Biodegradable Polymer Membranes Applied in Guided Bone/Tissue Regeneration: A Review

Jiaolong Wang 1,2, Lina Wang 2,3, Ziyu Zhou 1, Hanjian Lai 2, Pan Xu 2, Lan Liao 1,* and Junchao Wei 2,*

1 Department of Prosthodontics, Affiliated Stomatological Hospital of Nanchang University, Nanchang 330006, China; 406531513386@email.ncu.edu.cn (J.W.); 406531514649@email.ncu.edu.cn (Z.Z.)
2 College of Chemistry, Nanchang University, Nanchang 330031, China; 5901213058@email.ncu.edu.cn (H.L.); 5503113042@email.ncu.edu.cn (P.X.)
3 College of Science, Nanchang Institute of Technology, Nanchang 330029, China; linawang@nit.edu.cn
* Correspondence: liaolan5106@ncu.edu.cn (L.L.); weijunchao@ncu.edu.cn (J.W.);
Tel.: +86-0791-8635-0706 (L.L.); +86-0791-8396-8830 (J.W.)

Academic Editor: Jianxun Ding
Received: 27 February 2016; Accepted: 24 March 2016; Published: 29 March 2016

Abstract: Polymer membranes have been widely used in guided tissue regeneration (GTR) and guided bone regeneration (GBR). In this review, various commercially available membranes are described. Much attention is paid to the recent development of biodegradable polymers applied in GTR and GBR, and the important issues of biodegradable polymeric membranes, including their classification, latest experimental research and clinical applications, as well as their main challenges are addressed. Herein, natural polymers, synthetic polymers and their blends are all introduced. Pure polymer membranes are biodegradable and biocompatible, but they lack special properties such as antibacterial properties, osteoconductivity, and thus polymer membranes loaded with functional materials such as antibacterial agents and growth factors show many more advantages and have also been introduced in this review. Despite there still being complaints about polymer membranes, such as their low mechanical properties, uncontrollable degradation speed and some other drawbacks, these problems will undoubtedly be conquered and biodegradable polymers will have more applications in GTR and GBR.

Keywords: biodegradable polymer; GTR; GBR; membrane; collagen; polylactide

1. Introduction

Guided tissue regeneration (GTR) was first described in the 1950s by Hurley, who physically separated soft tissues from areas of active bone formation in the spine with a barrier membrane [1]. In the 1980s, GTR was introduced to periodontal tissue regeneration to stop cell migration from gingival connective tissue and epithelium to the periodontal defect, and has been adopted in treating periodontal lesions to generate new attachments [2,3]. Subsequently, a membrane technique used to generate new bone around implants based on the principle of GTR was defined as guided bone regeneration (GBR) [4]. Currently, GBR is one of the most common and promising augmentation techniques to regain sufficient width and height of the jawbone at oral implant sites, or to preserve alveolar sockets after tooth extraction [5–8]. For GTR and GBR techniques, whether or not the graft material is filled, a special barrier membrane plays a key role to prevent epithelial or undesirable tissues migration into the defective area [9], and consequently it allows sufficient time for bone, cementum, and periodontal ligament regeneration [10]. The ideal membrane for periodontal guided tissue and bone regeneration should have the following properties: biocompatibility, space maintenance ability, cell occlusiveness, integrated by the host tissues, and clinical manageability [11,12]. Generally,
the membranes used in GTR and GBR are roughly divided into two types: bioabsorbable and non-resorbable membrane. Each membrane has been extensively applied in clinic. Currently, much attention is still paid to the development of the new types of ideal GBR and GTR membrane [9].

Non-resorbable membranes include expanded polytetrafluoroethylene (e-PTFE, Gore-Tex®), high-density polytetrafluoroethylene (d-PTFE), and titanium-reinforced high-density polytetrafluoroethylene (Ti-d-PTFE) membranes [13]. The e-PTFE membranes have been accepted as the gold standard materials with excellent biocompatibility, leading to significant bone regeneration in numerous clinical studies. However, stiff e-PTFE membranes may result in soft tissue dehiscence, and thus make themselves susceptible to exposure with subsequent progression of infection [14]. The following commercially dense PTFE membranes might be impervious to bacteria, since their porosity is less than 0.3 microns. Besides, titanium frame made the Ti-d-PTFE membranes able to be trimmed to desired shapes, and shaped for tenting and space maintenance (Table 1) [13]. However, a second surgery is still necessary to remove them. Bioabsorbable membranes have the advantage of not requiring surgical removal. The main challenge of bioabsorbable membranes is to match its resorption time with the periods of tissue formation. The structural integrity of the membrane should be maintained during the maturation of the newly formed tissue and it varies according to the application, i.e., 4–6 weeks for GTR for bone and periodontal ligament cells to fill the space but ≥6 months for GBR to support new bone formation and maturation [15]. Hence, an optimal persistence and stability of membranes in vivo should be guaranteed in the range from four weeks to several months. In this review, the recent progress of bioabsorbable membranes used in GTR and GBR is reviewed. Depending on their origins, they can be sorted into natural polymers, such as xenogeneic-derived collagen, and synthetic polymer materials, for example, poly(lactic acid), and polymer composites, which refer to a combination of two or more different materials to obtain specific mechanical, chemical, and physical properties [16].

Table 1. The most commonly used commercially available non-resorbable polymeric membranes.

| Commercial Membrane | Materials                 | Properties                                           | Comments                                           |
|---------------------|---------------------------|------------------------------------------------------|----------------------------------------------------|
| Gore-Tex            | Expanded PTFE             | Good space maintainer; Relatively stiff; Handling    | Longest clinical experience                        |
| High-density Gore-Tex | High-density PTFE         | Porosity of less than 0.3 microns creates impervious barrier to bacteria | Most cost-effective; A non-surgical removal when in an open technique |
| Gore-Tex-Ti         | Titanium-reinforced PTFE  | Titanium frame may be trimmed and shaped to create additional space for bone growth | Ideal for ridge augmentation and grafting bony defects missing one or more walls |

2. Resorbable Membranes Based on Natural Polymer

Natural polymers exhibit good biocompatibility, safety, biodegradability, and therefore have gained much attention as GTR and GBR materials. More importantly, their inherent bioactivity, the ability to present receptor-binding ligands to cells, susceptibility to cell-triggered proteolytic degradation and natural remodeling, are advantageous properties compared to synthetic polymers [17]. However, the inherent bioactivity of these natural polymers has its own downsides, including a strong immunogenic response associated with most natural polymers, complexities associated with their purification and the possibility of disease transmission [17]. Collagen and chitosan are the most frequently studied natural polymers for GTR and GBR applications, especially collagen membrane.

