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REVIEW

Hybrid polymer biomaterials for bone tissue regeneration

Bo Lei[1], Baolin Guo[1], Kunal J. Rambhia[2], Peter X. Ma (✉)[1,2,3,4,5]

[1]Frontier Institute of Science and Technology, Xi'an Jiaotong University, Xi'an 710054, China; [2]Department of Biomedical Engineering, University of Michigan, Ann Arbor, MI 48109, USA; [3]Department of Biologic and Materials Sciences, University of Michigan, Ann Arbor, MI 48109, USA; [4]Macromolecular Science and Engineering Center, University of Michigan, Ann Arbor, MI 48109, USA; [5]Department of Material Science and Engineering, University of Michigan, Ann Arbor, MI 48109, USA

Abstract **Native tissues possess unparalleled physiochemical and biological functions, which can be attributed to their hybrid polymer composition and intrinsic bioactivity. However, there are also various concerns or limitations over the use of natural materials derived from animals or cadavers, including the potential immunogenicity, pathogen transmission, batch to batch consistence and mismatch in properties for various applications. Therefore, there is an increasing interest in developing degradable hybrid polymer biomaterials with controlled properties for highly efficient biomedical applications. There have been efforts to mimic the extracellular protein structure such as nanofibrous and composite scaffolds, to functionalize scaffold surface for improved cellular interaction, to incorporate controlled biomolecule release capacity to impart biological signaling, and to vary physical properties of scaffolds to regulate cellular behavior. In this review, we highlight the design and synthesis of degradable hybrid polymer biomaterials and focus on recent developments in osteoconductive, elastomeric, photoluminescent and electroactive hybrid polymers. The review further exemplifies their applications for bone tissue regeneration.**

Keywords hybrid polymer; bone regeneration; tissue engineering; biomaterials

Introduction

The extracellular matrix (ECM) of native tissues is composed of a hybrid polymer nanostructure at the molecular level, organized with different biopolymers and nanocrystallites [1]. Due to their hybrid and well-organized structure, both hard and soft native tissues demonstrate excellent physicochemical properties including viscoelasticity and strength. They also demonstrate excellent biological activity including cellular biocompatibility and tissue-inductive ability [2]. Development of new biodegradable biomaterials by mimicking the physicochemical properties and biological activity has therefore gained increasing attention in recent years [3]. Biomimetic polymer hybrid biomaterials play an important role because they can be synthesized with highly tailored physicochemical properties and bioactivity, through combining different polymers and inorganic phases at the multiple levels [4]. In past decades, biodegradable natural-based polymers (collagen, silk, alginate, chitosan, hyaluronic acid) and synthetic polymers (poly(lactic acid): PLA, poly(glycolic acid):PGA, poly(lactic-co-glycolide): PLGA, Poly(ϵ-caprolactone):PCL, Polyhydroxyalkanoates: PHA) have been widely studied and their promising biomedical applications are also well demonstrated [5–8]. These polymers have been hybridized in many forms including 3D scaffolds, hydrogels, microspheres, and their composites [9–14]. Hybrid hydrogel-microsphere polymers with osteoconductive properties have also been synthesized [15–17].

In addition to the hybrid structure, osteocondutive property and electroactive ability are also very important for the application of hybrid polymers to regenerate bone [18]. Regeneration of bone can be accomplished by a combination of osteoinductive materials, regenerative cells and osteogenic growth factors. Local and long-term treatment with bone morphogenetic protein 7 (BMP-7) was accomplished by encapsulation of bioactive protein in PLGA microspheres. In combination with a nanofibrous and porous scaffold, treatment with BMP-7 significantly enhanced *in vitro* osteogenic differentiation and *in vivo* bone regeneration [19].

Pure biomedical polymers such as those listed above cannot mimic the mechanical properties of native tissues

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Correspondence: Peter X. Ma, mapx@umich.edu

especially the strength, elasticity and modulus, due to intrinsic shortcomings. Nevertheless, they provide certain advantages. It is possible to use these polymers to design precise micro and nanoscale environments that are beneficial for cell attachment, proliferation and differentiation. They can also be tailored for tunable drug delivery. Because of these advantages, they are being developed widely for tissue regeneration. To improve their mechanical and osteogenic properties, bioactive ceramic-based nanophases (bioactive glass and calcium phosphate) and various polymers (natural and synthetic polymers) have been hybridized [20–27]. To induce elastomeric behavior, highly elastomeric hybrid polymers were also synthesized through incorporating inorganic phase into biodegradable elastomers [28]. In particular, siloxane-based biodegradable hybrid polymer elastomers were developed with significantly enhanced mechanical properties and biocompatibility [29–31]. In recent years, electric stimulation has been shown to exhibit a positive effect on tissue regeneration through enhancing cell proliferation and differentiation [32]. Therefore, conductive components such as carbon-based materials and polymer semiconductors were added to fabricate electroactive hybrid polymer biomaterials for tissue regeneration applications [33].

This work reviews the design, fabrication, and properties of biodegradable hybrid polymers with a focus on their osteoconductive functions, elastomeric property, and electroactivity. The prospective application of hybrid materials for bone tissue regeneration is also covered in this review.

