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Enabling Proregenerative Medical Devices via Citrate-Based Biomaterials: Transitioning from Inert to Regenerative Biomaterials

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Regenerative medicine aims to restore tissue and organ function without the use of prosthetics and permanent implants. However, achieving this goal has been elusive, and the field remains mostly an academic discipline with few products widely used in clinical practice. From a materials science perspective, barriers include the lack of proregenerative biomaterials, a complex regulatory process to demonstrate safety and efficacy, and user adoption challenges. Although biomaterials, particularly biodegradable polymers, can play a major role in regenerative medicine, their suboptimal mechanical and degradation properties often limit their use, and they do not support inherent biological processes that facilitate tissue regeneration. As of 2020, nine synthetic biodegradable polymers used in medical devices are cleared or approved for use in the United States of America. Despite the limitations in the design, production, and marketing of these devices, this small number of biodegradable polymers has dominated the resorbable medical device market for the past 50 years. This perspective will review the history and applications of biodegradable polymers used in medical devices, highlight the need and requirements for regenerative biomaterials, and discuss the path behind the recent successful introduction of citrate-based biomaterials for manufacturing innovative medical products aimed at improving the outcome of musculoskeletal surgeries.

1. Introduction

Regenerative medicine aims to develop therapeutic options for repairing, regenerating, and restoring damaged tissues and organs to their normal physiological function and anatomy. However, achieving this goal has proven to be challenging and the field remains primarily an academic discipline with only a few products on the market. Challenges include the lack of proregenerative biomaterials, a lengthy and complex regulatory pathway to ensure treatment safety and efficacy, and user adoption due to differences in handling or delivery of innovative medical devices. In the United States of America, the success of medical device technology and innovation heavily relies on the regulations set and enforced by the Food and Drug Administration (FDA).[1–4] The FDA categorizes medical devices into three classes: Class I, II, and III, based on their level of risk. Class I devices are considered low-risk and

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require general controls, while Class II devices are moderate to medium-risk and require general and special controls. Class III devices are high-risk and require general controls and premarket approval. In addition to their risk classification, medical devices can also be categorized as permanent or nonpermanent implants. Biodegradable implants, in particular, are of interest due to their ability to degrade in vivo over time.[5–6] This property allows for the breakdown of large, complex molecular structures into smaller molecules that can be absorbed by the body, minimizing negative long-term responses from the host tissue.[7–8]

The first biodegradable medical device, approved by the FDA in 1971, was the Dexon absorbable suture produced by Davis & Geck and it was based on poly(glycolic acid) (PGA).[9] Up until the first half of 2020, a total of nine biodegradable polymers had been used in implantable medical devices cleared or approved by the FDA for marketing in dental, orthopedic, cardiovascular, and drug delivery applications. These polymers include poly(glycolic acid) (PGA), poly (lactic acid) (PLA), poly(caprolactone) (PCL), poly(dioxanone) (PDS), poly(trimethylene carbonates) (PTMC), poly(hydroxybutyrate) (PHB)/poly(hydroxyvalerate) (PHV), tyrosine-based polyarylates, poly(anhydrides), and poly(urethanes) (PU).[10–13] Although there are limitations in the design, production, and marketing of biodegradable polymeric medical devices, the aforementioned polymers have dominated the medical device market for the past 50 years.[9] Despite advances in biomaterial science and engineering, there are remarkably few synthetic biodegradable polymers commercially available for the fabrication of implantable medical devices.[14] Furthermore, the widespread use of these polymers in medical devices is not necessarily due to their superior properties for intended applications, but rather their successful track record in marketed devices, which can lead to shorter times and lower cost for bringing incrementally better products to market. It should be noted that most of these polymers lack inherent properties that support biological processes, such as cell adhesion and differentiation and do not intrinsically aid tissue regeneration.

To facilitate the development and clinical utilization of regenerative devices and fully unlock the potential of regenerative medicine to significantly enhance patient outcomes, it is imperative to create biomaterials with inherent proregenerative properties. These biomaterials would not only demonstrate the feasibility of bioabsorbable medical implants capable of providing mechanical support but also actively supporting tissue regeneration. The successful development and commercialization of Citregen, a citrate-based biomaterial comprising a polydiolcitrate with hydroxyapatite (HA), offers insight into a path for novel medical devices designed for tissue and regenerative engineering applications. Citrate, the building block monomer for citrate-based biomaterials (CBBs) is a naturally occurring metabolite of our body and a major player in the structural and architectural components of bone.[15–16] Citregen's crosslinked polymer network and ceramic content mimics bone's extracellular matrix. Upon degradation, Citregen slowly releases citrate, calcium, and phosphate, which play a significant role in bone regeneration.[17] So far, CBBs have been used for the fabrication of a variety of medical devices for orthopedic surgery applications, including the Citrelock Tendon Fixation Device System (K200725),[18] Citrefix Suture Anchor System (K203334),[19] Citrespline and Citrelock ACL Reconstruction System (K210239),[20] and Citrelock Duo Fixation Device (K232592).[21] Given the successful clinical translation of CBBs, they are currently under development for devices that are designed for the regeneration of bone defects. Unlike the current biodegradable synthetic polymers used in FDA-approved or -cleared medical devices that only offer mechanical support, CBBs have the potential to actively promote tissue regeneration.[22] This transition from inert to regenerative biomaterials is a significant step in the use of biomaterials for regenerative medicine applications.

1.1. Overview of Current Synthetic Biodegradable Polymers Used for FDA-Approved or -Cleared Medical Devices

Over the past 50 years, numerous synthetic biodegradable polymers have been utilized for various biomedical applications. Nevertheless, only a select few have been incorporated into medical devices that have received FDA clearance or approval for clinical use. **Figure 1** and **Table 1** provide a comprehensive summary of the current synthetic biodegradable polymers employed in FDA-regulated medical devices.

1.1.1. Poly (glycolic acid) (PGA), Poly (lactic acid) (PLA), and their Copolymers

PGA, the simplest linear and aliphatic polyester, was first synthesized by Carothers in 1932 (**Figure 2**).[23] It can be produced through the polycondensation of glycolic acid or the ring-opening polymerization of glycolide. The former method yields only low molecular weight PGA, while the latter is used for industrial production of high molecular weight PGA. PGA exhibits high crystallinity (45–55%), a high melting point (220–225 °C), and low solubility in organic solvents (**Table 2**).[24] The first synthetic and absorbable suture, Dexon (K830889), was fabricated using PGA (Davis & Geck in 1971), and it received FDA approval in 1983.[25–26] PGA sutures retain ≈50% of their strength after 2 weeks, lose 100% of their strength after 4 weeks, and are completely absorbed within 4–6 months.[25] PGA was also used in the development of internal bone fixation devices, Biofix (K843428), by Kirschner Medical Corporation in 1984.[27–28] However, PGA implants were usually found to induce local inflammatory responses due to the rapid degradation and the accumulation of its acidic degradation products.[29]

Copolymers of glycolic acid and the more hydrophobic monomer lactic acid (PLGA) were developed in the 1960s. These copolymers offered better strength retention and were used in the development of sutures, such as "Polyglactin 910 (K833081)" and "Vicryl (K851086)" (Ethicon in 1984 and 1985) that were able to retain 75%, 50%, and 25% of their strength after 2, 3, and 4 weeks, respectively.[30–32] PLGA was also used in the development of drug delivery capsules (Lupron Depot (NDA 19-943), AbbVie) in 1989.[33–34] PLGA bone fixation devices such as LactoSorb (K953194) (Biomet Inc. in 1995) and RapidSorb (K093464) (Depuy Synthes in 2010) with different GA and LA ratios have been widely used in oral and maxillofacial surgery.[35–38]