2.1. Membrane Based on Collagen

Collagen membranes, mostly types I and III, have several superior properties such as good tissue integration, fast vascularization, biodegradation without foreign-body reaction, chemotactic action
for fibroblasts, hemostatic property, weak immunogenicity, osteoblastic adhesion and their proven biocompatibility and capability of promoting wound healing. Therefore, collagen membranes attract much interest in GTR and GBR research [15,18–23].

Different types of commercially collagen membranes, such as Bio-Gide®, Ossix®, Biomend® and BiomendExtend®, varying from collagen types, physical or chemical structures, have been designed (Table 2). These collagen membranes can be resorbed via enzymatic degradation by collagenases/proteases, and macrophage/polymorphonuclear leukocyte-derived enzymes [14], and bacterial proteases [24,25]. For example, Bio-Gide® (GeistlichPharma AG, Wolhusen, Switzerland), one of the most important commercial collagen membrane, is composed of porcine type I and type III collagen fibers. It comprises a bilayer structure with an outer compact smooth layer and an inner porous layer. When used for GBR, the porous and compact layers can not only enable osteogenic cell migration to make bone ingrowth possible, but also prevent the invasion of fibroblasts [26]. It was observed that Bio-Gide® collagen membranes rapidly adsorb the TGF-β activity released from autogenous bone chips, a molecular process that might contribute to guided bone regeneration [27]. Besides, the degradation of monolayer Bio-Gide® and bilayer Bio-Gide® had no difference [14].

### Table 2. The most commonly used commercially available resorbable collagen membranes.

| Commercial Name (Manufacturer) | Collagen Type | Collagen Source | Resorption Rate |
|-------------------------------|--------------|----------------|-----------------|
| Non-cross-linked collagen membrane |              |                |                 |
| CollaTape/CollaPlug/CollaCote (Integra LifeSciences Corp., Plainsboro, NJ, USA) | Type I | Bovine tendon | 10–14 days |
| Periogen (Collagen Corporation, Palo Alto, CA, USA) | Type I and III | Bovine dermis | 4–8 weeks |
| Bio-Gide (Geistlich, Wolhusen, Switzerland) | Type I and III | Porcine skin | 2–4 weeks |
| Tutodent (Tutogen Medical GmbH, Neunkirchen, Germany) | Type I | Bovine pericardium | 8–16 weeks |
| Cross-linked collagen membrane |              |                |                 |
| OsseoGuard (Zimmer Biomet, Inc., Carlsbad, CA, USA) | Type I | Bovine tendon | 6–9 months |
| OsseoGuard Flex (Zimmer Biomet, Inc., Carlsbad, CA, USA) | Type I and III | Bovine dermis | 6–9 months |
| Ossix Plus (Datum Dental Ltd., Lod, Israel) | Type I | Porcine tendon | 4–6 months |
| BioMend (Zimmer Biomet, Inc., Carlsbad, CA, USA) | Type I | Bovine tendon | 8 weeks |
| BioMendExtend (Zimmer Biomet, Inc., Carlsbad, CA, USA) | Type I | Bovine tendon | 18 weeks |
| RCM6 (ACE Surgical Supply Co. Inc., Brockton, MA, USA) | Type I | Bovine tendon | 26–38 weeks |
| Mem-Lok (BioHorizons IPH, Inc., Birmingham, England) | Type I | Bovine tendon | 26–38 weeks |
| Neomem (Citagenix Inc., Montreal, QC, Canada) | Type I | Bovine tendon | 26–38 weeks |
| OssGuide (Bioland, Cheongju, Korea) | Type I | Porcine pericardium | 6 months |

Although these native collagen membranes have excellent cell affinity and bio-compatibility [28], and similar bone regeneration capacity to that of non-resorbable membrane [29], they have obvious drawbacks for GTR and GBR applications, including the loss of space-maintaining ability in humid conditions [14,30], risks of a disease transmission to human for animal-derived collagen [31], inferior mechanical strength, and too rapid biodegradation [32]. It has also raised certain ethical and cultural issues [33]. These limitations, such as poor mechanical properties and rapid degradation, are associated with the shortened functional period, greater susceptibility to infection, and the regeneration of new tissue [34,35]. Hence, in order to reinforce the mechanical and biodegradable stability to comprise the biocompatibility for use as GBR and GTR membranes, various chemical, physical, and biological cross-linking methods have been introduced to cross-link collagen. Among the
chemical cross-linkers, glutaraldehyde (GTA), 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide (EDC), polyepoxy, diphenyl-phosphorylationazide, etc. are the most commonly used. For instance, BioMend® (BioMend Extend®) (Zimmer Biomet, Inc., Carlsbad, CA, USA) and Rapi-Gide® (DalimTissen, Seoul, Korea), commercially available membranes, are cross-linked by GTA and EDC, respectively. Via cross-linking, the tensile strength of collagen was enhanced and their degradation time may be prolonged [36]. However, the residual reagents or secondary products during collagen implant degradation may have toxic effects, and thus limit their applications [32]. In addition, certain polysaccharides have also shown a degree of success to cross-link collagen membrane [36,37], such as Ossix Plus® (Datum Dental Ltd., Lod, Israel) membrane. Physical treatments such as dehydrothermal treatment [38–40], heat treatment, ultraviolet irradiation, gamma irradiation and microwave irradiation, and biological methods (e.g., transglutaminase) may be used as an alternative to introduce cross-link efficiently [32,41]. Cross-linked collagen membrane can maintain block bone substitutes dimensionally stable in comparison with the use of non-cross-linked collagen in the early healing period of lateral onlay graft (Figure 1) [40].

![Figure 1](image-url)

**Figure 1.** Clinical photographs of the experimental sites: (a) A full-thickness flap was elevated, and the bone bed was prepared by perforating the cortical bone; (b) Assigned bone substitutes and membranes were applied. The left block is bovine hydroxyapatite incorporated into a non-cross-linked collagen matrix, and the right block is porcine hydroxyapatite incorporated into a cross-linked collagen matrix; (c) The bone substitutes were covered by the membranes (red arrow), which were stabilized using two pins (yellow arrow). Both membranes are cross-linked collagen membrane; (d) An occlusal view of the opposite side. The non-cross-linked collagen membrane is applied. Reprinted with permission from John Wiley and Sons [40].

Although cross-linking of collagen endows it with more advantages, there still are some problems with cross-linked collagen; for example, cross-linked membranes display prolonged membrane integrity with surrounding tissues and blood vessels compared with the non-cross-linked membranes [42]. These chemically and enzymatically cross-linked collagen membranes showed delayed angiogenesis in rats and dogs [29,40]. Some research showed that chemically cross-linked collagen membrane demonstrated more adverse events and insufficient bone regeneration compared to the non-cross-linked collagen membrane [43]. All in all, how to balance the contrary sides of cross-linking collagen membranes between stability and functional remodeling [41] through the
considerable complexity and diversity in their structure, their linking degrees, their assembly and their function remains a challenge.