Synthesis and properties of hybrid polymers

Osteoconductive hybrid polymers

Osteoconductive hybrid polymer biomaterials can be fabricated by incorporating osteoconductive materials into biodegradable polymers. Biodegradable polymers typically have low elastic modulus and poor osteoconductive activity [34]. Bioactive inorganic biomaterials including bioactive glass (BG) and calcium phosphate (CP) have high conductive activity and bone-bonding ability, and their enhanced potential for bone regeneration have been well described in the literature [35–39]. Therefore, BG and CP-based nanoparticles have been added into various polymers to fabricate osteoconductive hybrid polymers for bone tissue regeneration [40–43]. CP-based polymer hybrid biomaterials have been fabricated successfully by melting, solvent-casting and *in situ* precipitation [44]. Most reports showed that addition of low content-CP-based nanoparticles can efficiently improve the mechanical strength and modulus of polymers and improve osteoconductive bioactivity [44]. Bioactive glass nanoparticles (BGN) have an amorphous structure and typical chemical composition of SiO_2-CaO-P_2O_5 that enable the controlled biodegradation and high bone-bonding activity for *in vivo* implanting applications [45]. By the facile solvent-casting method, BGNs with different morphology and size were added into various polymers including gelatin, chitosan, PLA, PCL, PLGA [41,46–48]. These hybrid BGN-polymers significantly enhanced compressive strength, tensile strength, elastic modulus, biominerialization, and osteoblast biocompatibility (Fig. 1). Although BGN-polymer nanocomposites have been developed well in past years, the nanoparticle-based polymer composites still showed uncontrolled biodegradation and mechanical properties *in vivo* due to the low interface strength between nanoparticles and polymers. These are known challenges associated with certain BGN-polymer nanocomposites.

Advances have been made in hybrid polymer materials to maintain controlled degradation and mechanical properties while also enhancing *in vitro* osteoconductive activity [49]. Gelatin-apatite hybrid nanofibrous scaffolds fabricated by thermally induced phase separation were

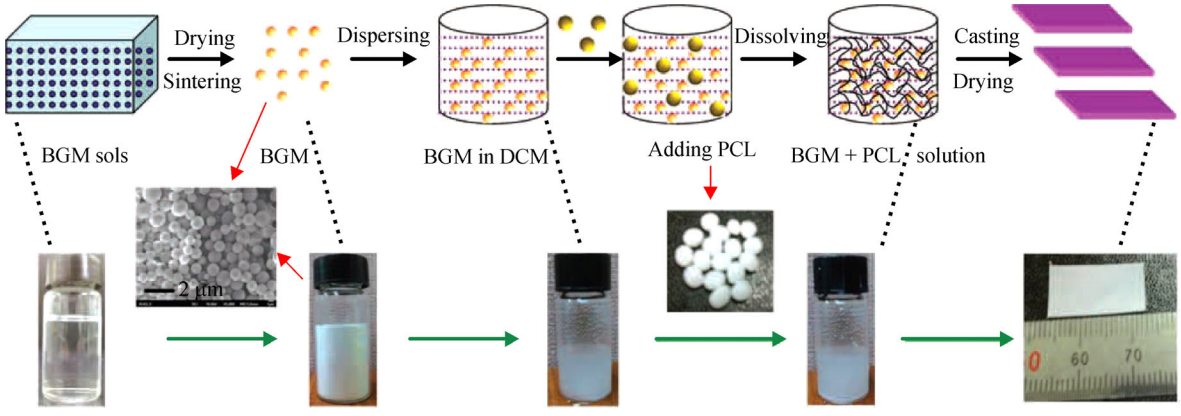

Fig. 1 Bioactive glass particles reinforced PCL osteoconductive hybrid polymers. Reproduced from Ref. [41] with permission.

evaluated for biominerialization in simulated body fluid (SBF) [49]. The gelatin-apatite hybrid scaffolds demonstrated significantly enhanced mechanical strength and enhanced expression of osteogenic genes in cells. Additionally, the hybrid scaffold was coated with biological apatite nanocrystals through an electrochemical deposition technology (Fig. 2) [50]. The apatite layer thickness could be tailored efficiently by the electrochemical parameters. The deposited hybrid polymer scaffolds also showed enhanced physiochemical properties and osteoconductive activity.

Agglomeration of BGNs within the polymer matrix is a challenge associated with hybrid polymers, as these materials may exhibit unfavorable mechanical and physiochemical properties [43]. To overcome this limitation, silica-based bioactive glass sol (SBGS) at the molecular level has been used to develop hybrid polymer biomaterials for applications in tissue regeneration. For example, SBGS-reinforced gelatin, chitosan, polyethylene glycol (PEG) and PCL hybrid polymers have been fabricated successfully through one-step hybridization process [51–57]. SBGS reinforced hybrid polymers showed significantly improved mechanical properties including strength, toughness, controlled biodegradation and biominerialization, as well as high osteoblastic activity. The SBGS-reinforced gelatin hybrid polymer was synthesized through typical sol-gel process, and the interface strength between organic and inorganic phase was controlled by siloxane coupling agents (Fig. 3). The resulting SBGS-gelatin hybrid showed strong compressive strength, mimicking native bone tissue and providing evidence for its potential application in bone fixation and repair [51]. SBGS-based gelatin hybrid scaffolds and nanofibrous scaffolds were fabricated through alkaline treatment technology and thermal-induced phase separation (Figs. 4–6). Significantly improved mechanical properties and biocompatibility of SBGS-gelatin hybrids were observed [41,43,51,58–60]. The SBGS-based hybrid polymer biomaterials have shown promise for bone tissue regeneration.

Additional advances have been reported in the use of carbon biomaterial-polymer hybrids as osteoconductive scaffolds for bone regeneration. Carbon nanomaterials are often synthesized as single sheets, referred to as graphene, or hollow structures referred to as carbon nanotubes (CNTs). CNTs can be single-walled or multi-walled, consisting of concentric tubular layers of graphene. One study compared CNT-PLLA scaffolds with graphene-PLLA scaffolds and reported that both carbon nanomaterial hybrids enhanced *in vivo* bone regeneration but graphene-PLLA scaffolds showed more osteoconductive capacity than CNT-PLLA scaffolds [61]. Polymeric scaffolds reinforced with ultrashort (US)-single walled CNTs enhanced both ectopic and *in situ* bone regeneration in rabbit subcutaneous and femoral condyle models [62]. Adsorption of ampiphilic comb-like polymer (APCLP) to CNTs allowed for more homogenous integration of carbon nanotubes into a bacterial cellulose (BC) scaffold [63]. In a mouse calvarial defect model, this hybrid CNT-BC scaffold improved bone formation and expression of osteocalcin. Vertically aligned CNTs combined with hydroxyapatite were made to be superhydrophilic and subsequently dispersed in poly (D, L, lactic acid) (PDLLA). The resulting hybrid scaffold showed suitable mineralization and cytocompatibility *in vitro* and demonstrated enhanced *in vivo* bone regeneration capacity in a rat calvarial defect model [64]. In addition to increasing

