227] some of which are currently used in the market for drug development and assessment. Yet, mainstream applications require scalable fabrication techniques. Figure 5 summarizes some of advantages and constraints of commonly utilized polyesters for cardiac engineering.

Biofabrication techniques also provide a distinctive opportunity to fabricate unique bioengineered designs for *in vivo* and *in vitro* models. Currently, electrospinning, laser ablation, micromolding, 3D stamping and 3D printing are some of the most common methods of scaffold fabrication. However, due to relatively long crosslinking time of polyesters[12, 22, 94, 129, 220] additional methods of high throughput fabrication such as droplet-based bioprinting, extrusion bioprinting and stereolithographical bioprinting could be applied to obtain higher resolution features, in a more reproducible manner. Delivery of the biomaterials into affected tissue could also be improved by enhancing the shape-memory properties of the designed scaffold. Currently an open-heart surgery is required for application of cardiac patches *in vivo*, which requires a longer recovery time and could result in in-patient post-surgical complications. Shape-memory properties of designed scaffold will enables application of cardiac patches with minimal invasiveness. [18] Finally, more thorough understanding of long-term effects of these constructs *in vivo* is vital to enable transition into clinical trials.

In summary, recently developed polyesters have demonstrated a great potential for fabrication of *in vitro* cardiovascular models[102, 232, 264], as well as implantable patches and grafts[18, 23, 99, 248, 293]. Given their potential, more research in this area is needed to explore novel chemistries, fabricate the models in higher throughput and functionalize them with application-specific bioactive compounds for regenerative medicine or drug delivery purposes.

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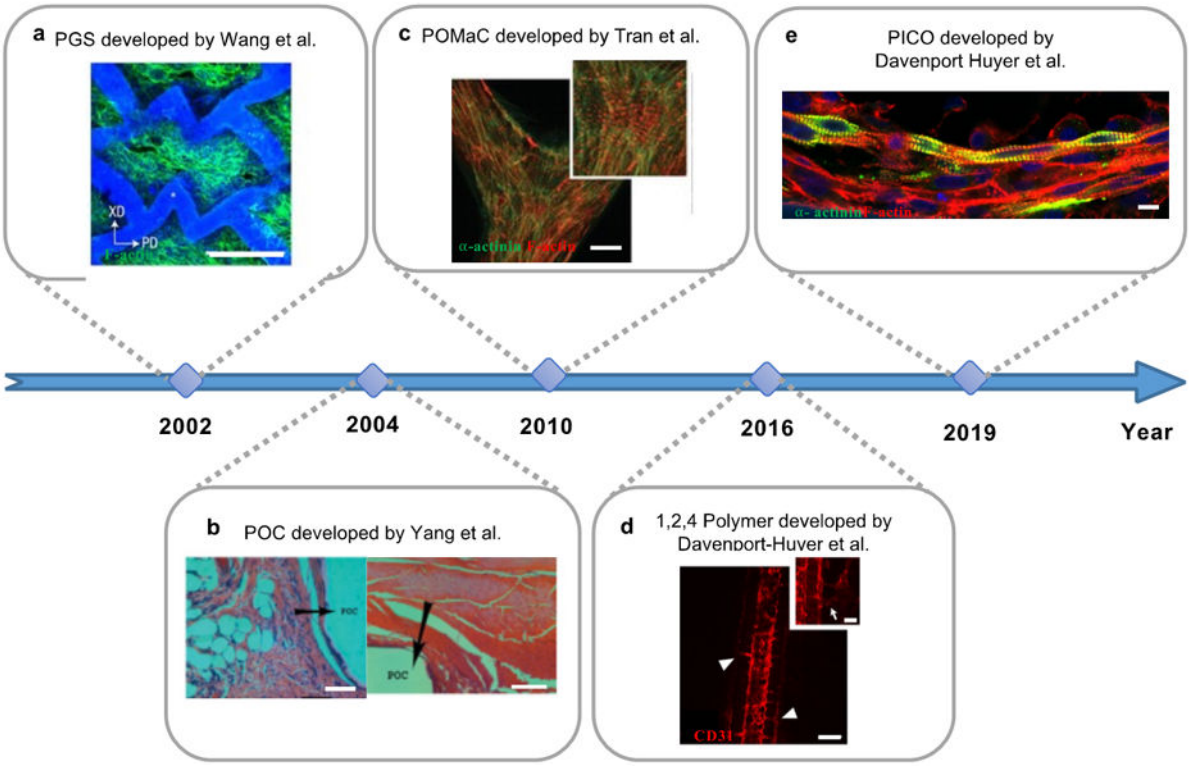