2.2. Membrane Based on Chitosan

In the past 20 years, chitosan, 1,4-linked 2-amino-2-deoxy β-D-glucan, an alkaline linear and cationic polysaccharide obtained from the deacetylation of chitin, has been shown to be an attractive candidate material for GTR and GBR membranes due to its low cost, superior biocompatibility, non-antigenicity, appropriate degradation rate, flexibility in hydrated environments, hemostatic activity, antimicrobial and wound healing potential [44–47]. Chitosan membranes were compatible with cells in vitro and able to facilitate bone regeneration in rat calvarial defects [48]. Chemical cross-linking is an effective method to increase its mechanical strength and reduce its degradation speed [49]. Chitosan membranes cross-linked with genipin showed less inflammatory reaction and resulted in faster healing times when compared with GTA [50]. Histological observations show that most non-cross-linked and genipin-cross-linked chitosan membranes became infiltrated by fibrous tissue by 16 and 20 weeks, respectively, whereas BioMend Extend® collagen membranes showed an much earlier infiltration timing at the 12-week time point [49]. It was reported that genipin-cross-linked chitosan electrospun mats exhibited only 22% degradation after 16 weeks in vitro test, which was much slower compared to 34% degradation for non-cross-linked mats [51]. Besides, the ultimate tensile strength of the cross-linked mats was 32 MPa, about 165% higher than that of the non-cross-linked mats [51]. These results suggest that genipin-cross-linked chitosan membranes might have potential to meet the clinical requirements for GBR applications.

Another attractive characteristic is its inherent antibacterial property; therefore, chitosan is also widely used as an antibacterial agent, either alone or blended with other natural polymers [52]. However, research on its antibacterial application in GBR and GTR is scarce. Chitosan nanoparticles could adhere to mucosal surfaces, and thus prolong the residence time and evaluate drug permeation at drug absorption sites [53]. It was reported that chitosan nanoparticles acted synergistically with chlorhexidine in collagen membranes for periapical guided tissue regeneration [53]. These results suggested that antibacterial property of chitosan could be used to improve regenerative procedures in periapical surgery.

2.3. Membrane Based on Gelatin

Gelatin, a soluble protein derived from partially denatured collagen, has received great attention owing to its availability, easy handling and cost efficiency [54]. Attractive properties of gelatin, such as good biocompatibility, low immunogenicity, plasticity, adhesiveness, promotion of cell adhesion and growth, and low cost, make it ideally suitable as a biomaterial for tissue engineering, GBR and GTR [55]. However, gelatin exhibits poor mechanical properties and fast degradation. An efficient method to improve its mechanical properties and stability is to cross-link gelatin with EDC and N-hydroxyl succinimide (NHS) [56], heat treatment [57], and GTA [58]. Although the tensile properties of the gelatin fibrous membrane can be greatly enhanced by cross-linking with EDC/NHS, the cross-linked membranes in the moist state showed a high elastic characteristic but an extremely lower Young’s modulus [56]. Therefore, gelatin is seldom used alone to function as a GBR and GTR membrane.

2.4. Membrane Based on Silk Fibroin (SF)

Silk fibroin (SF), a natural protein that can be extracted from silk worms (e.g., Bombyx mori) or spiders [59], has many attractive properties, including good biocompatibility, good oxygen and water vapor permeability, and biodegradability [60], and thus has been a candidate material for bone and periodontal regenerative applications. A recent study reported that in the calvarial defect of rabbits with SF nanofiber membrane, a complete bony union across the defects was observed after eight weeks, while at 12 weeks, the defect can be completely healed with new bone [61]. In addition, SF provides remarkable strength and toughness to provide enough stability, which benefits for space
maintenance for bone ingrowth while preventing membrane collapse [61]. The tensile strength of the wet SF membrane was higher than the tensile strength of the wet EDC-cross-linked collagen and PTFE membranes. The bone formation of the SF membrane was also higher than those of the other two membranes observed by µ-CT and histological analysis [62]. All these results strongly suggest that the SF membrane could be useful as a barrier membrane for GBR and GTR.

3. Resorbable Membranes Based on Synthetic Polymer

Most of current resorbable synthetic polymer membranes on the market are based on aliphatic polyesters, such as poly(lactic acid) (PLA), poly(glycolic acid) (PGA), poly(ε-caprolactone) (PCL), poly(hydroxyl valeric acid), and poly(hydroxyl butyric acid), as well as their copolymers. The use of these membranes may be subject to drawbacks such as inflammatory foreign-body reactions associated with their degradation products [63]. Some studies found a reduced defect fill when applying PLA and PGA membranes as opposed to e-PTFE membranes [64,65]. More importantly, they are generally not as biologically active as natural polymers [17]. However, due to their excellent biocompatibility, controllable biodegradability, low rigidity, malleability, processability, and drug-encapsulating ability [64,66–68], they have been widely considered for orthopedic applications both in theoretical experiments and clinic, especially in GBR and GTR procedures.

3.1. Polylactic Acid (PLA) and Polylactic acid/Polyglycolic Acid Copolymer (PLGA)

Polylactic acid (PLA) is one of the most common and important polymers used in GTR and GBR procedures because of its suitable mechanical properties and biocompatibility. In order to regulate the degradation rate and hydrophilicity of PLA, copolymers of lactide and ε-caprolactone, glycolide, etc. have been synthesized. Polylactic acid/polyglycolic acid copolymer (PLGA) is a well-known alternative for PLA in orthopedic applications. Both PLA and PLGA have been used commercially as membranes, such as Resolut Adapt®, Vicryl®, Epi-Guide® and Vivosorb®, and every membrane may have its own properties (Table 3). For example, Guidor® Matrix Barrier (Sunstar Americas, Inc. near Chicago, IL, USA), the first and most widely studied alloplastic matrix and barrier technology available, is bi-layered, and it is made from a homogenous blend of two polymers, poly-D,L-lactide (PDLLA) and poly-l-lactide (PLLA), doped with acetyl tri-n-butyl citrate [69]. GUIDOR® Matrix Barrier could maintain its barrier function for a minimum of six weeks, while it is gradually resorbed in 13 months [69]. Resolut Adapt® and Resolut Adapt® LT (W.L. Gore and ASSOC, Flagstaff, AZ, USA) membranes were made by PLGA, and they can remain substantially integrity for 8–10 weeks and 16–24 weeks, respectively, in order to meet GBR and GTR different demands.