PLA was first discovered by Carothers in 1920s, but it was not commercially used until 1989 when Grubers developed a method

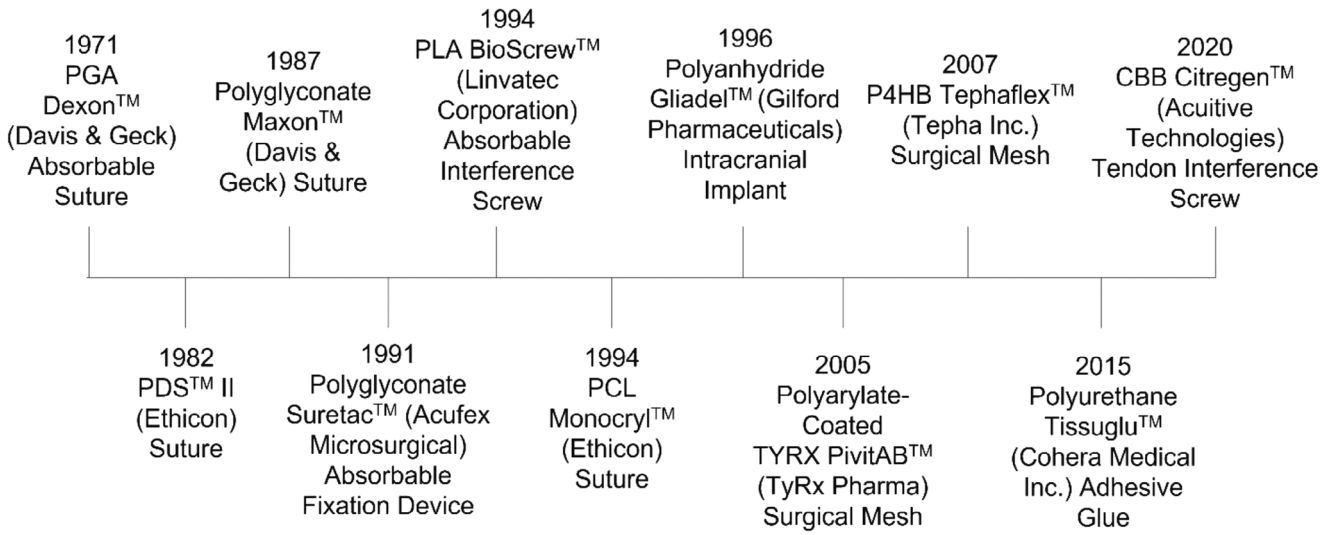

Figure 1. Timeline of distinct synthetic and biodegradable polymers first used in FDA-approved or -cleared medical devices.

to extract lactic acid from corn. PLA can be synthesized through the polycondensation of lactic acid or ring-opening polymerization of lactide. Lactic acid exists in two stereoisomeric forms, D-LA and L-LA. Both PDLA and PLLA are semicrystalline, while PDLLA is completely amorphous.[39] Amorphous PDLLA has often been used in drug delivery systems, such as Atridox (NAD 05-751) (Tolmar Therapeutics, Inc. in 1998) that deliver doxycycline hyclate for the treatment of periodontitis.[40–41] Semicrystalline PLLA, with a crystallinity of 37%, has been used for sutures and orthopedics devices that require high mechanical strength and toughness. Due to its ability to stimulate collagen synthesis, PLLA has also been used as a bio-stimulatory dermal filler (Sculptra (P030050), Galderma Laboratories LP in 2004).[42–43] Abbott Vascular received FDA premarket approval (PMA) for the everolimus-eluting coronary artery stent system, Absorb GT1 (P150023) to treat patients with coronary artery disease (CAD) in 2015.[44] This drug-eluting bioresorbable vascular stent (BVS) consists of PLLA struts coated with a PDLLA layer that contains the drug. The FDA investigated an increased rate of major adverse cardiac events in patients who received the Absorb GT1 stent.[45] As of the date of this manuscript, these devices are no longer available on the market.

PGA, PLA and their copolymers have been extensively used in many medical devices with relatively good success. Examples of these devices include sutures and meshes, dental and orthopedic fixation devices, skin grafting materials, vascular stents, and drug delivery systems (Table 1). However, there are challenges that need to be addressed. For example, PLA and PGA have limited capacity to support cell adhesion and cell proliferation in vitro.[46] In addition, the degradation products of PGA and PLA, glycolic acid and lactic acid, are relatively strong acids that can accumulate at implantation sites, causing a chronic inflammatory response.[3] PGA, PLA, and their copolymers are used more than any other synthetic biodegradable polymer for medical devices.[47]

Table 1. Overview of current synthetic biodegradable polymers used for FDA-approved or -cleared medical devices.

Synthetic biodegradable polymers	Major applications in FDA-approved/cleared medical devices
Polyglycolic acid (PGA) and Polylactic acid (PLA) and their copolymers	Dental and orthopedic fixation devices,[27,35–36] sutures,[25,30] staples,[160] drug delivery capsules,[33,40] skin replacement materials,[161] barrier membranes,[162–163] dermal injectable fillers,[42] cardiovascular stents[45]
Polydioxanone (PDS)	Orthopedic fixation devices,[53] sutures,[50] meshes,[164] wound clips[165]
Poly(trimethylene carbonates) (PTMC)	Sutures,[51,58] meshes,[166] orthopedic fixation devices[167]
Polycaprolactone (PCL)	Implantable contraceptive drug devices,[65] orthopedic screws, sutures[70]
Polyanhydride	Drug delivery system[76]
Amino acid-based polymers	Meshes for hernia repair,[168] antimicrobial pacemaker pouch,[169] cardiovascular stents[170]
Polyhydroxybutyrate (PHB) and polyhydroxyvalerate (PHV)	Orthopedic fixation devices,[91] sutures,[93] meshes[171]
Biodegradable Polyurethane (PU)	Tissue adhesives,[101] wound dressings[105]
Poly(octamethylene citrate) (POC)	Orthopedic fixation devices[17]

Table 2. Physical properties of current synthetic and biodegradable polymers used in FDA-approved medical devices.

Polymer	Crystallinity [%]	Glass transition temperature [°C]	Melting temperature [°C]	Tensile Modulus [GPa]	Solubility	Degradation time [months]	Degradation products	References
Poly(glycolic acid) (PGA)	45–55	35–40	220–225	6.9	Soluble in highly fluorinated solvents such as hexafluoroisopropanol (HFIP)	4–6	Glycolic acid	[24]
Poly(lactic acid) (PLA)	PDLLA amorphous	PDLLA 50-53	PDLLA N/A	PDLLA 1.9-2.4	Soluble in a range of organic solvent.	< 6	Lactic acid	[39]
	PLLA 37%	PLLA 55-65	PLLA 173—178	PLLA 1.2-2.7		12-36		
Poly(dioxanone) (PDO/PDS)	55%	−10	110-115	1.5	Low solubility in organic solvent	6-12	Glyoxylic acid	[48]
Poly(trimethylene carbonate) (PTMC)	amorphous	−17	N/A	2.4	Insoluble in organic solvent	6-12	Carbon dioxide and 1,3-propanediol	[56]
Poly(ε-caprolactone) (PCL)	Up to 69%	−5	58–63	0.4	Soluble in chloroform, dichloromethane, carbon tetrachloride, benzene, toluene, cyclohexanone and 2-nitropropane	> 24	Hydroxycaproic acid	[64]
Poly(anhydride)	N/A	68	120–122	N/A	Insoluble in common organic solvent	Wide time range	Diacid	
Amino acid-based polymers	Wide range	Wide range	Wide range	Wide range	Low solubility in organic solvent	Wide time range	Amino acid	[80]
Polyhydroxybutyrate (PHB)	P3HB >50%	P3HB 0-27	P3HB 173–180	P3HB 2.5	Slightly soluble in chloroform, dichloromethane, dichloroethane at room temperature	P3HB several years	3-Hydroxybutyric acid or 4-hydroxybutyric acid	[88–90]
	P4HB	P4HB -51	P4HB 60	P4HB 0.07		P4HB 2-13		
Polyurethane	Wide range	Wide range	Wide range	Wide range	Wide range	Wide time range	Hydroxy acids, alcohols, amines and carbon dioxide	[96,97]
Poly(octamethylene citrate) (POC)	amorphous	5	N/A	0.0035	Insoluble in all organic solvents once crosslinked	Wide time range	1,8-Octanediol, citric acid	[107]

