Design of biodegradable polyurethanes and the interactions of the polymers and their degradation by-products within *in vitro* and *in vivo* environments

X. Zhang¹, K.G. Battiston¹, J.E. McBane², L.A. Matheson³, R.S. Labow³, J. Paul Santerre¹,4,*

¹Institute of Biomaterials and Biomedical Engineering, University of Toronto, Toronto, ON, Canada; ²Children’s Hospital of Eastern Ontario Research Institute, Ottawa, ON, Canada; ³University of Ottawa, Ottawa, ON, Canada; ⁴Faculty of Dentistry, University of Toronto, Toronto, ON, Canada

*Corresponding author: paul.santerre@dentistry.utoronto.ca

3.1 Fundamentals of polyurethane degradation

From before and on out to 2015 polyurethanes (PUs) have been used extensively in numerous biomedical applications. Their lasting popularity has been a direct result of their segmented block copolymeric chemistry, which provides a wide range of versatility in terms of tailoring physical properties, biocompatibility, and degradation rates. The literature cites many examples of early PU devices showing signs of degradation (i.e., valves [1], vascular prostheses [2], and PU-coated silicone breast implants [3–5]), leading many research groups to question the safety of PU devices and to continue the quest for more biocompatible PUs without compromising their desirable physical properties.

3.1.1 Polyurethane chemistry influences stability

It is important to recognize that the chemical composition and the resulting surface domain organization of PU materials will ultimately affect degradation [6]. Classical PUs are formulated with a desired stoichiometry from all three major components: (1) an aliphatic or aromatic diisocyanate (DI), (2) a long chain oligomeric diol (soft segment), and (3) a low molecular weight chain extender [7]. In PU-based materials, a microphase segregation process leads to the formation of regions enriched in either hard or soft segments, directly impacting the dimensional stability of the elastomer [8].

3.1.2 Polyurethane bulk degradation

Although original PUs used in biomedical applications were widely accepted as flexible, durable, and relatively biocompatible, they have also been singled out as being
problematic in terms of their long-term stability in vivo. Polyether PUs were generally recognized as hydrolytically stable at neutral and basic pH and had been extensively evaluated for use in long-term implantable devices [9,10]. It was not until Pellethane® was used in marketed devices, such as pacemaker lead insulators, that several oxidation failure mechanisms were discovered to affect the polyether soft segment [11]. A synergistic effect of chemical degradation and physical damage was proposed since the brittle surface layer is more susceptible to cracking under repeated strains (i.e., physiological movement of tissues, limbs, or fluids). In addition, polyether PU devices containing metal parts, such as pacemaker leads, have been subject to metal ion oxidation because of redox reactions and catalysis with corrosion products in combination with H₂O₂ released by cells on the surface during the foreign body response (FBR) [12,13].

Early on, Stokes et al. put forth a description of a failure mechanism affecting polyether PUs under strain, termed environmental stress cracking (ESC) [14]. This description implicated factors from the in vivo environment: oxidative processes, residual stress, ether content in the soft segment, and the presence of cells associated with the FBR, as well as an unknown biological element. Many subsequent studies embraced the ESC theory and built on it, to understand the molecular mechanisms associated with cleavage of the polymer chains. Anderson’s group focused on the oxidative mechanism of ESC and was the first to use inflammatory cells to study the biodegradation of PUs [15].

3.1.3 Hydrolytic degradation

Other groups focused on the nature of the biodegradation products and investigated the hydrolytic pathway of PU chain cleavage. A number of reports described the generation of potentially carcinogenic aromatic diamines from polyester urethanes (PEUs) that had been used in the Meme breast implant [16,17].

Subsequent reports proposed that hydrolytic enzymes associated with monocyte-derived macrophage (MDM) activity are as important as oxidation in the degradation of PUs. Santerre and coworkers demonstrated that cholesterol esterase (CE) preferably degraded ester linkages immediately adjacent to the hard segment rather than catalyzing the hydrolysis of the urethane linkage in the hard segment to generate toluenediamine [18]. The group went on to identify oligomeric degradation products from the polymer to gain a greater understanding of the polymer’s breakdown by CE [19]. Through a series of experiments with radiolabeled DIs and the degradative enzyme CE [20–26], it was determined that biodegradation showed a strong dependence on hard segment chemistry and molecular weight. Stable H-bonded microdomains in the hard segment are thought to create a protective structure for cleavage points favored by the enzyme. In vivo experiments also confirmed an association between polymers with increased hard segment content and improved biostability (i.e., methylene diphenyl diisocyanate (MDI)-based polycarbonate PUs reported for Corethane® materials) [27,28]. However, the role of hydrolytic enzymes in the FBR and in vivo biodegradation had not been fully defined in those early studies.

3.1.4 Molecular mechanisms at the cell–material interface

In most cases, the actual chronic tissue interface is layered as follows: the biomaterial surface, adsorbed protein, MDMs and/or foreign body giant cells, a fibrotic capsule
Design of biodegradable polyurethanes and the interactions of the polymers

composed primarily of collagen-containing phagocytic cells and fibroblasts, and then subsequently the native tissue [29]. It is not surprising that white blood cells have emerged as the predominant cell type coordinating the biodegradation process. The temporal variation in the acute and chronic inflammatory response describes polymorphonuclear neutrophils (PMNs) appearing within minutes, but not lasting more than 48 h [15,30]. Adherent PMNs, a source of initial reactive oxygen species (ROS), have been shown to be differentially activated based on material chemistry [31–33]. For this reason, PMNs have been linked to biodegradation; however, it is unclear what the extent of their involvement is given their short life span at the cell–material interface. A comparison of PMNs versus MDMs for their destructive potential toward a radio-labeled PEU determined that there was 25 times more radiolabel release elicited by MDMs [25].

3.1.5 Environmental biodegradation

A model of environmental biodegradation has been described in such a way that the central interaction between the cells and the materials is a cyclic process that influences two critical end points that have significant clinical impact: degradation of the biomaterial and chronic inflammation [7]. The model shows how an external perturbation, such as mechanical strain, metal ions, or other factors, influences the material morphology by redefining the interactions between the polymer chains. The external perturbation disrupts the PU surface microenvironment, which dictates the type, amount, and conformation of protein adsorbed onto the material surface. Taken together all of these factors influence the response of the cells, in turn altering the inflammatory process feeding back to the material.

3.2 Design of new degradable polyurethanes inspired by biodegradation mechanisms

The study of PU degradation mechanisms has motivated the development of novel degradable PU materials from 2005 to 2015, particularly in the area of tissue engineering (TE) applications. Specifically, chemical linkages that are susceptible to oxidative, hydrolytic, or enzymatic degradation have been incorporated into the segmented block copolymeric structure of new PU materials to achieve desirable degradation processes.

3.2.1 Degradable polyurethanes designed with hydrolytically susceptible soft segments

Guan et al. have developed poly(ester urethane) urea (PEUU) and poly(ether ester urethane) urea (PEEUU) [34], both designed to be degraded by cleavage of their soft segment bonds. The PEEUU used polyethylene glycol (PEG) in a copolymer with polycaprolactone (PCL)–PEG–PCL soft segment rather than pure PCL, as in PEUU [34]. The addition of PEG into the soft segment of PEEUU contributed to increased
hydrophilicity and a faster hydrolytic degradation rate of the polymer when compared to PEUU. Despite the slight difference in hydrophilicity and change in degradation behavior for the two materials, both PEUU and PEEUU scaffolds demonstrated desirable mechanical properties (tensile strength and breaking strains) comparable to those of the canine thoracic aorta [34]. Two other interesting examples consisting of poly(ether carbonate urethane) ureas (PETCUUs) were developed by Wang and coworkers [35]. While both PETCUUs were synthesized with butanediisocyanate (BDI) and putrescine as in the PEUU and PEEUU materials discussed above, one of the PETCUUs contained a triblock copolymer of poly(trimethylene carbonate)–poly(ethylene oxide)–poly(trimethylene carbonate) (PTMC–PEO–PTMC) as the soft segment, while the other one included a pentablock copolymer PTMC–PEO–PPO–PEO–PTMC (PPO, polypropylene oxide) as the soft segment [35]. PTMC was chosen for its low modulus and relative hydrophobicity [35,36], which helped maintain the mechanical integrity of the polymer for an extended period of time. The PEO (highly hydrophilic) or PEO–PPO–PEO (moderately hydrophilic) provided the ability to change the rate of degradation and cell adhesion behavior [37–40]. These polymers demonstrated comparable cell compatibility, as smooth muscle cells (SMCs) cultured in an 8-week study with both PETCUUs showed similar morphology and viability [35]. Cell adhesion could be further enhanced with the incorporation of an Arg–Gly–Asp–Ser (RGDS) surface modification [35].