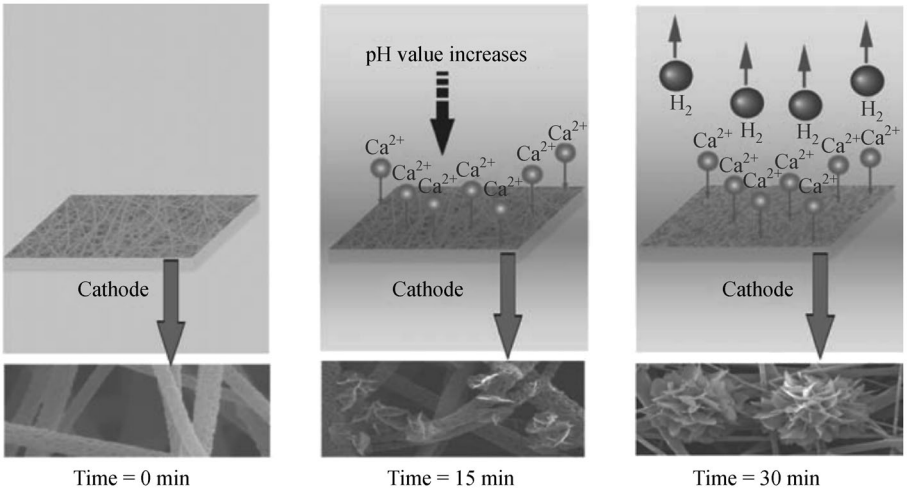

Fig. 2 Schematic illustration of a hypothesized mechanism for the growth of calcium phosphate crystals over time. When a deposition voltage is applied, pH in the vicinity of electrode increases, and some calcium phosphate crystals deposited onto the surface of PLLA nanofibers. Further increase of deposition time leads to the generation of hydrogen bubbles and larger flower-like crystals. Reproduced from Ref. [50] with permission.

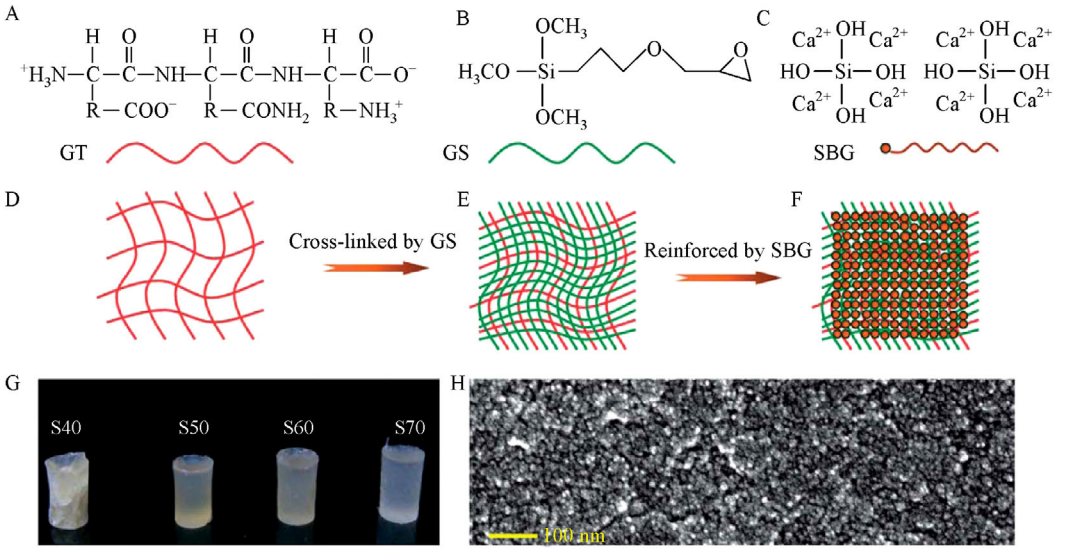

Fig. 3 Formation mechanism of the biomimetic siloxane-gelatin (SGT) hybrid bone implants. (A–C) Molecular structure and composition of gelatin (GT) (A), siloxane (GS), silicate bioactive glass sol (S); (D–F) GT (D) polymer matrix was cross-linked by GS (E), and then hybridized with the SBG sol at the molecular and nanoscale levels (F); (G and H) semi-transparent SGT hybrid implants with different SBG weight percent, formed after condensation and drying. Reproduced from Ref. [51] with permission from the Royal Society of Chemistry.

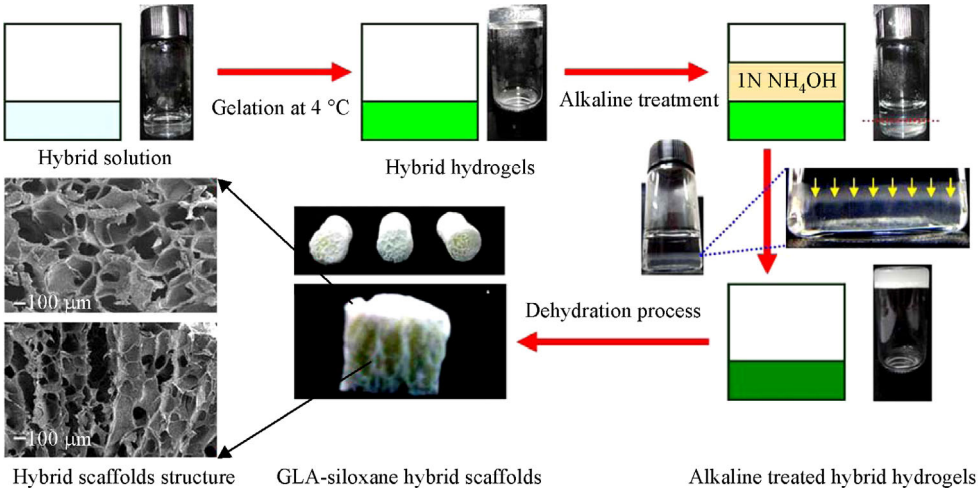

Fig. 4 Schematic diagram showing an experimental procedure for producing anisotropic porous gelatin-silica hybrid polymer scaffolds by ammonium hydroxide treatment. Reproduced from Ref. [68] with permission.

hydrophilicity, functionalization of CNT-polymer hybrids may improve mechanical characteristics and cytocompatibility of scaffolds and was reported to enhance *in vitro* and *in vivo* bone regeneration [65–67].

