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Biodegradable polyphosphazenes for regenerative engineering

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Regenerative engineering is a field that seeks to regenerate complex tissues and biological systems, rather than simply restore and repair individual tissues or organs. Since the first introduction of regenerative engineering in 2012, numerous research has been devoted to the development of this field. Biodegradable polymers such as polyphosphazenes in particular have drawn significant interest as regenerative engineering materials for their synthetic flexibility in designing into materials with a wide range of mechanical properties, degradation rates, and chemical functionality. These polyphosphazenes can go through complete hydrolytic degradation and provide harmlessly and pH neutral buffering degradation products such as phosphates and ammonia, which is crucial for reducing inflammation in vivo. Here, we discuss the current accomplishments of polyphosphazene, different methods for synthesizing them, and their applications in tissue regeneration such as bones, nerves, and elastic tissues.

Introduction

The term "regenerative engineering" was first introduced by Laurencin and Khan in 2012. For the first time, regenerative engineering converged the technology advancements in advanced material science, stem cell science, and areas of development biology toward the regeneration of complex tissues [1]. Since the inception of regenerative engineering, many resources have been devoted to advancing the field [2–30].

Building on the idea of tissue engineering introduced by Y.C. Fung in 1987, which focuses primarily on the restoration and repair of individual tissues and organs, regenerative engineering seeks the regeneration of complex tissues and biological systems [22]. Traditional tissue engineering approaches have used biomaterials from a limited pool of biodegradable and non-biodegradable polymers and ceramics for tissue repair. Through years of technological advancements, biomaterials have expanded to include polymers that can be designed with a range of mechanical properties, degradation rates, and chemical functionality. Polyphosphazenes are a great example of the concept of regenerative engineering.

Polyphosphazene synthesis dated back to a report published by Stockes in 1987 [31]. It was the first inorganic backbone polymer developed on a broad scale since the discovery of silicon in 1940s. However, the polyphosphazene synthesized by Stockes exhibited poor environmental stability and progressive degradation into phosphate, ammonia, and hydrogen chloride [32]. Hence, the versatility of polyphosphazenes was not fully appreciated until the first successful linear polyphosphazenes reported by Allcock and coworkers in 1965 [33, 34]. Since then, hundreds of different polyphosphazenes have been reported [33, 35]. The architecture of polyphosphazenes can be broadly categorized into two types: poly(organo)phosphazenes, and cyclo-polyphosphazenes.

Poly(organo)phosphazene, also often referred to just as polyphosphazenes unless specified, is a linear polyphosphazene with alternating phosphorus and nitrogen backbones with two

organic side groups attached to each phosphorus atom. This type of polyphosphazene is the one that Allcock and coworkers reported in 1965. The design flexibility of polyphosphazenes allow for the substitution of hundreds of different organic side groups which makes the polymer applicable to different areas such as regenerative engineering, drug delivery, vaccine delivery, energy storage, and filtration [36–40].

More recently, cyclo-polyphosphazenes have drawn significant research interest. Cyclo-polyphosphazenes are made directly from reacting hexachlorophosphazene (HCCP) with multifunctional nucleophiles without opening the ring structure of the HCCP. The architecture of cyclo-polyphosphazenes primarily lends itself to drug delivery and energy storage applications [41, 42]. For the scope of this review paper, we will focus more on the linear polyphosphazenes as this type of polyphosphazene can degrade completely into non-toxic byproducts and have more synthesis flexibility to tailor different kinds of tissue regeneration such as bone, nerve, ligament, meniscus, and tendon regeneration.

Synthesis of polyphosphazene

For the synthesis of linear polyphosphazene, the methods can be summarized into two categories: one by obtaining poly(dichloro) phosphazene (PDCP), followed by macromolecular substitution of PDCP with different nucleophiles, whereas the other one is by directly synthesizing polyphosphazenes via condensation reactions. While the most widely used route to polyphosphazene is by macromolecule substitution of poly(dichloro)phosphazene (PDCP), the direct synthesis method to polyphosphazenes provide access to synthesize polyphosphazenes that are difficult to obtain by macromolecular substitution of PDCP, such as alkyl/acryl-substituted polyphosphazenes [43].

Synthesis of poly(dichloro)phosphazene (PDCP) precursor

Thermal ring-opening method

The first synthesis of poly(dichloro)phosphazene (PDCP) was prepared by Stockes in 1897 [31]. Due to its inability to dissolve in solvent and instability in the atmosphere, no practical use was found for this polymer [32]. The first practical use of PDCP was not discovered until 1965. The first linear soluble PDCP was synthesized by Allcock and Kugel by heating hexachlorophosphazene (HCCP) at 250 °C under vacuum [33, 34]. The proposed mechanism of the thermal ring-opening polymerization is illustrated in Fig. 1. The reaction is a cationic chain-growth polymerization [35, 44]. The polymerization is initiated at 250 °C and terminated before cross-linking occurs. The resulting PDCP is a linear polymer that has good solubility in various solvents such as tetrahydrofuran (THF), benzene, and toluene [32, 33, 45]. However, this method for producing PDCP is difficult to control and generally has a low yield between 40 and 60% [45]. Hence, significant research has been done to lower the polymerization temperature, which translates to more controlled polymerization and improved yield.