3.2.2 Degradable polyurethanes developed with blended soft segments

Given the need for degradable scaffolds to enable new tissue regeneration, to allow for timely scaffold decomposition, and to achieve mechanical criteria, a series of novel degradable PUs were developed with blended soft segments. For example, the partial replacement of the polyester units with polycarbonate elements in the soft segment has resulted in polymers (PECUU) with degradation properties in between those of the PEUU described above and a poly(carbonate urethane) urea (PCUU) [41]. Polyester hydrolysis can induce acidic by-product release [42], which further catalyzes the degradation process, where the weak acidic by-products can be quickly converted into alcohol in the decomposition process of polycarbonate [42]. Following a similar logic, Niu and colleagues generated a novel PU by coupling PCL with PEG for its soft segment [43]. Degradation of the PU material occurred over 20 weeks in vivo, with no significant elevation of pH in the local tissue [43]. Scaffolds made with this polymer also provided excellent mechanical support and important structural cues that facilitated better nerve regeneration in a rat nerve injury model [43]. Moreover, to better modulate the degradation kinetics of the materials, PUs with different soft segments were mixed together to generate novel composite PUs. In one study, PEG–hexamethylene diisocyanate (HDI)–desamino tyrosine tyrosyl hexyl ester (DTH) and PCL–HDI–DTH (both containing the same hard segment, HDI, and chain extender, DTH, but PEG versus PCL as respective soft segments) were blended at different ratios by electrospinning [44]. While the incorporation of HDI and the amino acid-based DTH were selected to improve the biocompatibility of the polymers [44], the biodegradability of
the materials depended on PCL and PEG (with PCL being more hydrophobic than PEG). It was observed that a higher ratio of PEG–HDI–DTH to PCL–HDI–DTH resulted in faster degradation of the composite polymer [44]. As well, electrospun scaffolds were shown to decompose faster than films made with the same material chemistry [44].

### 3.2.3 Degradable polyurethanes with varying chain extenders

Wagner et al. substituted the chain extender putrescine in PEUU, discussed above, with the enzymatically sensitive diamine peptide–Ala–Ala–Lys [45], aiming to develop an elastase-sensitive PU. Elastase-sensitive PU scaffolds with oriented pores supported muscle-derived stem cell growth [45], suggesting its potential use in TE applications.

Furthermore, elastomeric PUs with flexible degradability were prepared with PCL, HDI, and varying chain extenders [46,47]. Specifically, three new PUs, PU-S, PU-M, and PU-F, with bioactive isosorbidediol (1,4:3,6-dianhydro-α-d-sorbitol) (ISO), bis(2-mercaptoethyl) ether, and ISO combined with 3,7,11-trimethyl-2,6,10-dodecatrien-1-diaminobutane amide (TDD), respectively, used as chain extenders were synthesized [46,47]. These chain extenders acted as labile units and introduced different levels of polymer chain mobility into the polymeric materials [46].

Another attractive PEUU that showed controlled degradability based on its unique arginine-containing chain extender was reported by He et al. [48]. More specifically, HDI was reacted with the hydroxyl group in glycerol α-monoallyl ether (GAE) to form a prepolymer, which was then chain extended with l-Arg hydrochloride alkylenediester (Arg-x-Cl) via a urea bond to produce the PEUU [48]. The degradation rate of this arginine-derived PEUU could be adjusted by varying the proportion of Arg-x-Cl in the polymer, since Arg-x-Cl bears hydrolytically susceptible ester bonds [49]. In addition, the arginine-containing PEUU could elicit desirable cellular responses because the cationic arginine moiety not only plays a role in nitrogen metabolism and production of nitrogen oxide (NO) but also regulates the inflammatory response in vivo [50–56].

### 3.2.4 Degradable polyurethanes generated from novel chemistries

Degradable PUs synthesized with novel chemistries have demonstrated other attractive characteristics such as injectability, exclusive stimuli sensitivity, and anti-inflammatory properties. A novel injectable PU consisting of a flowable lysine triisocyanate (LTI)–PEG prepolymer and a polyester triol was prepared by Adolph and colleagues [57]. The polymer was designed to be degraded through hydrolysis of ester bonds (polyester triol) and oxidation initiated by peroxidase expressed by MDMs interacting with the biomaterial in vivo [58]. The study showed that the injection of the PU resulted in wound healing rather than fibrosis in rat excisional wounds after 7 days [57].

Since production of ROS is a common biological response in cell–material interactions on biomaterial implantation [59], PUs designed to degrade by a ROS-dependent mechanism could be more advantageous in TE applications. Martin and coworkers have fabricated a series of poly(thioketal) urethanes (PTKU) that could be exclusively
degraded by cell-generated ROS [59]. Briefly, poly(thioketal) (PTK) (synthesized with 2-mercaptoethyl ether (MEE), acetone, and 1,4-butanedithiol) was reacted with hard segment HDI trimer (HDIt) to yield PTKU [59]. It was found that PTKU degradation in the oxidative environment promoted the release of hydroxyl radicals, which acted as a positive feedback to further attack the thioketal bond and decompose the compound into its original monomers [59]. Additionally, ether oxidation also contributed to the overall degradation of the polymer [59]. The mechanism of degradation for PTKU was verified by assessing the response of the material to ROS released from activated murine-derived RAW267.4 macrophages and oxidative medium after 10 days in vitro. However, the material remained nonreactive to hydrolysis in phosphate-buffered saline (PBS) for 25 weeks [59]. PTKU demonstrated greater cell infiltration for subcutaneous wounds in a rat model when compared to standard PEU control [59].

Work by Santerre et al. has conceived degradable polar hydrophobic ionic (D-PHI) PUs, which possess excellent anti-inflammatory characteristics [60,61]. The novel D-PHI PU was synthesized from a lysine-based polycarbonate divinyl oligomer (DVO), which consists of a poly(hexamethylene carbonate) diol (PCN) soft segment and lysine diisocyanate (LDI)/2-hydroxyethyl methacrylate (HEMA) hard segments and anionic/hydrophobic acrylate monomers (methacrylic acid (MAA) and methyl methacrylate (MMA)) [60]. PCN was chosen as the soft segment not only because it provides high tensile strength while being biodegradable but also because it yields relatively low proinflammatory degradation products such as carbon dioxide and alcohols [7,62]. The traditional hard segment is substituted by HEMA, which was incorporated into the material to confer cross-linking functionality to the DVO. The vinyl groups generated reactivity with MAA and MMA via the terminal ends of the oligomeric polycarbonate chain and thus enhanced the mechanical strength of the material [60]. Additionally, MMA and MAA were introduced to induce procell adhesion and cell–material interactions, because they generated hydrophobic and anionic function integrated with the nonionic polar nature via the polycarbonate [63]. D-PHI displayed a more controlled degradation rate in vivo as compared to PLGA, and maintained its physical structure [64]. In addition, D-PHI promoted a wound-healing phenotype of monocytes with and without protein coating [65,66] and demonstrated good compatibility with vascular SMCs (VSMCs) [67], endothelial cells (ECs) [68], and human gingival fibroblasts (HGFs) [68].