Figure 1. Timeline of recent developments of soft polyester elastomers suitable for cardiovascular applications.

a. F-actin filament of cells attached on a poly(glycerol sebacate(PGS)-based patches seeded with cardiomyocytes. [21] Scale bar, 200 mm. Copyright 2008, Nature publication Group. [21] **b.** H&E staining of Poly(1,8-octanediol citrate) (POC) samples implanted *in vivo.* Copyright 2004, John Wiley & Sons. [22] Scale bar, 100 mm**. c.** Immunostaining of α-actinin and F-actin on cardiac patch made from poly(octamethylene maleate (anhydride) citrate (POMaC) and seeded with cardiomyocytes. Copyright 2015, Science publications. [23] Scale bar, 30 mm**. d.** 1,2,4 polymer developed in Radisic lab. [12] Engineered poly(octamethylene maleate (anhydride) 1,2,4-butanetricarboxylate) 1,2,4 polymer-based micro-scaled tube, AngioTube, seeded with endothelial cells and stained for CD31 to illustrate lumen sprouting. [12] Copyright 2021, Nature Publication Group. [24] Scale bar, 100 mm. Inset scale bar, 20 mm**. e**. Poly(itaconate-co-citrate-co-octanediol) (PICO)-based cardiac patch seeded with cardiomyocytes and stained for cardiac marker α-actinin and general filament marker, F-actin. [25] Copyright 2022, John Wiley & Sons. [25]