The temperature for ring-opening polymerization of HCCP can be lowered by the addition of catalysts. This catalyst

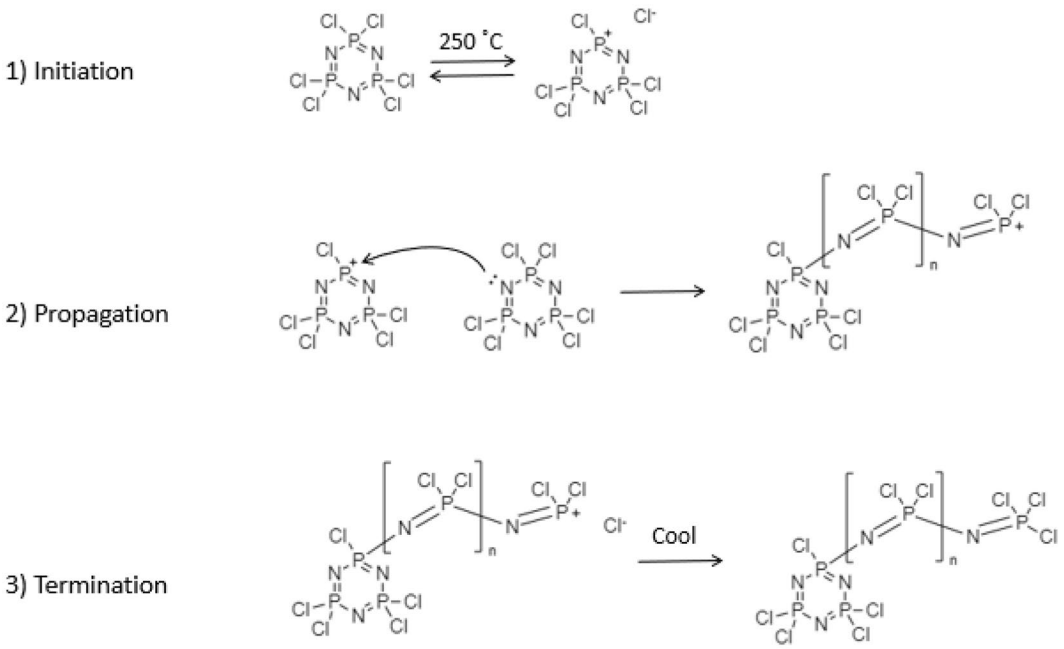

Figure 1: Mechanism of thermally induced ring-opening polymerization of hexachlorophosphazene (HCCP).

can be a small amount of Lewis acids, such as $AlCl_3$ or BCl_3. For instance, using boron trichloride (BCl_3) as the catalyst and 1,2,4-trichlorobenzene (TCB) as the solvent, the reaction temperature can be lowered to 150 °C and give soluble PDCP with over 80% yield [44]. Youn S.H. et al. reported that when using over 2.0 wt% of $AlCl_3$ as the catalyst, the polymerization temperature is lowered to 240 °C, and linear PDCP can be obtained with over 90% yield. However, it is worth noting that PDCP synthesized using $AlCl_3$ as catalyst was reported to have a lower molecular weight around 10^4 Da as compared to a molecular weight of 10^5 Da when synthesized without the catalyst and polymerized at 250 °C [46]. Reported by Magill and coworkers, using $HSO_3(NH_2)$ as the catalyst, TCB as the solvent, and with the presence of $CaSO_4{\cdot}2H_2O$ as a promoter, the polymerization temperature can be lowered to 214 °C [47, 48]. Successful ring-opening polymerization of HCCP to PDCP has also been reported to be done at ambient temperatures using silylium ions ($SiEt_3^+$) as the catalyst, and 1,2-dichlorobenzene was used as the solvent. A complete conversation of HCCP to PDCP was observed [34, 43].

Condensation polymerization method

Two different methods of PDCP synthesis via condensation have been reported. One of the methods is the non-living thermal condensation polymerization method developed by de Jeager and coworkers. In this method, PDCP can be synthesized from P-trichloro-*N*-(dichlorophosphoryl) monophosphazene ($Cl_3P{=}N{-}P(O)Cl_2$) by losing $P(O)Cl_3$ at a high temperature around 230 °C, shown in Fig. 2(2). Resulting polyphosphazenes have a broad PDI [31].

The other method is the living cationic condensation method developed by Allcock and Manners. In this method, the PDCP produced has a narrower PDI than the uncatalyzed thermal ring-opening method [32]. During the reaction, $Cl_3P{=}NSi(CH_3)_3$ can be catalyzed at room temperature using a small amount of Lewis acids such as PCl_5, shown in Fig. 2(2). The resulting molecular weight of the PDCP can be precisely controlled by the ratio of initiator and monomers. Since this reaction is a living polymerization, another different polymer can be coupled to the end of the PDCP [49, 50].

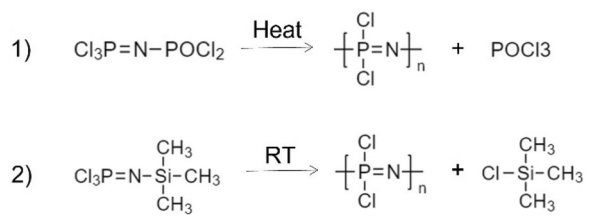

Figure 2: Condensation polymerization method for synthesizing PDCP. (1) Thermal condensation method; (2) Living cationic condensation method.

Synthesis of linear polyphosphazene via macromolecule substitution of PDCP

The PDCP, obtained either by ring-opening polymerization method or condensation reaction method, is extremely sensitive to moisture and must be carefully stored under anhydrous conditions before the macromolecular substitution [43]. Due to the high reactivity of the P–Cl bond, poly(organo)phosphazene can be obtained by macromolecular substitution of PDCP using nucleophiles such as primary amines, alkoxides, and aryloxides, shown in Fig. 3. Poly(alkyl/acryl) polyphosphazenes can be achieved by macromolecular substitution of PDCP using organic nucleophiles such as RMgX or RLi. However, such reactions are often difficult and are preferably synthesized using the direct synthesis method described below [51]. Over 300 different nucleophilic substitutions of PDCP have been reported, and these nucleophiles can be used either alone or in combination to give hundreds of different linear polyphosphazenes with the properties of the polymer tailored toward specific applications [32, 52, 53].