These novel chemistries have been strongly considered for use in TE applications and as such they have been optimized for multiple design features both in terms of the chemistry and the processing of the materials. A list of key factors affecting PU performance in orthopedic, cardiovascular, and connective TE is provided in Table 3.1.

### 3.3 *In vivo* testing of polyurethanes from 2005 to 2015

*In vivo* testing in animal models is essential for implanted biomaterial devices (e.g., scaffolds) to determine biodegradation, mechanical compatibility, FBR, and biocompatibility of the material with host tissue or device function.
Table 3.1  Factors affecting degradable PU performance in tissue engineering applications

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Notes</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Orthopedic</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Processing</td>
<td>Some applications require the polymer to be injectable and cured in situ.</td>
<td>[69]</td>
</tr>
<tr>
<td>Elasticity</td>
<td>Sufficient elasticity required to ensure intimate contact with bone when used to fill a defect.</td>
<td>[70]</td>
</tr>
<tr>
<td>Mechanical strength</td>
<td>Compressive modulus &gt;1 GPa, compressive strength around 100 MPa. For highly porous polymers, this may be achieved with an appropriate filler material.</td>
<td>[69,71,72]</td>
</tr>
<tr>
<td>Degradation</td>
<td>Some studies have suggested &gt;18 months, depending on rate of new bone growth. Nontoxic degradation by-products.</td>
<td>[70]</td>
</tr>
<tr>
<td>Hydrophilicity</td>
<td>Reduced hydrophilicity has been proposed as a means to reduce degradation rate, allowing more time for new bone to form. However, more hydrophilic materials have shown greater calcium deposition than hydrophobic PUs in some cases.</td>
<td>[70,73]</td>
</tr>
<tr>
<td>Porosity</td>
<td>Porosity can influence the rate of PU degradation and the ability of cells to infiltrate the scaffold.</td>
<td>[70,71]</td>
</tr>
<tr>
<td>Osteoconductivity</td>
<td>Must promote new bone formation at a rate that outpaces PU degradation. This can be enhanced through inclusion of calcium-complexing agents and drugs (e.g., lovastatin) in some cases.</td>
<td>[70,74]</td>
</tr>
<tr>
<td><strong>Cardiovascular</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mechanical properties</td>
<td>Materials must be suturable, elasticity depending on the application, and have sufficient modulus without being too stiff (e.g., cardiac tissue has modulus of 10–50 kPa, tensile strength of 3–15 kPa, and strain of 22–90%).</td>
<td>[75,76]</td>
</tr>
<tr>
<td>Degradation</td>
<td>Slower degrading materials have performed better than faster degrading PUs. Nontoxic degradation by-products.</td>
<td>[76]</td>
</tr>
<tr>
<td>Porosity</td>
<td>Porosity must be sufficient to allow tissue infiltration, not compromise rate of degradation, and promote cell attachment and growth.</td>
<td>[60,77,78]</td>
</tr>
<tr>
<td>Nonactivating chemistries</td>
<td>For blood contacting PUs, chemistries that reduce platelet and white blood cell activation are essential.</td>
<td>[61,65,79,80]</td>
</tr>
<tr>
<td><strong>Connective tissue</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mechanical properties</td>
<td>PUs should have mechanical properties that mimic those of native tissue (compliance, modulus, strain).</td>
<td>[81,82]</td>
</tr>
<tr>
<td>Degradation</td>
<td>Appropriate degradation rate to support new tissue formation. Nontoxic degradation by-products that could also activate cells to promote positive remodeling outcomes.</td>
<td>[57,58,83]</td>
</tr>
<tr>
<td>Porosity</td>
<td>Must allow for new tissue ingrowth.</td>
<td>[84,85]</td>
</tr>
<tr>
<td>New tissue formation</td>
<td>Inclusion of bioactive agents, such as ECM components (e.g., ECM digest) can promote tissue infiltration.</td>
<td>[82,86,87]</td>
</tr>
<tr>
<td>Nonactivating chemistries</td>
<td>In addition to white blood cell interactions, new PUs should prevent fibroblast to myofibroblast differentiation to support healthy tissue regeneration instead of scarring.</td>
<td>[57]</td>
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</table>
3.3.1 In vivo testing of polyurethanes to assess biodegradation and the foreign body response

Preliminary in vivo biodegradation and the FBR are often assessed by subcutaneously implanting a PU disk (porous or nonporous). While the cage implant model has often been used to study biodegradation and the FBR because of the advantage of allowing removal of the PU, surrounding cells/tissues and exudates [88–90], it presents a significant perturbation to the implant site. A cageless subcutaneous implant allows for direct contact with host cells and in the case of porous scaffolds leads to cell infiltration, reflecting more of what would be seen in TE applications [64,91]. Recent studies have shown that D-PHI lost only 20% of its original mass after 100 days of implantation in a rat model, suggesting a relatively slow and controlled degradation rate [64]. In a mouse system, it was found that 14 day D-PHI explants showed good cell infiltration and matrix deposition as well as a pro-wound healing cytokine profile (compared to 1-day explants) [91]. Both studies favored D-PHI as a good scaffold for TE as it allowed for tissue ingrowth while maintaining structural support.

Using a 14-day subcutaneous implant, Da Silva et al. compared aqueous anionic PU dispersions (PUD) (with PCL and PEG soft segment and isophorone diisocyanate (IPDI) and hydrazine (HZ) hard segment) with or without montmorillonite clay nanoparticles (NPs) [92]. The number of cells infiltrating the PUD scaffolds decreased from day 1 to day 14 but did not significantly change between formulations, suggesting that by day 14 the FBR had been resolved [92]. Dey et al. compared a cross-linked urethane-doped polyester (CUPE) scaffold to a poly-l-lactic acid (PLLA) scaffold in a subcutaneous rat model system. It was found that after 1 week, the CUPE scaffold had a thinner fibrous capsule when compared to the PLLA scaffold, suggesting a more modest FBR [93].

3.3.2 In vivo wound healing assays

Dermal TE using PU scaffolds/membranes requires the precise reconstitution of the skin bilayer. In an ovine full thickness wound model, which tested a PU (biodegradable temporizing matrix; BTM-2) [94], the Integra™ dermal regeneration template was compared to BTM-2. It was found that by 29 days all wound sites had healed comparably [94].

Hafeman et al. recently compared two PEUs prepared from LTI versus HDIt for use in skin TE, looking at the in vivo degradation of the two PEUs in a full excision model [58]. Both PUs showed limited inflammation; however, the LTI scaffold degraded significantly faster than the HDIt scaffold at 28 days, suggesting that it may be better for skin TE [58] as this rate is aligned with the desired design specifications.

3.3.3 In vivo polyurethane soft tissue engineering

Soft tissue TE scaffolds are temporary templates that are gradually degraded and replaced by the host’s own cells and tissue. New methods in in vivo imaging provide an
attractive strategy for determining structural and mechanical changes in PU scaffolds without explanting or sacrificing the animal. This allows for longer term monitoring of the scaffold’s compatibility and host tissue integration. Park et al. used multimodality imaging to compare degradation rates of PEUU scaffolds versus polydioxanone scaffolds [95]. They found that mechanical and histological assessments of explants correlated well with ultrasound shear wave imaging and photoacoustic imaging data [95].

Cardiac biomaterials for TE have been a major PU research area for years. Many PU trileaflet heart valves have been developed, but most of these have failed due to calcification and stiffening. More recently, Thomas and Jayabalan developed a calcification-resistant high flex life polyurethane urea (HFL18-PU) for use as a trileaflet valve [96]. The long-term in vivo biodurability testing (subcutaneous implant in rabbit) showed little FBR with an absence of PMNs and MDMs after 3 months, and by 6 months there was no change in weight, color, or surface pitting and minimal changes in mechanical properties, suggesting that the implant was not degraded [96]. Stachelek et al. evaluated a cholesterol-modified PU as a valve cusp that can promote EC adhesion [97]. They found that bovine blood outgrowth ECs (BOECs) could adhere to the PU valve cusps and that the BOEC-seeded valves implanted in an ovine model system appeared translucent with no abnormalities when compared to the unseeded valves, which appeared opaque with visible thrombi [97].