| Commercial Name (Manufacturer) | Materials | Properties | Function Time | Resorption Rate |
|--------------------------------|-----------|------------|---------------|----------------|
| Guidor (Sunstar Americas, Inc. near Chicago, IL, USA) | Poly-D,L-lactide and Poly-l-lactide, blended with Acetyl tri-n-butyl Citrate | 2-layer | ≥6 weeks | 13 months |
| Resolut Adapt (W.L. Gore and ASSOC, Flagstaff, AZ, USA) | Poly-D,L-lactide/Co-glycolide | Good space maintainer | 8–10 weeks | 5–6 months |
| Resolut Adapt LT (W.L. Gore and ASSOC, Flagstaff, AZ, USA) | Poly-D,L-lactide/Co-glycolide | Good space maintainer | 16–24 weeks | 5–6 months |
| Epi-Guide (Curasan, Inc., Kleinostheim, Germany) | Poly-D,L-lactic acid | 3-layer Self-supporting | 20 weeks | 6–12 months |
| Vivosorb (Polyganics, Groningen, The Netherlands) | Poly(0.1-l-lactide-ε-caprolactone) can also be used as a nerve guide | | 10 weeks | 24 months |

PLGA membrane have shown similar result in extraction wound healing by GBR protocol compared with collagen membrane [70]. Besides, some study reported that both Gore-Tex® and
Resolut Adapt\textsuperscript{\textregistered} membranes in combination with bioactive glass were equally effective in enhancing the periodontal regeneration [71]. However, in a randomized controlled trial, PLGA membrane can not maintain the horizontal thickness of regenerated bone as well as Ti-e-PTFE membrane, and the latter membrane revealed less soft tissue complications [72].

PLA and PLGA membrane prepared by most fabrication techniques were stiff, which impeded their medical applications [73], while this drawback can be solved by introduction of softeners, such as \textit{N}-methyl-2-pyrrolidone (NMP). Some studies recently have shown that NMP could soften PLGA membranes and accelerate the maturation of preosteoblastic cells and bone regeneration [73–76]. When the NMP released, the membrane would turn re-stiffness again. Besides, its contents have a positive role on these PLGA membranes with regard to bone ingrowth [76]. When combined with deproteinized bovine bone mineral, this PLGA can perform similarly to native collagen [73]. In addition, 3 wt \% lauric acid can provide a remarkable plasticizing effect on PLGA because of weak intermolecular interactions in PLGA, and the elongation at break (16.1\%) is much higher than that of pure PLGA (9.1\%) [77].

Although PLA- and PLGA-based membranes are non-cytotoxic and biodegradable, the releases of oligomers and acid byproducts during degradation may trigger inflammation reactions and foreign body response \textit{in vivo} [73,78,79], and thus many studies have been carried out to tune its properties, for example, blending with hydroxyapatite (as shown in Section 4.2.).

3.2. Polycaprolactone (PCL)

Due to its biocompatibility, low cost and high mechanical strength, polycaprolactone (PCL) is an attractive biomedical polymer and has been extensively studied in bone tissue engineering [80–82]. Only a few studies have studied PCL-based GTR membranes [83,84]. PCL does not produce a local acidic environment during the degradation procedure compared with PLA and PLGA. However, the complete bioresorption \textit{in vivo} of PCL membranes is approximately 2–3 years, which is too long for application in GTR and GBR treatment [13]. Furthermore, its hydrophobicity reduces cell adhesion and proliferation. Therefore, PCL is always blended or copolymerized with other polymers before biomedical application (as shown in Section 4.1.).

3.3. Polyethylene Glycol (PEG)

Polyethylene glycol (PEG), as an important biodegradable, cell-occlusive, and biocompatible polymer, has also been a candidate for GBR and GTR membranes [85–87]. PEG hydrogel showed a high biocompatibility and tissue integration in rats, and degradation was dependent on PEG composition [86]. In a randomized controlled trial, PEG hydrogel membrane was as successful as collagen membrane in the treatment of peri-implant bony dehiscences with simplified clinical handling [87]. In addition, recent studies found that PEG membranes exhibited perspective potential for staged augmentation of challenging lateral ridge defects and preservation of the ridge contours [23,88–90].

4. Resorbable Membranes Based on Polymer Composites

4.1. Polymer Blends

As polymer membranes have several essential criteria for GBR and GTR success, including biocompatibility, proper degradation profiles, adequate mechanical and physical properties, and sufficient strength to avoid membrane collapse and assure sufficient barrier function [12], single polymer cannot meet all the criteria. For example, natural polymers always lack sufficient mechanical strength and degradation profiles, while synthetic polymers are biologically inert. It has been reported that some polyester-based membranes become stiffer and brittle after placement in PBS or artificial saliva solution [91]. It is still a challenge to develop membranes with sufficient mechanical properties, predictable degradation rate, and structure that mimics closely the native extra cellular
matrix (ECM) [92]. It may be an efficient solution to blend two kinds or more of polymers to hinder their respective limitations and show more positively synergistic effects.

4.1.1. Blends of Natural Polymers

Although chitosan is natural polymer, its bioactivity was not as well as protein polymers, and its mechanical properties are poor. Many works have been carried out by blending chitosan with other polymers to improve the mechanical properties and bioactivity of scaffolds composed of several components. For example, gelatin contains free carboxyl groups on its backbone, and it is easy to blend with chitosan to form a network by hydrogen bonding. It was shown that the ability to support cell adhesion and proliferation of gelatin/chitosan membranes was better than gelatin or chitosan alone [93]. Besides, after proanthocyanidin cross-linked, gelatin/chitosan became more stable and possessed higher mechanical properties compared with gelatin and chitosan/gelatin membranes [93]. A tri-layered membrane with a central chitosan layer sandwiched by two collagen membranes containing 20 wt % HA was fabricated [94]. The hydroxyapatite/chitosan/gelatin membranes not only promote human bone marrow mesenchymal stem cells (hBMSCs) proliferation, but also enhance progression of osteogenic differentiation [95]. These results suggest that such gelatin/chitosan or collagen/chitosan membranes are promising candidate for guided tissue and bone regeneration applications which possess sufficient mechanical and structural properties to function as a barrier membrane, and that the proteins promoted osteogenic differentiation.

4.1.2. Blends of Synthetic Polymers

PLGA is well known for having a good influence on the reconstruction of various tissues because of its superior cytocompatibility. However, because of its weak mechanical strength, it is hard to maintain the shape of a PLGA scaffold during various in vitro and in vivo experiments. Thus, PLGA have been blended with other polymers, for example, PCL/PLGA composite scaffolds were manufactured by mixing PCL and PLGA in the same ratio, and their compressive strength and modulus were much higher than that of pure PLGA scaffolds [96].