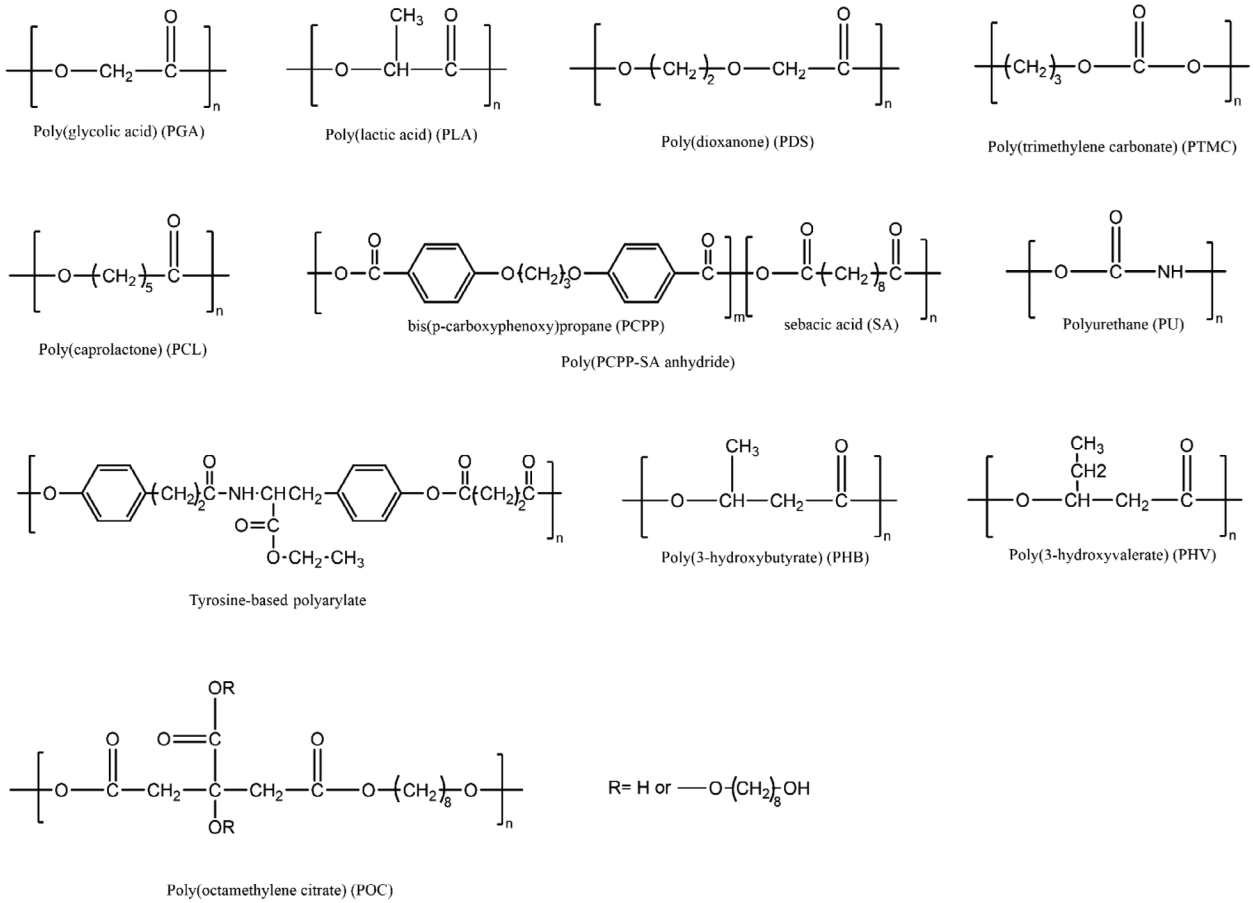

Figure 2. Chemical structures of current synthetic and biodegradable polymers used in FDA-approved or -cleared medical devices.

1.1.2. Polydioxanone (PDS)

PDS, a poly(ether ester), is synthesized by ring-opening polymerization of p-dioxanone. It is semicrystalline (55%) with a glass transition temperature ranging from −10 to 0 °C, and a melting temperature of 110–115 °C.[48] PDS is a nonantigenic and non-pyrogenic polymer, eliciting minimal tissue reaction following implantation.[49] Furthermore, its inherent flexibility allowed PDS to be the first biodegradable polymer that could be fabricated into a monofilament fiber. In 1982, PDS was introduced as the first monofilament synthetic absorbable suture, PDS II (N18331), developed by Ethicon. Compared to PGA and PLA sutures, the monofilament configuration of PDS allows the sutures to easily go through tissues, thereby reducing tissue reactivity and the risk of wound infection.[50] PDS II sutures (Ethicon in 1981) lose 50% of their initial breaking strength after 3 weeks and are completely absorbed within 6 months.[51–52] PDS has also been used in the development of suture clips as well as orthopedic pins marketed under the name OrthoSorb (K901456) (Johnson & Johnson International).[53–54] However, PDS clips or staples have been associated with high rates of surgical site infection, postoperative fever, and pain, with suboptimal clinical performance and poor safety record, possibly due to the acidic degradation product, glyoxylic acid, released into the body.[55]

1.1.3. Poly(trimethylene Carbonates) (PTMC)

PTMC is an aliphatic polycarbonate synthesized through ring-opening polymerization of trimethylene carbonate. It has an amorphous structure, rendering it a flexible and soft polymer with a relatively low glass transition temperature of −17 °C. This characteristic makes it less suitable for bulk applications that demand high mechanical strength.[56] To overcome this limitation, researchers have developed A-B-A block copolymers in a 2:1 glycolide/TMC ratio, with a TMC center block (B) and glycolide end blocks (A). This copolymer, referred to as polyglyconate, has been used as Maxon (P840051) sutures (Davis & Geck in 1987).[57] Maxon sutures offer greater flexibility than pure PGA sutures and are fully absorbed within ≈6 months.[51] Medtronic has further formulated polyglyconate with dioxanone to create Biosyn (K000037) sutures, which received FDA clearance in 2000.[58–59] Polyglyconate has also been used to develop Acufex (K911837) orthopedic fixation devices by Acufex Microsurgical, Inc. in 1991.[60] Unlike other ester-based degradable polymers, PTMC releases diols and carbon dioxide instead of acidic compounds from its degradation products. Studies have shown that PTMC is susceptible to enzymatic degradation in vivo.[61]