Similar to dermal patches for TE, cardiac patches to repair cardiac tissue can also be made of PUs. Fujimoto et al. used a PEUU scaffold to replace a surgical defect in the right ventricular outflow tract of a rat heart [98]. After 12 weeks, the PEUU scaffold showed host tissue ingrowth, which was not apparent in a comparison to expanded polytetrafluoroethylene patches [98].

### 3.3.4 In vivo polyurethane bone tissue engineering

PUs designed for bone replacement applications need to be subjected to weight-bearing in vivo studies. For instance, Dumas et al. used a rabbit weight-bearing unicortical plug defect model system to evaluate an allograft bone that uses a 2-component biodegradable PU as a binder [72]. Within 6 weeks there was extensive cellular infiltration into the graft and new bone formation [72].

Adhikari et al. developed a biodegradable injectable PU for orthopedic applications [99]. The group chose to evaluate both the preformed PU and the in vivo injected PU to determine degradation and biocompatibility using an ovine model [99]. The preformed and injected PUs were well tolerated by the sheep and both showed evidence of new bone growth and controlled polymer degradation after 6-month implantation [99].

Other biodegradable PUs for bone TE have incorporated drugs to enhance wound healing and bone regeneration and prevent bacterial contamination. For example, a group prepared a biodegradable PU with lovastatin to promote BMP-2 expression to stimulate bone formation [74]. A rat plug defect in vivo model was used where a 3 mm defect was created in the femur and the biomaterial was formed into a 3 × 5 mm cylinder implanted into the defect. The femurs were then explanted at 2 and 4 weeks for X-ray microtomography evaluation [74]. By 4 weeks, there were
increases in bone regeneration using the lovastatin/PU, which was not seen at the 2-week time point [74].

3.4 Coculture using degradable polyurethanes from 2005 to 2015

Bone and soft tissues are complex multicellular structures requiring oxygen, nutrients, and cell signaling cues to allow cells to form functional tissues. The oxygen diffusion limit of 150 μm [100] limits the size of in vitro TE constructs without vascularization. Often coculture is employed to promote prevascularization of the TE graft (reviewed in [101]).

3.4.1 Polyurethane coculture systems for liver tissue engineering

Salerno et al. cocultured human hepatocytes with human umbilical vein ECs (HUVECs) on a polyetheretherketone PU membrane to promote vascularization of an in vitro engineered liver tissue [102]. There was improved hepatocyte function and the formation of luminal structures occurred within 3 days of coculture on the PU versus hepatocyte-only samples [102]. Another study demonstrated that coculturing bone marrow-derived mesenchymal stromal cells with hepatocytes greatly reduced the secretion of stress enzymes by the hepatocytes and that the cells attached better to nanofiber PU versus unstructured PU [103].

3.4.2 Polyurethanes coculture systems for cardiac tissue engineering

Surprisingly, the use of cocultures with degradable PUs in cardiac TE systems has been limited when vascular grafts are excluded from the research. A study by Parrag et al. used murine-derived embryonic stem cells (mESCs) and mouse embryonic fibroblasts (MEFs) to TE cardiomyocyte-derived tissues. mESCs are pluripotent cells that require proper cues to differentiate into specific cell types. In the study, Parrag et al. showed that both the coculture of mESCs with MEFs and the use of aligned microfibrous PU scaffolds provided the cues necessary to induce mESC differentiation to a functioning cardiomyocyte phenotype [104].

More recently, the Santerre lab used the coculture of primary cells with monocytes/MDMs to promote a wound-healing milieu to encourage cell attachment, infiltration, and proliferation on D-PHI PU films and scaffolds for TE vascular graft applications [67,91,105–107]. In the context of blood vessel TE, it was found that by coculturing monocytes with ECs on D-PHI films that the ECs attached better and spread out more while displaying more EC functional markers than EC monocultures (CD31) [91]. VSMCs benefited from coculture with monocytes on both film and porous scaffold forms of D-PHI [67,106,107]. On porous scaffolds, the monocyte coculture helped VSMCs migrate within the pores and increased deposition of extracellular matrix (ECM) proteins [107]. A recent study found that monocyte-conditioned medium could also promote VSMC attachment to
D-PHI, while allowing VSMC differentiation marker expression [106]. This suggests that it is the cytokines and signaling cues released from the monocyte (i.e., paracrine effects) rather than cell–cell contact alone that contribute to a desirable VSMC phenotype [106].

### 3.4.3 Polyurethane coculture system for dermal and other soft tissue engineering

Dermal TE grafts meet a critical need for nonhealing wounds and burn repair. For dermal TE, a vascularized bilayer of fibroblasts and keratinocytes is the ultimate goal. Li et al., using Novo Sorb™ PU variant BTM-2, showed that keratinocytes could form a monolayer over the BTM-2 scaffold preseeded with dermal fibroblasts [94]. In a 2014 follow-up paper, the Greenwood group described their coculture system (fibroblasts then keratinocytes) on BTM as a cultured composite skin, suggesting that the BTM-2 construct may be moving closer to the clinic [108].

Gingival atrophy, where the root is exposed leading to tooth sensitivities and caries, is a prevalent disorder that requires better graft options [109]. The Santerre group recently published that a D-PHI PU is compatible with HGFs cultured in a medium-perfused bioreactor [110]. The coculture of HUVECs with HGFs was subsequently tested to see if HUVECs could vascularize the PU scaffolds. HUVEC clusters could be seen at the end of the 28-day test and the cocultures had modulated cytokine activities depending on the ratio of HUVEC:HGF [105].

### 3.4.4 Polyurethane coculture systems for bone tissue engineering

Bone has been one of the largest research areas for PUs and coculture systems (coculture strategies in bone TE, reviewed by Janardhanan et al. [111]). Duttenhoefer et al. coseeded human endothelial progenitor cells (EPCs) with mesenchymal stem cells (MSCs) onto a porous bioresorbable elastomeric PU scaffold containing NPs of hydroxylapatite (HA) to induce vascularization and encourage osteogenic differentiation [112]. The presence of EPCs promoted more tubular structures per mm² and greater EC marker-expressing tubular structures [112]. In another study, Hofmann et al. showed that coculturing human osteoblasts with HUVECs promoted vascularization of a degradable PU scaffold and stable cell differentiation after more than 14 days in culture [113]. Together, these studies suggest that coculture is beneficial for promoting cell attachment, desirable cell phenotypes, and tissue vascularization in the context of bone TE.