A series of PDLLA/PLGA electrospinning membrane system with appropriate degradation rate and excellent cell-occlusiveness were prepared for GTR, and the in vitro cytologic research revealed that PDLLA/PLGA composite membranes could efficiently inhibit the infiltration of human embryonic kidney 293T cells. Besides, the subcutaneous implant test on Sprague-Dawley (SD) rat showed that PDLLA/PLGA (70/30, 50/50) composite membranes could function well as a physical barrier to prevent cellular infiltration within 13 weeks, implying that PDLLA/PLGA composite membranes could serve as a promising barrier membrane for guided tissue regeneration [92]. Besides, PLA/PCL, PLGA/PCL and many other synthetic polymer composites may also have bright future in GBR and GTR [96–98].

4.1.3. Blends of Natural Polymer and Synthetic Polymer

Natural polymers always possess much better biocompatibility or bioactive properties, for example gelatin, has many integrin-binding sites for cell adhesion and differentiation [99,100]. When blend the natural polymers with synthetic polymers, it may combine both the advantages of natural and synthetic polymers. PCL-gelatin blend, a new biomaterial with good biocompatibility and improved mechanical, physical, and chemical properties, has been successfully used in neural tissue engineering [101], cartilage tissue engineering [102,103], GBR and GTR applications [99,100,104–106]. However, phase separation between PCL and gelatin is a headache to prepare composites with excellent resultant performance. Acetic acid could effectively mediate the miscibility of PCL and gelatin, and thus it was generally used to form homogeneous nanofibers with improved performance [106,107]. The biodegradation time of the membranes was also appropriate for tissue regeneration [106].

Many chitosan-based hybrid systems have been prepared to increase the cell adhesion, proliferation, and differentiation ability of polyester membranes or scaffolds. When compared to
pure PLLA electrospun membrane, PLLA/chitosan electrospun composite membranes showed more potential for clinical application due to their faster degradation rate and non-fibroblast penetration property. The degradation rate was up to 20% in six weeks, while PLLA electrospun membrane was almost non-degradable [108]. Aligned PCL–PEG nanofibers were incorporated into porous chitosan scaffolds to improve the orientation of collagen fibers in regenerated periodontium (Figure 2) [109]. Ku et al. [110] designed PLLA/chitosan multilayered membrane composed of the outer layers of chitosan mesh for ease of cell adherence and the middle layer of nanoporous PLLA for sufficient mechanical strength. The membrane maintained its integrity for up to eight weeks while allowing gradual degradation. These results suggest that these chitosan/polyester membranes may be suitable for use in GBR and GTR.

![Diagram](image)

**Figure 2.** The schematic process of fabricating PCL–PEG nanofibers embedded 3D scaffold by incorporating PCL–PEG nanofibrous mats (aligned or random) into porous chitosan scaffold. The optical image displays a representative section view of the scaffold with width of 103.38 ± 49.54 µm between layers. Reprinted with permission from Elsevier [109].

### 4.2. Bio-Ceramic/Polymer Composites

In order to develop attractive biomaterials for GBR and GTR, considerable attention has been paid to biomimetic bone extracellular matrix (ECM) structure, composites of polymer and bio-ceramics component [111]. The latter component refers to hydroxyapatite (HA) [112], carbonated hydroxyapatite (CHA) [113], bioactive glass (BG) [114], β-calcium phosphate (β-TCP) [115,116] and so on, which is known for its good osteoinductive, osteoconductive properties and excellent biocompatibility [117]. Among the available bioactive ceramics, except for its superior osteogenic and angiogenic effects [118,119], BG can regenerate not only hard tissues, but also soft tissues [120], and thus BG has received increasing attention in periodontal regeneration, since the periodontal tissues consist of both hard tissues (i.e., cementum and alveolar bone) and soft tissues (i.e., gingiva and PDL). It has been shown that the incorporation of bioactive ceramics can significantly enhance mineralization and cell activities on polymer membranes, indicating favorable osteoconductivity and/or osteoinductivity for GTR and GBR applications [45,83,114,121,122]. Besides, these bioactive materials can improve the mechanical properties [123]. The 10–30 wt % nanoapatite in the membrane demonstrated higher tensile strength (0.61 MPa) compared with pure PLGA (0.49 MPa) [77]. Moreover, the addition of bio-ceramics can neutralize the acidic degradation products from the polymers such as PLA and chitosan by the alkali groups [45,47,124]. These composite membranes are assumed to have the ability to preserve the structural and biological functions of the damaged hard tissues in a more efficient and biomimetic way [125]. Zinc HA powders were introduced into a heat treated cross-linked gelatin membrane, which exhibited greater bone formation than collagen membrane did. It was Zinc HA that stimulated...
bone formation through the actions of zinc ions accelerating the proliferation and differentiation of osteogenic cell [57,126]. A biomimetic coating of apatite on a collagen template can be considered an efficient alternative [127]. Biomimetic precipitation process has been used to form apatite coating on collagen formulations [128–130]. This emphasizes the need for polymer/bio-ceramics composite materials that can combine the advantage of both materials.

5. Resorbable Membranes Containing Functional Materials

5.1. Polymer Membranes Loaded with Antibacterial Agents

The development of periodontitis is mainly related to bacteria activities. Moreover, bacterial infections are currently considered to be the major reason for the failure of GTR and GBR membranes in clinical applications. Antibacterial properties attached to GTR and GBR membranes is one of the greatest interests in the war against implant-related infections, representing the broadest group of anti-infective biomaterials [131]. Membranes loaded with antibiotics have been designed for local drug release to overcome the adverse effects of conventional systemic drug administration. For example, metronidazole (MNA)-loaded polymeric membrane showed a significant improvement on the periodontal and bone regeneration following GTR and GBT [100,106,107,132]. The PCL/gelatin electrospun membrane loaded with 30% MNA had the best comprehensive properties including superior biocompatibility and antibacterial ability [100]. Moreover, acetic acid was introduced to effectively connect strong interaction between PCL, gelatin, and MNA [106,107]. The controlled and sustained release of MNA from the membranes significantly prevented the colonization of anaerobic bacteria [106].

In additional to antibiotics, non-antibiotic antibacterial agents also possess a superior antibacterial ability and have been used in GTR and GBR. Lauric acid loaded PLGA-CaP hybrid membranes [77] and ZnO-loaded PCL or PCL/gelatin electrospun membranes [133] have been designed for GTR and GBR. Chitosan nanoparticles and chlorhexidine have also been added in collagen membranes to endow antibacterial activity for periapical guided tissue regeneration [53].

Generally, antibiotics were directly blended with membranes, resulting in a high burst release and short release period that could not effectively prevent bacterial infections. Hence, it is important to develop novel GTR and GBR membranes with sustained and controlled release of antibacterial agents, especially when used for patients with a predisposition to these kinds of complications: smokers, patients with diabetes mellitus, and so on [134–136].