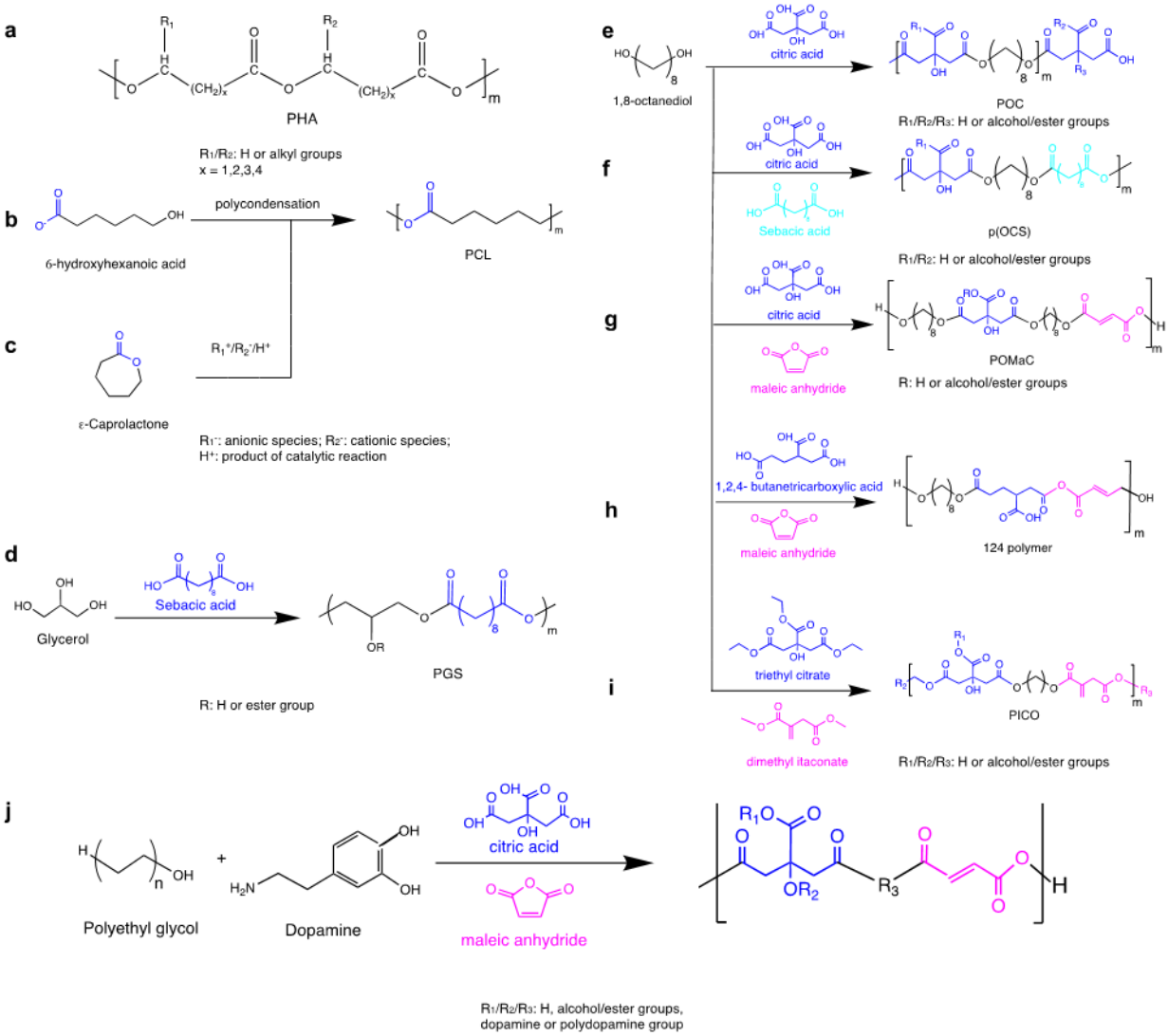

Figure 2. General polycondensation synthesis scheme of common polyesters for soft tissue engineering.

Polyesters are the product of condensation of an alcohol group (shown in black) and a carboxylic containing monomer (shown in blue) along with other organic monomers (shown in pink) **a.** Chemical structure of polyhydroxyalkanoates (PHA) groups. Given their natural source, length of carbon chains might be variable in different PHAs. [127] Poly(ε-caprolactone) can be fabricated by different chemistries such as **b.** polycondensation, or **c.** ring-opening via anionic, cationic or other catalytic agents. [61] **d.** Polyglycerol sebacate (PGS) polymer is synthesized from one-pot synthesis of glycerol and sebacic acid. [128] Other commonly used polyesters such as **e.** POC, **f.** p(OCS) **g.** POMaC, **h.** 1,2,4 polymer, and **i.** PICO are made from the reaction of 1,8-octanediol and **e.** citric acid[79], **f.** citric acid and sebacic acid **g.** citric acid and maleic anhydride[94], **h.** 1,2,4-butanetricarboxylic acid and maleic anhydride[12], and **i.** triethyl citrate and dimethyl itaconate[129], respectively**. j.** A type of adhesive polyester made from polycondensation of polyethylglycol (PEG), dopamine, citric acid and maleic anhydride. [126]