Like all the other nucleophilic reactions, some substitution of PDCP cannot achieve 100% due to the bulkiness of the nucleophiles or strongly electron-donating groups in the reagent [32]. However, the remaining unreacted P-Cl bond can be substituted using less hindered reagents. It is important to note that ensuring a complete replacement of Cl atoms is critical, as unreacted P-Cl can quickly react with moisture in the air to form P-OH bonds, and uncontrolled cross-linking and degradation can occur, which compromise the property of the designed polyphosphazene [43].

Direct synthesis of polyphosphazenes via condensation reaction method

There have also been reports that polyphosphazenes can be prepared without the need for PDCP. Initially developed by Wisian-Neilson and Neilson, alkyl/acryl-substituted polyphosphazene can be made directly by thermal polycondensation of

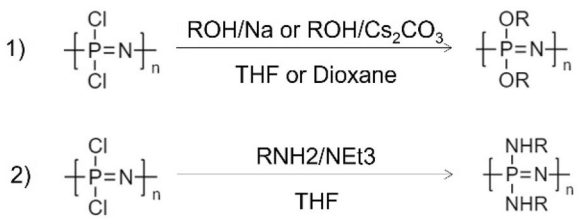

Figure 3: Macromolecular substitution of PDCP.

$(CH_3)_3SiN=P(R_2)\text{-}OR_1$, shown in Fig. 4(1) [51]. Since then, this method has been expanded to the cationic initiator and with $BrR_1R_2P=NSi(CH_3)_3$ or $ClR_1R_2P=NSi(CH_3)_3$, and the reaction can be carried out at room temperature, shown in Fig. 4(2) [54, 55]. This method is a more feasible way to synthesize alkyl/acryl-substituted polyphosphazenes, as they are quite difficult to obtain by macromolecular substitution of PDCP [43].

Polyphosphazenes can also be prepared directly by anionic polymerization of N-silylphosphoranimines in the presence of N-methylimidazole and fluoride ion as initiator, shown in Fig. 4(3). However, this reaction is not a true living anionic polymerization and has a polydispersity between 1.3 and 2.3 when synthesized at 125 °C [56]. Another similar research reported by Steinke and coworkers showed that using water instead of fluoride ion as the initiator, the polymerization exhibit living polymerization kinetic, and the resulting polymer has a much lower polydispersity (< 1.15).

Synthesis of cyclomatrix polyphosphazenes by polycondensation method

Cyclo-polyphosphazenes, also called cyclomatrix polyphosphazenes are made by rapid one-step precipitation polycondensation of HCCP and multifunctional nucleophiles, shown in Fig. 5. Unlike synthesis of linear polyphosphazenes that required anhydride reaction conditions due to the high moisture sensitivity of the PDCP, the reaction for synthesizing cyclo-polyphosphazenes can proceed at ambient conditions. Due to the high density of the P-Cl reaction site at each HCCP molecule, the resulting cyclo-polyphosphazenes can be highly dense determiners [41]. Based on the substitution groups and the reaction conditions, cyclo-polyphosphazenes can self-assemble into different geometries, such as various sizes of microspheres, hollow spheres, nanotubes, nanofibers, and sheets [57–65]. Some of these geometries have sparked significant interest in biological applications such as drug delivery, as they are capable of encapsulating drugs in the microporous structure of the cyclo-polyphosphazenes and can release the drug in a controlled fashion as the cyclo-phosphazenes slowly go through hydrolysis [66]. Some researchers reported using of the cyclo-polyphosphazenes are made using the drug as the nucleophiles, as well as the drug that is encapsulated in the cyclo-polyphosphazene matrix, which significantly increases the drug load [67].

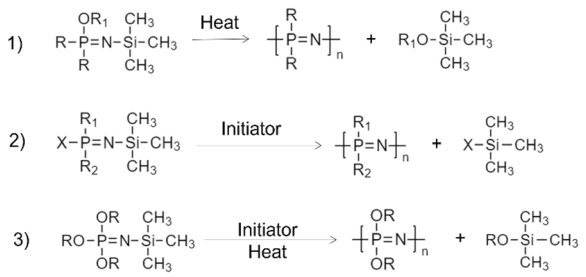

Figure 4: Direct synthesis of polyphosphazenes via condensation reaction method. (X: Br, Cl, or OR').

Applications of polyphosphazenes for regenerative engineering

Polyphosphazenes and polyphosphazenes blends for bone regeneration

Among the development of polyphosphazenes for regenerative engineering, an important application would be in bone regeneration. Annually, more than half a million bone graft surgeries are performed in the US alone and over two million are performed worldwide [68, 69]. Traditional bone graft options such as autografts and allografts pose challenges such as donor site morbidity, pain, inability to harvest large tissue volumes, or risk of disease transmission and possibility of immune rejection.

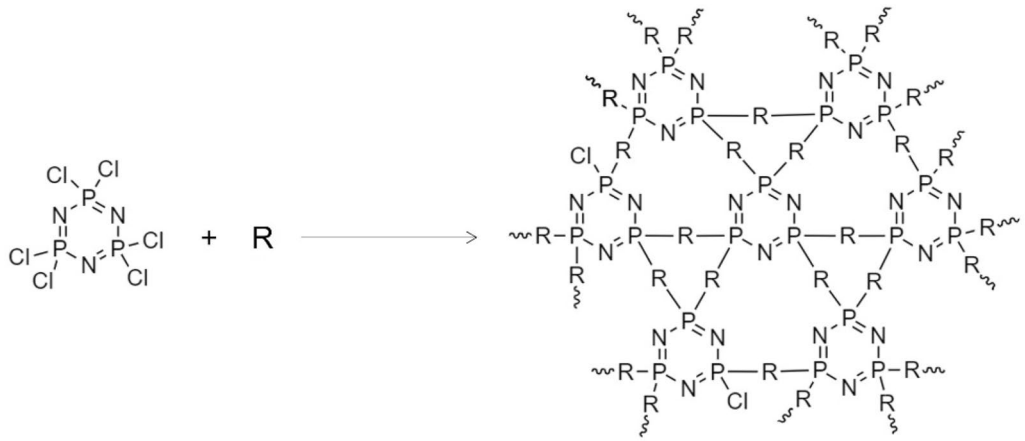

Figure 5: Synthesis of cyclo-polyphosphazenes. (R: multifunctional nucleophiles).

