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# Biomedical Applications of Biodegradable Polymers

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## Abstract

Utilization of polymers as biomaterials has greatly impacted the advancement of modern medicine. Specifically, polymeric biomaterials that are biodegradable provide the significant advantage of being able to be broken down and removed after they have served their function. Applications are wide ranging with degradable polymers being used clinically as surgical sutures and implants. In order to fit functional demand, materials with desired physical, chemical, biological, biomechanical and degradation properties must be selected. Fortunately, a wide range of natural and synthetic degradable polymers has been investigated for biomedical applications with novel materials constantly being developed to meet new challenges. This review summarizes the most recent advances in the field over the past 4 years, specifically highlighting new and interesting discoveries in tissue engineering and drug delivery applications.

## INTRODUCTION

A biomaterial is defined as any natural or synthetic substance engineered to interact with biological systems in order to direct medical treatment.[1] Biomaterials must be biocompatible meaning that they perform their function with an appropriate host response.[2] In order to meet the needs of the biomedical community, materials composed of everything from metals and ceramics to glasses and polymers have been researched. Polymers possess significant potential since flexibility in chemistry gives rise to materials with great physical and mechanical property diversity. Degradable polymers are of utmost interest since these biomaterials are able to be broken down and excreted or resorbed without removal or surgical revision.

While natural polymers like collagen have been used biomedically for thousands of years, research into biomedical applications of synthetic degradable polymers is relatively new, starting in the 1960s.[3,4] In the fifty years since, successes have been numerous, but grand challenges still exist in both the basic and translational elements of biomaterial design. From a basic science perspective, the capacity to modulate biomaterial chemistry to convey unique material properties is endless yet requires significant time and resources to complete the research. As biomaterials are applied in the clinical setting, numerous issues arise that cannot be adequately identified and addressed in previous *in vitro* and model *in vivo* experiments. The host response to both tissue engineering and drug delivery devices depends on the chemical, physical and biological properties of the biomaterials. When these

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materials are also biodegradable, there exists the additional issue of continuing changes in the material properties induced by degradation over time. These changes can cause long-term host responses to these biomaterials to be greatly different than the initial response. These issues are non-trivial and have contributed to the slow evolution of biodegradable polymer biomaterials as a field of research.

In order to better address the many issues in biomaterial design and expedite progress, biomaterial scientists have fundamentally changed their approach to the research. Especially in the last ten years, there has been a shift in paradigm from investigators working independently on narrow research goals to collaborative teams that facilitate solving greater objectives. By combining researchers with expertise in chemistry, biology, materials, engineering and clinical practice, biomaterials research has been able to advance more rapidly in the past few years.[5–13]

In the design of biodegradable biomaterials, many important properties must be considered. These materials must (1) not evoke a sustained inflammatory response; (2) possess a degradation time coinciding with their function; (3) have appropriate mechanical properties for their intended use; (4) produce non-toxic degradation products that can be readily resorbed or excreted; and (5) include appropriate permeability and processability for designed application.[14] These properties are greatly affected by a number of features of degradable polymeric biomaterials including, but not limited to: material chemistry, molecular weight, hydrophobicity, surface charge, water adsorption, degradation and erosion mechanism. Due to the wide-ranging use of polymeric biomaterials, a single, ideal polymer or polymeric family does not exist. Instead a library of materials is available to researchers that can be synthesized and engineered to best match the specifications of the material's desired biomedical function.

Biomaterial applications of biodegradable polymers have already been extensively reviewed in the past so no attempt will be made to provide a further exhaustive review. Instead, the reader is referred to comprehensive articles in Advances in Biochemical Engineering/ Biotechnology[15] and Progress in Polymer Science[16] which include research prior to and including 2006. This review will focus on the numerous advancements made in the development of hydrolytically and enzymatically degradable polymers over the past 4 years.

## HYDROLYTICALLY DEGRADABLE POLYMERS

Hydrolytically degradable polymers are materials that possess hydrolytically labile chemical bonds in their backbone and can be broken down without secondary influence as shown in Fig. 1. The broken bond yields two species with one product gaining a hydrogen atom and the other gaining a hydroxyl group. A number of degradable polymers possess bonds that are susceptible to hydrolysis including esters, anhydrides, acetals, carbonates, amides, urethanes and phosphates. One of the major features that conveys significant impact on the capacity of these polymeric families to function as biomaterials is their relative degradation rates and erosion mechanisms. An extensive investigation into a number of different degradable polymeric families showed that the degradation rates (Table 1) can vary twelve-fold from very hydrolytically unstable (polyphosphazenes) to extremely hydrolytically stable (polyamides).[17] It should be noted with certain families' (polyphosphazenes and polyanhydrides) degradation rate can be greatly modulated based on polymer chemistry conveying significant flexibility in material properties for these families. Degradation rates are incorporated with other factors like water diffusion, monomer solubility and diffusion, and device geometry and size, to determine how a degradable polymeric biomaterial will erode. Erosion is typically categorized as surface erosion, bulk erosion or a combination of the two.[18] Surface erosion is characterized by the rate of polymer degradation and mass

relief at the water-device interface being much greater than the rate at which water diffuses into the bulk of the material leading to a device that degrades almost entirely at its surface. Bulk erosion is characterized by the reverse in which water diffusion is much faster than degradation leading to degradation and subsequent mass loss occurring throughout the bulk of the material. These categorizations are extremely important in determining which material is best for a desired application. For example, in sustained drug delivery a material that can undergo surface erosion may be desired since stable, near zeroth-order release can be maintained and payload release kinetics can be more easily tailored.[19] Whereas for applications requiring a permeable membrane like in tissue engineering, bulk eroding materials would allow for necessary hydrolytic diffusion.[20] The following sections discuss a number of hydrolytically sensitive polymers and their biomedical applications.

## Poly(α-esters)

Poly(α-esters) are a class of polymers that contain an aliphatic ester bond in their backbone. While a number of polyesters are commercially available and all are theoretically degradable, the hydrolytically stable nature of the ester bond (Table 1) means only polyesters with reasonably short aliphatic chains can be utilized as degradable polymers for biomedical applications. While these polymers are often mildly hydrophobic, ester bond stability causes them to undergo bulk erosion.[21] Due to the relative ease of their synthesis (via ring-opening or condensation polymerization) and commercial availability, poly(α-esters) have been the most heavily researched degradable biomaterials to date.[22]

**Polyglycolide—**Polyglycolide or poly(glycolic acid) (PGA) was one of the very first degradable polymers ever investigated for biomedical use. With a melting point ($T_m$) greater than 200 °C, a glass transition temperature ($T_g$) of 35 – 40 °C and very high tensile strength (12.5 GPa),[23] PGA found favor as the degradable suture DEXON® which has been actively used since 1970.[24] From 1984 to 1996, PGA was marketed as an internal bone pin under the name Biofix®, but since 1996 Biofix has been converted to a poly(L-lactide) base for better long-term stability.[25,26]

Due to PGA's rapid degradation and insolubility in many common solvents, limited research has been conducted with PGA-based drug delivery devices. Instead, most recent research has focused on short-term tissue engineering scaffolds and the utilization of PGA as a filler material coupled with other degradable polymer networks. PGA is often fabricated into a mesh network and has been used as a scaffold for bone,[27–30] cartilage,[31–33] tendon,[34,35] tooth,[36] vaginal,[37] intestinal,[38] lymphatic,[39] and spinal regeneration.[40] While there has been research conducted into a wide range of applications, there exists significant issues with PGA. Rapid degradation leads to loss of mechanical strength and significant local production of glycolic acid. While glycolic acid is bioresorbable by cells via the citric acid cycle,[41] high level of glycolic acid have been linked to a strong, undesired inflammatory response.[42–44] In addition, PGA has mechanically failed as a biomaterial when used to facilitate colonic anastomosis formation[38] and prevent intrapericardial adhesions.[45]

**Polylactide—**Since polylactide (PLA) possesses chiral molecules, polylactides come in four forms: poly(L-lactic acid) (PLLA), poly(D-lactic acid) (PDLA), poly(D,L-lactic acid) (PDLLA) – a racemic mixture of PLLA and PDLA, and meso-poly(lactic acid). As far as use in biomedical research, only PLLA and PDLLA have shown promise and have been extensively studied.

PLLA has a $T_g$ of 60 – 65 °C, a melting temperature of around 175 °C and a mechanical strength of 4.8 GPa.[46] The additional methyl group in PLA causes the polymer to be much more hydrophobic and stable against hydrolysis than PGA. High molecular weight PLLA

has been shown to take greater than 5 years to be completely resorbed *in vivo*.[47] Due to the slow degradation time, limited research has been recently conducted into drug delivery by PLLA systems alone.[48–51] In order to reduce degradation time, investigators have either developed modification techniques or have blended or copolymerized PLLA with other degradable polymers. One interesting modification technique has been through the use of radiation.[52,53] This process works by creating radicals in the ester alpha carbon which upon rearrangement shortens the polymer backbone through the removal of an ester bond and the release of carbon dioxide. Recombination of carbon radicals induces branching and cross-linking causing a decrease in crystallinity due to the modified polymers possessing unique molecular architectures. Shortening of the polymer and decrease in crystallinity work in concert to facilitate more rapid device degradation. While this process is very predictable, allowing for fine tuning of PLLA degradation behavior, even heavily irradiated PLLA is not completely absorbed until months after being delivered *in vivo*. This holds promise for drug eluting depots (i.e. birth control delivery devices), but more research must be done in order for PLLA to be more widely used for short-term controlled delivery applications. Under the product name Fixsorb®, PLLA has been used as a bone fixator.[54] PLLA has also been extensively utilized in tissue engineering applications ranging from scaffolds for bone,[55–58] cartilage,[59,60] tendon,[61] neural,[62,63] and vascular [64] regeneration. Specifically, Dr. Peter Ma's group has produced some very exciting research on the design of PLLA-based patient specific scaffolds (Fig. 2).[65] A CT image of a digit was converted to a 3-D structured wax mold through layer-by-layer printing. By utilizing a solvent-extraction process and paraffin spheres, a 3-D PLLA scaffold that matched the structure of the digit was manufactured. The authors were able to uniquely control the nano-, micro- and macro-structure of the scaffold. This promising technique has the potential to be used for a number of different degradable polymers and parameters could be optimized for a wide-range of applications. Composite materials include PLLA combined with PDLLA,[66] poly(lactide-*co*-glycolide),[67] poly(caprolactone),[68,69] poly(ethylene glycol),[70] collagen,[71] and chitosan.[72]

PDLLA is an amorphous polymer due to the random positions of its two isomeric monomers within the polymer chain yielding a slightly lower $T_g$ of 55 – 60 °C and lower mechanical strength of 1.9 GPa.[23] While possessing more desirable degradation properties than PLLA, PDLLA still takes over a year to properly erode which has kept it from being researched as a particle-based delivery vehicle. Instead PDLLA has been commonly used as a drug delivery film for inorganic implants,[73–76] and as a tissue engineering scaffold.[77–79] Like PLLA, PDLLA has been often combined with other degradable polymer like poly(lactide-*co*-glycolide),[80] poly(ethylene glycol),[81,82] and chitosan[83] to create composites with desirable material properties.