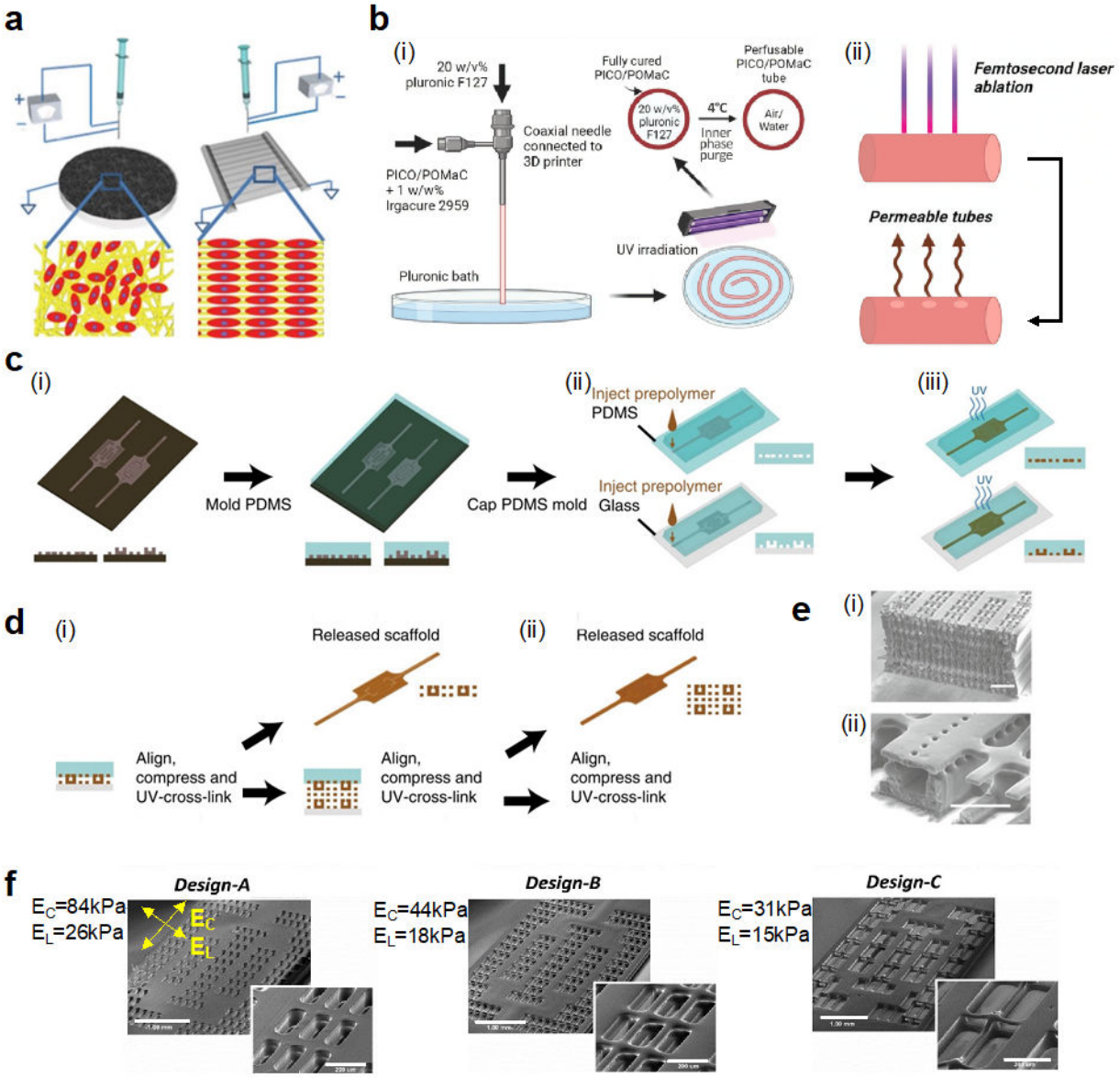

Figure 3. Microfabrication approaches to tune micro-scale structure of polyester elastomers; **a.** Electrospinning of PGS/PCL composite to create random or aligned fibers. Copyright 2014, Wiley Publication Group. [239] **b.** Creation of PICO/POMaC-based microtubes by **(i)** coaxial 3D printing in a Pluronic bath, followed by **(ii)** laser ablation to create micro-holes and provide higher permeability. Copyright 2022, Wiley Publication Group. [232] **c.** AngioChip assembly through **(i)** soft-lithography of SU-8 positive molds to create PDMS negative mold, **(ii)** reversible bonding of PDMS to PDMS or PDMS to glass, and injection of POMaC prepolymer into microchannels, **(iii)** UV treatment of for partial cross-linking and solidification. Copyright 2018, Nature Publication Group. [248] **d.** 3D stamping of AngioChip by **(i)** uncapping the top PDMS from both platforms, aligning the channels and stacking them up, and gently pressing under UV light to bond the layers, **(ii)** detaching the top PDMS mold and repeating the process to get multilayers. Copyright 2018, Nature Publication Group. [248] **e.** SEM image of a microchannel in (i) multi-layered AngioChip and