Synthetic bone substitutes have gained significant attraction for their ability in large quantity, lack of antigenicity, and the ability to be customized based on each patient. Among all the biodegradable polymers developed for bone regeneration, polyphosphazenes are especially worth mentioning as it can be easily modified and tailored to the physicochemical properties of the bone regeneration. Extensive studies have shown that polyphosphazenes have great biocompatibility [70–74]. Polyphosphazenes can also go through complete hydrolytic degradation and degrades into ammonia, phosphate, and corresponding side groups. These degradation products provide a natural buffer, which can sufficiently decrease any acute inflammation that could occur in the implant site [39, 53].

Currently, most of the pioneered research of utilizing polyphosphazenes for bone regeneration was done by the collaboration between Laurencin and Allcock's group. Significant efforts have been made to improve the performance of polyphosphazenes as bone regeneration material, shown in Fig. 6. The first generation of biodegradable polyphosphazenes was designed with an imidazole side group. Imidazole side group was chosen for its biocompatibility, ability to confer hydrolytic instability to the backbone, and non-toxic and neutral degradation product [52]. The imidazole-substituted polyphosphazenes showed significant enhancement in alkaline phosphate (ALP) activity as compared to poly (lactic acid-co-glycolic acid) (PLAGA). However, with the increase in the content of imidazolyl side groups, there is a decrease in the MC3T3-E1 cell attachment and growth, suggesting potential toxicity to the cells [75].

The second generation of polyphosphazenes focused on amino acid ester-substituted polyphosphazenes. Like imidazole-substituted polyphosphazenes, amino acid ester-substituted polyphosphazenes are hydrolytically sensitive. However, amino acid ester-substituted polyphosphazenes have better biocompatibility as compared to imidazole-substituted polyphosphazenes [76, 77]. Reported by Laurencin et al., poly (ethyl glycinato) (methylphenoxy)phosphazenes showed an increase in the content of ethyl glycinato group favored increased cell attachment and growth, whereas poly (imidazolyl)(methylphenoxy)phosphazenes showed a decrease in the cell attachment and growth with increasing content of imidazolyl group [78]. Study has also shown that the rate of degradation rate can be controlled by co-substituting the amino acid ester-based polyphosphazenes with a hydrophobic and steric hindrance side group [79].

In 2010, investigated by Weikel et al., amino acid ester-substituted polyphosphazenes and PLAGA blends were studied as a bone regeneration material, as PLAGA is a well-established and commercially available biodegradable polymer

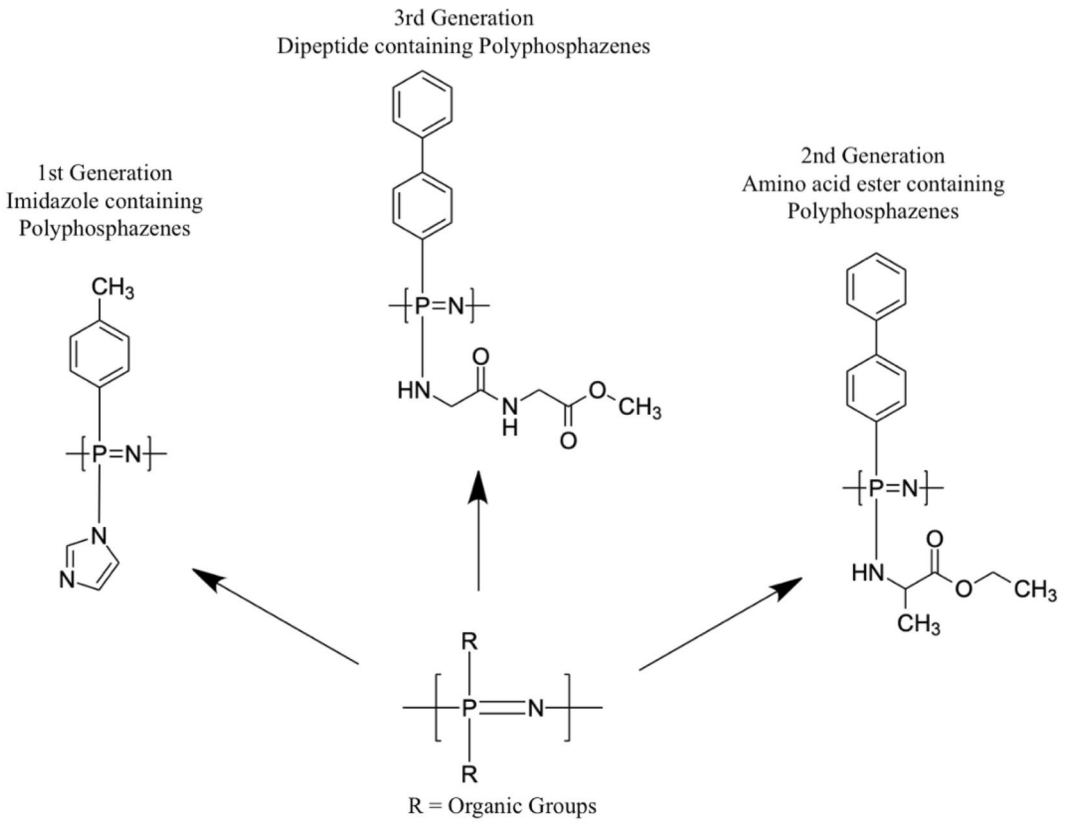

Figure 6: Different generation design of polyphosphazenes for bone regeneration [52]. Reprinted with permission from American Chemical Society.