### 3.5 Degradable polyurethanes cultured with stem cells for tissue engineering applications

Since mature cells usually have limited expansion abilities in vitro [114], stem cells have become a promising substitute for mature cells in tissue repair and regeneration when assessed with a variety of PUs and stem cell culture systems.
3.5.1 **Biodegradable polycaprolactone-containing polyurethanes seeded with stem cells**

Stem cell interactions with PCL-containing PEU or PEUU scaffolds (degraded via hydrolysis) have been studied for TE applications, and in particular using immunomodulating and multipotent MSCs [115–117]. Zahedmanesh and colleagues have seeded MSCs on 3D fibrin–PU composite scaffolds, with the PU synthesized from HDI, PCL, and ISO, and incorporation of a fibrin gel [118]. A 10% triaxial compression of the scaffold matrix combined with interfacial shear promoted chondrogenesis of MSCs, as indicated by their elevated expression of collagen and proteoglycans after 14 days in culture (in the presence of TGF-β-dexamethasone) [119]. In addition, the importance of mechanical stimulation in modulating the behavior of MSCs has been reported by Liu et al., who cultured MSCs on degradable PU scaffolds (generated using PCL/l-lactide, 1,4-butanediol (BDO), and BDI) [120]. Moreover, Laschke et al. reported culturing adipose-derived stem cells (ASCs) either as 3D spheroids or single cells on PEU scaffolds (which has the same chemistry as the PU used in Zahedmanesh’s study) combined with HA [121]. ASC spheroids were shown to encourage significantly more new vasculature formation than single ASCs (40% vs. 20%). The results corresponded well to the findings in Kuo’s study, where it was reported that human MSC aggregates proliferated more and showed greater osteogenesis/chondrogenesis potential than single cells on PU after 7 days in culture [122]. The investigators then carried out a study to determine if the differentiation of ASCs on HA–PEU before implantation would affect their angiogenic capacity [123]. They found that osteogenic preconditioning of ASCs significantly impaired their ability to generate new microvessel networks [123]. In addition, dedifferentiation of preconditioned ASCs was evident with a reduction in mineralized matrix after 14 days in a mouse implant model [123]. Since the structure of electrospun fibrous scaffolds can be controlled to resemble natural ECM by adjusting the processing parameters [124], Gugerell and coworkers have incorporated ASCs into two PCL-containing electrospun PUs. Both remained degradable by hydrolysis (with ester bonds more susceptible than urethane and urea linkages) [125]. The two PU polymers were poly(ε-caprolactone-courethane-co-urea) (PCLUU) and poly [(l-lactide-co-ε-caprolactone)-co-(l-lysine ethyl ester diisocyanate)-block-oligo(ethylene glycol)-urethane] (PLLEGU), with PLLEGU showing more degradability (34.3%) than PCLUU (2.4%) after 44 weeks in PBS [125]. ASCs were shown to be able to adhere, proliferate, and differentiate into adipocytes on both scaffolds (with lipid droplet formation after 21 days). However, they exhibited a more physiological morphology on PCLUU (more spread) than on PLLEGU (elongated) [125].

3.5.2 **Commercial degradable polyurethanes used in stem cell culture**

Commercial PUs have also been studied for use with stem cell culture. For instance, electrospun commercial PU (Desmopan® 9370A) scaffolds were fabricated with
high porosity (84%) and an average fiber diameter of 360 nm [126]. Human ESCs were cultured on PU scaffolds in neuronal proliferation (1–17 days) and differentiation medium (18–47 days), and the results indicated successful transformation of the ESCs to dopaminergic tyrosine hydroxylase-positive neurons [126]. More importantly, ESCs seeded on PU scaffolds showed expression of neuronal markers (MAP2ab, β-tubulin III), neurite outgrowth, and formation of cell–cell/cell–PU fiber connections [126]. On the other hand, the reference culture (without the PU fiber, but with the same proliferation/differentiation medium) promoted differentiation along the astrocyte lineage [126]. Therefore, the electrospun commercial PU could provide topographical cues to guide ESCs and allow them to differentiate into neuronal cells [126].

3.5.3 Injectable degradable polyurethanes cultured with stem cells

Injectable PU gels, containing a hydrophilic PEG segment and hydrophobic poly (serinol hexamethylene urethane), have been developed by Ritfeld et al. for seeding with MSCs [127]. In this specific design, the PU gel could act as a scavenger for ROS via its urethane groups and thus protect MSCs from oxidation-mediated cell death in vivo [127].

3.6 Degradable polyurethanes used in drug delivery systems

PU-based drug delivery systems can be manipulated to have site-specific release (via cell targeting designs) and controllable drug release kinetics [128].

3.6.1 Degradable polyurethane-based growth factor delivery systems

Growth factors have been covalently coupled to PUs (such as PEU and PEUU) such that the materials are degraded mainly via hydrolysis of the soft segment (cleavage of ester bonds). It is believed that biologics anchored to PUs can be released following Fick’s diffusion kinetics, breakdown of the polymers, or a combination of both. For example, Guan et al. loaded basic fibroblast growth factor (bFGF) with the addition of heparin and bovine serum albumin to stabilize bFGF [129,130]. A biphasic release behavior with an initial fast release followed by a slow release over 4 weeks was observed in PEUU/bFGF scaffolds without heparin. However, with the incorporation of heparin into the material, drug release in the burst phase was increased within the first 24 h [129]. Similarly, insulin-like growth factor-1 and hepatocyte growth factor were introduced into the same PEUU by Wagner’s group [131]. Proteins in this case showed complex multiphasic release profiles, influenced
by the rates of degradation and the different protein/polymer interactions of the different segments of the block copolymers [131]. Li and coworkers have coupled platelet-derived growth factor (PDGF) to a polyester triol-based PU [132]. The PDGF–PU system yielded a two-stage release profile as seen in Guan’s study. Most importantly, the Guan, Wagner, and Li studies all showed sustained bioactivity of the released growth factors [129,131,132].

### 3.6.2 Commercial degradable polyurethane-based anti-inflammatory/anticancer drug delivery systems

Anti-inflammatory/anticancer drugs have been incorporated into and delivered with IPDI-based PUs or commercially available PUs. Moura et al. reported on mixing the anti-inflammatory dexamethasone acetate (ACT) with PU (prepared with hard segments, IPDI and HZ; soft segments, PCL and PEG) [133]. ACT was seen to be continuously released from the PU matrix following an approximately linear relationship over 120 days, indicating drug release mechanisms that implicated both polymer degradation (hydrolysis of ester linkages in PCL) and Fickian diffusion [133]. Babanejad and coworkers designed highly soluble carboxylated PU (CPU) NPs by substituting HZ in the PU used by Pinto et al. (2012) with dimethylol propionic acid (DMPA) and BDO [134]. The anticancer drug raloxifene hydrochloride (R-HCl) was complexed with CPU by interactions of cationic amino groups from R-HCl with the anionic CPU [134]. The results suggested Fickian diffusion release kinetics from the NPs, with a sustained drug release up to 24.19 ± 4.35% after 4 weeks in vitro [134].

### 3.6.3 Degradable polyurethane-based gene delivery systems

Nonviral transfection vectors are providing a promising alternative to viral vectors due to their ease of production and low immunogenicity. Cationic amine groups can effectively bind DNA with strong electrostatic force and therefore have been coupled to PUs via hydrolytically degradable ester or urethane bonds [135]. Positively charged polymers also have a pH buffering effect, which would assist the escape of vectors and increase the efficiency of transfection [136–139]. One example of an amine-containing PU was synthesized with LDI, PEG, and 2-diethylaminoethylamine (DEAE) via an aminolysis reaction [140]. Cationic amino groups in the PU established strong interactions with DNA molecules, which allowed condensation of DNA into nanoscale structures for endocytosis. As well, the cationic groups protected the NPs from nuclease degradation [140]. Tseng and Tang also developed a similar poly(amine ester glycol urethane)–PAEGU based gene carrier, with the hard segment being BDI rather than LDI [135]. PAEGU DNA carrier was determined to be an efficient and safe tool, with a high transfection rate (35% transfection) and cell viability (90%) when cultured with human fibroblasts for 24 h [135].
3.6.4 *Stimuli-sensitive polyurethane drug delivery systems*