**Poly(lactide-co-glycolide)—**Random copolymerization of PLA (both L- and D,L-lactide forms) and PGA, known as poly(lactide-*co*-glycolide) (PLGA), is the most investigated degradable polymer for biomedical applications and has been used in sutures, drug delivery devices and tissue engineering scaffolds. With a number of commercial manufacturers and easy polymer processability, researchers do not have to be polymer synthesis experts in order to utilize PLGA in their work. One particular advantage is that since PLA and PGA have significantly different properties, careful choice of copolymer composition allows for optimization of PLGA for intended applications. Property modulation is even more significant for PLGA copolymers since with 25 – 75% lactide composition, PLGA forms amorphous polymers which are very hydrolytically unstable compared to the more stable homopolymers.[41,84] This is evident in the degradation times of 50:50 PLGA, 75:25 PLGA, and 85:15 PLGA being 1–2 months, 4–5 months and 5–6 months, respectively.[85]

PLGA has been used as a suture material since 1974[86] under the product name Vicryl® (Ethicon), a 10:90 PLGA braided construct. More recently a modified version, Vicryl

Rapide®, has come to market. Vicryl Rapide® degrades much more quickly than traditional Vicryl® since it is irradiated during production. Panacryl® (Ethicon) is another product, which has a higher LA/GA ratio (90:10) than Vicryl®, which undergoes more rapid degradation. Unfortunately, Panacryl® has seen a significant drop in recent use due to public concern that it induces significant inflammation after implantation even though a recent report refutes this argument.[87] While Ethicon produces the most widely used PLGA sutures, Polysorb® (Syneture) and Purasorb® (Purac Biomaterials) are also commonly used suture materials composed of PLGA.

With rapid degradation compared to other polyesters, PLGA has been utilized extensively in drug delivery applications. PLGA has been used to deliver chemotherapeutics,[88,89] proteins,[90–92] vaccines,[93–95] antibiotics,[96–98] analgesics,[99,100] anti-inflammatory drugs[101,102] and siRNA.[103–105] Most often PLGA is fabricated into microspheres,[90–95,97,98,101] microcapsules,[106–108] nanospheres[88,89,95,96,100] or nanofibers[109,110] to facilitate controlled delivery of encapsulated or adsorbed payloads. Depending on the composition of the PLGA used and the interactions between payload and polymer, drug or protein release profiles can vary.[54] Unfortunately, bulk erosion of the polymer prevents significant modulation of the release rate. Water diffusion in, payload dissolution and subsequent diffusion out is not controlled by polymer degradation rate and often PLGA delivery devices have a significant bolus release of their payload. Additionally, hydration of the entire matrix can often damage or deactivate hydrolytically sensitive encapsulated materials through constant water exposure and the high acidity of PLGA degradation products.[111,112] The use of surface eroding polymers is better for zeroth-order and controlled release kinetics as well as payload protection.

PLGA demonstrates great cell adhesion and proliferation properties making it an excellent candidate for application in tissue engineering. PLGA has been fabricated into scaffolds by a number of different techniques including gas foaming,[113,114] microsphere sintering,[115–117] porogen leaching,[118–120] electrospinning,[121–124] polymer printing,[125,126] or a combination of these techniques[80,127,128] in order to create unique nano- and microstructured materials that can facilitate tissue development. Polymer printing in particular is a novel technique that holds great promise in the design of tissue engineering scaffolds. Dr. James Dunn's group has demonstrated the capacity of 3D printing with PLGA.[126,129] As shown in Fig. 3, very complex designs with controllable features can be generated to mimic structured tissue like villi for smooth muscle tissue engineering.[126] The ability to utilize this technology with other degradable polymers holds promise in allowing for the design of organ-like structures that until now have been impossible to replicate. PLGA scaffolds have been used in the engineering of bone,[10,79,115,116] cartilage,[60,92,117] tendon,[117,123,130,131] skin,[108,122,132] liver,[133–135] and nerve tissue.[136–138]

**Polyhydroxyalkanoates—**Polyhydroxyalkanoates are biodegradable polyesters that can be produced by both bacterial and synthetic routes. The most common polymer is poly(3-hydroxybutyrate) (PHB), a semi-crystalline isotactic polymer that undergoes surface erosion due to the hydrophobicity of the backbone and its crystallinity.[139] PHB has a glass transition temperature around 5 °C and a melting temperature from 160 – 180 °C.[140] Hydrolytic degradation of PHB results in the formation of D-(−)-3-hydroxybutyric acid, a normal blood constituent.[141] The biocompatibility, processibility and degradability of PHB make it an excellent candidate for use in long-term tissue engineering applications[142–147] Unfortunately, the stability of PHB makes it a poor candidate for controlled delivery applications.

To widen the applicability of PHB as a biomaterial, most commonly PHB is copolymerized with 3-hydroxyvalerate to create PHBV. PHBV is less crystalline than PHB with a lower

melting temperature of 80 – 160 °C and a glass transition temperature in the range of −5 – 20 °C depending on HV content.[148] PHBV has been used in tissue engineering of bone,[147,149,150] cartilage,[151] tendon,[152] skin,[143,153] and nerves.[143,147] While the addition of HV content improves the biomaterial potential of PHB, rate of degradation is still too low for other biomedical applications. Significant research is underway to speed degradation rates through copolymerizing or blending PHB or PHBV with PLLA,[153] PDLLA,[154,155] PLGA,[114,156–158] poly(dioxanone),[159] poly(caprolactone),[160–162] and polyethers.[163–165]

**Polycaprolactone—**Polycaprolactone (PCL) is a semicrystalline polyester with great organic solvent solubility, a melting temperature of 55 – 60 °C and glass transition temperature of −54 °C.[166] Due to PCL's very low *in vivo* degradation rate and high drug permeability, it has found favor as a long-term implant delivery device. Capronor® is a commercial contraceptive PCL product that is able to deliver levonorgestrel *in vivo* for over a year and has been on the market for over 25 years.[167] Current research is being conducted into the development of micro- and nano-sized drug delivery vehicles, but the degradation rate (2–3 years) is a significant issue for pure PCL products to be FDA approved for this use. Instead PCL is often blended or copolymerized with other polymers like PLLA,[68,168,169] PDLLA,[170,171] PLGA[104,172,173] and polyethers[174–176] to expedite overall polymer erosion.

While somewhat limited in drug delivery applications, tissue engineering implications of PCL are numerous. PCL has low tensile strength (~23 MPa), but very high elongation at breakage (4700%) making it a very good elastic biomaterial.[41] PCL's processability allows for the formation of scaffolds composed of adhered microspheres[177,178] electrospun fibers,[179–181] or through porous networks created by porogen leaching.[182–184] PCL and PCL composites have been used as tissue engineering scaffolds for regeneration of bone,[182,185,186] ligament,[187,188] cartilage,[133,189] skin,[177,181,190] nerve,[184,191,192] and vascular tissues.[183,193,194] A recent advancement using PCL hybrid scaffolds has been used in interfacial tissue engineering. Lee and coworkers have shown that if distinct scaffold regions are seeded with appropriate cells harvested from cartilage or ligament sources (Fig. 4), complex tissue interfaces like the bone-ligament interface can be regenerated.[195]

**Poly(propylene fumarate)—**Poly(propylene fumarate) (PPF) is a high-strength polymeric biomaterial that while technically a polyester, it possesses the unique ability to be cross-linked through the unsaturated bonds in its backbone. Since PPF can be cross-linked, polymer degradation is dependent on molecular weight, cross-linker and cross-linking density.[196] PPF is a liquid injectable which becomes solid upon cross-linking, therefore it has found favor in biomedical applications such as filling bone defects[197–199] and the depot, long-term delivery of ocular drugs.[200–202] For osteogenic tissue engineering, PPF is often mixed with ceramics like hydroxyapatite[203–205] or alumoxane[206–208] to create stronger, more-bioactive scaffolds. Recent research has focused on the use of PPF to fill irregular shaped bone defects like ear ossicle[209] or mandibular defects.[210] In both circumstances PPF-based scaffolds allow the design of structures that may not be attainable from non-cross-linkable degradable polymers.

## Polyanhydrides

Polyanhydrides are a class of surface eroding polymers that contain two carbonyl groups bound together by an ether bond and have been almost exclusively studied for biomedical applications. While originally developed as textile fibers in the 1930s, their hydrolytic instability precluded their wide-spread usage.[211] Beginning in the 1980s, polyanhydrides were investigated for the biomaterial potential,[212] eventually leading to their FDA approval as drug delivery vehicles in 1996.[213] One particularly unique property of polyanhydrides is

that the degradation of the anhydride bond is highly dependent on polymer backbone chemistry. In fact degradation rate can vary by over six orders of magnitude based on monomer chemistry (Table 1). Surface erosion and control over degradation rate allows for precision tuning of payload release rate which is why polyanhydrides have found significant favor in drug delivery applications. Polyanhydrides have been used for the delivery of chemotherapeutics,[214,215] antibiotics,[216,217] vaccines,[218–221] and proteins.[106,222,223] Polyanhydrides are often fabricated into microparticles[106,218,220,222] or nanoparticles[214,215,219,221,223] to allow for injectable, oral or aerosol delivery. Aliphatic homo-polyanhydrides, such as poly(sebacic anhydride) (pSA), have been found to have limited applications due to their rapid degradation. In order to retard polymer degradation and extend payload delivery, aliphatic diacid monomers have been copolymerized with hydrophobic aromatic diacid monomers[218,222,224–226] or aliphatic fatty acid dimers (FAD).[227,228] By varying aromatic monomer content, Determan and coworkers have fabricated polyanhydride particles that release their payload over a few days to a couple of years, as shown in Fig. 5.[19] Additional research in polyanhydrides has focused on novel monomer development to allow for the replacement of SA due to its high acidity in solution (pH 4.2).[229] A monomer of interest is 1,8-bis-(*p*-carboxyphenoxy)-3,6-dioxaoctane which is an aromatic diacid monomer that contains a triethylene glycol backbone that together convey amphiphiliticity.[230,231] Copolymerizing this polymer with traditional aromatic diacid monomers yields degradable polymers that can be used as long-term delivery vehicles that have shown to stabilize acid-sensitive payloads like recombinant proteins.[220,223]

While polyanhydrides have been extensively investigated for drug delivery applications, their low molecular weights yield poor mechanical properties precluding their use in tissue engineering. In order to increase their strength, methacrylated polyanhydrides have been studied as injectable, cross-linkable biomaterials. Methacrylic groups are typically incorporated by reacting diacids with methacryloyl chloride to create dimethacrylate monomers.[232] Dimethacrylate monomers exist as liquids (i.e. dimethacrylic sebacic anhydride) or soft solids (i.e. dimethacrylic 1,3-bis-*p*-(carboxyphenoxy)hexane) which can be injected and cross-linked into solid scaffolds for tissue engineering applications.[233] Cross-linked polyanydrides have been mostly studied for utilization in drug delivery and structural support for bone tissue engineering,[234,235] but due to monomer flexibility have the potential to be used in other tissue engineering applications as well.