for bone regeneration [72]. However, PLAGA suffers from drawbacks such as acidic degradation product and bulk erosion mechanism that can lead to inflammatory responses, foreign body reaction, and unexpected structure failure [80]. Polyphosphazene and PLAGA blend materials were hence designed in the hope to address these issues. Numbers of research have shown that the polyphosphazenes effectively neutralized the acidic degradation product of the PLAGA, and the blends significantly improved cell proliferation and ALP activity as compared to PLAGA [72, 81]. However, the ethyl glycinato-substitute polyphosphazenes cannot form a complete miscible blend with PLAGA due to the lack of H-bonding sites, which compromises the mechanical properties of the blends. Hence, the third generation of dipeptide-substituted polyphosphazenes was developed.

By replacing the ethyl glycinato side group with glycylglycine ethyl ester side group, the polyphosphazenes showed significant improvement in the miscibility with PLAGA. A single glass transition temperature was found in the polyphosphazenes and PLAGA blends, and intermolecular H-bonding was observed in FTIR around 1677 cm^{-1} [82, 83].

More interestingly, two unique pore-forming abilities were discovered in these dipeptide-substituted polyphosphazenes and PLAGA blends, shown in Fig. 7 [85]. When the polyphosphazene was co-substituted with glycylglycine ethyl ester and ethyl phenyl alanato, porosity was observed after 4 weeks, and after 7 weeks, interconnected porous structures extended to the whole area. However, when the polyphosphazene was co-substituted with glycylglycine ethyl ester and phenylphenol, the blend materials self-assembled into interconnected microspheres [84].