5.2. Polymer Membranes Loaded with Growth Factors

Growth factors are critical signaling molecules that instruct cells behavior through binding to specific transmembrane receptors on the target cells, and one may achieve tissue regeneration by enabling control over growth factor delivery [137]. GBR and GTR membrane can act as a localized controlled release system for growth factors, hence to encourage the differentiation of osteogenic progenitor cell types in the secluded space under the membrane [104]. In the past decades, controlled drug delivery systems and biomaterial scaffolds with various osteogenic factors, especially bone morphogenetic proteins (BMPs), are widely used clinically to promote bone regeneration [138]. BMPs have an unparalleled, dose-dependent potential to augment alveolar bone by triggering the angiogenesis, migration, and proliferation of mesenchymal stem cells, and their differentiation to osteoblasts and chondroblasts. Still, the appropriate methods and optimal doses to allow safe use of recombinant human bone morphogenetic protein-2 (rhBMP-2) is a challenge [139]. PCL/PLGA/β-TCP GBR membrane loaded with rhBMP-2 was successfully prepared via 3-D printing method, realizing sustained release of rhBMP-2 up to 28 days; meanwhile, after four and eight weeks in vivo test, the implantation of rhBMP-2 loaded membrane induced much more new bone formation and led to almost entire healing of 8 mm calvarial defects within eight weeks [115]. When incorporating BMP-2 in the core and silk fibroin/chitosan/HA as the shell layer of a nanofiber with two different shell thicknesses
Schematic Representation of the Preparation of SCHB2-Thick and SCHB2-Thin Nanofibrous Membranes through Coaxial Electrospinning and Their Influence on human marrow mesenchymal stem cells. Reprinted with permission from American Chemical Society 2015 [140].

6. Resorbable Membranes Based on Other Polymer

Although a minor application, platelet-rich fibrin (PRF) in a compressed membrane-like form has also been used as a substitute for commercially available barrier membranes in GTR treatment [142]. PRF is composed of a biopolymer fibrin, and acts as a potent source of growth factors to facilitate the tissue regeneration. However, its rapid degradability within two weeks or less at implantation sites, attaches the disadvantages to application in GBT and GTR for sufficient periods of time [143]. Cross-linking treatments, regardless of methodology, can provide resistance against enzyme-dependent degradation while simultaneously sacrificing the bioactivity of the PRF. Thus, appropriate cross-linking treatment may be a solution to make PRF suitable for GBR and GTR, as long as balance its degradability time and sufficient bioactivity. Freshly prepared human PRF was first compressed with dry gauze and subsequently with a hot iron. Kawase et al. [143] employed the heat treatment to prepare PRF membrane, which appeared plasmin-resistant and remained stable for longer than 10 days in vitro compared to gauze-compressed PRF. This technique reduces the rate of biodegradation without sacrificing its biocompatibility. Therefore, PRF membranes have promising potential applied as a barrier membrane in the GTR treatment.

Salicylic acid-based poly(anhydride-esters) (SAPAE) has been a promising candidate under issue to improve diabetes’ bone or periodontal tissues regeneration [144]. SAPAE have been synthesized

(SCHB2-thick and SCHB-thin), the release rate of BMP-2 and the concentration of BMP-2 in the release medium were higher for SCHB2-thin membranes because of reduced shell thickness. Compared with SF/CS and SF/CS/HA membranes, BMP-2 obviously promoted osteogenic differentiation of hBMSCs (Figure 3) [140]. Stromal cell-derived factor-1α (SDF-1α) regulates the migration of hBMSCs in a dose-dependent manner [141]. Compared to the bare membranes, SDF-1α loaded membranes yielded a six-fold growth in the amount of bone formation [104]. These membranes with adequate mechanical properties and the capacity to release growth factors with tailor-made kinetics have potential for optimizing clinical application of GBR and GTR.
by chemically incorporating salicylic acid, a nonsteroidal anti-inflammatory drug, that reduces the production of pro-inflammatory cytokines within a polyanhydride [145]. Subramanian et al. [146] tested SAPAE membrane as a physical barrier and localized salicylic acid delivery system to restrict BMP-2 activity to a specified region. The data indicated that SAPAE polymer membranes have potential application in GBR and GTR procedures and as a barrier to excessive bone formation for diabetes.

7. Conclusions and Perspectives

Different types of biodegradable membranes are commonly used in GTR and GBR, as barrier devices to isolate the epithelium from bone tissue to favor bone regeneration. In this review, the advantages and disadvantages of polymer membranes were introduced. The non-degradable e-PTFE membranes have disadvantages such as non-resorbability and the need for a second surgical operation, and thus biodegradable membranes including natural and synthetic polymers showed many exciting advantages. Natural polymer membranes have excellent biological properties, such as cell adhesiveness and biodegradability, however, they are characterized by low mechanical strength and short degradation cycle. As a control, membranes based on biodegradable synthetic polymers possess tuned biodegradation, sufficient mechanical strengths, low rigidity, manageability and processability, while their biological activity is generally not as good as natural polymers. They may also be subject to drawbacks including inflammatory foreign-body reactions associated with their degradation products.

Despite the various drawbacks of biodegradable polymers, they are irreplaceable in GTR and GBR. More and more studies will be carried out on biodegradable polymers and their blends or composites. For example, to some extent, polymer membranes often sacrifice their early angiogenesis and osteogenesis. Thus, future works should address how to effectively promote the osteogenic activities of these membranes when long barrier function time is needed, and hence reach the balance among physiochemical, mechanical and biological properties. Bioactive ceramics that can significantly enhance mineralization and cell activities, combined with biodegradable polymers will be researched more and more. In addition, special membranes with various functional materials, such as antibacterial agents and growth factors, and membranes with tunable degradation speed, mechanical properties and controlled release behaviors will be designed accurately according to clinical demand.

Acknowledgments: This work was financially supported by the National Natural Science Foundation of China (No. 51463013), the Natural Science Foundation of Jiangxi Province of China (No. 20151BAB206011), the Health and Family Planning Commission Science Foundation of Jiangxi Province of China (No. 20161082) and Natural science foundation of Nanchang institute of technology (2012KJ028).

Author Contributions: Junchao Wei and Lan Liao conceived and designed the structure and main content of the article. Jiaolong wang, Lina Wang and Junchao Wei write the article. Ziyu Zhou, Hanjian Lai and Pan Xu helped analyze the documents.

Conflicts of Interest: The authors declare no conflict of interest.