Elastomeric hybrid polymers

Many tissues in the body possess elastomeric properties. Therefore, the development of biomaterials that demonstrate highly elastomeric behavior has garnered much attention. Elastomeric materials are of particular interest because of their biomimetic mechanical properties, which enable their use in the complicated *in vivo* load environment [69]. Current biodegradable elastomers include physically crosslinked polymers such as polyurethanes and polyesters, chemically crosslinked polymers such as poly(glycerol sebacate) (PGS) and poly(citrate diol) (PCD) [70]. These biodegradable elastomers have shown highly tunable degradation, moderate biocompatibility and good elastomeric mechanical behavior [70]. They have

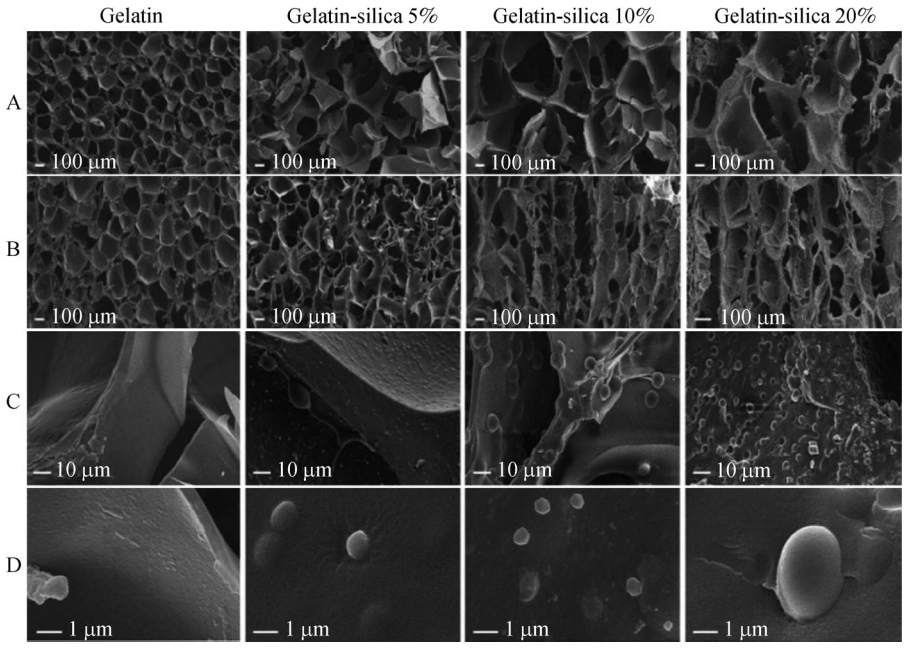

Fig. 5 Porous morphology of gelatin-silica hybrid polymer scaffolds. (A, C) Transverse direction; (B, D) Axial direction. Reproduced from Ref. [68] with permission.

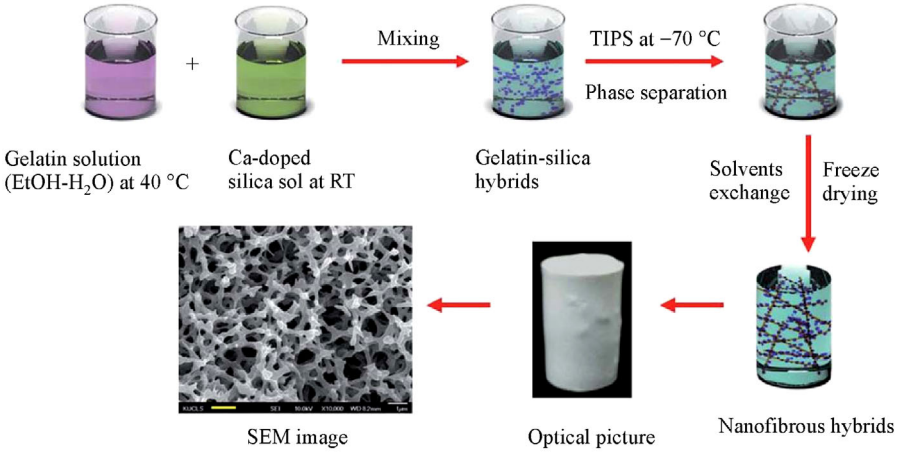

Fig. 6 Schematic diagram showing an experimental procedure for producing nanofibrous gelatin-silica hybrid scaffolds by the thermally induced phase separation (TIPS) technique using the mixtures of the gelatin solution and sol–gel derived silica sol. Reproduced from Ref. [59] with permission from the Royal Society of Chemistry.

demonstrated promising applications in regeneration of soft tissue due to their low mechanical strength or poor bioactivity [70]. To make these elastomers effective for a wider number of biomedical applications, developing hybrid polymers has become an attractive option to obtain biodegradable elastomers with optimized properties to meet different tissue-specific requirements.