1.1.4. Polycaprolactone (PCL)

PCL was first synthesized through a ring-opening polymerization of ϵ-caprolactone in 1930s by Carothers.[62] Its degradation properties were discovered in the 1970s and became commercially available due to efforts at Union Carbide to identify synthetic polymers that can be degraded by microorganisms.[63] PCL is a semicrystalline polymer with a relatively high crystallinity of up to 69% and exhibits a low glass transition temperature of −60 °C and a melting temperature range of 58–63 °C.[64] The degradation product of PCL is hydroxycaproic acid. The slow degradation rate of PCL has made it suitable for use in long-term implants and controlled drug release systems. For example, the biodegradable contraceptive capsule, Capronor system, has demonstrated controlled release of levonorgestrel for over a year.[65] However, limited cellular interactions, hydrophobicity, and suboptimal mechanical properties associated with PCL-based medical devices can present compatibility challenges with host tissues, thereby constraining their broader applicability in tissue engineering.[66–68] Further modifications to PCL, including copolymerization, have enhanced its utility and expanded its range of applications in medical devices. For example, the copolymer of caprolactone and glycolide has been used in absorbable monofilament sutures and marketed as Monocryl (K930772) by Ethicon in 1994.[69] This suture loses ≈20–30% breaking strength after 2 weeks and is completely absorbed 91–119 days after implantation, with minimal tissue reaction.[70] Furthermore, a copolymer consisting of caprolactone and lactide was employed in the manufacture of ZipE (K162429) knotless tissue repair and attachment devices by Ziptek, LLC in 2017.[71]

1.1.5. Polyanhydrides

Polyanhydrides were initially studied for textile applications in the 1950s by Hill and Carothers.[72] In 1983, Langer and his colleagues investigated their use for controlled drug delivery.[73] Polyanhydrides were synthesized by polycondensation of diacid molecules. Their mechanical properties, degradation behaviors, and other physical properties can be adjusted by altering the chemical composition of reacting monomers, such as aliphatic monomers, unsaturated monomers, aromatic monomers, and linear fatty acid monomers. Aliphatic polyanhydrides degrade within days, while some aromatic polyanhydrides degrade over several years.[74] Surface erosion during degradation inhibits pitting and cavity formation in the bulk material, making polyanhydrides promising materials for drug delivery applications.[75] A polyanhydride copolymer, consisting of 20% carboxyphenoxy propane and 80% sebacic acid was used in Gliadel (NDA 20-637) brain tumor implants (Guilford Pharmaceuticals in 1996) for the controlled delivery of carmustine or bis-chloroethylnitrosourea (BCNU).[76–77]

1.1.6. Amino Acid-Based Polymers

Poly(amino acids) have been considered promising candidate materials for biomedical applications due to their biomass origin, unique physical properties, and ease of functionalization.[78] However, limited processability, thermal degradation upon melting, insolubility in common organic solvents, swelling in aqueous solution, and antigenicity of polymers containing multiple amino acids have restricted their use in biomedical applications.[79] To overcome these limitations, amino acid-modified polymers were introduced in 1987 by Langer and colleagues via polycondensation reaction between amino acid and other polymers.[80] Since then, more amino acid-derived polymers, especially tyrosine-based polymers,[81–82] have been developed for medical devices.[83] Tyrosine-based polycarbonates have been developed for orthopedic implants.[84] In 2010, the first tyrosine-based, polyarylate-coated meshes (PivitAB (K093524) developed by TyRx Pharma) for hernia repair received regulatory clearance from the FDA.[85]

1.1.7. Polyhydroxybutyrate (PHB) and Polyhydroxyvalerate (PHV)

PHB/PHV, the first known bioplastics, were discovered in 1926 by a French researcher, Maurice Lemoigne, through his work with the bacterium *Bacillus megaterium*.[86] Unlike the synthetic polymers discussed so far, which are obtained through manual chemical synthesis routes, PHB/PHV can only be synthesized by microorganisms.[87] Currently, two PHB derivatives are available for biomedical applications: poly(3-hydroxybutyrate) (P3HB) and poly(4-hydroxybutyrate) (P4HB). P3HB homopolymer exhibits high crystallinity (above 50%) and a high melting point (173–180 °C), making it suitable for use in orthopedic devices due to its stiffness and slow degradation rate.[88] P3HB undergoes complete absorption in vivo over several years. In contrast, P4HB is less crystalline and more flexible with an elongation of 100%.[89] P4HB degrades in vivo within 8–52 weeks. The degradation products of P3HB and P4HB are D-3-hydroxybutyric acid and D-4-hydroxybutyric acid, respectively, which naturally exist in many organs, including the brain, heart, lung, liver, and muscle.[90] The first commercial P4HB-based device was a bioresorbable mesh, TephaFLEX (K070894), developed in 2007 by Tepha, Inc.[91–92] In 2009 Aesculap, Inc. introduced the first P4HB absorbable suture, MonoMax (K100876), that was cleared by the FDA for clinical use.[93–94]

1.1.8. Biodegradable Polyurethane (PU)

Polyurethanes were discovered by Dr. Otto Bayer in the 1930s and they comprise a large family of polymers containing urethane groups in the backbone.[95] They are synthesized by polycondensation of polyols and diisocyanates. The mechanical properties and degradation rate of PU can be adjusted by varying the chemical composition or the feed ratio of polyols and diisocyanates.[96] Biodegradable polyester-based urethane polymers (PEU) have gained significant interest in the field of implantable medical devices due to their robust mechanical properties and good biocompatibility.[97] Recent research has focused on incorporating biodegradable groups or linkages on PU backbone to tailor its degradation behavior for biomedical applications.[98–100] In 2015, TissuGlu (P130023) surgical adhesive, the first PEU-based device, developed by Cohera Medical Inc., received FDA PMA.[101–102] Although TissuGlu surgical adhesive has been