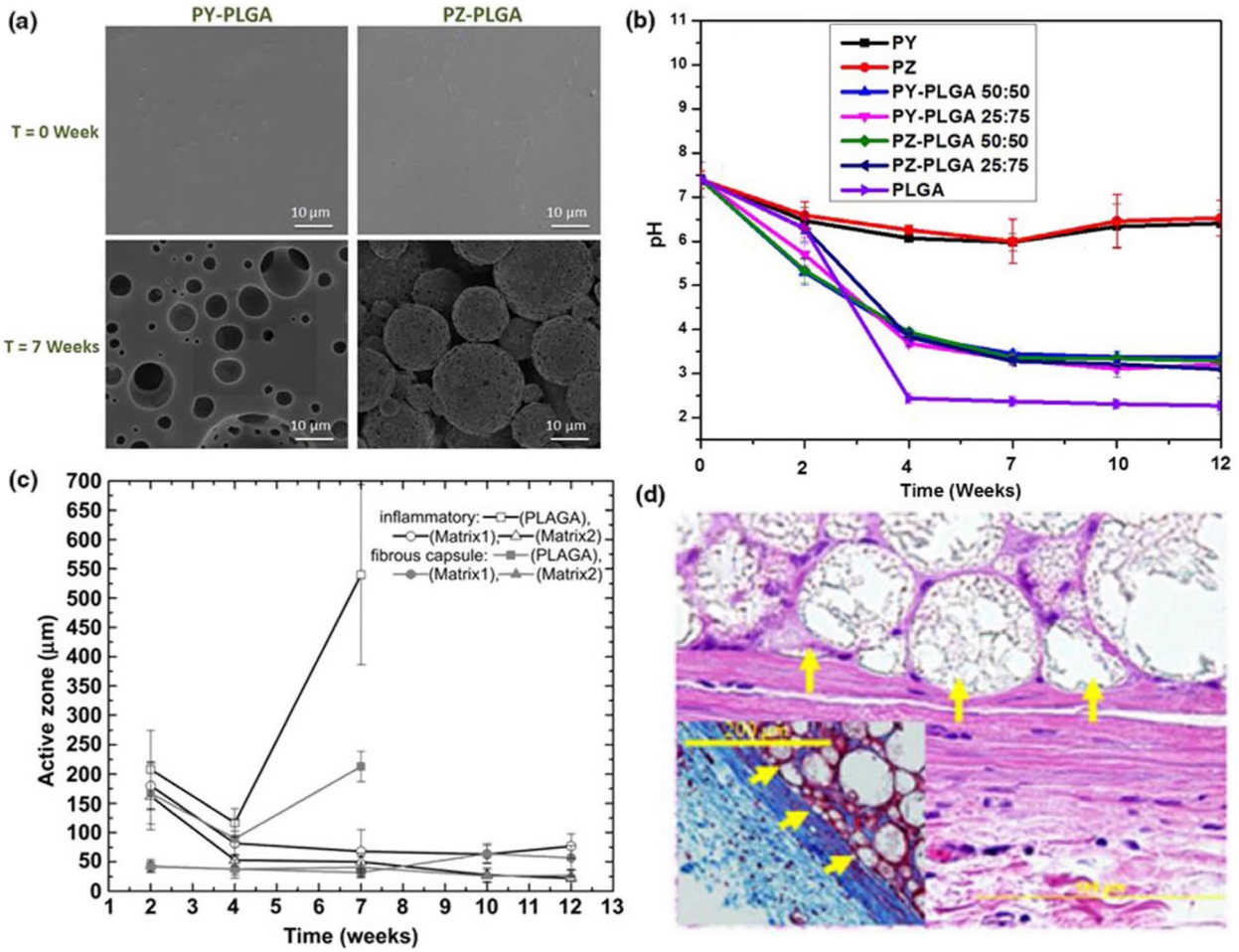

Figure 7: (a) SEM image displaying surface morphology of polyphosphazene-PLGA blends [84]. (b) Hydrolytic degradation study of PY, PZ, PLGA and their respective blends in PBS medium at physiological conditions. PLGA showed a lower pH value than the polyphosphazene polymers as PY and PZ exhibited a near-neutral pH and demonstrated the ability to neutralize the degradation products of PLGA [84]. Reprinted with permission from American Chemical Society. (c) PZ-PLGA 25:75 (matrix1) and PZ-PLGA 50:50 (matrix2) exhibited minimal tissue responses as compared to PLGA. The blends showed less inflammatory responses, and the thickness of the fibrous capsules remained at low level.[82]. Reprint with permission from Elsevier and Rightslink (d) H & E-stained section illustrating the in vivo biocompatibility of the PZ-PLGA. The histological image is also demonstrating the formation of polymer spheres with pore system and collagen tissue infiltration within the pores [85].

The latter type of erosion is quite distinctive, and the mechanism was explained by Deng et al.. As the blend material degrades, intermolecular H-bonding between polyphosphazenes and PLAGA breaks down, and the polyphosphazenes would self-assemble and form intramolecular H-bonding, resulting in rearrangement of polyphosphazenes into spheres. This unique in situ pore-forming ability allowed the infiltration of cells within the pores during the culture and enhances the cell-material interactions without sacrificing the mechanical properties of the blend material in the initial stage. This brings a paradigm shift in the initial sintered microsphere bone scaffold design [86–88].

Recently, the in vivo performance of the dipeptide-based polyphosphazenes and PLAGA blends were evaluated in a rabbit critical-sized bone defect model, shown in Fig. 8 [89]. It was shown that 3D matrices stemming from polyphosphazene–PLGA blends exhibited effective bone ingrowth and minimal inflammatory responses (Fig. 9).

Polyphosphazenes for nerve regeneration

Compared to other types of trauma, nerve injuries are uniquely complicated as mature neurons do not replicate, and peripheral nerve injuries can only be regenerated under certain conditions [90]. In medical practice, nerve injuries are generally repaired by autologous nerve grafting. However, harvesting nerve from the donor suffers from drawbacks such as multiple surgical

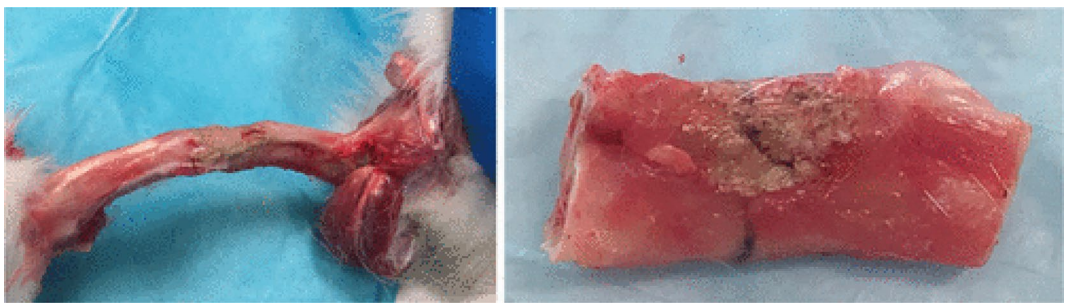

Figure 8: PNGEGPhPh-PLGA implanted bone after 4 weeks. Adapted from Ref. [89]. Reprint permission from American Chemical Society.