PGS-PCL hybrid elastomers have been developed successfully by solvent electrospinning. The incorporation of PCL significantly enhanced formation of the nanofibrous structure and the hybrid materials showed mechanical properties in the range of human aortic valve tissues [71]. Gelatin was also added into PGS elastomer to fabricate hybrid polymers for tissue regeneration. The addition of gelatin significantly enhanced the mechanical properties and bioactivity of PGS elastomers [72]. Although polymer-polymer hybrid elastomers have been well developed, their limited elastomeric behavior and

mechanical strength still prevent their wide application in bone tissue regeneration.

To overcome the limitations of polymer-based elastomers, inorganic phase reinforced hybrid polymer elastomers have been developed in recent years [73–75]. As osteoconductive biomaterials, hydroxyapatite nanoparticles were incorporated into PCD-based elastomers to fabricate composites for orthopedic implants [76]. Uniform distribution of HA in the polymer matrix significantly enhanced the mechanical properties and osteoconductive biocompatibility of PCD-HA hybrid elastomers. Melt-derived bioglass particles were also introduced into PGS elastomers to improve their range of biomedical applications [77]. Bioglass particles efficiently enhanced the elastomeric strain and cellular biocompatibility of PGS. These hybrid elastomers still have the intrinsic problem of poor interface intensity between the inorganic phase and polymers. Therefore, our group introduced bioactive silica into PCD elastomers through a one-step thermal polymerization method [30,31,78,79]. The inorganic silica phase was bonded with the PCD polymer chain through covalent bonds. The resulting hybrid polycitrate-silicon (PCS) elastomers demonstrated significantly improved elastomeric behavior, mechanical strength and cellular biocompatibility (Fig. 7) [30]. SBGS-based PGS hybrid elastomers were also fabricated successfully through the direct hybridization of SBGS and PGS solution [29]. SBGS-PGS hybrid elastomers exhibited significantly enhanced mechanical properties, biominerialization and cellular biocompatibility (Fig. 8). The inorganic phase-grafted PGS and PCD hybrid elastomers have shown promise for applications in bone tissue regeneration.

Electroactive hybrid polymers

Conducting polymers are organic polymers that possess electrical, magnetic and optical properties that are similar to metal, while maintaining desirable mechanical properties as well as ease of processing of polymers [80,81]. Recently, it was found that conductive polymers could tune the properties of cells in electrically sensitive tissues under electrical stimulation, including neural, muscle, cardiac, and bone [82–84]. Regenerative biomaterials for the treatment of bone diseases that need surgical intervention have attracted more attention, particularly with extended life expectancies. Scaffolds that regulate cellular behavior

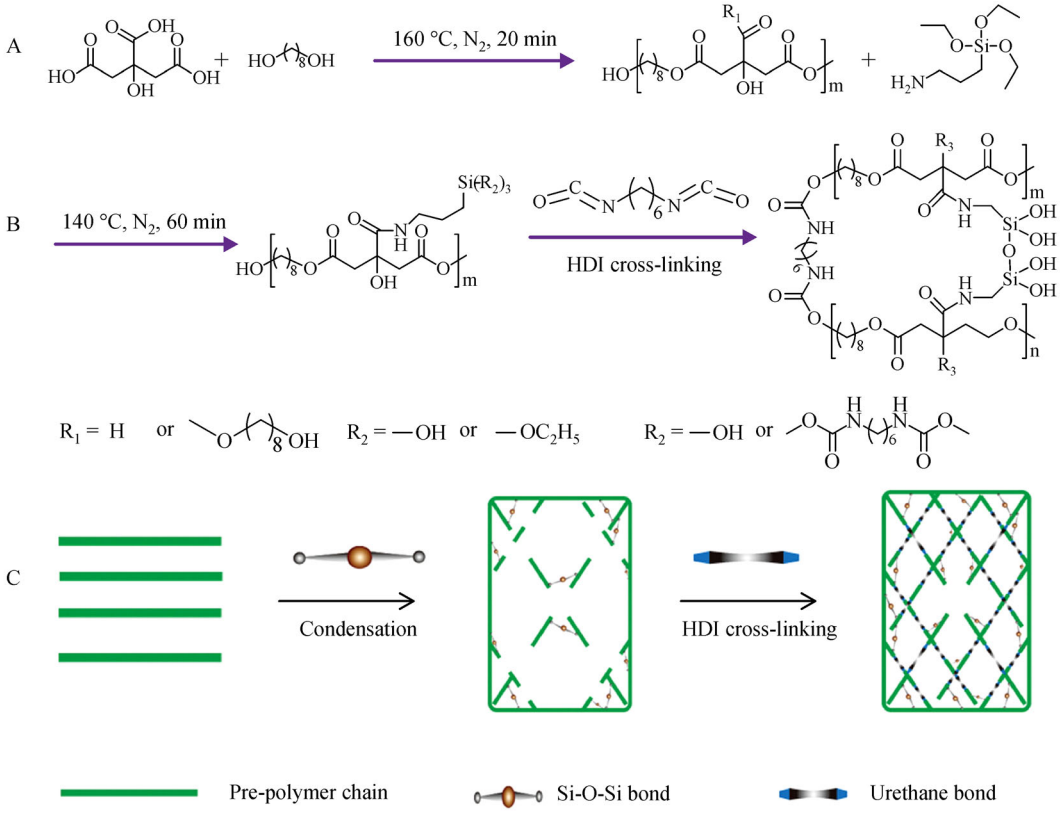

Fig. 7 Synthesis of multifunctional silica-poly(citrate)-based hybrid prepolymers and elastomers. (A,B) Fabrication of multifunctional silica-poly (citrate) (MSPC) and crosslinked MSPC (CMSPC) elastomers by polycondensation of citric acid (CA), 1,8-octylene glycol (OD), aminosilane (AS), as well as the chemical crosslinking with hexamethylene diisocyanate (HDI) and (C) schematic diagram showing the formation of CMSPC hybrid elastomers matrix. Reproduced from Ref. [30] with permission.