## Polyacetals

Polyacetals are degradable polymers in which two ether bonds are connected to the same carbon molecule (geminal). The molecular closeness of the normally stable ether bonds conveys hydrolytic instability close to that seen for polyanhydrides (Table 1) and gives polyacetals surface eroding properties. Polyacetals are normally subdivided into two subgroups: polyacetals and polyketals. While all geminal-diether polymers are technically polyacetals, the namesake is normally reserved for polymers with only one of the two other geminal bonds possessing an R group. Polyketals instead have both other geminal bonds with R groups. Both polyacetals and polyketals have gained traction in biomedical research recently since their degradation products possess no carboxylic acids yielding significantly milder pH microenvironments[236] and their degradation is acid-catalyzed.[236–238] Milder pH microenvironments allow for the delivery of acid- and hydrolytically-sensitive payloads. Dr. Niren Murthy's group has shown acid-catalyzed degradation allows for intracellular payload delivery, since particle-based delivery vehicles are stable under normal physiological pH (7.4), but rapidly degrade when they reach lysosomal pH (4 – 5), as shown in Fig. 6.[237] So far polyketal microparticles and nanoparticles have been used to directionally deliver siRNA,[238] DNA,[239] and proteins[237,240–244] in the treatment of acute inflammatory

disease,[237,242] ischemic heart disease,[244] and cancer,[241] as well as in the delivery of vaccines.[240,243]

For most implant applications, polyacetals have found limited use since they are often unable to be synthesized at high enough molecular weights to meet mechanical strength needs. A notable exception is Delrin® (polyoxymethylene) which is the homopolymer of formaldehyde that can be polymerized by acid or anionic catalysis to high molecular weights. Delrin®-based implants found favor as tilting disc valves in the repair of faulty heart valves in the late 1960s.[245] Unfortunately, it was found that these implants swelled when they were used *in vivo* and other materials have since replaced Delrin® in artificial valves.[246] Also, the degradation product of Delrin® is formaldehyde which is toxic. In order to create tissue engineering scaffolds from polyacetals, cyclic polyacetal monomers with two ester acrylate end groups have been synthesized that can then be crosslinked.[247] Cyclic polyacetal homopolymers and those copolymerized with poly(ethylene glycol) diacrylate have shown preliminary promise as osteogenic biomaterials for bone tissue engineering.[248,249]

### Poly(ortho esters)

Poly(ortho esters) are hydrophobic, surface eroding polymers that have three geminal ether bonds. Like polyacetals, control of poly(ortho ester) backbone chemistry allows for the synthesis of polymers with varied acid-catalyzed degradation rates and material properties. They have been specifically developed for drug delivery applications by the ALZA Corporation in the early 1970's.[250] Research in poly(ortho esters) is still ongoing in the academic community. While four classes of poly(ortho esters) have been developed, inherent issues with POE I – III have led to nearly all research focusing on POE IV. POE IV incorporates short segments of lactic or glycolic acid into the polymer backbone in order to expedite degradation since POE I – III possess much too slow erosion rates to be clinically relevant as drug delivery vehicles.[250] POE IV polymers have been used for the delivery of analgesics,[251] DNA vaccines[252,253] and antiproliferative drugs.[254] There capacity to be used as tissue engineering scaffolds is limited due to their weak mechanical properties and their capacity to induce a mild to moderate inflammatory response.[255]

### Polycarbonates

Polycarbonates are linear polymers that have two geminal ether bonds and a carbonyl bond. While this bond is extremely hydrolytically stable (Table 1), research has shown *in vivo* degradation to be much more rapid presumably due to enzymatic degradation which causes these polymers to be surface eroding.[256] The most extensively studied polycarbonate is poly(trimethylene carbonate) (PTMC) which has a Tg of −17 °C.[257] PTMC is an elastomeric aliphatic polymer with great flexibility and a slow degradation profile, but poor mechanical strength. Its degradation into biocompatible, non-acidic 1,3-propanediol and carbonic acid make it an ideal candidate for drug delivery applications. PTMC has been fabricated into microparticles,[258,259] discs,[260,261] and gels[262–264] for the delivery of angiogenic agents[264] and antibiotics.[260,261] To enhance the delivery potential of PTMC it is often copolymerized with PLA,[265,266] PCL,[265] polyether,[266–268] or poly(L-glutamic acid)[269,270] to allow for the fabrication of sutures,[265] micelles,[266–268] and polymersomes[267,269,270] with superior mechanical and degradation properties for delivery of chemotherapeutics[266–268,270] and antibiotics.[265]

In addition to PTMC, new polycarbonates have been recently researched for tissue engineering applications. One approach in order to create stiffer polycarbonates than PTMC is the use of cyclohexane or propylene instead of trimethylene in the monomer backbone.[271] Another approach has been attaching bulky side groups through an ester bond to the β-

carbon of the backbone.[272] A particularly interesting novel polycarbonate has been created using the glucose metabolism intermediate dihydroxacetone (DHA).[273] When DHA is copolymerized with methyl poly(ethylene glycol), the resulting rapidly-gelating, rapidly-degrading (100% mass loss within days) copolymer has been shown to assist the body in clotting through the development of new vascular tissue[274] and the prevention of seromas, fluid filled gaps commonly created following ablative or reconstructive surgeries.[275] The continued exploration of new polycarbonates holds potential for the expansion of this class of degradable polymers in biomedical applications.

Other polycarbonates that are used as fixators and in tissue engineering scaffolds are tyrosine-derived polycarbonates. These polymers are variations of poly(amino acids) in which amino acid like backbones are connected by carbonate bonds giving them strong mechanical properties while maintaining the biocompatibility of their degradation products. The most extensively studied of these pseudo poly(amino acids) are poly(desaminotyrosyl-tyrosine alkyl ester carbonates) (PDTEs). Due to aromatic groups in the polymer backbone, PDTEs possess significant mechanical strength allowing for their use in load-bearing applications. PDTEs have a variable pendant alkyl chain allowing for modulation of their thermal and mechanical properties with $T_g$s of 50 – 81 °C, $T_m$s of 75 – 118 °C, tensile strengths of 50 – 70 MPa and stiffnesses of 1 – 2 GPa.[276] Their processibility has allowed for fabrications of scaffolds composed of films,[276–281] fibers,[282] and gels.[283,284] PDTEs have been investigated for their potential in tissue engineering of bone,[277,278,280] vasculature,[283] and muscle.[281] Slow degradation ($M_w$ half life of over 200 days[285]) and minimal mass loss of PDTEs allows for them to maintain their physical properties for very long times making them good candidates for slow regenerative processes.

## Polyurethanes

Polyurethanes are biocompatible, biostable, moldable, strong polymers that possess ester bonds with geminal amide bonds that have a degradation rate similar to polyesters and polycarbonates (Table 1). They are typically synthesized by polycondensation of diisocyanates with alcohols and amines.[286] Polyurethanes are composed of hard and soft segments that can undergo microphase separation allowing for these polymers to handle physical stresses very well.[287] Polyurethanes have been used extensively in prostheses like cardiac assist devices,[288] small vascular shunts [289] and tracheal tubes.[290,291] A commercial polyurethane product, NovoSorb™ (PolyNovo®), is a two component system that cures *in situ*. The self setting system is an injectable liquid that polymerizes at physiological temperatures creating a biomaterial that has been shown to be mechanically similar to bone cements, but also promotes favorable cell adhesion and proliferation.[292] Under most conditions pure polyurethanes are degradation resistant making them poor candidates for drug delivery and many tissue engineering applications. In order to expand the biomedical potential of polyurethanes they have been utilized in multi-degradable group or combination polymers which will be discussed later in this review.

## Polyphosphazenes

Polyphosphazenes are a unique class of degradable polymers in that their backbone is completely inorganic consisting of phosphorous and nitrogen bonded linearly through alternating single and double bonds. While these polymers have been synthesized with high molecular weights since the mid 1960s,[293] only in the past two decades have they been investigated in biomedical research.[294] What distinguishes these materials is that they are highly flexible both physically and chemically. With two phosphorous side groups open to conjugation via esterification, etherification or amidification, over 500 different polyphosphazenes have been synthesized to date.[295] While the phosphonitrilic backbone is not intrinsically hydrolytically sensitive, careful choice of side groups greatly impacts the

degradation rate (Table 1). Certain side groups, like amino acid esters, glucosyl, glyceryl, glycolate, lactate and imidazole, have been found to sensitize hydrolysis of the backbone to allow for the design of clinically relevant biomaterials. In addition to control over degradation rates, physical properties of the polymer are also greatly affected by side group substitution. By changing disubsituted polyphosphazene side groups for one particular system, thermal and mechanical properties were greatly varied with $T_g$ −10 – 35 °C, contact angle 63° – 107°, tensile strength 2.4 – 7.6 MPa, and modulus of elasticity 31.4 – 455.9 MPa.[296] Another unique feature is that polyphosphazenes degrade into neutral products that have been found to have a pH buffering effect when combined with polymers, like polyesters, that have highly acidic degradation products.[297] A commercially available product Polyzene-F® (poly[bis(trifluoroethoxy)phosphazene], CeloNova BioSciences) has shown tremendous potential as stent coatings[298] and embolizing microspheres,[299] and was FDA approved in 2008. While original research found the material to cause limited inflammation,[300] a more recent study showed a significant, sustained foreign body response that is of concern.[301] More research into this phenomenon is warranted before Polyzene-F® can be used clinically.

Polyphosphazenes have shown significant promise in drug delivery and tissue engineering applications. The large library of side groups and the processibility of polyphosphazenes has allowed for them to be fabricated into particles,[302–304] micelles,[305–309] microneedle coatings,[310,311] and gels.[312–315] They have been used in the delivery of anti-inflammatory drugs,[306] chemotherapeutics,[307,309,315] growth factors,[313,316] DNA,[302–304] proteins,[312,314] and vaccines.[305,308,310,311] One particular promising application has been in the design of biodegradable microneedle coatings to deliver vaccines.[310] Andrianov and coworkers have shown polyphosphazene-vaccine covered metallic cones can be used to pierce the skin to deposit rapidly degrading polymer films (~90% in 15 minutes) into the dermis layer (Fig. 7). An added benefit of utilizing polyphosphazene as the delivery vehicle is that prior research has found that certain polyphosphazenes are strongly immunoactivating and hold great potential as adjuvants, non-specific immune boosting substances.[305,308] This research has shown the induction of stronger immune responses than comparable intramuscular injections without the pain and strong inflammation seen with traditional needle use providing promise for this new technology.

While many rapidly degrading polyphosphazenes have shown promise in drug delivery applications, more hydrophobic side group substitutions have allowed for the use of polyphosphazenes in tissue engineering applications. Polyphosphazene scaffolds have been composed of films,[317,318] fibers,[319–322] and sintered microspheres.[323] These matrices have been used to assist in nerve regeneration,[317,319,322] but recent research has almost exclusively focused on orthopedic applications of polyphosphazenes.[318,320,321,323] Often polyphosphazenes have been blended with polyesters to increase mechanical strength and provide a moderate pH microenvironment for developing tissues. Interestingly, miscible blends of poly[(glycine ethyl glycinato)$_1$ (phenylphenoxy)1 phosphazene] and PLGA that are originally cast as films undergo varied rates of degradation of the principal components under aqueous conditions.[13] As the PLGA degrades and erodes from the matrix the more hydrophobic polyphosphazene reforms into a scaffold with a microstructure very similar to adhered microspheres. Porous scaffolds of adhered microspheres have been used heavily in tissue engineering applications since they allow for the infiltration of host cells into the scaffold that will eventually become new tissue. Having biomaterials with the strength and flexibility of films that can form into porous scaffolds over time greatly enhances the biomedical potential of these materials.

## Polyphosphoesters

Polyphosphoesters form another interesting class of biomaterials that is composed of phosphorous-incorporated monomers. These polymers consist of phosphates with two R groups (one in the backbone and one side group) and can be synthesized by a number of routes including ring opening polymerization, polycondensation, and polyaddition. Originally developed in the 1970s,[324,325] polyphosphoesters have great biocompatibility and similarity to biomacromolecules like RNA and DNA. Relatively rapid hydrolytic cleavage (Table 1) of the phosphate bonds in the backbone leads to the production of bioresorbable or excretable phosphates, alcohols and diols. While a commercial polyphosphoester-based microsphere delivery device (PACLIMER®) has shown promise in Phase I/II trials for the treatment of ovarian and lung disease, MGI Pharma discontinued further research with the product after purchasing the original development company, Guilford Pharmaceuticals. Polyphosphoesters are divided into two different classes: polyphosphonates (alkyl/aryl R groups) and polyphosphates (alkoxy/aryloxy R groups). Due to the flexibility in choosing R groups, polymers of significantly varying physical properties and degradation rates can be synthesized. In order to enhance physical properties, polyphosphoesters are commonly copolymerized with polyethers and polyesters. Polyphosphoesters and polyphosphoester composites have shown significant promise as chemotherapy[326–328] and DNA,[329–331] delivery devices. Polyphosphoesters have also been utilized as scaffolds in the engineering of bone tissue.[328,329,332–335] These polymers have been formed into particles,[328,330] micelles,[326,327] films[329,331] and gels[332–335] for these applications. Recent research utilizing polyphosphoesters has been limited, but their chemical flexibility and similarity to biomacromolecules gives them great promise for future applications.