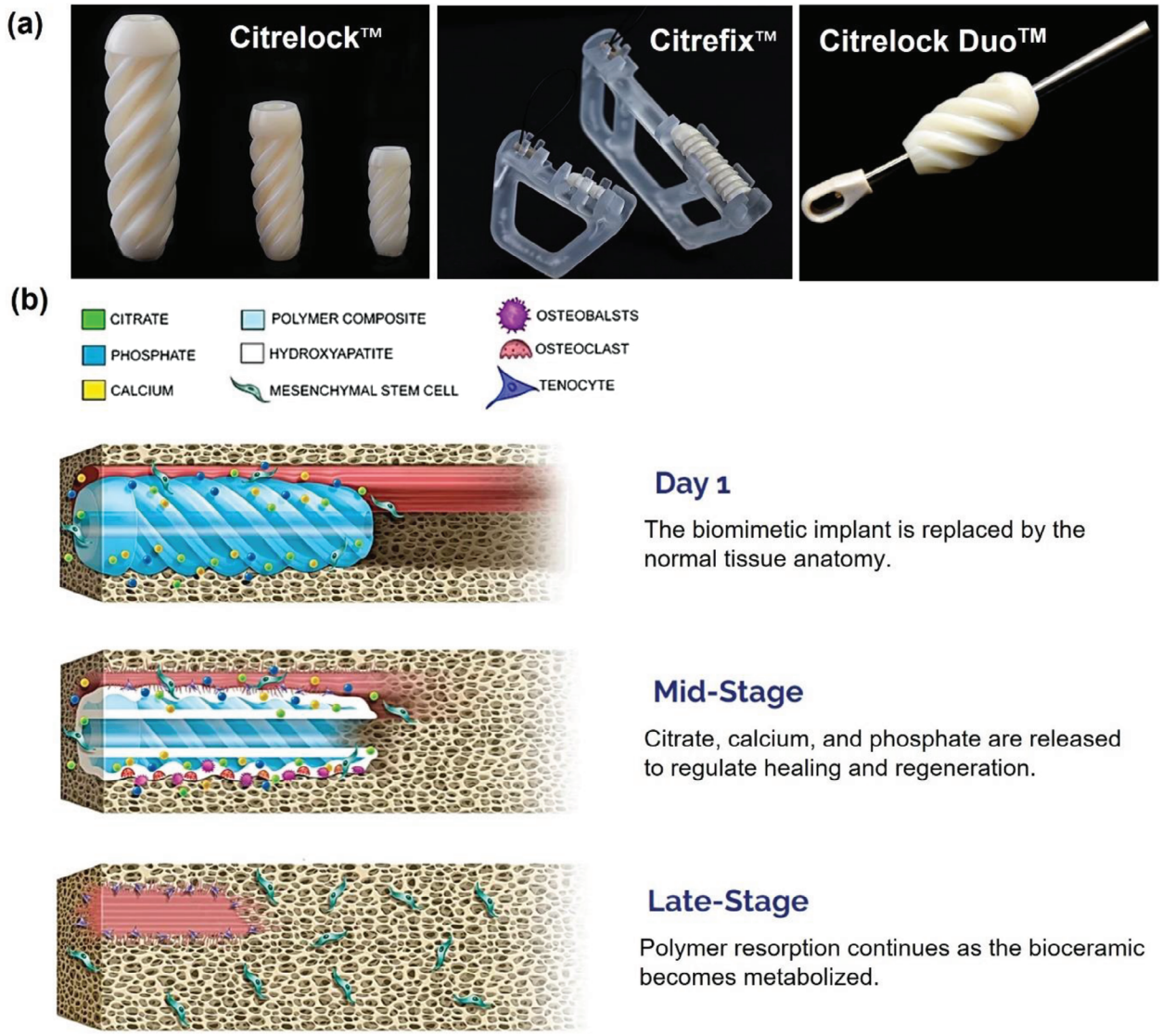

Figure 3. a) Citregen-based devices include the Citrelock Tendon Fixation Device System, the Citrefix Knotless Suture Anchor System and Citrelock Duo Fixation Device. b) Citregen undergoes controlled and homogeneous resorption through polymer hydrolysis, releasing citrate, calcium, and phosphate molecules. This process prevents bulk degradation and chronic inflammation, facilitating natural bone remodeling. Reproduced with permission from Acuitive Technologies, Inc. (https://www.acuitivetech.com/technology).

shown to increase tensile strength and reduce surgery time compared to progressive tension sutures, its application has been associated with high reintervention rates and increased puncture volume due to recurring seromas, which can negatively impact patient-specific convalescence.[103–104] PEUs have also been used in absorbable wound dressings. NovoSorb (K172170) by PolyNovo Biomaterials Pty Ltd. received FDA regulatory clearance in 2017.[105–106]

1.2. Citrate-Based Polymers

In 2020, the FDA granted 510k clearance to medical devices fabricated using Citregen, a biomaterial based on citrate-containing polymers originally developed and reported by Yang et al. in 2004.[107] Citregen is a composite of poly(octamethylene citrate) (POC) and hydroxyapatite, the latter component at a percent content similar to that found in bone. This composite has demonstrated significant potential for bone regeneration.[17] Citregen is used for the fabrication of the soft tissue fixation device Citrelock and the knotless suture anchor Citrefix (**Figure 3**).[19,18,108–109] The Citrelock tendon fixation device system is a tenodesis screw with controlled resorbable properties currently used for tendon fixation in foot and ankle procedures. Citrefix consists of a Citregen resorbable biomimetic anchor body and a PEEK eyelet (Figure 3). In 2023, versions of Citrelock were introduced into the market to target sports medicine applications: 1) Citrelock ACL, a fixation device first used in a patient for anterior cruciate ligament reconstruction surgery in June, 2023,[20] and 2) Citrelock Duo a fixation device that received FDA clearance in September, 2023 for

biceps tenodesis and tendon transfer procedures (Figure 3).[21] The regulatory clearance of these products for clinical use is a milestone for the biomaterials science and engineering community as they feature the first thermoset synthetic biodegradable polyester used in FDA-cleared medical devices since the introduction of biodegradable polymers for medical use 50 years ago. Citregen provides biomimetic mechanical properties and a proregenerative microenvironment for the surrounding tissues through the release of citrate, calcium, and phosphate.[17] Tailorable mechanical and degradation properties together with the release of degradation products deemed useful for supporting tissue function opens up possibilities for next-generation biomaterials in regenerative engineering and medicine.[22,107]

As demonstrated with Citregen, citric acid is an innovative building block to create innovative polymeric biomaterials. Citric acid is readily available and has a well-established safety record in various consumer and professional products. Crystalline citric acid was first isolated in 1784 by Scheele.[110] In 1937, it was discovered to be a key intermediate in the Krebs cycle,[111] and was established as a component of almost all biological systems shortly thereafter. Industrial production of citric acid begins with the discoveries of Wehmer in 1893 and Currie in 1917. Wehmer demonstrated that Citromyces produced citric acid in a medium containing inorganic salts and sugars, while Currie showed that *Aspergillus niger* accumulated large amounts of citric acid.[112]

The salt form of citric acid, citrate, is naturally present in the body, particularly in bone, where citrate content is 5–25 times greater than that found in other tissues. In fact, ≈80% of the body's total citrate content is in bone.[16] Citrate is essential for the structure of apatite nanocrystals, which are responsible for the significant properties of bone, such as stability, strength, and resistance to fracture.[15] Citric acid is also present in other organs, such as the liver, kidney, and brain, where it helps with energy metabolism, mineral adsorption, and the prevention or treatment of kidney stones.[113] The incorporation of co-monomers, particularly diols, into citric acid enables the creation of citrate-based biomaterials (CBBs) with customizable mechanical and degradation properties, as well as antioxidant, and anti-inflammatory properties. POC was the first CBB introduced in 2004 by Yang et. al. as a novel elastomer for tissue engineering applications.[107] 1,8-octanediol, the largest aliphatic diol that is water-soluble, was chosen as co-monomer to react with citric acid via thermal condensation to form a hydrolysable polyester elastomer. Both reaction time and temperature were tuned to achieve controllable mechanical and degradation properties, which allow the CBBs to be used for various biomedical applications. So far, CBBs alone or combined/modified with other biomaterials have been extensively studied in tissue engineering, including skin, muscle, cardiovascular, bladder, cartilage, ligament, and bone regeneration.[22,114–116] A comprehensive summary of citrate-based polymers used for biomedical applications is presented in **Table 3**.