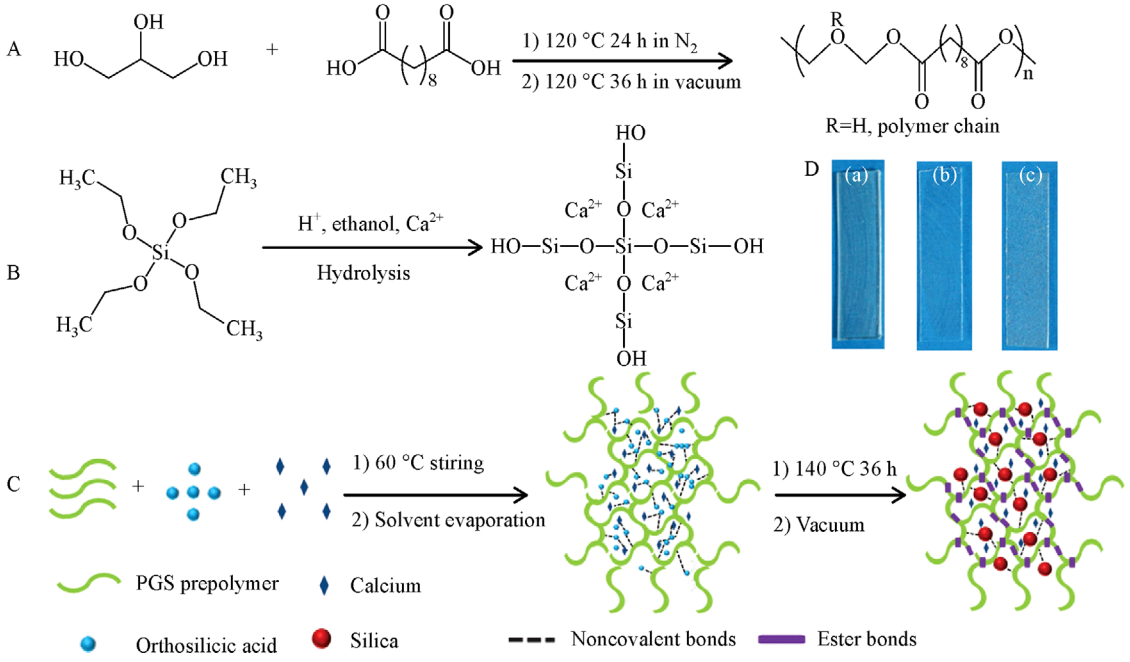

Fig. 8 Schematic illustration for preparing poly(glycerol sebacate)-silica-calcium (PGSSC) hybrid elastomers. (A) Synthesis of PGS pre-polymers; (B) formation of silica-based bioactive glass sols; (C) fabrication of PGSSC hybrid elastomers; (D) optical images of PGS and PGSSC hybrid elastomers: (a) PGS; (b) PGS15mol%Si (PGS15Si); and (c) PGS-15mol%Si-20mol%Ca (PGS15Si20Ca). Reproduced from Ref. [29] with permission from the Royal Society of Chemistry.

are particularly interesting for such applications [85–87]. A 3-D conductive scaffold that can locally deliver an electrical signal is needed. 3D conductive scaffolds were prepared using poly(3,4-ethylenedioxythiophene) poly(4-styrene sulfonate) (PEDOT:PSS), gelatin, and bioactive glass [88]. Introduction of PEDOT:PSS enhanced the physiochemical stability and improved mechanical properties of the composite. Increasing the content of PEDOT:PSS in the scaffolds improved cell viability. Together, these results indicated that these conductive scaffolds exhibited more favorable structural properties for bone repair. The use of conducting polymers loaded with a bioactive molecule has been an emerging approach to functional biomaterial use in tissue regeneration. Chondroitin sulfate (CS)-doped polypyrrole (PPy) was coated via an *in situ* chemical oxidative polymerization onto the non-conductive polylactide to fabricate novel osteogenic scaffolds [89]. Electrical conductivity of PPy-coated polylactide (PPy-PLA) scaffolds was obvious, but it decreased with time due to de-doping.

Applications in bone tissue regeneration

Biomaterials-based bone regeneration aims to develop bioactive bone-substitutes that repair damaged issue and restore tissue functionality. Native bone ECM is a hybrid structure that consists of a polymer and inorganic phase. Therefore, biodegradable hybrid polymer biomaterials with representative nanostructures are desirable for bone tissue regeneration [90]. Inorganic phase reinforced hybrid biomaterials with multifunctional properties have demonstrated enhanced bone-binding ability, osteoblast activity, and bone regeneration potential as compared to pure biodegradable polymers [91]. Here, we review the recent development of biodegradable hybrid polymer biomaterials for osteoblastic proliferation, differentiation, and *in vivo* bone regeneration.

Silicon-based BG particles with microscale and nanoscale sizes have been employed to enhance biomineralization and biocompatibility [41,43]. As shown in Fig. 6, hybrid polymers reinforced with BG microparticles or nanoparticles could efficiently induce deposition of biological apatite after soaking in SBF [41]. Osteoblast attachment was also improved on the hybrid BGN-PCL, as compared to PCL scaffold alone [43]. In addition to bioactive glass-based hybrid polymer, the apatite-based polymer also showed enhanced osteoblastic activity (Fig. 9). After 1 and 4 weeks culture of MC3T3-E1 cells on nanofibrous gelatin-apatite hybrid scaffolds (NF-gelatin/apatite) and pure NF-gelatin scaffolds, cells grown on the hybrid scaffolds showed significantly increased expression of genes for bone sialoprotein (BSP) and osteocalcin (OCN) (Fig.10) [49]. *In vivo* experimentation demonstrated that the incorporation of osteoconductive components can significantly improve bone formation. For example, compared with pure poly