## Combination Polymers

A growing trend in degradable polymer research is the development of combination polymers. These are polymers in which monomers contain multiple degradable groups. Unlike copolymerization of different monomers, the molecular proximity of these groups yields functionally novel biomaterials. These materials often have properties that cannot be obtained by single degradable group polymer families or through simple copolymerization. With the goal of developing new polymers, this research area has yielded a large number of new families which will not be completely reviewed in this section. Below are a couple examples of interesting degradable combination polymer families that have been recently developed.

Poly(ester ether)s are an interesting class of degradable polymers in which typically an ether bond in incorporated into the backbone of a polyester in order to expedite hydrolytic cleavage of the ester bond. One very common poly(ester ether) is polydioxanone (PDO). PDO is a colorless, semicrystalline polymer synthesized by ring- opening polymerization of *p*-dioxanone that has a $T_g$ about −10 to 0 °C and a $T_m$ of 115 °C.[336] While quicker degrading than longer aliphatic polyesters of similar backbone length, PDO can still be considered a slow degrading polymer (6 – 12 months for complete mass loss).[23] With a low modulus (1.5 GPa),[23] but good flexibility and strength maintenance (1 – 2 months) PDO has been commercialized as the monofilament suture PDS® for nearly 30 years.[337] In an effort to create faster degrading polyesters, research has been conducted into the synthesis of poly(ether ester)s via polycondensation. This is carried out by the use of a catalyst to create alternating blocks from dicarboxylic acids and diols. Oligomeric ethylene glycol (n = 2 – 4) and *trans*-β-hydromuconic acid are condensed to create low molecular weight poly(ether ester)s (4,000 – 6,000 g/mol) that are amorphous and have low $T_g$s (−36 – −32 °C).[338,339] These polymers are liquid at room temperature and possess cross-linkable double bonds in their backbone making them promising biomaterials for filling non-uniform defects. By creating random copolymers between cross-linkable and non-cross-linkable (adipic acid)

monomers, control over cross-linking density can be obtained. These materials are able to be synthesized with Young's Moduli varying three orders of magnitude (0.02 – 20 MPa).[339] Also, the liquid poly(ester ether)s are able to be fabricated into complex architectures not easily obtainable by solid polyesters.[339]

Poly(amide ester)s are cationic, degradable polymers originally investigated for their biomedical potential in the 1990s by Robert Langer.[340] The most widely studied sub-group of these polymers are poly(β-amino esters) (PBAEs) which are synthesized by a Michael Addition reaction of diester diacrylates and primary or secondary amines.[341,342] Due to having control over both components' backbone chemistry a wide range of PBAEs can be synthesized. The fidelity of the reaction and the library of polymers that can be synthesized have led to the use of combinatorial research methods to identify polymers that show particular promise as biomaterials.[343–346] In one particular study, over 2,000 polymers were synthesized and screened combinatorially.[345] PBAEs show tremendous promise in DNA delivery due to their positively charged amide bonds[347–350] and in tissue engineering since they can be synthesized with high molecular weights and hydrolytically stable bonds allowing for long-term maintenance of their mechanical strength.[351–353]

While copolymers and blends of polyesters and polyanhydrides have been studied for a few decades, the synthesis of poly(anhydride ester)s for biomedical applications have only been investigated for the last decade.[354] The original impetus for their development was the creation of prodrug polymers. If commonly used aromatic diacid monomers have two internal ester bonds instead of ether bonds, their degradation products are resorbable carboxylic diacids and salicylic acid, a non-steroidal anti-inflammatory drug and the active compound of aspirin. Polycondensation of salicylate-containing diester diacids yields poly(anhydride ester)s very similar to classical polyanhydrides with moderate hydrophobicity, surface erosion and good processability.[354,355] These polymers have been found to have $T_g$s lower than physiological temperatures (12 – 34 °C),[354,356,357] and are often copolymerized with traditional aromatic diacid monomers to improve mechanical properties.[356,358] Since this original discovery, salicylic acid-derived poly(anhydride ester)s and their composites have since been fabricated into particles,[357,359] fibers,[358] and films[355,356,360,361] for biomedical application. They have been used in the prevention of biofilm formation,[360,361] the prevention of bone resorption,[356,359] and the creation of a local anti-inflammatory effect.[356,360]

Polyurethanes have shown some applicability in biomedical research, but their hydrolytic stability limits their potential. In order to expedite degradation, ester bonds have been introduced into the polymer backbone. Poly(ester urethane)s are typically synthesized by reacting diisocyanates with polyester diols or triols composed of glycolide, lactide or caprolactone to create the soft segments of the polymer.[362] Often the hard segments are composed of polypeptides or diols or triols of 3-hydroxybutyrate in order to give biomaterials that are degradable, but still relatively hydrolytically stable.[362,363] In order to better commercialize the aforementioned PolySorb™, more recent research has focused on including degradable ester groups into the injectable prepolymers. This has allowed for development of biomaterials that has shown promise in bone[364] and articular cartilage regeneration.[365] Another commercialized poly(ester urethane) is the highly porous Degrapol® (Ab Medica)which has shown promise in engineering tracheal soft tissue[366,367] and bone tissue.[368]

## ENZYMATICALLY DEGRADABLE POLYMERS

Enzymatically degradable polymers are materials that possess bonds that while technically hydrolytically sensitive, in reality require catalysis to undergo meaningful degradation under

physiological conditions. Most of these polymers contain ether or amide bonds which have hydrolytic degradation rates much lower than the polymers discussed in the previous section (Table 1). This section details a number of these polymeric families and their application as biomaterials.

## Synthetic Polyethers

Synthetically-derived polyethers are highly biocompatible polymers that have been used in polymeric drug delivery and tissue engineering for over 30 years.[369] Nearly all biomedical research with synthetic polyethers has focused on the use of poly(ethylene glycol) (PEG) and poly(propylene glycol) (PPG), while a limited amount of work has been conducted using poly(tetrahydrofuran).[370–373] Polyethers do not readily undergo hydrolytic degradation and while bacterial etherases have been discovered,[374,375] human equivalents of these enzymes have yet to be identified. Instead polyether chains are normally dissociated from the biomaterial and removed via the excretory system. Due to a near absence of *in vivo* degradation and the fear of accumulation, it is recommended that polyethers with lower molecular weights be utilized for biomedical applications. In addition to issues associated with high molecular weight PEG, very low molecular weight PEG has been found to induce bodily harm. Specifically, tetraethylene glycol and PEG 200 have been shown to induce clastogenic effects (chromosomal disruption) in Chinese hamster epithelial liver cells.[376] Most research with synthetic polyethers has focused on triblock Pluronic ([PEG]n-[PPG]m-[PEG]n), cross-linkable oligomers or these polymers in union with many of the previously mentioned hydrolytically degradable polymers.

Pluronic is of particular interest because PEG is hydrophilic while PPG is hydrophobic allowing for the formation of very small micelles (10 to 100 nm in diameter)[377] by self assembly in water. These micelles allow for high payload loading (30 wt%)[378] of hydrophobic drugs into the core while the hydrophilic shell makes the particles easy to administer. Drug delivery devices composed of Pluronic micelles have been used to deliver chemotherapeutics,[379–381] antibacterials,[382,383] antidiuretics,[384] anti-inflammatory drugs,[385] and DNA.[386] Pluronic has also been formulated into hydrogels. These hydrogels possess relatively weak mechanical properties (maximum shear storage modulus of 13.7 kPa at 20 wt% Pluronic)[387] making them candidates for drug delivery[388–391] and soft tissue engineering.[392,393]

In order to enhance the mechanical strength of polyether-based hydrogels, cross-linkable oligomers are synthesized by reacting PEG with excess acryloyl chloride or methacryloyl chloride yielding the products PEG diacrylate (PEGDA) or PEG dimethacrylate (PEGDMA), respectively. PEGDA and PEGDMA can then be polymerized by their double bond yielding cross-linked networks which upon degradation yield poly(acrylic acid) or poly(methacrylic acid) and PEG. PEGDA hydrogels (shear storage modulus of 68 kPa at 20 wt%)[394] and PEGDMA hydrogels (shear storage modulus of 125 kPa at 20 wt%)[395] are stronger than their Pluronic counterparts. PEGDA, PEGDMA and PEGDA/PEGDMA hydrogels have been used in the delivery of chemotherapeutics,[396] hormones,[397] antibacterials[398] and anti-inflammatory drugs[399] as well as scaffolds in the engineering of cartilage,[400,401] bone,[402–404] endothelial,[405] and vascular tissues.[406]

While synthetic polyethers have shown some promise when utilized by themselves, they have much greater biomedical potential when utilized in combination with other degradable polymers. PEG is commonly used to cap (PEGylation) or coat other degradable polymers in order to convey steric stabilization limiting the interactions between the device and the host. This is especially important in preventing phagocytosis, cellular uptake, of particle-based delivery vehicles.[407–409] Unlike polyanhydrides and polyesters, PEG does not initiate the complement cascade which is known to facilitate particle phagocytosis.[410] PEG

incorporation has been used to enhance the biocompatibility and delivery properties of polyanhydrides,[411–414] poly(ortho esters),[415] PLA,[416–419] PLGA,[420–423] and PCL.[424–427] Of particular interest is the work being conducted with poly(ether anhydride)s. The addition of a low molecular weight PEG shell to polyanhydride micro- and nanoparticles conveys "virus-like" behavior and allows for them to pass through mucosal membranes much more rapidly than uncoated particles.[428,429] Being able to transport drug delivery devices across mucosal barriers is important in improving therapeutic efficacy against diseases like cystic fibrosis[430] and lung cancer [414] (lung mucosa) and HIV[431] (vaginal mucosa).

PEGDA and PEGDMA have also been heavily researched in composite systems with other acrylated and methacrylated degradable polymers, most commonly polyesters,[432–434] polyanhydrides,[232,234,235,435,436] and chitosan,[437,438] a polysaccharide that will be discussed later in this review. The polyether diacrylate monomers give the cross-linked network hydrophilicity while the other degradable components convey significantly greater mechanical strength (compressive moduli as great as ~ 100 MPa)[232] than cross-linked polyether diacrylate homopolymers. Greater strength and component flexibility has lead to the use of these composites in a wide range of tissue engineering applications including in the regeneration of ligament,[433] cartilage,[434] bone, [232,432] and epithelial tissue.[437]

## Proteins and Poly(amino acids)

Proteins are essentially high molecular weight polymers composed of amino acid monomers joined by amide bonds. They often occur in three-dimensional folded structures and are one of the most common materials found in the human body. Proteins and amino acid-derived polymers have been utilized as biomaterials in sutures, scaffolds and drug delivery devices. While amide bonds are hydrolytically stable, the body possesses a wide-array of proteases that can rapidly degrade proteins.