Intelligent stimuli-sensitive PUs designed from 2005 to 2015 are emerging as promising tools for targeted drug delivery. One example is the pH-sensitive biodegradable PCLH–PUs developed by Zhou et al. for targeted antitumor drug release \[141\]. Briefly, the pH-responsive PU was synthesized with soft segments PCL and pH-sensitive PCL-hydrazone–PEG-hydrazone–PCL macrodiol (PCLH); hard segments LDI, BDO, and l-lysine derivative tripeptide (LDT); and end-capped with hydrazone-linked methoxyl-PEG \((m\text{-PEG-Hyd})\) \[141\]. In PCLH–PU, \(m\text{-PEG-Hyd}\) was introduced to shield the polymeric micelles from plasma proteins or phagocytotic cells in blood circulation \[142\], and could be cleaved in the low pH environment of tumor tissue, enabling efficient internalization of micelles by cancer cells. Song and colleagues also developed tumor-cleavable PUs by reacting PCL and LDI with an l-cysteine-derived diamine chain extender bearing a redox-responsive disulfide bond, clickable alkynyl groups (Cys-PA), and a detachable pH-sensitive methoxyl-PEG unit \[143\]. The hydrophobic core of the micelles was formed mainly by PCL to entrap water-repelling biologics (doxorubicin (DOX)) \[143\]. What made this latter multisensitive drug carrier unique was that a model targeting ligand, folic acid (FA), was conjugated to the alkyne groups on the PU via facile click chemistry, which improved the drug efficacy toward HeLa cells (FA-receptor positive) after 4 h *in vitro* \[143\]. With a similar design logic, He and coworkers have incorporated reduction-sensitive bis(2-hydroxyl ethyl) disulfide (DHDS) into their polymers to generate paclitaxel (PTX)-coupled PU (PTX–PU) micelles, for on-demand drug delivery \[144\]. The rate of drug release (via polymer disintegration) was designed to be modulated by the redox-sensitive disulfide content DHDS in the material \[144\]. *In vitro* studies showed effective uptake of drug micelles within 1 h by tumor cells \[144\].

3.7 *Physical forms and processing of degradable polyurethanes*

Many fabrication methods exist for processing degradable PUs, whose final forms affect their degradability \[145\].

3.7.1 *Porous polyurethane scaffolds*

Many biomedical applications require PUs to be in the form of 3D constructs. For TE in particular, a porous scaffold architecture is necessary to permit cell and tissue ingrowth as well as to allow for integration with the host. Different porosity values, pore sizes, and pore interconnectivities are required for different TE applications. The method of solvent casting and particle leaching is popular for fabricating PU scaffolds due to its ease of use and versatility. In this method, the PU is dissolved in an appropriate solvent and cast into a porogen-filled mold. The most commonly used porogens are salts and sugar, but polymer particles and paraffin can also be
Scaffold geometry can easily be manipulated by the design of templates made of solvent-compatible materials that are fabricated in the required shape. Care must be taken with this approach to ensure that residual solvent is removed to avoid cytotoxicity.

A degradable PU fabricated from a prepolymer of PCN:LDI:HEMA (1:2:2) and cross-linked in the presence of MMA and MAA has been processed into porous scaffolds (80–90% porosity, 100–400 μm macropores, 1–5 μm micropores) using the aforementioned porogen leaching technique [68,78]. In this system, NaHCO₃ provides a macroporous structure, while PEG (Mₙ 600) supports the formation of micropores in the scaffold walls to facilitate nutrient diffusion. For this PU, the prepolymer (PCN:LDI:HEMA) is dissolved in the MMA and MAA monomer mixture, while the microporogen increases the salt-loading capacity, obviating the need for a solvent.

Another scaffold fabrication technique is thermally induced phase separation (TIPS) [34,46,84,147–149]. TIPS involves decreasing the temperature of a polymer solution to obtain a polymer-rich and polymer-poor phase. Following phase separation, the solvent is removed using one of a number of methods (freeze drying, evaporation) resulting in the formation of pores in the polymer structure. TIPS can also be combined with the use of porogens to increase void fraction, have better control over pore size, or improve pore interconnectivity.

Studies with degradable PUs have investigated the parameters involved in the TIPS process on the final scaffold properties achieved. Using a PU synthesized from HDI, PCL, and ISO, the use of dimethyl sulfoxide (DMSO) or N-methylpyrrolidone (NMP) as solvents resulted in scaffolds with a nonporous polymer layer that excluded nonsolvent from the bulk of the scaffold (DMSO) or a dense, irregular pore structure (NMP). The latter had low pore interconnectivity, as demonstrated by a high porosity but low water permeability [46]. Dimethylformamide (DMF), however, resulted in larger, open, and interconnected pores. The use of a cosolvent with DMF, which leads to the formation of micropores in the walls of macropores due to liquid-induced phase separation, also influenced the scaffold properties, with tetrahydrofuran (THF) producing larger pores and greater pore interconnectivity than ethanol or isopropanol.

While investigating the use of other processing parameters with TIPS using a PU (BDI, PCL, and putrescine) dissolved in DMSO, it was shown that pore size increased with an increase in quenching temperature (0 > −20 > −80 °C) and that porosity was higher when using a lower PU concentration (5% > 10% PU in DMSO) [84]. The freezing phase of TIPS can further be modified using a temperature gradient to achieve oriented pore structures [150].

### 3.7.2 Electrospun polyurethane scaffolds

Detailed descriptions of the theory and setup with electrospinning systems can be found in reviews by Pham et al., Bhardwaj et al., and Rutledge et al. [151–153]. A generic setup consists of a PU solution held in a syringe connected to a syringe pump, a high voltage source, and a collector [151]. The high voltage source is used to induce charge into the polymer solution, which is attracted toward the collector of opposite
polarity. As the polymer solution travels from the needle tip of the syringe to the collector, the solvent evaporates, resulting in the deposition of polymer micro- or nanoscale fibers.

Degradable PUs based on HDI, PCL, and chain extenders of either 2-aminoethanol (PEUU) or a diesterdiphenol derivative of tyrosine (PEU) were electrospun using different electrospinning parameters, and provided a case study for the importance of both polymer type and electrospinning parameters on the final formed scaffold [154]. Below certain concentrations (<30 wt% in dimethylacetamide (DMAc) and <20% in DMAc/acetone 60/40), electrospinning of these PUs results in only beads, while elevating the concentration results in a polymer solution too viscous to electrospin [154]. In contrast, the use of 1,1,1,3,3,3-hexafluoroisopropanol (HFIP) as the electrospinning solvent generates uniform fibers with no beading at concentrations greater than 20%. HFIP is considered a good solvent for the electrospinning of highly hydrogen bonded polymers, such as PUs, as the hydroxyl group interacts with hydrophilic hard segment domains through hydrogen bonding, while fluoride is able to interact with the hydrophobic soft segments, allowing for a well-dispersed polymer solution with reduced chain entanglements. The appropriateness of the solvent was also dependent on the polymer type, since the PEU, but not PEUU which experiences greater hydrogen bonding, could be reliably electrospun with 50:50 DMF:THF [154].

Modifications to the traditional electrospinning setup have also been reported to further customize PU scaffolds. Hybrid scaffolds have been achieved using a dual-syringe system where simultaneous electrospinning of PLGA and a PEUU is used to produce a scaffold with one polymer providing mechanical stability, and the other antibiotic release [155]. Wet electrospinning has also been reported, wherein during the electrospinning of a PEUU (based on PCL, BDI, and putrescine) cell culture medium was electrosprayed, resulting in the incorporation of biological factors that improved the ability of the formed scaffold to support cellular infiltration [83]. Reactive electrospinning, achieved by placing a UV source above the mandrel, can be used with PU formulations that are UV sensitive, such as Pellethane® modified with reactive pentenoyl groups [156]. Electrospinning can also perturb the surface distribution of chemical functional groups. While fluorinated components of PUs are typically reported to demonstrate significant surface segregation [157]. In the latter work Blit and colleagues introduced cell adhesive chemistries onto the surface of a degradable polycarbonate urethane via fluorinated surface carrier oligomers. However, others have reported that the electrospinning process results in perfluoro-polyether components of a PU to aggregate in the electrospinning solution, which results in a minimized surface fluorine content due to the fluorinated segments being frozen in the fiber core during the rapid evaporation of solvent that occurs during electrospinning [158], thereby influencing the potential for surface degradation by chemically changing the surface.