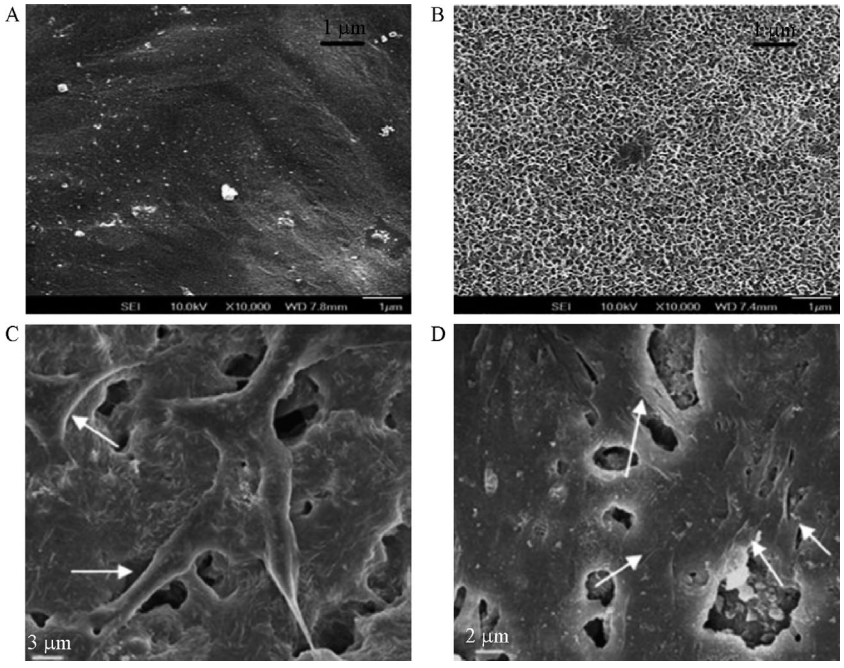

Fig. 9 *In vitro* biomineralization activity and osteoblast biocompatibility (MC3T3-E1) of BG micro-nanoscale particles-PCL hybrid polymers. (A, B) Apatite formation on surface of PCL (A) and BG-PCL (B) after soaking in SBF for 7 days; (C, D) Cell attachment morphology on the surface of PCL (C) and BG-PCL (D) after culture for 3 days. Reproduced from Refs. [41] and [43] with permission.

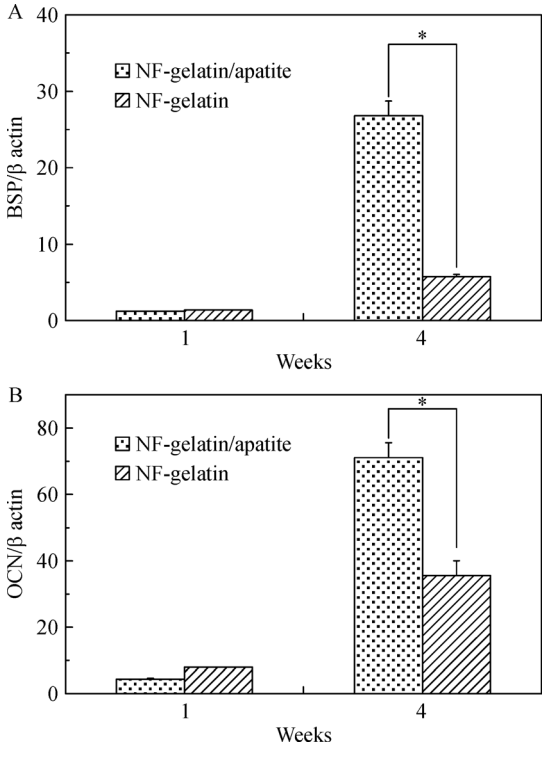

Fig. 10 Quantitative RT-PCR results of bone sialoprotein (BSP)(A) and osteocalcin (OCN)(B) gene expression. MC3T3-E1 cells were cultured on NF-gelatin and NF-gelatin/apatite scaffolds for 1 and 4 weeks. The *Y*-axis of the figure is the gene expression results normalized by β actin. * represents statistically significant differences ($P < 0.05$). Reproduced from Ref. [49] with permission.

(lactide-co-glycolide) (PLGA), amorphous tricalcium phosphate nanoparticles reinforced PLGA (PLGA-TCP) nanocomposites enhanced the rapid regeneration of bone defects in a New Zealand white rabbit model (Fig. 11) [92].

As compared to osteoconductive particle-based hybrid polymers, silica-based sol-polymers possessed uniform nanostructure distribution and inorganic-organic interface, which could mimic the structure of native bone ECM. Silica-based chitosan hybrid polymer has been used to guide bone tissue regeneration successfully [93]. As compared to pure chitosan, new bone formation was significantly enhanced by the hybrid polymer while the hybrid membrane was degraded after 3 weeks implantation at bone defect sites (Fig. 12). A significantly higher rate of bone formation was observed for the hybrid (93%) but not the chitosan membrane (60%) [93]. Due to the inherent elastomeric behavior of native bone, elastomeric hybrid biomaterials are appealing for applications in bone regeneration [94]. Our group developed silicon-based polymer elastomers with controlled biodegradation for applications in bone regeneration [29–31]. The results demonstrated that poly(citrate-siloxane) (PCS) hybrid elastomers significantly enhanced attachment and proliferation of various cells, including cells derived from both hard and soft tissue [30,31]. PCS-based hybrid polymer could also significantly enhance osteoblastic differentiation, cellular biominerialization of MC3T3-E1 cells [78,79]. PCS-based hybrid biomaterials have shown