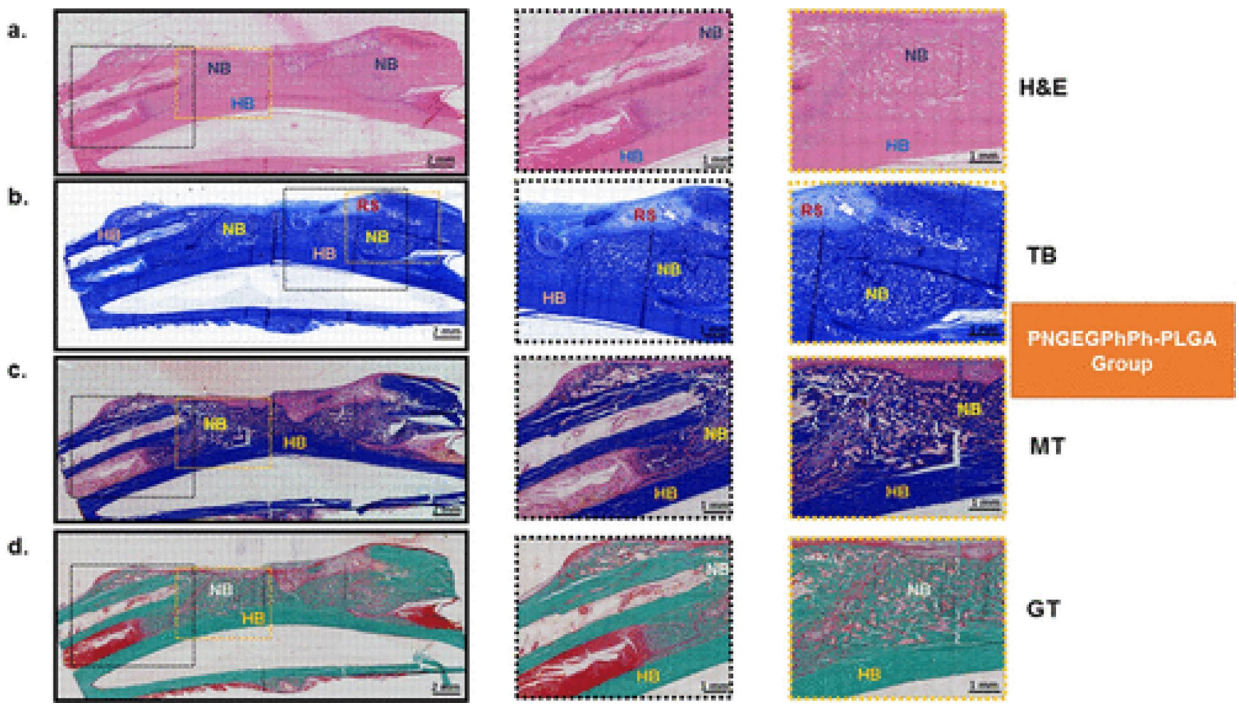

Figure 9: Comparison of (a) H&E, (b) TB, (c) MT, and (d) GT stained images of polyphosphazene–PLGA blend matrices for a 6-week critical-sized defect model. The blend matrices showed more promising translational capability, as they exhibited more rapid bone regeneration than the PLGA scaffolds 6 weeks post-surgery and implantation. NB, new bone; HB, host bone; RS, residual scaffolds. Scale bar = 2 mm (first column) and scale bar = 1 mm (second and third column) [89]. Reprint permission from American Chemical Society.

procedures and loss of function at the donor site [91]. To address these limitations, many researchers investigated biodegradable polymers and non-degradable polymers, and biodegradable polymers have received a great deal of attention for their biocompatibility and degradability. In the early days, some success was observed using polyphosphazene-based materials for the development of nerve guides [92, 93]. Reported by Langone et al., poly[(ethylalanato)$_{1.4}$(imidazolyl)$_{0.6}$ phosphazene] (PEIP) showed promising signs of establishing continuity of a complete lacerated sciatic nerve when tested in vivo.

To further improve the performance of the polymer scaffold for nerve regeneration, some research suggested that utilizing materials that have electrical conductivity would have positive effects on nerve regeneration. However, the majority of the conductive polymers are unable to degrade for in vivo applications, which poses risk for inflammation and surgical removal [94]. Ideally, highlighted that polymer used for neural tissue regeneration must be both conductive, to facilitate electrical synapses, and degradable [95].

Recently, an electrically conductive poly [(glycine ethyl ester) (aniline pentamer) phosphazene] (PGAP) was reported by Zhang et al., where the aniline pentamer (AP) give the polyphosphazene electrical conductivity. The material displayed electrical conductivity around 2×10^{-5} S/m in the semiconducting region when doped with camphorsulfonic acid. This electrically conductive polyphosphazene was compared with poly-DL-lactic acid (PDLLA) and AP in vitro, and no cytotoxicity was observed in vitro to RSC96 Schwann cells, shown in Fig. 10 [95]. The biodegradability of the PGAP was investigated in vitro and compared with the non-conductive version of its parent