1.2.1. Musculoskeletal and Craniofacial Regenerative Engineering

As described in the aforementioned paragraph, Citregen is the first CBB commercialized for innovative resorbable tissue fixation devices used in musculoskeletal surgeries. Nevertheless, there is significant ongoing research to better control the mechanical properties, osseointegration, and osteoconduction of CBBs. One approach involves increasing the crosslinking density of CBBs by introducing additional functional groups into the polymer network. For example, the addition of azide and alkyne groups to POC enable the formation of a double polymer network, resulting in POC-M-click-HA scaffolds with a maximum load of 880.8 ± 14.5 N.[117] Adhering mussel-inspired tannic acid (TA) onto a HA surface created citrate-based tannin-bridged bone composites (CTBCs), exhibiting significantly improved compression strengths of up to 323.0 ± 21.3 MPa compared to 229.9 ± 15.6 MPa for POC-HA.[118] An alternative strategy is to use smaller HA particles. The POC-HA nanocomposite displays much higher compression strength with reduced degradation time and better osseointegration compared to the microcomposite.[119–120] This nanocomposite has also been used to create a tri-component graft for anterior cruciate ligament (ACL) reconstruction.[121] To further support graft fixation and tissue integration, a porous POC-HA scaffold was created using a salt-leaching method that improved cell migration and tissue infiltration leading to increased osteointegration and new bone formation.[122]

Bone cements used in orthopedic surgeries have suboptimal properties, including lack of resorption to facilitate new bone formation, systemic toxicity due to nonreacted monomers, significant heat generation, mechanical mismatch with bone, and complicated handling due to constraints in polymer curing times upon mixing of the reactants. To address these problems, Huddleston et al. developed in injectable CBB that solidifies upon exposure to physiological body temperature.[123] Methacrylated POC (mPOC) combined with HA and the thermal initiator V70 creates a body heat-activated injectable bone cement suitable for minimally invasive bone fracture repair procedures. Incorporating HA into mPOC, up to percentages comparable to that found in bone, enables control of mechanical properties and biological responses without significant heat generation during the in situ polymerization.[123] This injectable polymer-ceramic composite could potentially serve as a biocompatible alternative to conventional PMMA-based bone cements, such as Kyphon Actiovs 10.[123]

Citrate, a degradation product of CBBs, can fuel hMSCs and facilitate their osteogenic differentiation via a mechanism referred to as "metabonegenic" regulation.[115,124–125] Given that phosphate is also an important energy substrate, phosphoserine (PSer), and glycerophosphate (GP) have also been incorporated as phosphate donors into POC and citrate-based hydrogels, such as poly(poly-ethyleneglycol citrate-*co*-*N*-isopropylacrylamide) (PPCN). The resultant POC-phosphoserine (or POC-PSer)/HA and POC-GP/HA) or PPCN-phos gels have demonstrated enhanced bone regenerative capabilities when compared to POC/HA or PPCN in rodents and rabbits.[125–127]

A thermoresponsive PPCN-gelatin (PPCNg) scaffold has been investigated for craniofacial bone regeneration. PPCNg's cell compatibility was leveraged to encapsulate various cell types, such as immortalized calvarial mesenchymal progenitor cells (iCALs) and immortalized murine adipocyte (iMAD) progenitor cells transduced to overexpress bone morphogenetic protein 9 (BMP-9).[128–129] These PPCNg-cell constructs consistently demonstrated significant osteogenesis and accelerated closure

Table 3. Overview of current studies on development of citrate-based materials for biomedical applications.

Material	Application	Refs
Poly(octamethylene citrate) (POC)	Tissue engineering	[107,131,134,136,137,154,156]
Poly(1,2-propanediol-sebacate-citrate) (PPSC)	Tissue engineering	[172]
POC-citric acid-sebacic acid (p(OCS))	Tissue engineering	[173–174]
Poly(octamethylene maleate citrate) (POMC)	Tissue engineering	[175]
Poly(octamethylene maleate (anhydride) citrate) (POMaC)	Tissue engineering cardiovascular engineering	[142,176–177]
Urethane-doped CBBs (CUPEs)	Tissue engineering	[138]
POC-lentivirus	Tissue engineering	[178]
Poly(1,2-propanediol-*co*-1,8-octanediol-*co*-citrate) (PPOC)	Tissue engineering	[179]
Poly(diol 4-ketopimelateco-diol citrate)	Tissue engineering	[180]
Poly (silicone-citrate) (PSC)	Tissue engineering	[181–182]
POC-polyhedral oligomeric silsesquioxances (POSS)	Tissue engineering	[183]
POC-*co*-Pluronic F127 (POFC)	Tissue engineering	[184–186]
POC-PLLA	Tissue engineering	[187–188]
Poly(octamethylene-*co*-*L*-cysteine citrate)-*co*-polylactide BPLP-PLLA	Tissue engineering	[189]
Poly(caprolactone-diol-citrate) (PCC)	Tissue engineering	[190]
Poly(polyethylene glycol citrate-*co*-*N*-isopropylacrylamide) (PPCN)	Tissue engineering	[145,191]
POC-HA	Bone regeneration	[119,17]
POC-TCP	Bone regeneration	[192]
POC-glycerophosphate calcium (GP-Ca)	Bone regeneration	[126]
POC-beta calcium silicate	Bone regeneration	[193]
Silica grafted POC	Bone regeneration	[194]
POC-gallium	Bone regeneration	[195]
POC-Click-HA	Bone regeneration	[196–197]
POC-M-click-HA	Bone regeneration	[117]
POC-HA-tannic acid-silver nanoparticles	Bone regeneration	[118]
Poly(ethylene glycol) maleate citrate (PEGMC)/HA	Bone regeneration	[198]
PPCN-BMP9	Bone regeneration	[130,199]
PPCN-gelatin-BMP9	Bone regeneration	[128]
PPCN-SR/P/c-RGD	Bone regeneration	[127]
BPLP-HA	Bone regeneration	[200]
Methacrylated POC (mPOC)/HA	Bone regeneration	[123,201]
Poly(1,8-octamethylene-citrate-co-octanol) (POCO)	Cardiovascular engineering	[143]
POC-heparan sulfate	Cardiovascular engineering	[202]
POC-collagen	Cardiovascular engineering	[203]
All-trans retinoic acid (atRA)-POC	Cardiovascular engineering	[204]
Methacrylated poly(1,12 dodecamethylene citrate) (mPDC)	Cardiovascular engineering	[139–141,205]
POC-poly(acrylic acid)	Wound healing	[146]
Poly(L-lactic acid)-poly(citrate siloxane)-curcumin polydopamine (PPCP)	Wound healing	[206]
Poly(citrate-glycolsiloxane) (PCGS)	Wound healing	[207]
PPCN-SDF-1	Wound healing	[152]
PPCN-A5G81	Wound healing	[151]
PPCN-HKUST-1	Wound healing	[153]
Panthenol citrate (PC) and poly (panthenol citrate polyethylene glycol citrate *co*-*N*-isopropylacrylamide) (PC-PPCN)	Wound healing	[208]
Citrate-based mussel-inspired bioadhesives (iCMBAs)	Wound healing	[148–149,209–211]

(*Continued*)

Table 3. (Continued).