(ii) features of each layer. Scale bar represents **(i)** 500μm and **(ii)** 200μm. Copyright 2018, Nature Publication Group. [248] **f.** SEM images of an AngioChip containing micro-holes with different sizes. The scaffold has shown different mechanical elasticity and anisotropy based on the size of the macro-porosity. Scale bars represent 1mm and 200μm (inset) for design A, 1mm and 200μm (inset) for design B and 1mm and 300μm (inset) for design C. Copyright 2016, Nature Publication Group. [99]

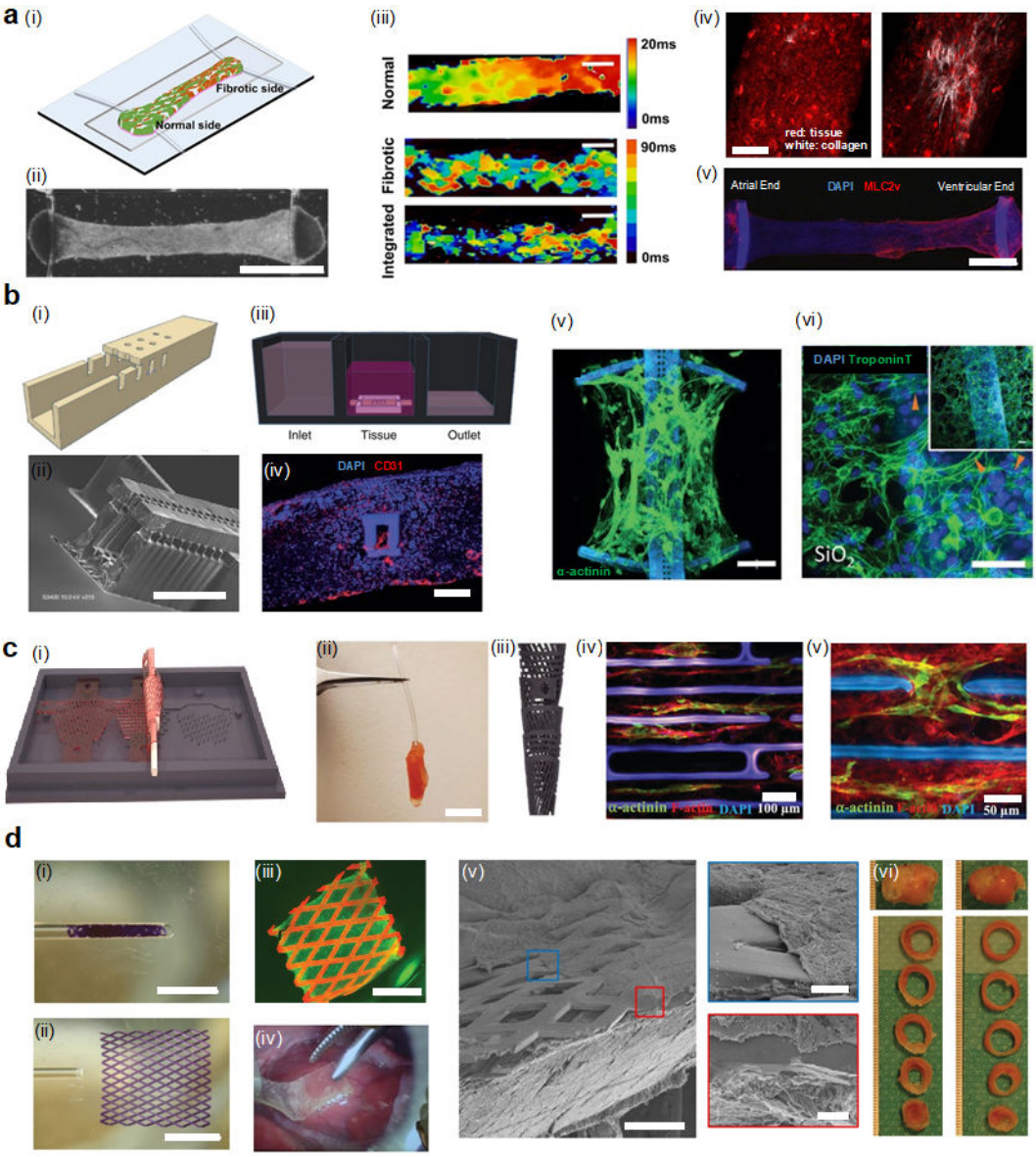

Figure 4. Applications of polyester elastomers in cardiovascular tissue engineering and organs-on-a-chip