Another modification involves removing the potentially cytotoxic solvent from the electrospinning equation in a process called melt electrospinning [159]. This process involves tight control of temperature, and for the case of a PU based on BDI, PCL, 1,4-butanediamine (BDA), and BDO involved temperatures of 220–240°C [160].
While thermal degradation of PUs is generally not considered an issue for biomedical applications due to the range of temperatures expected, when processing degradable polymers at high temperatures thermal degradation can occur, which can release toxic degradation by-products into the body, depending on the hard and soft segment components of the PU. In a study by Karchin et al. [160], degradable PUs made of PCL:LDI:BDA (1:2:1) underwent degradation, yielding weak and oxidized fibers following melt electrospinning, while a PU of PCL:BDI:BDO (1:4:3) could successfully be electrospun with good quality fibers.

3.7.3 Polyurethane nanoparticles

Several methods have been reported for the synthesis of PU NPs. Using a soft segment of PCL diol with either PLLA diol or polyethylene butylene adipate (PEBA) diol, hard segment of IPDI and DMPA, as well as triethylamine (TEA) and ethylenediamine (EDA), NPs of <50 nm diameter were fabricated using a waterborne procedure [161]. In this method, the soft segment components and IPDI are first reacted to form a prepolymer, after which DMPA is added with 0.27% methyl ethyl ketone. To neutralize the carboxylic acid groups of DMPA, TEA is added, followed by end-capping of the polymer with EDA in water under vigorous stirring to form the NPs (final stoichiometric ratio of IPDI:oligodiols: DMPA:EDA:TEA of 3.52:1.1:1.52:1).

The use of oil/water (O/W) emulsions has also been employed to fabricate PU NPs [162–165]. In this method, the diisocyanate (IPDI) is first dissolved in an oil/surfactant mixture (90/10, saturated medium chain triglyceride/polysorbate 80 [polyoxyethylene 20-sorbitan monooleate]). Addition of the aqueous phase with PEG 400 (diamine or diol) to the O/S mixture in dropwise fashion (to obtain 90% aqueous component) occurs under mechanical stirring to obtain nanoemulsions, followed by heating to 70°C to allow polymerization and achieve PU or PU urea NPs, which can be isolated by ultracentrifugation [165]. This method works by having IPDI present in the core of oil nanodroplets in the O/W nanoemulsion, which react with the diols or diamines at the surface of the oil droplet, resulting in the formation of the NPs with a size distribution from 40 to 100 nm.

Core–shell PU NPs can also be prepared by appropriate choice of isocyanate [166]. Blocked amphiphilic prepolymers were prepared by Cheong et al., where the hydrophobic block is composed of IPDI–polytetramethylene adipate polyol (PTMA) and the hydrophilic block is MDI–DMPA. The resulting polymer is added dropwise to water under stirring, resulting in a core–shell structure with the hydrophobic IPDI–PTMA in the core and hydrophilic MDI–DMPA in the shell (80–100 nm diameter) [166].

3.7.4 Effect of processing parameters on polyurethane biodegradation characteristics

While the chemistry of the PU itself is of critical importance in determining the biodegradability of the PU, the final form it takes can also alter its degradation
Design of biodegradable polyurethanes and the interactions of the polymers

characteristics. Increasing the porosity of the scaffolds enhances cellular and tissue infiltration, but the greater surface area associated with the porous form may also increase the rate of degradation [167]. For some polymer scaffolds, the degradation rate has been shown to increase slowly with increases in porosity up until 80%, after which a sharp increase in degradation rate is seen [167]. Likewise, PCL nanofibers demonstrated an increase in degradation with decreasing electrospun fiber diameter due to the associated increase in surface area. Furthermore, the process of electrospinning resulted in reduced surface hydrophilicity of PCL nanofibers, thereby generating decreased water uptake and thus reduced degradation versus other processing techniques. This emphasizes the importance of processing parameters on surface chemistry that can ultimately influence degradation properties [168].

Nanocomposites involve the inclusion of NPs into otherwise familiarly processed PUs, which can be in the form of films or electrospun or porous scaffolds. In addition to providing bioactivity to the PU material [169–173], inclusion of NPs in the polymer matrix can also alter the degradation characteristics. Nanocomposites involving the inclusion of a polyhedral oligomeric silsesquioxane (POSS) integrated within a poly(carbonate–urea) urethane (POSS–PCU) resulted in shielding of the soft segment from oxidative and hydrolytic degradation [174]. The inclusion of POSS in a poly(caprolactone/carbonate) urethane urea also allowed for a more controlled degradation rate, specifically demonstrating the ability to protect the mechanical properties of the polymer under hydrolytic degradation [175]. Gold and silver NPs have also been incorporated into PU materials to alter degradation kinetics. The inclusion of gold NPs (30.2–113 ppm) in a polyether-type waterborne PU was shown to increase the biostability of the PU by acting as a free radical scavenger [176].

### 3.8 Monomers and oligomers used in degradable polyurethanes

The monomers and oligomers used in the design of degradable PUs are summarized in Table 3.2.

### 3.9 Summary

Block copolymeric/degradable PUs provide significant advantages over classical degradable polyesters because of their chemical diversity, which yields uniquely compatible materials with respect to the biological responses to implants, and provides the field with a versatile range of physical properties when compared to other classes of biomaterials. Their attributes will enable many practical solutions to medical devices that are currently not afforded by other contemporary biomaterials. Hopefully this review will inspire the exploration of new PU chemistries with respect to biological interactions.
Table 3.2 Monomers and oligomers used in degradable PUs

<table>
<thead>
<tr>
<th>Monomer</th>
<th>Chemical structure</th>
<th>Comment</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Polyisocyanate</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MDI</td>
<td><img src="image" alt="MDI chemical structure" /></td>
<td>• Toxic aromatic diamine degradation products</td>
<td>[27,28,166]</td>
</tr>
<tr>
<td>BDI</td>
<td><img src="image" alt="BDI chemical structure" /></td>
<td>• Yields putrescine following degradation, a polyamine essential for cell growth</td>
<td>[35,82,84,120,135,160]</td>
</tr>
<tr>
<td>HDI</td>
<td><img src="image" alt="HDI chemical structure" /></td>
<td>• Diamines released on degradation are toxic to human liver and kidney, though less toxic than aromatic diamines from MDI or TDI</td>
<td>[44,46–48,118,154]</td>
</tr>
<tr>
<td>LTI</td>
<td><img src="image" alt="LTI chemical structure" /></td>
<td>• Hydrolytic, esterolytic, and oxidative degradation • Nontoxic degradation by-product (lysine)</td>
<td>[57,58]</td>
</tr>
<tr>
<td>HDIt</td>
<td><img src="image" alt="HDIt chemical structure" /></td>
<td>• Hydrolytic, esterolytic, and oxidative degradation • Slower in vivo degradation than LTI-based PUs • Degradation releases cyanuric acid</td>
<td>[58,59]</td>
</tr>
<tr>
<td>Polyurethane Type</td>
<td>Description</td>
<td>References</td>
<td></td>
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</tbody>
</table>
| LDI               | Nontoxic degradation by-product (lysine)  
Methyl ester provides steric hindrance of hydrolysis sites | [60,125,140,141,143,160] |
| IPDI              | Lower toxicity than aromatic diisocyanates  
Reduced hydrolytic degradation vs. HDI-based PUs due to asymmetrical structure | [92,133,161,165,166] |
| DMPA              | Hydrophilic, and thus expected to increase susceptibility to hydrolytic degradation | [134,161,166] |
| Soft segment      | Most susceptible to oxidative degradation  
Can increase PU hydrophilicity, thus increasing hydrolytic degradation | [34,43,44,57,92,125,133,135,140,165] |
| PEG               | Most susceptible to hydrolytic degradation  
Slow degrading, but faster than just hydrolysis due to autocatalytic bulk degradation from lower pH due to acidic degradation by-products | [34,43,44,46,47,82,84,92,115–118,120,125,133,143,154,160,161,168,174] |
<table>
<thead>
<tr>
<th>Monomer</th>
<th>Chemical structure</th>
<th>Comment</th>
<th>References</th>
</tr>
</thead>
</table>
| PTMC      | ![PTMC structure](image) | - Has been shown to undergo surface degradation, which may allow for maintenance of mechanical properties for prolonged periods  
- Slow degradation rate | [35]        |
<p>| PEO       | <img src="image" alt="PEO structure" /> | - Can be used to accelerate hydrolytic degradation due to high hydrophilicity | [35]        |
| PPO       | <img src="image" alt="PPO structure" /> | - Less hydrophilic than PEO, thus maintains slower hydrolysis rate | [35]        |
| GAE       | <img src="image" alt="GAE structure" /> | - High GAE content results in higher cross-link density, reducing enzymatic biodegradation rate | [48]        |
| Polyester triol | <img src="image" alt="Polyester triol structure" /> | - Composition of the polyester triol (ε-caprolactone, glycolide, lactide) can be modified to tailor degradation rate | [57,132]    |</p>
<table>
<thead>
<tr>
<th>Polymer</th>
<th>Description</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>PTK diol</td>
<td>Stable under aqueous conditions, but selectively degraded through cell-generated ROS</td>
<td>[59]</td>
</tr>
<tr>
<td>PCN</td>
<td>More resistant to oxidative degradation than PEU, but can be designed to be prone to hydrolytic degradation</td>
<td>[60]</td>
</tr>
<tr>
<td>L-Lactide</td>
<td>Releases acidic degradation by-products</td>
<td>[120,125]</td>
</tr>
<tr>
<td>PCLH macrodiol</td>
<td>Confers pH sensitivity, increases susceptibility to hydrolytic degradation, undergoes bulk degradation, hydrolysis rate inversely correlated to pH</td>
<td>[141]</td>
</tr>
<tr>
<td>PLLA diol</td>
<td>Most susceptible to hydrolytic degradation, acidic degradation by-products</td>
<td>[161]</td>
</tr>
</tbody>
</table>
Table 3.2  Continued