Material	Application	Refs
Sildenafil citrate-loaded polyvinyl alcohol PEG (SC-PVA-PEG)	Orally dissolving films	[212]
BPLP-PLGA	Bioimaging	[213]
Poly (citric acid-octanediol-polyethylene glycol) (PCE)-graphene (PCEG) nanocomposites	Muscle regeneration	[133]
POC-PEG-PEI	Muscle regeneration	[214]
Folic acid-coated CUPEs (fCUPEs)	Nerve regeneration	[157]
F127-polycitrate-polyethyleneimine	Nerve regeneration	[158]

of critical-sized calvarial defects in murine models. Addition of graphene oxide to PPCNg resulted in an injectable composite scaffold (GO-P) that retained its thermoresponsive properties while promoting the proliferation and differentiation of mesenchymal stem cells (MSCs). Studies performed in rodents described the formation of well-mineralized and vascularized trabecular bone, especially when BMP-9-transduced MSCs were incorporated into the GO-P scaffolds. These findings collectively highlight the multifaceted potential of PPCNg as a scaffold for bone regenerative engineering and medicine applications.[130]

Porous POC scaffolds have been investigated for cartilage regenerative engineering.[131–132] POC scaffolds promoted chondrocytes adhesion, proliferation, and differentiation with increased glycosaminoglycan (GAG) and collagen type II content, supporting their use for cartilage regeneration.[131] When compared to PCL and poly(glycerol sebacate) (PGS) scaffolds, POC scaffolds exhibit superior performance in terms of supporting chondrocyte growth and cartilaginous tissue development.[132] A conductive, biodegradable, and elastic poly (citric acid-octanediol-polyethylene glycol)(PCE)-graphene (PCEG) nanocomposite was developed with the aim of regenerating skeletal muscle tissue. This PCEG nanocomposite improved myoblast attachment, proliferation, and myogenic differentiation, facilitating muscle fiber, and blood vessel formation in a skeletal muscle lesion model. These results support the potential use of these biomaterials for enhancing skeletal muscle tissue repair.[133]

1.2.2. Cardiovascular Regenerative Engineering

The surface energy of CBBs supports desirable protein adsorption and cell attachment. Their compatibility with human aortic smooth muscle cells (HASMC) and human aortic endothelial cells (HAEC) led to the evaluation of POC for cardiovascular tissue engineering.[107] POC was coated onto ePTFE vascular grafts to increase their surface energy. The resulting POC interface demonstrated reduced thrombogenicity and macrophage infiltration and enhanced endothelialization, expanding its use to small-diameter blood vessels.[134–135] The immobilization of heparin onto POC-coated ePTFE or POC-ECM composites further demonstrated the potential to reduce thrombosis and promote re-endothelialization.[136–137] Due to its high elasticity, POC thin-walled tubes can withstand burst pressure of 1300 mmHg, which is comparable to that of native human saphenous veins (1680 ± 307 mmHg). The introduction of a strong hydrogen bonding forming group, urethane bond, to POC further increase its elasticity, burst pressure, and suture retention.[138] Furthermore, a methacrylated poly(1,12-dodecamethylene citrate) (mPDC) was developed for 3D-printing bioresorbable vascular stents with thinner struts than those of the PLLA-based bioresorbable polymer stent Absorb (Abbott).[139–141] Poly(octamethylene maleate (anhydride) citrate)) (POMaC) was utilized for tissue delivery via injection. Cardiomyocyte-seeded POMaC patches significantly improved cardiac function following myocardial infarction in a rat. In a porcine model, authors achieved successful minimally invasive delivery of human cell-derived patches to the epicardium, aorta, and liver.[142] Cardiac patches based on conductive polymers offer attractive features that may prevent abnormal remodeling of heart tissue after a myocardial infarction. However, limited elasticity and high impedance interfaces hinder their mechanical and electrical performance. The biodegradable elastomer poly(1,8-octamethylene-citrate-co-octanol) (POCO) was integrated with the bioresorbable metal, molybdenum, to develop a bioresorbable, highly conductive, elastic cardiac patch (BCEP).[143] The BCEP's hybrid material structure was configured in a thin serpentine geometry that yielded elastic mechanical properties that could withstand physiologically relevant cardiac tissue contractions. Ex vivo studies demonstrated cardiac cell compatibility and the detection of electrocardiogram (ECG) signals and electroconductive pathways. The antioxidant, antimicrobial, and proangiogenic properties of CBBs can prevent chronic inflammation and implant-associated infection, properties that are desirable for cardiovascular engineering.[144–145]

1.2.3. Skin Regenerative Engineering

The need for better materials and products to promote wound healing and the mechanical, chemical, and biological properties of CBBs have motivated research efforts on the application of CBBs to skin regeneration. Electrospun POC and poly (acrylic acid) (PAA) nanofibers that mimic the dermis structure can promote fibroblasts attachment, spreading, and the formation of cellular sheets. POC/PAA scaffolds with sustained release of platelet derived growth factor (PDGF-$\beta\beta$) also promote fibroblasts migration and proliferation.[146] By copolymerizing POC with poly(lysine) and subsequently electrospinning with PCL, an elastomeric, photoluminescent, and antibacterial hybrid polypeptide-based nanofibrous matrix was created, which inhibits multidrug-resistant (MDR) bacteria and enhances wound healing.[147] An injectable and antimicrobial citrate-based

mussel-inspired bioadhesive (iCMBA) with strong wet strength, was developed for sutureless wound closure.[148] The addition of a second network by introducing clickable crosslinkers or magnesium oxide (MgO) to form coordinate bonds with iCMBA enhance wet adhesion strength without compromising its antibacterial and antifungal capabilities.[149–150] Copolymerization between CBBs and *N*-isopropylacrylamide (NIPAAm) creates a thermoresponsive hydrogel, PPCN, with intrinsic antioxidant properties that are useful for treating diabetic wounds, which typically have a high oxidative stress microenvironment.[145] Various formulations of PPCN have been reported for biomedical applications including: 1) PPCN with a covalently conjugated laminin-derived peptide (A5G81), 2) PPCN with entrapped stromal cell derived factor-1 alpha (SDF-1) that is slowly released, and 3) PPCN with entrapped copper metal organic framework HKUST-1 for sustained copper ion release.[151–153] The incorporation of A5G81 into PPCN hydrogel enhances integrin-mediated spreading, migration, and proliferation of dermal and epidermal cells. This synergistic effect promotes accelerated tissue regeneration in diabetic wounds, leading to faster healing and improved outcomes.[151] The sustained release of SDF-1 from PPCN promotes dermal tissue regeneration, accompanied by an increase in blood vessel perfusion. The use of this combined chemokine-antioxidant dressing is a novel approach for the treatment of chronic wounds, potentially addressing this challenging clinical condition.[152] The PPCN-HKUST-1 composite system enabled the sustained release of copper II ions while providing an antioxidant microenvironment for cells due to the PPCN. This hydrogel-particle composite was the first study to use a metal organic framework (MOF) in a biomedical application. The PPCN-HKUST-1 combination reduced the cytotoxicity of copper ions and promoted key processes such as cell migration, angiogenesis, and collagen deposition, leading to accelerated wound healing in diabetic mice. The use of metal organic frameworks in combination with a hydrogel offers a promising approach for efficient local delivery of target ions and holds potential as an innovative dressing for the treatment of diabetic wounds.[153]

1.2.4. Bladder Regenerative Engineering

Due to its cell compatibility, elasticity, and degradation properties, POC has been utilized for partial bladder regeneration.[154] Human mesenchymal stromal cells (hMSC) and $CD34^+$ hematopoietic progenitor cells were seeded onto a POC nonporous scaffold (referred to as the film) to create a native smooth muscle milieu for partial bladder regeneration. POC films serve as a strong, watertight, and flexible substrate that support the growth and proliferation of MSCs. The mechanical characteristics of the POC films can be engineered to mimic native bladder elasticity, enabling the MSCs to undergo repeated contraction and expansion cycles. Regenerated tissue treated with MSC and urothelial cells (MSC/UC) seeded on POC films exhibit more muscle bundles and higher expression of bladder smooth muscle contractile proteins relative to MSC/UC and POC films alone.[154] In contrast to intestinal tissue, POC films offer several advantages for bladder regeneration by eliminating inherent composition variability and mitigating inflammatory responses.[155] However, future research is necessary to achieve faster angiogenesis and innervation for complete tissue function restoration. The combination of $CD34^+$ hematopoietic stem/progenitor cells (HSPCs) with MSCs seeded on POC films results in enhanced urothelium growth, blood vessel formation, and ingrowth of peripheral nerve in the regenerated bladder tissue.[156]