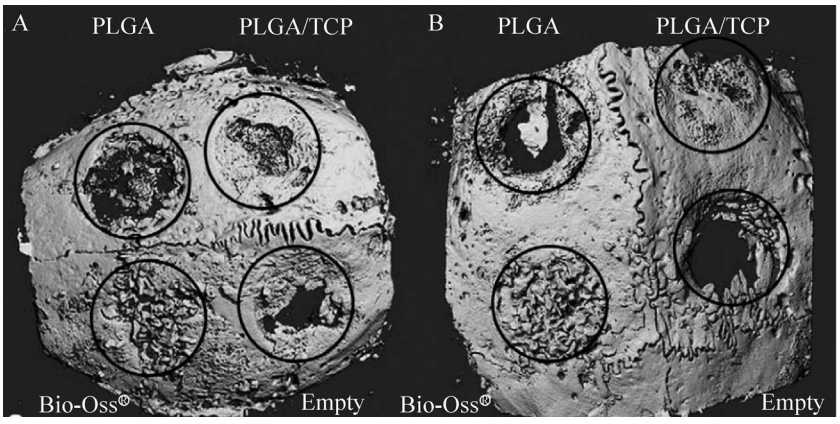

Fig. 11 Micro-computed tomography of the cranial defects (diameter = 6 mm) in New Zealand White rabbits after 4-week implantation using PLGA, PLGA/TCP composites. (A, B) Two examples of the CT of the entire cranial bone are shown. Defect margins and treatment modalities are indicated. Adapted from Ref. [92] with permission.

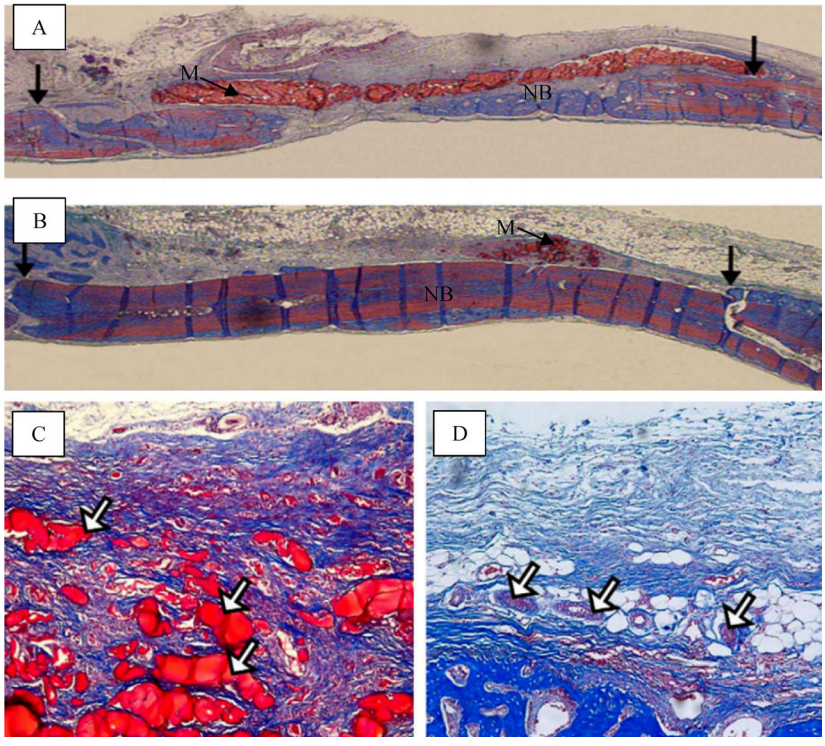

Fig. 12 Optical micrographs of the rat bone tissue regeneration responses after the 3 weeks implantation of the membranes: (A, C) pure chitosan and (B, D) the chitosan–silica xerogel hybrid. The fresh-formed bone tissue was revealed in blue, the calcified bones and materials were stained in red. Reproduced from Ref. [93] with permission.

promising potential for *in vivo* bone tissue regeneration. Additional *in vivo* experiments should be carried out to evaluate the potential value of PCS-based hybrid biomaterials.

Proliferation and osteogenic differentiation of human adipose stem cells (hASCs) on the coated and conductive scaffolds was compared to non-coated polylactide scaffolds under electrical stimulation. The conductive hybrid scaffolds greatly enhanced hASC proliferation compared to pure PLA scaffolds [89]. Alkaline phosphatase (ALP) activity of hASCs seeded on PLA-PPy scaffolds was generally higher; however, electrical stimulation did not

show a significant effect on hASCs. These results highlighted the potential application of PPy-coated PLA scaffolds for bone regeneration. Mesenchymal stem cells (MSCs) have great potential and are commonly used progenitor cells in bone tissue engineering. Osteogenic differentiation of MSCs can be guided by various types of biomaterials. Our group found that the electroactive biodegradable copolymers can enhance osteogenic differentiation of bone marrow derived MSCs (BMSCs) [95]. These copolymers were composed of polylactide and tunable contents of conductive aniline tetramer. Culture of BMSCs on the electroactive copolymer films indicated that these copolymers were not cytotoxic, in fact proliferation of BMSCs was significantly enhanced. Osteogenic differentiation of BMSCs showed that the electroactive copolymers greatly promoted osteogenic differentiation compared to pure PLA with respect to expression of ALP, OPN, and Runx2 and deposition of calcium measured by von Kossa staining. The electroactive copolymer surface can adsorb more protein than pure PLA, which may be a factor that enhanced proliferation and differentiation of MSCs. These results indicated that the electroactive degradable polymers based on polylactide and aniline tetramer have great potential as scaffolding materials for bone regeneration.

Summary and perspectives

Degradable hybrid polymer biomaterials with osteoconductivity, biomimetic elastomeric behavior and electroactivity have shown promise in applications in bone tissue repair and regeneration. However, to meet the requirements of efficient bone regeneration, there are still many areas in need of improvement for these polymer hybrid biomaterials. First, high osteoinductive activity should be incorporated into these hybrid polymers. Second, maintaining high mechanical strength of hybrid polymers while preserving their elastomeric behavior should be prioritized. Third, other functions including antibacterial activity and bioimaging ability should be also considered in the design of next generation hybrid polymer biomaterials.

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Compliance with ethics guidelines

Bo Lei, Baolin Guo, Kunal J. Rambhia, and Peter X. Ma declare that they have no financial conflicts of interest. This manuscript is a review article and does not involve a research protocol requiring approval by a relevant institutional review board or ethics committee.

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