References
1. Hurley, L.A.; Stinchfield, F.E.; Bassett, C.A.L.; Lyon, W.H. The role of soft tissues in osteogenesis. J. Bone Jt. Surg. Am. 1959, 41, 1243–1266.
2. Gottlow, J.; Nyman, S.; Karring, T.; Lindhe, J. New attachment formation as the result of controlled tissue regeneration. J. Clin. Periodontol. 1984, 11, 494–503. [CrossRef] [PubMed]
3. Villar, C.C.; Cochran, D.L. Regeneration of periodontal tissues: Guided tissue regeneration. Dent. Clin. North Am. 2010, 54, 73–92. [CrossRef] [PubMed]
4. Dahlin, C.; Senneryby, L.; Lekholm, U.; Linde, A.; Nyman, S. Generation of new bone around titanium implants using a membrane technique: An experimental study in rabbits. Int. J. Oral Maxillofac. Implants 1989, 4, 19–25. [PubMed]
5. Moses, O.; Pitaru, S.; Artzi, Z.; Nemcovsky, C.E. Healing of dehiscence-type defects in implants placed together with different barrier membranes: A comparative clinical study. Clin. Oral Implants Res. 2005, 16, 210–219. [CrossRef] [PubMed]
6. Lee, J.-Y.; Lee, J.; Kim, Y.-K. Comparative analysis of guided bone regeneration using autogenous tooth bone graft material with and without resorbable membrane. J. Dent. Sci. 2013, 8, 281–286. [CrossRef]

7. Beilittum, I.; Artzi, Z.; Nemcovsky, C.E. Clinical evaluation of particulate allogeneic with and without autogenous bone grafts and resorbable collagen membranes for bone augmentation of atrophic alveolar ridges: Bone augmentation with allo- and autografts and collagen membrane. Clin. Oral Implants Res. 2010, 21, 1242–1250. [CrossRef] [PubMed]

8. Retzepi, M.; Donos, N. Guided bone regeneration: Biological principle and therapeutic applications. Clin. Oral Implants Res. 2010, 21, 567–576. [CrossRef] [PubMed]

9. Dimitriou, R.; Mataliotakis, G.I.; Calori, G.M.; Giannoudis, P.V. The role of barrier membranes for guided bone regeneration and restoration of large bone defects: Current experimental and clinical evidence. BMC Med. 2012, 10, 1–24. [CrossRef] [PubMed]

10. Sowmya, S.; Bumgardener, J.D.; Chennazhi, K.P.; Nair, S.V.; Jayakumar, R. Role of nanostructured biopolymers and biocermamics in enamel, dentin and periodontal tissue regeneration. Prog. Polym. Sci. 2013, 38, 1748–1772. [CrossRef]

11. Abou Neel, E.A.; Bozec, L.; Knowles, J.C.; Syed, O.; Muddera, V.; Day, R.; Hyun, J.K. Collagen—Emerging collagen based therapies hit the patient. Adv. Drug Deliv. Rev. 2013, 65, 429–456. [CrossRef] [PubMed]

12. Zupancic, S.; Kocbek, P.; Baungartner, S.; Kristl, J. Contribution of nanotechnology to improved treatment of periodontal disease. Curr. Pharm. Des. 2015, 21, 3257–3271. [CrossRef] [PubMed]

13. Gentile, P.; Chiono, V.; Tonda-Turo, C.; Ferreira, A.M.; Ciardelli, G. Polymeric membranes for guided bone regeneration. Biotechnol. J. 2011, 6, 1187–1197. [CrossRef] [PubMed]

14. Gielkens, P.F.M.; Schortinghuis, J.; de Jong, J.R.; Raghoebear, G.M.; Stegenga, B.; Bos, R.R.M. Vivosorb®, Bio-Gide®, and Gore-Tex® as barrier membranes in rat mandibular defects: An evaluation by microradiography and micro-CT. Clin. Oral Implants Res. 2008, 19, 516–521. [CrossRef] [PubMed]

15. Kozlovsky, A.; Aboodi, G.; Moses, O.; Tal, H.; Artzi, Z.; Weinreb, M.; Nemcovsky, C.E. Bio-degradation of a resorbable collagen membrane (Bio-Gide®) applied in a double-layer technique in rats. Clin. Oral Implants Res. 2009, 20, 1116–1123. [CrossRef] [PubMed]

16. Gloria, A.; Ronca, D.; Russo, T.; D’Amora, U.; Chierchia, M.; De Santis, R.; Nicolais, L.; Ambrosio, L. Technical features and criteria in designing fiber-reinforced composite materials: From the aerospace and aeronautical field to biomedical applications. J. Appl. Biomater. Biomech. 2011, 9, 151–163. [CrossRef] [PubMed]

17. Nair, L.S.; Laurencin, C.T. Biodegradable polymers as biomaterials. Prog. Polym. Sci. 2007, 32, 762–798. [CrossRef]

18. Klinger, A.; Asad, R.; Shapira, L.; Zuberb, Y. In vivo degradation of collagen barrier membranes exposed to the oral cavity. Clin. Oral Implants Res. 2010, 21, 873–876. [PubMed]

19. Thoma, D.S.; Villar, C.C.; Cochran, D.L.; Hämerle, C.H.F.; Jung, R.E. Tissue integration of collagen-based matrices: An experimental study in mice. Clin. Oral Implants Res. 2012, 23, 1333–1339. [CrossRef] [PubMed]

20. Owens, K.W.; Yukna, R.A. Collagen membrane resorption in dogs: A comparative study. Implant Dent. 2001, 10, 49–58. [CrossRef] [PubMed]

21. Rothamel, D.; Schwarz, F.; Sager, M.; Herten, M.; Sculean, A.; Becker, J. Biodegradation of differently cross-linked collagen membranes: An experimental study in the rat. Clin. Oral Implants Res. 2005, 16, 369–378. [CrossRef] [PubMed]

22. Rothamel, D.; Schwarz, F.; Fienitz, T.; Smeets, R.; Dreiseidler, T.; Ritter, L.; Happe, A.; Zöller, J. Biocompatibility and biodegradation of a native porcine pericardium membrane: Results of in vitro and in vivo examinations. Int. J. Oral Maxillofac. Implants 2012, 27, 146–154. [PubMed]

23. Benic, G.I.; Haemmerle, C.H.F. Horizontal bone augmentation by means of guided bone regeneration. Periodontol. 2000 2014, 66, 13–40. [CrossRef] [PubMed]

24. Sela, M.N.; Babitski, E.; Steinberg, D.; Kohavi, D.; Rosen, G. Degradation of collagen-guided tissue regeneration membranes by proteolytic enzymes of Porphyromonas gingivalis and its inhibition by antibacterial agents. Clin. Oral Implants Res. 2009, 20, 496–502. [CrossRef] [PubMed]

25. Sela, M.N.; Kohavi, D.; Krausz, E.; Steinberg, D.; Rosen, G. Enzymatic degradation of collagen-guided tissue regeneration membranes by periodontal bacteria. Clin. Oral Implants Res. 2003, 14, 263–268. [CrossRef] [PubMed]