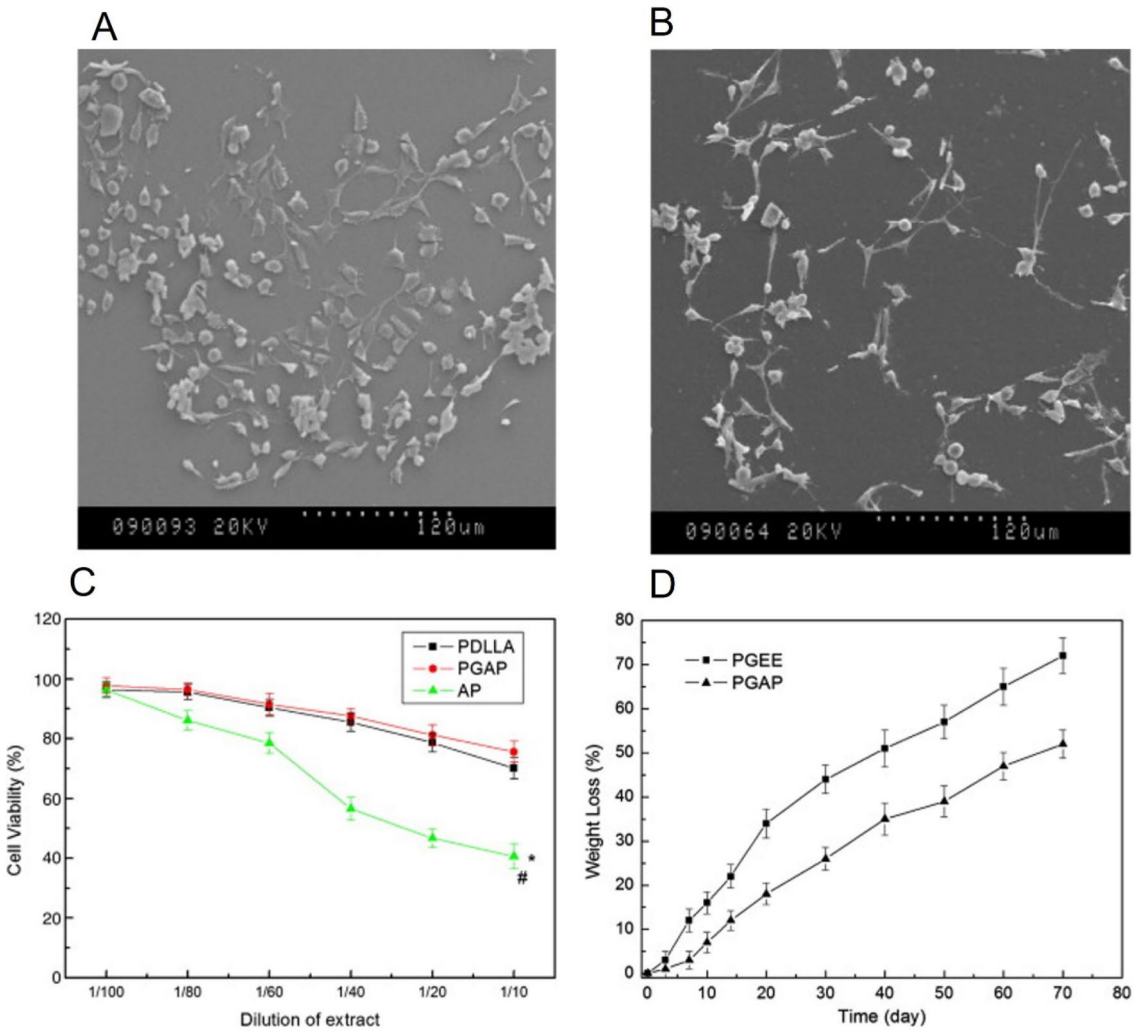

Figure 10: (A) SEM images of RSC96 cells seeded on the PGAP film after 3 days of incubation. (B) SEM images of RSC96 cells seeded on the PDLLA film after 3 days of incubation. (C) The viability of RSC96 cells in vitro (cells were treated with different concentration extracted liquid of PGAP, poly-DL-lactic acid (PDLLA) and aniline pentamer (AP). (D) In vitro degradation study of PGEE compared to PGAP polymer membranes in 0.1 mol/L PBS at 37 °C and pH 7.4 [95]. Reprint permission from Elsevier.

polyphosphazene, poly [bis (glycine ethyl ester) phosphazene] (PGEE). About 50% mass loss was observed for PGAP. This value is smaller than the 70% mass loss observed with PGEE, and this decreased degradation rate is likely due to the hydrophobic side chain of AP sterically hindering the approach of water toward the backbone. Some other new polyphosphazene applications are currently being investigated for nerve repair, and amino acid ester-based polyphosphazenes are candidates [96].

Polyphosphazenes for ligament, meniscus, and tendon regeneration

Mechanically, ligament, meniscus, and tendon tissues are considered elastic tissues [96]. Since elastic tissues are poorly vascularized, oxygen and nutrient concentration are lower in these areas [97]. Like bone tissue repairs, elastic tissue regeneration often calls on autografts and allografts [98]. An ideal tendon or ligament tissue should contain enough initial biomaterial for the immediate bearing of the load onto the implant, as well as a degradation rate that matches the cell and tissue ingrowth [99]. Materials explored include animal-derived elastin, synthetic elastomers, and polymer-protein hybrids [100].

Polyphosphazene structure lends itself to the desired characteristics of elastic tissue implants. The low torsional barriers of polyphosphazene backbones and side groups create the possibility for very low glass transition temperatures down to − 100 °C, which is near its theoretical limit [101]. A slow-degrading, flexible polymer, coupled with crosslinkable side groups, such as polyphosphazenes, has the potential to meet the requirements for ligament and tendon replacement [70]. In 2013, Nichol et al. demonstrated that the glass transition temperature and hydrolytic behavior of the polyphosphazenes can be controlled by changing the alkyl ester chain length of the polyphosphazenes L-alanine and L-phenylalanine alkyl ester-substituted polyphosphazene [102]. They revealed that glass transition (T_g) temperatures of the polyphosphazene decreased as the alkyl ester chain length increased.

More studies surfaced in 2012. To improve the hydrophilicity of the tendon microenvironment-like matrices electro-spanned using polycaprolactone (PCL), Peach et al. surface-functionalized the matrices with poly [(ethyl alanato)$_1$ (*p*-methyl phenoxy)$_1$ phosphazene] (PNEA-mPh) [103, 104]. The study investigated the adhesion, cell-construct infiltration, proliferation, tendon differentiation, and long term cellular construct mechanical properties using human mesenchymal stem cell (hMSC). A study has shown that with the surface modification of the polyphosphazene, enhancement in cell adhesion and superior cell-construct infiltration was observed as compared to the non-modified ones. The surface-modified matrices show a more prominent tenogenic differentiation, have greater tenomodulin expression and superior phenotypic maturity as compared to the non-modified version [104]. These polyphosphazenes coated matrices have also shown positive results when tested in vivo using a rat rotator cuff tear model [103].

More research was suggested later by Nichol et al. in 2014 that polyphosphazene can be a great candidate for ligament or tendon repair [105]. In this research, polyphosphazenes was co-substituted using citronellol and alanine ethyl ester. Citronellol provides anti-inflammatory properties and permits the polyphosphazenes to crosslink, whereas alanine ethyl ester helps tune the hydrolysis rate of the final polymer. It was also discovered that increased steric hindrance at the α-carbon position of the amino acid ester increased both the modulus and tensile strength while allowing control of the hydrolytic degradation rate [106]. No in vitro or in vivo work was conducted in this research, but the tunability of these polyphosphazenes make them excellent candidates for further evaluation as ligament or tendon scaffold.

Outlook

As the field of regenerative engineering expands, the potential for biodegradable polymers increases. Polyphosphazenes pose great advantages over current existing biodegradable polymers as they have great flexibility in the structural design and can be tailored to meet the requirements of the specific application. The success of using polyphosphazenes as the regenerative material has been shown in different tissue regeneration, such as bone, nerve, ligament, meniscus, and tendon regeneration. The term "polyphosphazene" has also expanded from the original linear polyphosphazenes to include densely crosslinked cyclo-polyphosphazenes, in which the latter are just starting to see promising results in drug delivery. This review paper gave an overview of the most recent advancement in polyphosphazene synthesis and applications in different tissue regeneration, in the hope to spark new research around polyphosphazenes.

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Declarations

Conflict of interest On behalf of all authors, the corresponding author states that there is no conflict of interest.

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