a. Biowire is a cardiac-on-a-chip model that **(i)** enables studying complex disease mechanisms such as fibrosis. Copyright 2019, ACS Publication Group. [100] **(ii)** This model allows for a formation of a dense cardiac tissue in between parallel POMaC wires. Scale bar represents 1mm. Copyright 2019, Elsevier. [264] **(iii)** Comparison of electrical propagation patterns in healthy and fibrotic tissue. Scale bar represents 500μm. Copyright 2019, ACS Publication Group. [100] **(iv)** Collagen deposition was observed in the control sample (left) vs fibrotic Biowire model (right). Scale bar represents 100μm. Copyright 2020, Nature Publication Group. [290] **(v)** Different sides of the Biowire could be seeded with atrial and ventricular cardiomyocytes to study their crosstalk. Scale bar represents 0.5mm. Copyright 2019, Elsevier. [264] **b.** AngioTube is a polyester-based microtube. **(i)** fabricated by 3D stamping of a hollow bottom and flat top structures (Copyright 2021, Nature Publication

Group[24]) to give rise to **(ii)** micro-scaled porosity. Scale bar represents 200μm Copyright 2021, Nature Publication Group. [24] **(iii)** AngioTube is assembled on a polystyrene sheet and capped with a bottom-less 96-well plate to create gravity-driven flow. Copyright 2021, Nature Publication Group. [24] **(iv)** seeding of parenchymal tissue around the AngioTube. Scale bar represents 200μm. Copyright 2017, John Wiley & Sons. [227] **(v)** Immunostaining for cardiomyocyte marker, sarcomeric alpha-actinin (Scale bar represents 200μm. Copyright 2017, John Wiley & Sons. [227] **(vi)** Cardiac marker, Troponin-T, and nuclei marker, DAPI, staining of AngioTube after exposure to 50μgml^{-1} of SiO_2 nanoparticles for 24hr. Scale bar represents 50μm. Copyright 2017, John Wiley & Sons. [249] **c.** mm-scaled 3D left ventricle model **(i)** fabricated by rolling a flat seeded patch around a central mandrel to create **(ii)** a 3D model capable of containing fluid within its cavity. Scale bar 1cm. **(iii)** Computer aided (CAD) model of the fabricated *in vitro* left ventricle. **(iv)** staining of alpha-sarcomeric actinin and F-actin filaments on the scaffold and **(v)** cardiomyocyte crosstalk between different microgrooves due to the unique design of the patch. Scalebar **(iv)**100μm and **(v)**50μm. Copyright 2022, ACS Publication Group. [25] **d.** Flexible shape-memory scaffold that can be **(i)** rolled within a 1 mm diameter opening needle and **(ii)** injected *in situ*, while maintaining its original shape. Scale bar **(i)** and **(ii)** 5mm.**(iii)** CFDA (live/green) and propidium iodide (PI)(dead/red) staining of the patch seeded with cardiomyocytes after injection. Scale bar 2.5mm. **(iv)** implantation of stem-cell derived cardiomyocytes on porcine heart. **(v)**SEM images of seeded patch with after implantation on porcine epicardium. Scale bar 1mm (main) and 100μm (inset) **(vi)** comparison of myocardial thickness of rodent model with (left) and without (right) implantation of the patch. Copyright 2017, Nature Publication Group. [18]