**Collagen—**Collagen is the most abundant protein in the human body and is a major component of ligament, cartilage, tendon, skin and bone. It also forms the structural network of other tissues like blood vessels. Collagen is composed of polypeptide strands bearing tri-amino acid blocks of Glycine-X-Y where X and Y can be any of a number of different amino acids and are most commonly proline and hydroxyproline.[439] These polypeptides are formed into left-handed triple helix microfibrils that organize together in a number of different architectures to create collagen fibers with appropriate mechanical properties for their function. To date, at least 28 different types of collagen have been identified, however types I, II, III, and IV are the most heavily investigated with over 90% of all collagen being type I.[440]

Collagen has been extensively researched for various medical applications due to its biocompatibility, mechanical strength and enzymatic degradability by collagenases and metalloproteinases.[441] In addition, it is very processable with high solubility in acidic aqueous solutions allowing for the fabrication of collagen sponges,[442–444] tubes,[445,446] sheets,[447] powders,[448] and injectables.[449–452] Collagen has been used for centuries as a suture material of which one form, catgut, is still sometimes utilized in surgery,[453,454] but due to collagen suture's increased infection rates and inflammation, synthetic sutures are much more commonly used today. Collagen has also been used as a depot payload delivery device in the local extended release of antibiotics,[455,456] DNA,[457,458] siRNA,[459,460] and proteins.[461–463] In each case collagen had a burst release due to bulk erosion making it less ideal than the aforementioned surface eroding hydrolytically-sensitive polymers for drug delivery applications.

More recently collagen has found use as a haemostatic sealant.[464] Collagen is highly thrombogenic and plays a role in the body's natural clotting process by activating fibrogen

conversion into fibrin, heavily cross-linked mesh networks of fibrogen. Fibrin captures activated platelets to make a clot. By creating a collagen based sealent, wounds can be coated and blood flow halted much more quickly. The FDA has approved a couple of collagen-containing solutions, including Helistat® (Integra Life Sciences) and FloSeal® (Baxter), for the treatment of bleeding during surgery.

Due to collagen's structural integrity conveyed by its fibrous nature, a majority of biomedical research using collagen as a biomaterial has focused on its potential as a tissue engineering scaffold, specifically in load bearing applications. Collagen sponges have been used as tissue supports and scaffolds for nearly 50 years.[465] Due to collagen's ability to withstand high tensile loads (92.5 MPa ultimate tensile strength),[466] it has often been used in bone tissue engineering.[467–469] Composites of hydroxyapatite and collagen are utilized since these materials closely mimic the composition of natural bone.[470–472] Collagraft® (Angiotech Pharmaceuticals) is a synthetic bone-graft substitute composed of bovine type I collagen and hydroxyapatite/tricalcium phosphate granules which has been approved by the FDA and used clinically.[473] Collagen has also been widely researched as a tissue engineering scaffold for cartilage,[474–476] tendon,[477–479] and ligament.[480,481]

While often used for load bearing applications, collagen's biocompatibility and ease of use has lead to its investigation as a scaffold in skin engineering as well.[482–484] Due to collagen's ability to improve cellular adhesion and proliferation, burn treatment and reconstructive surgery is often conducted with an acellular collagen matrix taken from human cadavers which is marketed as Alloderm® (LifeCell). While Alloderm is the most commonly used commercial product for skin engineering and wound healing, several other FDA collagen-based products exist in the market place including Promogran® (Johnson & Johnson), Biobrane® (UDL Laboratories) and OrCel® (Ortec International) for this application. While these products provide excellent support to regenerating tissue, they lack many of the constituent structures found within skin like hair, nerves and glands as well as tissue layer separation necessary to truly replicate skin's three-dimensional structure. Several approaches to these problems have been proposed, but two concepts of particular interest are outlined. In order to develop sweat glands within regenerated skin, Huang and coworkers have developed growth-factor releasing collagen microspheres that can support differentiating sweat gland cells.[485] These constructs are then embedded into a keratinocyte/fibroblast co-culture with structural maintenance provided by a collagen matrix to create substructures within the developing skin that are maintained even after implantation *in vivo* (Fig. 8). In order to create keratinocyte-fibroblast separated layers, keratinocytes are normally cultured on top of a preformed fibroblast layer which is time-consuming and inefficient. A new method has been developed for creating controlled large pore scaffolds that allow for keratinocyte and fibroblast structures to separate naturally creating better skin mimicking constructs which are also well integrated into the collage scaffold.[486] These advances hold promise not only for collagen-based biomaterials and skin engineering but for tissue engineering as a whole since as the field moves towards creating and regenerating more complex structures like organs three-dimensional patterning of multiple tissue types will be paramount to continued success.

In order to improve collagen's potential as a biomaterial it has often been modified or combined with other degradable polymers. Modifications such as crosslinking,[487–489] association of bioactive molecules,[490,491] and enzymatically pre-treatment[492–494] have all led to novel collagen-based materials with expanded functionality. In composite materials, collagen has been combined with PLA,[60,495,496] PLGA,[60,497,498] PCL,[60,497,499] and chitosan.[500–502] These multi-polymer constructs are typically either polymeric blends or intermixed devices (ex: microparticles of one polymer dispersed in a fibrous scaffold of another polymer).

While heavily researched, collagen possesses many negative attributes limiting its biomedical potential and clinical utility. Collagen-based biomaterials have been known to induce a moderate immunological response *in vivo* due to its terminal region composition and a series of antigenic sites in the central helix.[503] The degree and nature of this response greatly depends on the source and post-processing of the collagen used. Other issues include the high cost of pure collagen, significantly varying physico-chemical properties and risk of transmitted infection from the grafting source. While current research is underway to produce recombinant human collagen,[504] animals and cadavers still remain the most common sources. Until alternative biological sources are created or purely synthetic collagen can be synthesized, wide spread clinical acceptance and use of collagen-based biomaterials does not seem likely.

**Elastin & Elastin-like Polypeptides—**Elastin is an insoluble, highly elastic polymer composed of heavily cross-linked tropoelastin molecules that is a major component of vascular and lung tissue and is responsible for the contraction of these tissues following stress. Soluble tropoelastin molecules are produced intracellularly by smooth muscle cells and fibroblasts and are cross-linked extracellularly to form their elastic polymeric network.[505] Since it is prevalent in vascular tissue, elastin has been found to not activate platelets making it a promising material for synthetic vascular grafts.[506,507] While some biomaterials research has been conducted with elastin, its ability to elicit an immune response and its insolubility have limited its use.[508]

In order to overcome the limitations inherent to elastin, synthetic elastins have been developed. Soluble recombinant human tropoelastin can be molded, coaservated and cross-linked at 37 °C to create soluble elastin with controlled architecture.[509,510] Also, tropoelastin undergoes an irreversible temperature transition (ITT) above 25 °C where its molecular organization goes from a disordered to ordered state. This transition gives synthetic elastin promise as a smart, injectable drug delivery system.[511,512]

Another attempt to utilize elastin-based materials as biomaterials has been in the investigation of elastin-like polypeptides (ELPs). ELPs are artificial polypeptides that are composed of pentapeptide repeats (VPGXG) similar to those found in elastin where X can be any of a number of different amino acids except proline.[513] While very flexible like elastin, ELPs are biocompatible and non-immunogenic. They also can be synthesized to undergo ITT, as well as respond to pH, ionic strength and light based on which amino acid is synthesized in the X position.[514] While once synthesized chemically, ELPs have been more recently produced in *E. Coli*.[515] Due to the variety of phase transitions that ELPs can undergo, they have been investigated as delivery vehicles for chemotherapeutics,[516,517] antibiotics,[518] and proteins.[519,520] Also, when cross-linked ELPs are seeded with chondrocytes they have been shown to possess dynamic sheer moduli (~ 1.7 kPa)[521] similar to normal cartilage. The elastic behavior of ELPs makes them uniquely suited for the engineering of soft tissues.[522–524]

**Albumin—**Albumin is an abundant water soluble blood protein comprising almost 50% of total plasma mass in the body. Albumin carries hydrophobic fatty acids in the blood stream as well as carefully maintains blood pH. Since Albumin is essentially ubiquitous in the body, nearly all tissues have enzymes that can degrade it making it a promising polymer for biomedical applications.[525] Albumin's solubility allows for the protein to be easily processed into a number of different shapes including fibers,[526,527] microparticles,[528,529] and nanoparticles.[530–532] Due to its serological compatibility and weak mechanical strength, albumin has been primarily investigated for payload delivery,[529–531] coating,[533,534] and suturing applications.[535,536] Currently, a bovine albumin-based adhesive marketed as BioGlue® (CryoLife) is FDA approved for vascular surgery.[535]

**Fibrin—**Fibrin, a large cross-linked biopolymer composed of fibronectin, is involved in the natural clotting process. In the presence of the enzyme thrombin, cleavage of an internal fibrin linker yields linear fibrils that laterally associate into nanofibers (10 – 200 nm) that form a clot. This clot is able to be degraded by a complex cascade of enzymes.[537] The use of fibrin as a biomaterial goes back centuries and it has been shown to be biocompatible, biodegradable, injectable and able to enhance cell proliferation.[538] Fibrin glues has been studied as a surgical supplement under the market name Evicil® (Ethicon) which has been FDA approved as a tissue sealant and haemostatic agent. Fibrin glues are prepared as solutions containing thrombin and fibronectin separately that are mixed right before application. Thrombin rapidly crosslinks the fibronectin into a fibrin clot closing the wound. Fibrin has also been investigated for use as a drug delivery device[539–542] and cell carrier.[543–545] Due to its potential for cross-linking, fibrin can be uniquely modified so that its material properties can be tailored to the desired application.[546]

**Natural Poly(amino acids)—**Natural poly(amino acids) are biodegradable, ionic polymers similar to proteins in that they possess amide linkages, but poly(amino acids) are only composed of one type of amino acid. The two most commonly studied natural poly(amino acids) as biomaterials are poly(γ-glutamic acid) and poly(L-lysine).

Poly(γ-glutamic acid) (γPGA) is a water soluble, biodegradable polyamide composed of both enantiomeric D- and L-glutamic acid units commonly produced by a number of different bacteria.[547–549] The biomaterial promise of γPGA centers on its reactive side carboxylate which allows for the covalent attachment of other functional groups and drugs. Benzyl ester,[550] sulfonate,[551] sulfide,[552] and chemotherapeutic attachment[553,554] have all allowed for its further development as a biomaterial. It has also been used in particle-based[555–558] delivery of antibiotics,[556] vaccines,[557,558] DNA,[555] and proteins.[556] As a homopolymer it is too physically weak to be used in supportive tissue engineering scaffolds, but as a cross-linked hydrogel it has found some promise in soft tissue engineering.[559,560] Often it is blended with other polymers like PLA,[561,562] PLGA,[563] PCL,[564] collagen,[565] and chitosan[566–568] to give composites that are mechanically strong but possess some hydrophilicity. While promising, research into γPGA as a biomaterial has been limited due to its scarcity.

Like γPGA, poly(L-lysine) is generated by bacteria and is currently being investigated as a tissue engineering scaffold and drug delivery device. It has been shown to possess intrinsic antibacterial,[569] antiviral,[570] and antitumor activity[571] that make it a very promising polymer. Unfortunately, it's very high positive charge causes it to be rather toxic which has limited its applications. It has found some use being blended with other degradable polymer like PLA,[572] PLGA,[573,574] PCL,[575] γPGA,[576,577] and chitosan.[578]

**Synthetic Poly(amino acids)—**Synthetic poly(amino acids) have been investigated for a number of biomedical applications due to their similarity to naturally occurring proteins. While several homo-and co-poly(amino acids) have been synthesized and evaluated; high crystallinity, low degradation rate, unfavorable mechanical properties and immunogenicity have kept a majority of these polymers from being utilized clinically.[579] However, two poly(amino acids) have been found to function as promising biomaterials: poly(L-glutamic acid) and poly(aspartic acid).