1.2.5. Nerve Regenerative Engineering

A folic acid-coated urethane-doped POC (fCUPE) tube was developed to demonstrate its effect on stimulating the release of growth factors important for Schwann cell migration and peripheral nerve regeneration.[157] The objective was to influence global DNA methylation levels that are associated with neurogenesis and neural stem cell differentiation, facilitating neurite formation and neuronal polarization through chemical-to-mechanical force transduction. Incorporating folic acid into cross-linked urethane-doped polyester nerve guidance conduits (NGCs) resulted in promising peripheral nerve regeneration and functional recovery that is comparable to that achieved with autografts. These findings support the potential of folic acid-releasing scaffolds as a cell niche for enhancing the repair of peripheral nerve injuries. Further research on the roles of folic acid in glial cells, adult neurons, and nerve regeneration can contribute to the development of strategies and biomaterials for treating various neurological disorders in both the peripheral and central nervous systems.[157]

A thermoresponsive hydrogel, composed of polycitrate-polyethylene glycol-polyethyleneimine (PCE) and F127 (FE@EVs), was developed for the delivery of extracellular vehicles (EVs) to enhance spinal cord repair after spinal cord injury (SCI).[158] The sustained release of EVs from the hydrogel played a crucial role in mitigating the microenvironmental factors associated with SCI, including the suppression of reactive fibrotic scar formation, reduction of inflammatory reactions, promotion of remyelination, and facilitation of axonal regeneration. Consequently, the FE@EVs hydrogel demonstrated significant improvements in tissue repair and motor functional restoration in the injured spinal cord. These findings highlight the potential of the FE@EVs hydrogel as a biocompatible and efficient EV delivery system for the treatment of SCI patients.

1.2.6. From Bench to Market

The 510(k) regulatory path has led to Citregen's successful utilization in the fabrication of bioresorbable tissue fixation devices. These devices include the Citrelock Tendon Fixation Device System (K200725),[18] Citrefix Suture Anchor System (K203334),[19] Citrespline and Citrelock ACL Reconstruction System (K210239),[20] and Citrelock Duo Fixation Device (K232592).[21] (Figure 3). The first two products are marketed worldwide by Stryker Corporation. The use of Citregen in these FDA-cleared devices highlights its potential for clinical translation in the field of regenerative engineering and medicine. By offering innovative solutions for tissue fixation and promoting the natural healing and regeneration process at the bone-soft tissue interface, Citregen contributes to advancing patient care and improving outcomes in musculoskeletal surgeries. This successful

translation of Citregen into FDA-cleared products that are on the market is a springboard to future applications and advances in regenerative medicine.

Identifying and defining biomaterial technology differentiation factor(s) is key to embarking on a path to partnerships for successful commercialization. In the case of CBBs, the versatility for chemical functionalization contributes to their controllable mechanical, biodegradation, and bioactivity properties, making CBBs highly attractive for engineering next-generation biomaterials for regenerative medicine. By incorporating functional groups or bioactive molecules, CBBs can be tailored to exhibit desirable characteristics such as enhanced biocompatibility, efficient, and controllable cargo loading and release kinetics, or specific cell-targeting capabilities. In addition to their chemical versatility, the mechanical properties of CBBs can be easily engineered to meet the requirements of several tissues and organs. The ability to mimic the mechanical properties of native tissues allows CBBs to create a conducive microenvironment for cell growth, migration, and differentiation, facilitating the regeneration of functional and structurally sound tissues. Furthermore, the biodegradable nature of CBBs ensures that they can be gradually metabolized and eliminated from the body over time (Figure 3). As CBBs degrade, they release degradation products that interact with the surrounding tissue, influencing cellular behavior and promoting tissue regeneration. Moreover, the degradation products of CBBs often possess bioactive properties, such as antioxidant, antimicrobial, metabonegenic, and proangiogenic capabilities that further contribute to their proregenerative potential. Continued research and exploration of CBB properties and capabilities will enable the development of innovative medical devices that can significantly advance the field and improve patient outcomes.

2. Challenges and Outlook

Synthetic biodegradable polymers such as PGA, PLA, and PCL have been widely used for decades in FDA-approved or -cleared medical devices ranging from solid implantable devices to injectable devices for drug release. Regulatory agencies in most developed nations have affirmed their safety, nontoxicity, and biocompatibility for many applications. However, despite their longstanding and proven track record, these polymers often exhibit mechanical, biological and physical properties that do not seamlessly align with the characteristics of the tissues they are intended to treat. Although these polymers were used for many feasibility and proof-of-concept experiments that launched the tissue engineering field, we recognized that these polymers have significant shortcomings that slow the development of regenerative medical devices. Therefore, the need to pursue innovative biomaterial technology remains. In this context, citrate-based biomaterials emerge as a highly promising and innovative option. These biomaterials present a host of distinctive and appealing advantages when compared to commonly used biodegradable polymers. The successful incorporation of Citregen in FDA-cleared medical devices has inspired innovation in the development of next-generation biomaterials and medical devices in the trauma and extremities sector, propelling the transition from inert to proregenerative biomaterials and devices. The global marketing of Citregen products by Stryker, coupled with the recognition of the underlying biomaterial technology by prominent market research firms, solidifies Citregen's role as a dominant driver in the musculoskeletal surgery sector. This recognition also highlights how a biomaterial technology can fuel a company's growth and leading role in the medical device technology industry.[159]

While citrate-based polymers have shown significant promise in meeting the requirements of various biomedical applications, there are challenges and limitations that biomaterials researchers need to address. It is important to understand and achieve control over the degradation behavior of the biomaterial to ensure its chemical, biological, and mechanical properties meet the specifications for the intended application. Comprehensive studies are needed to elucidate the interplay between degradation products and the surrounding tissue, including their effects on cellular processes, with the aim of promoting tissue regeneration. It is well known that cell metabolism plays a pivotal role in the differentiation of stem cells into specialized functional cells, orchestrating processes, such as cell proliferation, differentiation, and physiological responses. In addition to the recently discovered metabonegenic regulation of exogeneous citrate for stem cell differentiation into osteoblasts, the effects of citrate and other energy substrate molecules incorporated into biomaterials on the differentiation of stem cells into other cell lineages, tissue innervation, immune cell polarization, and vascularization are yet to be elucidated. Therefore, understanding these aspects of cell biology will be instrumental for the design and optimization of the next generation of regenerative biomaterials. More research is needed on manufacturing techniques such as 3D printing and injection molding to improve production scale up and facilitate the translation of biomaterial technologies. By addressing these challenges, researchers will help redefine the role of implantable medical devices for regenerative medicine applications.

Conflict of Interest

G.A.A. and J.Y. are coinventors on patents for citrate-based biomaterials. J.Y. and the Pennsylvania State University have a financial interest in Acuitive Technologies, LLC and Aleo BME. These interests have been reviewed by the University's Institutional and Individual Conflict of Interest Committees and are currently being managed by the University. Some of these patents have been licensed to companies where Dr. Ameer and Northwestern University have financial interests. These interests have been reviewed and are currently managed by Northwestern University.

Keywords

biomaterials, medical devices, regenerative engineering, regenerative medicine, synthetic biodegradable polymers

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