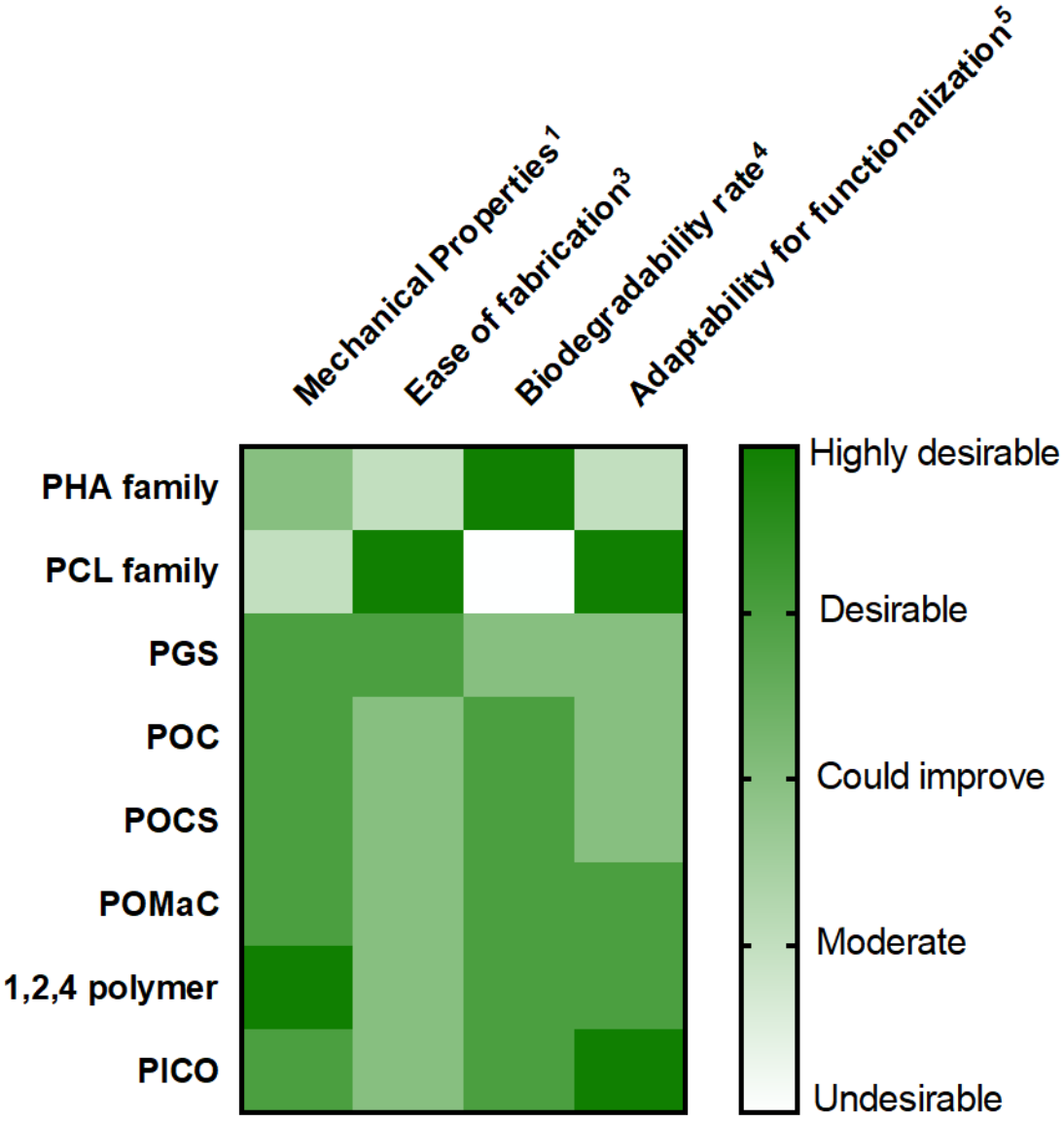

Figure 5. Comparison of advantages and shortcomings of each polyester group for fabrication of engineered cardiac tissues.