Poly(L-glutamic acid) (L-PGA) is different than γPGA since its amide linkage is made with the α-carbon amine group instead of the γ-carbon amine group. The shorter distance between amide bonds in L-PGA makes it more flexible than its γPGA counterpart. Also, synthetic techniques allow for L-PGA to be more easily produced. While L-PGA is typically synthesized as a linear polymer, the development of new synthesis techniques allows for the

creation of unique architectures like dendrimers.[580] L-PGA is very biocompatible and non-immunogenic and has been shown to be highly susceptible to degradation by lysosomal enzymes.[581,582] Due to its negative charge at physiological pH L-PGA has found significant promise as a DNA delivery device.[555,583] Also L-PGA's negative charge allows for the construction of layer-by-layer (LBL) film assembly with negatively charged polymers like poly(L-lysine),[584,585] and chitosan.[586] LBLs are relatively new drug delivery devices which alternate layers of charged polymer allowing for the repeated delivery of either positively or negatively charged payloads holding significant promise for future biomedical applications. Like γPGA, the reactive side carboxylate of L-PGA allows for conjugation. So far this has been used for the creation of soluble, long-lasting polymer-chemotherapy conjugates,[587,588] one of which is a Paclitaxel-conjugate marketed as OPAXIO® (Cell Therapeutics) that has shown promise in phase III clinical trials.[589] Conjugates with small molecules have yielded degradable MRI contrast agents.[590–592] Tian and coworkers have demonstrated the capacity of a L-PGA-gadolinium complex whose molecular weight keeps the contrast agent from diffusing out of the vasculature. When tested in rhesus monkeys, the vasculature contrast of subjects given the complex was much greater than those given a small molecular weight contrast agent (Magnevist) at 2 hours post-injection (Fig. 9).[593] This complex allows for the use of less contrast agent while getting clearer MRI of small vasculature which can lead to earlier detection of tumors, atherosclerosis, and gross hemorrhage. L-PGA has also been combined with other degradable polymers like PCL[594,595] and PTMC[269,270] for drug delivery applications and collagen[596] and chitosan[597] to create novel tissue engineering scaffolds.

Poly(aspartic acid) (PAA) is a highly water-soluble ionic polymer with a greater carboxylate content than PGA or L-PGA since it has one less carbon atom in its backbone. Like poly(glutamic acid), PAA has been found to be degradable by lysosomal enzymes.[598] It has been copolymerized with a number of degradable polymers (PLA,[599;600] PCL,[601] PEG,[600–602] etc.) to create materials that form micellar structures which have shown promise as smart delivery vehicles. PAA can also be easily converted to a hydrogel by high energy radiation which has shown promise in biomedical applications.[603]

## Polysaccharides

Polysaccharides are polymers composed of monosaccharide units joined together by glycosidic linkages, a type of ether bond. Their use as biomaterials has become much more common as new biological functions are identified for these materials. Also, the array of materials that can be investigated has increased due to new synthetic routes that have been developed for modifying polysaccharides. Their biodegradability, processability and bioactivity make polysaccharides very promising natural biomaterials.

**Human Origin—**Hyaluronic acid (HA) was originally isolated by Meyer and Palmer in 1934[604] and has shown significant promise as a biomaterial. HA is a linear anionic polysaccharide consisting of alternating units of N-acetyl-D-glucosamine and glucuronic acid making it a member of the glycosaminoglycan family. HA is the largest polymer in the family and has been found in molecular weights up to a few million.[605] It has been traditionally isolated from rooster combs and bovine vitreous humor. However, recent advances in microbiological techniques have led to the production of the first animal-free sodium hyaluronate which is synthesized by *Bacillius subtilis* and has been patented by Novozymes Biopharma. HA is water soluble and forms highly viscous solutions. Synovial fluid and vitreous humor have a large quantity of HA contributing to these tissues' viscoelastic properties. HA also plays an important structural role in articular cartilage and skin.

HA possesses several properties that make it unique. It has been shown to scavenge free radicals,[606] cause bacteriostasis[607] and assist in tissue repair.[608] These factors have made it a promising material for tissue engineering applications, but HA homopolymer is too weak and structurally fluid to create a supportive scaffold. To overcome this limitation, HA has been cross-linked with ethyl esters or benzyl esters yielding hydrogels which have been commercialized as HYAFF® (Fidia Farmaceutici). HYAFF® undergoes hydrolytic degradation that causes scission of the ester bond converting it back to hyaluronic acid. Depending on the extent of esterification, degradation rate can be varied from 1–2 weeks[609,610] to 4–5 months.[611,612] HYAFF® hydrogels are extremely versatile as shown by their capacity to be fabricated into sheets,[613] membranes,[614] sponges,[615] tubes[612,616,617] or fibers[618,619] and their usefulness as scaffolds for wound healing[618] and the regeneration of the trachea,[613] articular cartilage,[619] nasal cartilage,[615] respiratory epithelium,[614] vasculature,[612,616] and nerve tissue.[617] Other hyaluronic acid tissue engineering devices include injectables like SYNVISC ONE® (Genzyme) and ORTHOVISC® (Johnson & Johnson) which have been developed to be injected into the knee to relieve pain from osteoarthritis and improve joint mobility. A particularly novel injectable regenerative tissue scaffold has been developed by reacting hyaluronic acid with methacrylic anhydride creating injectable, cross-linkable methacrylated HA (MeHA). Dr. Jason Burdick's group has shown MeHA possesses tremendous promise as a supportive network for heart tissue that is recovering from infarction.[620] Figure 10 shows the ease of injecting the polymer into the heart wall as well as the thicker resulting walls from sheep given these scaffolds over untreated controls. Injectable, cross-linkable polymers like MeHA hold tremendous promise for a number of regenerative therapies especially in soft tissue engineering since they can fit defects or structural abnormalities *in vivo*.

HA has also shown promise as a payload delivery vehicle and has been formed into nanoparticles[621–624] and hydrogels[625–628] for this application. These constructs have been used to deliver chemotherapeutics,[622,624] antibiotics,[625] analgesics,[626] siRNA,[621] and proteins.[623,627,628] Composites of HA with PLA,[629,630] PLGA,[630–632] PCL,[633,634] PLL,[635–637] and chitosan.[638–641] have all been developed to create delivery vehicles with enhanced mechanical properties while retaining excellent biocompatibility.

Another human carbohydrate that has shown promise as a biomaterial is chondroitin sulfate (CS). CS is a glycosaminoglycan with very similar structure to HA (CS has a sulfate group in at least one of its side groups). It has been found to be a major component of the body's natural, hydrophilic would healing matrix produced by fibroblasts.[642] CS has also been shown to stimulate the metabolic response of cartilage,[643] possess anti-inflammatory properties[644] and connect cells to extracellular matrix components.[645] Due to CS's role in natural wound healing and chondrogenesis, it has been studied extensively as a hydrogel for wound dressings[135,646] and cartilage tissue engineering. In cartilage tissue engineering, the successful regeneration of cartilage requires a scaffold that causes the correct phenotypic development of seeded cells. Because CS plays a crucial role in the natural development of cartilage, CS[647,648] and CS composites with PCL,[649] PEG,[650,651] collagen,[649,652] hyaluronic acid[653] and chitosan[654] have been used to direct proper cellular chondrogenesis and successful regeneration of cartilage tissue.[655]

Other carbohydrates of human origin that are being considered as potential biomaterials include heparin, keratin and dermatan.

**Non-Human Origin—**In addition to polysaccharides of human origin, there exist a number of molecules from other sources that have shown promise as degradable polymeric biomaterials. While a number of candidates have been identified, two of particular interest are chitosan found in crustacean skeletons and alginic acid found in brown algae.

Chitin is a linear polysaccharide consisting of β-1,4 linked N-acetylglucosamine units that forms the exoskeletons of many arthropods. Chitin is structurally similar to hyaluronic acid and has shown a similar capacity to accelerate wound healing.[656] Chitin fibers,[657,658] sponges[659,660] and membranes[661] have all been investigated as wound dressing materials. Unfortunately, chitin is insoluble in many common solvents limiting its processability and potential in biomedical applications.

To overcome insolubility issues, chitosan, a chitin derivative, is created by deacetylation of chitin giving a polysaccharide composed of randomly located units of D-glucosamine and N-acetylglucosamine. A number of enzymes have been found *in vitro* to degrade chitosan including chitosanase, lysozyme and papain.[662] Physiologically, lysozyme is the primary degrading enzyme and chitosan degradation rate is dependent on the degree of acetylation and crystallinity.[663] Chitosan with lower acetylation percentages have been shown to last *in vivo* up to several months.[664] Side group modification has been found to be a secondary technique for modulating degradation rate. Chitosan undergoes significant hydrogen bonding which can be disrupted by the inclusion of bulky side groups like isobutyl leading to faster polymer degradation.[665] Due to chitosan's processability and versatility, it has been used in a wide range of biomedical applications.

Since chitosan is water absorptive, oxygen permeable and haemostatic, it has been extensively studied as a wound dressing over the past 20 years.[666–668] In addition, chitosan is much more bioactive than many of its degradable polymer counterparts leading to acceleration of wound healing. Induction of interleukin-8 production from fibroblasts,[669] stimulatation of macrophages,[670,671] and chemoattraction of neutrophils[672] by chitosan are all important steps necessary to initiate the body's wound healing cascade. Chitosan's intrinsic antibacterial property,[673] minimal foreign body reaction[664] and polymer degradation into N-acetylglucosamine (a major component of dermal tissue) also assist in rapid wound healing. Since chitosan by itself is mechanically weak, it is often crosslinked[669,674] or combined with other degradable polymers like PLA,[675] PLGA,[676,677] PEG,[437,678] collagen,[679,680] and alginate[681,682] which are formed into films,[437] membranes,[667,682] sponges,[673,678,679] particles,[676] fibers,[675,677,680] and gels[668,669,681] to create stronger bandages. Often times, antibiotics are trapped within chitosan and chitosan-based composite wound healing materials to prevent bacterial infection.[683,684] HemCon® dressings (HemCon Medical Technologies) are a FDA-approved chitosan-based wound dressing that is often used in combat,[685] emergency medicine[686] and dentistry.[687]

Chitosan has also been investigated as a delivery device. Chitosan is so hydrophilic that it almost always is either crosslinked[688,689] or blended with other degradable polymers to yield materials with physiologically relevant release rates. Some blended systems include chitosan with PLA,[690–692] PLGA,[690,692–695] PEG,[692,696–699] collagen,[700–702] γPGA,[703,704] and alginate.[705–707] Formation of the polymer composites into particles,[690–696,701,703,704,706,707] micelles,[698,699] fibers,[697] hydrogels,[705] and porous scaffolds[700–702] has allowed for the delivery of chemotherapeutics,[693,694,698] antibiotics,[704] anti-inflammatory drugs,[697]; antipsychotics,[690] immunosuppressants,[691] vaccines,[695,706] DNA,[696,699,702,703] siRNA,[692] and proteins.[700,701,705,707] Due to chitosan's positive charge and significantly high charge density, its ability to condense DNA has made it most promising as a DNA/gene delivery material. Also, chitosan has been found to be very mucoadhesive, so it has great potential for pulmonary drug delivery.[708–710]

The ease with which chitosan can be processed into porous matrices gives it promise as a tissue engineering scaffold. So far chitosan and chitosan-composites have been formed into membranes,[500,711–713] sponges,[443,714–716] fibers,[717–721] fused microspheres,[722–724] and hydrogels[725–729] for regenerative applications. Cellular and acellular scaffolds have been

used for the engineering of bone,[443,719,722–724] tendon,[717] ligament,[717,721] cartilage,[428,726,728] nerve[714,718,725,729] skin,[500,713,716,720] and vascular tissue.[711,712,715] By side group modification, deacetylation and polymer blending, chitosan can be incorporated into scaffolds with a wide range of physical properties but still retain the novel bioactive function of chitosan itself.