<table>
<thead>
<tr>
<th>Monomer</th>
<th>Chemical structure</th>
<th>Comment</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>PEBA diol</td>
<td><img src="image" alt="PEBA diol structure" /></td>
<td>• Hydrophobic, and thus reduces susceptibility to hydrolytic degradation</td>
<td>[161]</td>
</tr>
<tr>
<td>Chain extender</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Putrescine (BDA)</td>
<td><img src="image" alt="Putrescine structure" /></td>
<td>• Important mediator of cell growth and differentiation when released on degradation</td>
<td>[35,82,84,160]</td>
</tr>
<tr>
<td>HZ</td>
<td><img src="image" alt="HZ structure" /></td>
<td>• Can be used to bind targeting molecules to PU</td>
<td>[92,133]</td>
</tr>
<tr>
<td>LDT</td>
<td><img src="image" alt="LDT structure" /></td>
<td></td>
<td>[141]</td>
</tr>
<tr>
<td>BDO</td>
<td><img src="image" alt="BDO structure" /></td>
<td></td>
<td>[120,134,141,160]</td>
</tr>
</tbody>
</table>
| **HEMA** | ![HEMA](image) | • Confers cross-linking functionality to prepolymer  
• Increases susceptibility to hydrolytic degradation  
[60] |
| **DTH** | ![DTH](image) | • Nontoxic, noncarcinogenic peptide degradation by-products  
[44] |
| **ISO** | ![ISO](image) | • Provides enhanced biological activity, due to release of active agents on degradation that act as vasodilators and promote bone formation  
[46,47,118] |
| Bis(2-mercaptoethyl) ether (MEE) | ![MEE](image) | • Provides stability in aqueous medium, but susceptibility to oxidative degradation from cell-generated ROS  
• Limited in vitro cytotoxicity  
• Minimal host inflammatory response  
• Thiourea more susceptible to hydrolysis than urethane  
[46,47,59] |
Table 3.2  Continued

<table>
<thead>
<tr>
<th>Monomer</th>
<th>Chemical structure</th>
<th>Comment</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>DEAE</td>
<td><img src="image" alt="DEAE Chemical Structure" /></td>
<td>• Potential to increase cell viability and morphology</td>
<td>[135,140]</td>
</tr>
<tr>
<td>TDD</td>
<td><img src="image" alt="TDD Chemical Structure" /></td>
<td></td>
<td>[46,47]</td>
</tr>
<tr>
<td>Arg-x-Cl</td>
<td><img src="image" alt="Arg-x-Cl Chemical Structure" /></td>
<td>• Increased susceptibility to hydrolytic and enzymatic degradation due to presence of alkylene diester content</td>
<td>[48]</td>
</tr>
<tr>
<td>Diamine peptide–Ala–Ala–Lys</td>
<td><img src="image1" alt="Structure" /> • Introduces sensitivity to degradation mediated by elastase</td>
<td></td>
<td></td>
</tr>
<tr>
<td>-----------------------------</td>
<td>----------------------------------------------------------------</td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>m</em>-PEG-Hyd</td>
<td><img src="image2" alt="Structure" /> • Hydrazine bonds provide pH-sensitive degradation to target tumor environments (&gt;degradation at low pH)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><img src="image3" alt="Structure" /></td>
<td><img src="image4" alt="Structure" /> • Redox-sensitive disulfide bond, allows for triggered release of payloads due to intracellular glutathione • Nontoxic amino acid (cysteine) by-product</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cys-PA</td>
<td><img src="image5" alt="Structure" /></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DHDS</td>
<td><img src="image6" alt="Structure" /> • Disulfide bond allows for synthesis of reduction-sensitive PUs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2-Amino ethanol</td>
<td><img src="image7" alt="Structure" /> • Introduces both urea and urethane bonds, which have different sensitivities to hydrolytic degradation (urea &gt; urethane)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Continued*
### Table 3.2 Continued

<table>
<thead>
<tr>
<th>Monomer</th>
<th>Chemical structure</th>
<th>Comment</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diester diphenol derivative of tyrosine</td>
<td><img src="image1" alt="Chemical Structure" /></td>
<td>• Nontoxic amino acid tyrosine released on degradation</td>
<td>[154]</td>
</tr>
<tr>
<td>4-Pentenoyl chloride</td>
<td><img src="image2" alt="Chemical Structure" /></td>
<td>• UV-mediated cross-linking</td>
<td>[156]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Increased cross-linking expected to decrease degradation rate</td>
<td></td>
</tr>
<tr>
<td>TEA</td>
<td><img src="image3" alt="Chemical Structure" /></td>
<td></td>
<td>[161]</td>
</tr>
<tr>
<td>EDA</td>
<td><img src="image4" alt="Chemical Structure" /></td>
<td>• Provides hydrophobic character to PU</td>
<td>[161]</td>
</tr>
<tr>
<td>PTMA</td>
<td><img src="image5" alt="Chemical Structure" /></td>
<td>• Introduces hydrolyzable ester linkages</td>
<td>[166]</td>
</tr>
<tr>
<td>Other</td>
<td>POSS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>-------</td>
<td>------</td>
<td></td>
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</tr>
<tr>
<td></td>
<td><img src="image" alt="POSS Diagram" /></td>
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</tbody>
</table>

- Shields soft segment of polyurethanes from oxidation and hydrolysis [174]

<table>
<thead>
<tr>
<th>MAA</th>
<th><img src="image" alt="MAA Molecule" /></th>
</tr>
</thead>
</table>

- Increasing MAA content increases polymer swelling, which may yield greater hydrolytic sensitivity [60]

<table>
<thead>
<tr>
<th>MMA</th>
<th><img src="image" alt="MMA Molecule" /></th>
</tr>
</thead>
</table>

[60]
References


Design of biodegradable polyurethanes and the interactions of the polymers


Advances in Polyurethane Biomaterials


Behr J. The proton sponge: a trick to enter cells the viruses did not exploit. Chim Chim 1997;51:34–6.