To overcome these challenges, several strategies can be explored for development of novel chemical or fabrication techniques. Current polyesters seem to have a mechanical mismatch in terms of the visco-elastic properties with the myocardium, resulting in poor integration between the fabricated scaffolds and native myocardium. (Figure 5) The ability to fine-tune mechanical properties of polyesters using different molecular weights of monomers, degree of crosslinking and incorporation of porosity can be leveraged to achieve more cardiac-friendly constructs. Additionally, techniques such as surface modification can be applied to better mimic factors present in native ECM and establish cellular adhesion and communication with the biomaterial. Degradation kinetics along with the ability to incorporate a wide range of monomers in polymeric backbone allows for controlled release of different biochemical agents such as immunomodulatory[129, 138, 193], conductive[139], or adhesive compounds[126]. Incorporating other factors important in

mediating the inflammatory response of the body and tissue remodeling in the material will be beneficial for scaffolds designed to be implanted. For instance, following a myocardial infarction, spatiotemporal release of anti-inflammatory and proangiogenetic factors in the myocardium could enhance regeneration process and potentially restore the native tissue. [292] Other strategies such as co-polymerization of different polyester monomers could also be beneficial in such applications.

Table 1.

Summary of common soft polyester materials, their mechanical properties and degradation kinetics of pure polymer material (prior to fabrication). Below-mentioned values may be modified depending on porosity and design of engineered scaffolds in different applications.

Name	Young's Modulus	Tensile Strength	Elongation	Degradation	Reference
PHB *	74.45-554 MPa	1.3-87 MPa	3.8-26%	***In vitro***: less than 10% in 6 weeks	199-205
P4HB *	14.5-670 MPa	2.3-70 MPa	1000-1450%	***In vitro:*** less than 1% in 28 days **In vivo:** 6 to 12 months	43, 178, 206-207
P34HB *	13.9-902 MPa	1.23-24.3 MPa	7-17%	**In vivo:** no observed degradation over 8 moths	208-209
PHBV *	67.7-106.7 MPa	4.01-5.84	50.2-56.3%	***In vitro*:** up to 16% in 6 weeks.	210-213
PCL	30-241 MPa	25.1-29.4 MPa	450-772%	***In vitro*:** less than 1% in 6 months	206, 214-215
PLCL	8.4±0.9kPa	4.7±2.1 kPa	960±270%	***In vitro*:** ~40% in 50 weeks ***In vivo:*** 61% after 24 weeks	216-217
PGCL	292.98-263.26 MPa	288.5-380 kPa	43.7-59.2%	***In vitro*:** 20-40% in 40 days	218-219
PGS	0.282±0.0250 MPa	>0.5 MPa	267±59.4%	***In vitro*:**17 ± 6% after 60 days ***In vivo:*** 100 after 60 days	220-221
PGSA	0.05-1.38 MPa	0.05-0.5 MPa	42-189%	***In vitro:*** 15% after 10 weeks ***In vivo:*** fully degraded after 6 weeks	74
POC	0.49-3.92 MPa	6.1 ± 1.4 MPa	40-50%	***In vitro*** 100% after 15-68 week ***In vivo:*** 20% after 28 days	22, 81
POCS	0.19-1.1 MPa	0.2-0.6 MPa	160-230%	***In vitro:*** 9-70% in 4 weeks	11, 90
POMaC	0.04 - 0.29 MPa	245-611 kPa	48 - 534%	**In NaOH:** 100% after 4 to 12 hours ***In vitro:*** 100% after 12 weeks	94
1,2,4 polymer	44±7 kPa	34 ±13	99±32%	***In vitro*** 60% (porous) and 40% (pure polymer) after 14 days **Co-culture with cells:** 60% (porous) and 30% (pure polymer) after 14 days	12
PICO	36–1476 kPa	50 -320 kPa	10-45%	**In NaOH:** 25 to 80% (tunable) after 4 to 12 hours	129, 222
ITA polymer	N/A (liquid)	N/A	N/A	**Enzymatic environment**: 30-40% within 28 days.	138
Human left ventricle	60–800 kPa	2.51± 0.21 MPa	34.9±1.1%	N/A	223-224
Rat Left ventricle	20–54 kPa	200-400 kPa	100-175%	N/A	21
Rat aorta	0.17-0.98 MPa	0.40-1.88 MPa	318±27%	N/A	225-226

*These values might vary as natural sourced PHA polyesters have batch-to-batch variations.