Alginate is a linear copolymer composed of β-D-mannuronic acid and α-L-guluronic acid joined by a 1–4 glycosidic bond. The composition and patterning of the monomers is dependent on the source of the polysaccharide. The most common source of alginate is the cell wall of brown algae and it is normally extracted via a basic solution followed by acidic precipitation to achieve alginic acid. These polymers have been found to have molecular weights up to 500 kDa. Alginate has shown great promise in biomedical applications due to its capacity to form spontaneous gelation when exposed to divalent cations like calcium and the reactivity of its carboxylate side groups.

The simple and mild reaction conditions necessary for alginate hydrogel formation has led to their extensive use as drug and cell delivery devices, wound healing dressings and tissue engineering scaffolds. While some pure alginate hydrogel-based drug delivery devices have been used to deliver payloads,[730–733] most research has focused on composite systems of blends or intermixed constructs (e.g. particles within a hydrogel). Alginate-based drug delivery composites include the incorporation of PLGA,[734–737] PCL,[738,739] polyethers,[740–742] and chitosan[705,743–745] in order to effectively deliver chemotherapeutics,[735,739] antibiotics,[741] anti-inflammatory drugs,[734,738,740] calcium channel blockers,[744] and proteins.[705,736,737,742,745] Supportive alginate-based hydrogels have also been researched for the delivery of chondrocytes,[746] osteoblasts,[747] myoblasts,[748] fibroblasts,[749] keratinocytes,[749] and adipose-derived stem cells.[750] Alginate wound healing dressings have been FDA approved and marketed as AlgiDERM® (Bard Medical Division), AlgiSite M (Smith & Nephew), Hyperion Advanced Alginate Dressing (Hyperion Medical), KALTOSTAT® (ConvaTec), and Tegaderm® (3M).

While alginate alone is too mechanically weak to be used as a structural tissue engineering scaffold, it has shown significant promise when blended or copolymerized with other degradable polymers. Composites of PLGA,[751–753] collagen,[754–757] PLL,[758–762] and chitosan[746,753,763–765] with alginate have been formed into scaffolds composed of films,[760] sponges,[759] fibers,[763] adhered microspheres,[751,755,757,758,761,762] gel,[746,753,754,756,764] and freeze casted porous networks.[752,765] These constructs have been used in the regenerative engineering of bone,[752,757,759] cartilage,[746,751,753,756,765] corneal,[764] liver,[758,760] nerve,[761] vascular,[755] pancreas[762] and connective tissue.[754]

Modification of alginate through reactions with its carboxylate side groups have yielded novel, bioactive materials. Specifically, adding acetal aldehyde crosslinker yields a pH-sensitive contracting gel,[766] and adding laminin peptides causes better adhesion, cell spreading and neurite outgrowth.[767] Further investigation into adding functional groups is underway and will hopefully yield promising hybrid materials that can overcome some of the current limitations found with using alginate.

While possessing many great properties, alginate has two significant drawbacks as a biomaterial: limited *in vivo* degradation and poor cellular adhesion. Mammals do not produce alginate lyase, the enzyme that cleaves alginate polymers,[768] so the *in vivo* degradation of alginate is very slow. In order to overcome this issue, alginate is often either irradiated or oxidized through the use of gamma radiation or periodate, respectively. Low level radiation causes cleavage at the mannuronic-gluronic glycoside bond allowing for more rapid polymer degradation and material solvation.[769] Oxidation by periodate, an ion

composed of iodine and oxygen, causes the formation of a hemiacetal ring with an open urinate residue with a hydrolytic bond that can cleave much more quickly than the glycoside bond normally does.[770] In most tissue engineering applications the scaffold is designed to provide structure support as well as mimic natural extracellular matrix, so poor cell attachment is highly undesirable.[771] Most cells that do not interact with their surroundings tend to not differentiate and eventually die off. Side group modification of alginate with the peptides RGD[772,773] and GRGDSP[774,775] have lead to the development of scaffolds that interact more favorably with transplanted cells and host cells.

In addition to the polymers above, a variety of other polysaccharides, such as dextran, agarose, mannan and inulin have been investigated for potential as biomaterials.

## CONCLUSIONS

There currently exists a wide range of degradable polymers that hold potential as biomaterials. With advancements in polymer synthesis techniques, the paradigm of utilizing a few well characterized polymers (e.g. PLGA and collagen) for all biomedical applications has shifted to using polymers, both heavily researched and newly developed, that can fit certain niches (e.g. DNA and RNA association with phosphoesters and inherent bioactivity of chitosan). In addition, the emergence of combination polymers holds promise for the creation of novel materials that possess desired properties for highly specific applications. The further development of processing techniques, especially with the assistance of computer-aided technology, is allowing for the formation of particles and scaffolds with extremely complex architectures that can mimic their biological counterparts. While these developments in polymer research have been critical, it should be noted that the advancements in biological research has led to a better understanding of how biomaterials interact with the host on cellular, tissue, organ and systemic levels. The field of degradable polymeric biomaterials will only continue to progress if the recent creation of strong collaboration teams composed of chemists, biologists, material scientists, engineers and clinicians is encouraged.

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## Biographies

Dr. Bret Ulery received his B.S. and B.S.E. in Biochemistry and Chemical Engineering, respectively, from the University of Iowa in 2006. He was a graduate student in the Chemical and Biological Engineering department at Iowa State University from 2006 until he earned his Ph.D. in 2010. Since September 2010, he has served as a PostDoctoral Fellow in the Orthopaedic Surgery department and Institute for Regenerative Engineering at the University of Connecticut Health Center. His research interests include novel degradable polymer synthesis, composite tissue engineering scaffolds, and immunomodulatory biomaterials.

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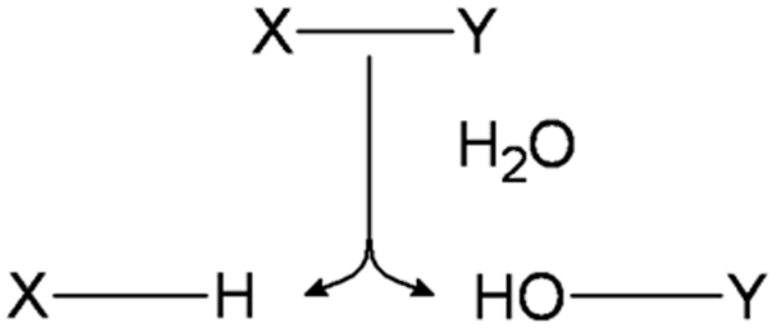



**Figure 1.**
The hydrolytically sensitive bond X-Y is cleaved by a water molecule yielding the products of X-H and HO-Y.

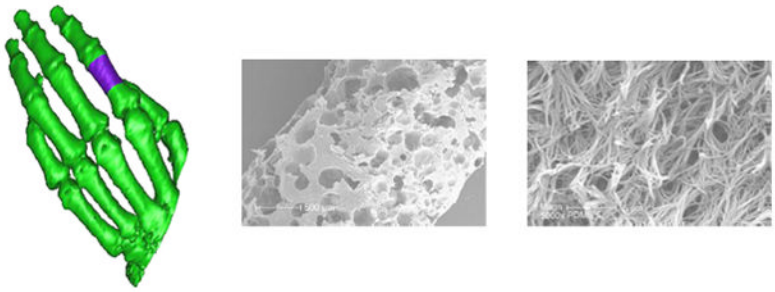


**Figure 2.**
Conversion of CT images into micro- and nanostructure controlled PLA scaffolds. A CT image of a hand (left) with a non-traditional defect (shown in purple) is converted into a wax mold which can be filled with PLA to create a scaffold with controllable pore size on the micro scale (center) and fiber size on the nano scale (right). (reprinted from [65] with permission from Elsevier.)

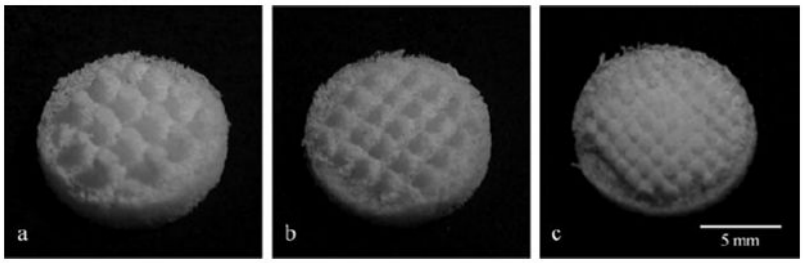



**Figure 3.**
PLGA scaffolds with villi architecture generated by indirect three-dimensional printing with villus diameter, height and intervillus spacing of (a) 0.5, 1, 0.5 mm; (b) 0.5, 1, 1 mm; (c) 1, 1, 1 mm, respectively. (reprinted from [126] with permission from Wiley.)

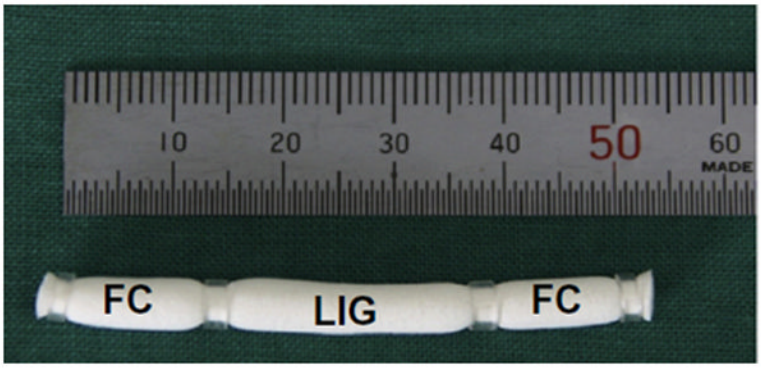



**Figure 4.**
Cylindrical porous poly(L-lactide-*co*-caprolactone) scaffold loaded with fibrochondryocytes (fibrocartilage sections) on either end with fibroblasts (ligament section) in the center in order to mimic the ligament-bone interfacial tissues. (reprinted from [195] with permission from Elsevier.)

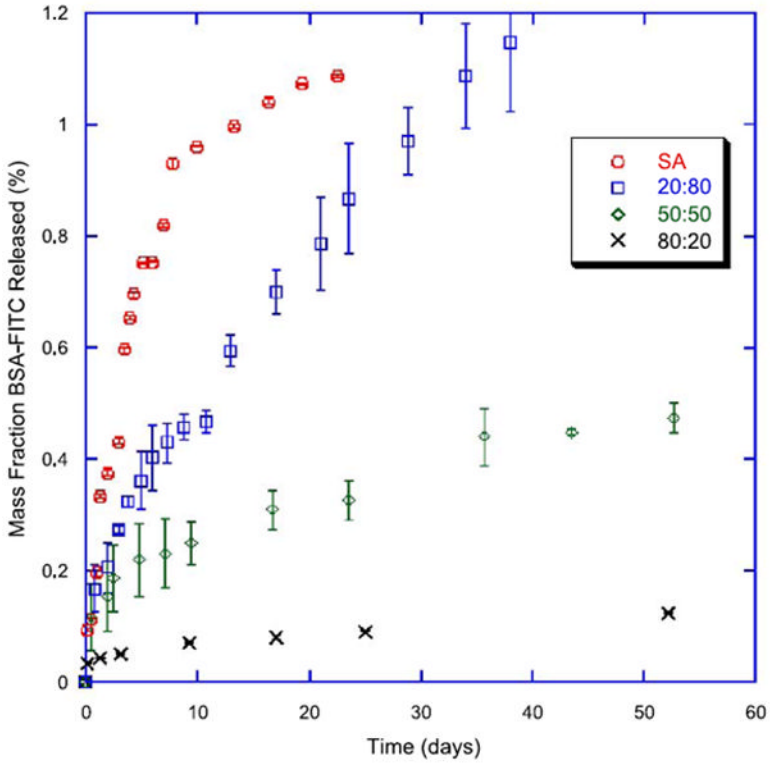



**Figure 5.**
*In vitro* release of bovine serum albumin from poly(sebacic anhydride-*co*-1,6-bis-*p*-carboxyphenoxy hexane) microparticles in phosphate-buffered saline (pH 7.4). (reprinted from [19] with permission from Elsevier.)

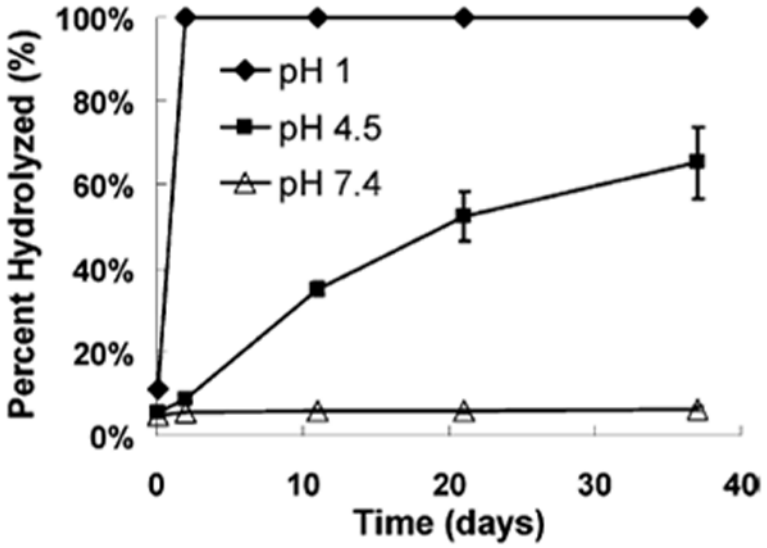



**Figure 6.**
*In vitro* hydrolysis of poly(cyclohexane-1,4-diyl acetone dimethyl ketal) is greatly influenced by surrounding pH evidenced by its half-life of 24.1 days in pH 4.5 and 4 years in pH 7.4. (reprinted from [237] with permission from the American Chemical Society.)

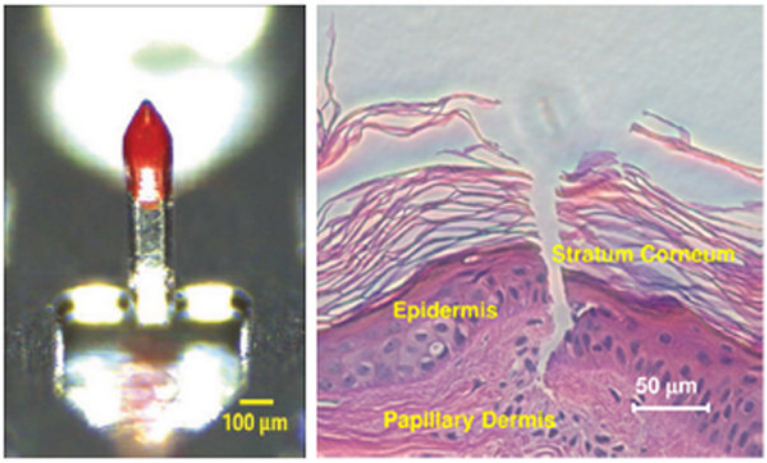



**Figure 7.**
Optical microscopy image of a polyphosphazene coated metallic microneedle (left) and histological section of porcine skin after coated microneedle insertion (right). (reprinted from [310])

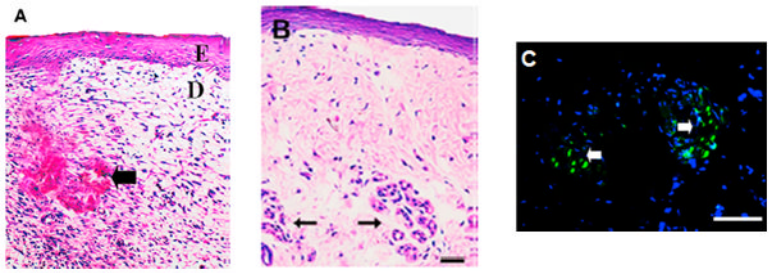



**Figure 8.**
Photomicrographs of keratinocyte-fibroblast co-culture engineered skin tissue with the addition of collagen microsphere supported sweat gland cell constructs. (A) Hemotoxylin and Eosin (H&E) staining after two weeks of *in vitro* co-cultivation showed differentiated tissue layers (E: epithelium and D: dermis) with a bud-like structure (black arrow) where sweat gland constructs were loaded. (B) H&E staining of six week post-implantation *in vivo* skin tissue showed the continued presence of bud-like structures in the dermis layer (black arrow). (C) Fluorescence microscope observation showed DiO-positive cells (green) confirming the presence of still viable sweat glands. (reprinted from [485] with permission from Elsevier.)

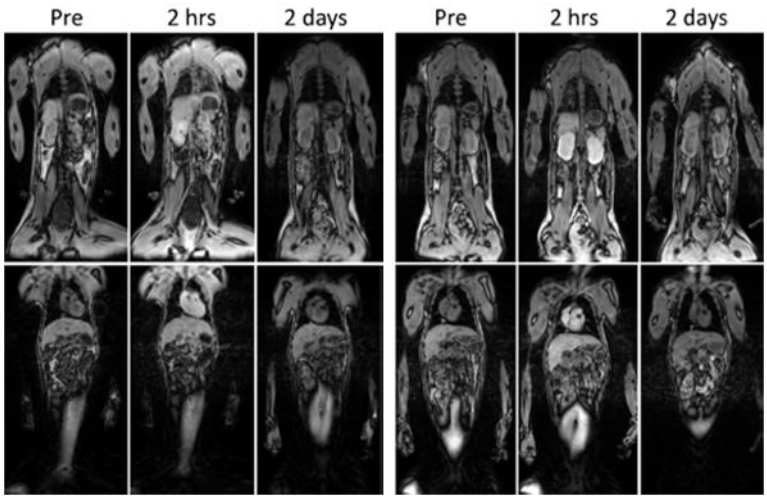



**Figure 9.**

Magnetic resonance imaging of rhesus monkeys before contrast injection and at 2 h and 2 days after injection of Magnevist at 0.1 mmol Gd/kg (left) and PG-Gd 0.01 mmol Gd/kg (right). Enhancements of blood vessel, heart, kidney and liver are clearly visualized at 2 h after PG-Gd injection at a tenth of the dose of Magnevist. By 2 days, the contrast agent has been mostly cleared with both contrast agents. (reprinted from [593] with permission from Wiley.)

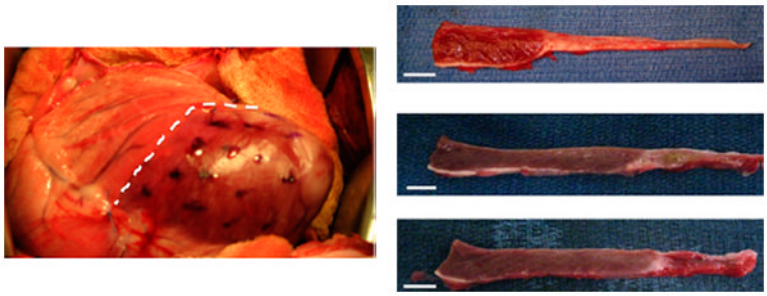
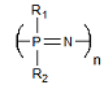
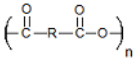
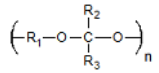
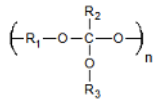
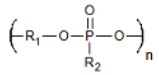
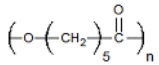
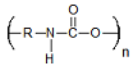
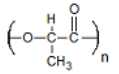
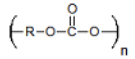
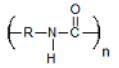


**Figure 10.**
MeHA injection into a sheet heart after infarction helps prevent subsequent myocardial damage. Multiple injections (dots) of MeHA were given into the infarcted area (right of dashed line) (left). Representative images of myocardial wall thickness 8 weeks post treatment with no scaffold (top right), MeHA High scaffold (middle right), and MeHA Low scaffold (bottom right). (reprinted from [620])

**Table 1**

Summary of different polymeric families' applications, advantages, disadvantages, degradation rate and structure.

| Polymer | Applications | Advantages | Disadvantages | λ, Degradation Rate Constant ($s^{-1}$) | Structure |
|---|---|---|---|---|---|
| Polyphosphazenes | Tissue Engineering<br>Vaccine Adjuvant | Synthetic Flexibility<br>Controllable Mechanical Properties | Complex Synthesis | $4.5 \times 10^{-2}$ –$1.4 \times 10^{-7}$ Ref. [776,13] |  |
| Polyanhydrides | Drug Delivery<br>Tissue Engineering | Significant Monomer Flexibility<br>Controllable Degradation Rates | Low Molecular Weights<br>Week Mechanical Properties | $1.9 \times 10^{-3} - 9.4 \times 10^{-9}$ Ref. [17,777] |  |
| Polyacetals | Drug Delivery | Mild pH Degradation Products<br>pH Sensitive Degradation | Low Molecular Weights<br>Complex Synthesis | $6.4 \times 10^{-5}$ Ref. [17] |  |
| Poly(ortho esters) | Drug Delivery | Controllable Degradation Rates<br>pH Sensitive Degradation | Week Mechanical Properties<br>Complex Synthesis | $4.8 \times 10^{-5}$ Ref. [17] |  |
| Polyphosphoesters | Drug Delivery<br>Tissue Engineering | Biomolecule Compatibility<br>Highly Biocompatible Degradation Products | Complex Synthesis | $1.4 \times 10^{-6}$ Ref. [778,779] |  |
| Polycaprolactone | Tissue Engineering | Highly Processable<br>Many Commercial Vendors Available | Limited Degradation | $3.5 \times 10^{-8}$ Ref. [17] |  |
| Polyurethanes | Prostheses<br>Tissue Engineering | Mechanically Strong<br>Handle Physical Stresses Well | Limited Degradation<br>Require Copolymerization with Other Polymers | $8.3 \times 10^{-9}$ Ref. [780] |  |
| Polylactide | Tissue Engineering<br>Drug Delivery | Highly Processable<br>Many Commercial Vendors Available | Limited Degradation<br>Highly Acidic Degradation Products | $6.6 \times 10^{-9}$ Ref. [17] |  |
| Polycarbonates | Drug Delivery<br>Tissue Engineering<br>Fixators | Chemistry-Dependent Mechanical Properties<br>Surface Eroding | Limited Degradation<br>Require Copolymerization with Other Polymers | $4.1 \times 10^{-10}$ Ref. [285] |  |
| Polyamides | Drug Delivery | Conjugatable Side Group<br>Highly Biocompatible Degradation Products | Very Limited Degradation<br>Charge Induced Toxicity | $2.6 \times 10^{-13}$ Ref. [17] |  |

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