26. Schlegel, A.K.; Möhler, H.; Busch, F.; Mehl, A. Preclinical and clinical studies of a collagen membrane (Bio-Gide). Biomaterials 1997, 18, 535–538. [CrossRef]
27. Caballé-Serrano, J.; Sawada, K.; Miron, R.J.; Bosshardt, D.D.; Buser, D.; Gruber, R. Collagen barrier membranes adsorb growth factors liberated from autogenous bone chips. *Clin. Oral Implants Res.* 2016. [CrossRef] [PubMed]

28. Sell, S.A.; McClure, M.J.; Garg, K.; Wolfe, P.S.; Bowlin, G.L. Electrospinning of collagen/biopolymers for regenerative medicine and cardiovascular tissue engineering. *Adv. Drug Deliv. Rev.* 2009, 61, 1007–1019. [CrossRef] [PubMed]

29. Schwarz, F.; Rothamel, D.; Herten, M.; Sager, M.; Becker, J. Angiogenesis pattern of native and cross-linked collagen membranes: An immunohistochemical study in the rat. *Clin. Oral Implants Res.* 2006, 17, 403–409. [CrossRef] [PubMed]

30. Hoogeveen, E.J.; Gielkens, P.F.M.; Schortinghuis, J.; Ruben, J.L.; Huysmans, M.-C.D.N.J.M.; Stegenga, B. Vivosorb as a barrier membrane in rat mandibular defects. An evaluation with transversal microradiography. *Int. J. Oral Maxillofac. Surg.* 2009, 38, 870–875. [CrossRef] [PubMed]

31. Döri, F.; Huszár, T.; Nikolidakis, D.; Arweiler, N.B.; Gera, I.; Sculean, A. Effect of platelet-rich plasma on the healing of intra-bony defects treated with a natural bone mineral and a collagen membrane. *J. Clin. Periodontol.* 2007, 34, 254–261. [CrossRef] [PubMed]

32. Ferreira, A.M.; Gentile, P.; Chiono, V.; Ciardelli, G. Collagen for bone tissue regeneration. *Acta Biomater.* 2012, 8, 3191–3200. [CrossRef] [PubMed]

33. Bunyaratavej, P.; Wang, H.-L. Collagen membranes: A review. *J. Periodontol.* 2001, 72, 215–229. [CrossRef] [PubMed]

34. Zhang, Y.; Mao, W.; Wang, J.; Li, Q.-L.; Mei, M.L.; Chu, C.H.; Xia, R.; Zhang, Z.-H. Antibacterial membrane with a bone-like structure for guided bone regeneration. *J. Nanomater.* 2015, 2015, 1–8. [CrossRef]

35. Tal, H.; Kozlovsky, A.; Artzi, Z.; Nemcovsky, C.E.; Moses, O. Long-term bio-degradation of cross-linked and non-cross-linked collagen barriers in human guided bone regeneration. *Clin. Oral Implants Res.* 2008, 19, 295–302. [CrossRef] [PubMed]

36. Zubery, Y.; Goldlust, A.; Alves, A.; Nir, E. Ossification of a novel cross-linked porcine collagen barrier in guided bone regeneration in dogs. *J. Periodontol.* 2007, 78, 112–121. [CrossRef] [PubMed]

37. Zubery, Y.; Nir, E.; Goldlust, A. Ossification of a collagen membrane cross-linked by sugar: A human case series. *J. Periodontol.* 2008, 79, 1101–1107. [CrossRef] [PubMed]

38. Drexler, J.W.; Powell, H.M. Dehydrothermal crosslinking of electrospun collagen. *Tissue Eng. Part C Methods* 2011, 17, 9–17. [CrossRef] [PubMed]

39. Lee, J.-H.; Lee, J.-S.; Baek, W.-S.; Lim, H.-C.; Cha, J.-K.; Choi, S.-H.; Jung, U.-W. Assessment of dehydrothermally cross-linked collagen membrane for guided bone regeneration around peri-implant dehiscence defects: A randomized single-blinded clinical trial. *J. PeriodontalImplant Sci.* 2015, 45, 229–237. [CrossRef] [PubMed]

40. Cha, J.K.; Joo, M.-J.; Yoon, S.; Lee, J.-S.; Choi, S.-H.; Jung, U.-W. Sequential healing of onlay bone grafts using combining biomaterials with cross-linked collagen in dogs. *Clin. Oral Implants Res.* 2016. [CrossRef] [PubMed]

41. Delgado, L.M.; Bayon, Y.; Pandit, A.; Zeugolis, D.I. To cross-link or not to cross-link? Cross-linking associated foreign body response of collagen-based devices. *Tissue Eng. Part B Rev.* 2015, 21, 298–313. [CrossRef] [PubMed]

42. Veríssimo, D.M.; Leitão, R.F.C.; Ribeiro, R.A.; Figueiró, S.D.; Sombra, A.S.B.; Góes, J.C.; Brito, G.A.C. Polyanionic collagen membranes for guided tissue regeneration: Effect of progressive glutaraldehyde cross-linking on biocompatibility and degradation. *Acta Biomater.* 2010, 6, 4011–4018. [CrossRef] [PubMed]

43. Annen, B.M.; Ramel, C.F.; Hämmerle, C.H.; Jung, R.E. Use of a new cross-linked collagen membrane for the treatment of peri-implant dehiscence defects: A randomised controlled double-blinded clinical trial. *Eur. J. Oral Implantol.* 2011, 4, 87–100. [PubMed]

44. Xu, C.; Lei, C.; Meng, L.; Wang, C.; Song, Y. Chitosan as a barrier membrane material in periodontal tissue regeneration. *J. Biomed. Mater. Res. B Appl. Biomater.* 2012, 100, 1435–1443. [CrossRef] [PubMed]

45. Mota, J.; Yu, N.; Caridade, S.G.; Luz, G.M.; Gomes, M.E.; Reis, R.L.; Jansen, J.A.; Walboomers, X.F.; Mano, J.F. Chitosan/bioactive glass nanoparticle composite membranes for periodontal regeneration. *Acta Biomater.* 2012, 8, 4173–4180. [CrossRef] [PubMed]

46. Dash, M.; Chiellini, F.; Ottenbrite, R.M.; Chiellini, E. Chitosan—a versatile semi-synthetic polymer in biomedical applications. *Prog. Polym. Sci.* 2011, 36, 981–1014. [CrossRef]
47. Qasim, S.B.; Delaine-Smith, R.M.; Fey, T.; Rawlinson, A.; Rehman, I.U. Freeze gelated porous membranes for periodontal tissue regeneration. *Acta Biomater.* 2015, 23, 317–328. [CrossRef] [PubMed]

48. Shin, S.-Y.; Park, H.-N.; Kim, K.-H.; Lee, M.-H.; Choi, Y.S.; Park, Y.-J.; Lee, Y.-M.; Ku, Y.; Rhyu, I.-C.; Han, S.-B.; et al. Biological evaluation of chitosan nanofiber membrane for guided bone regeneration. *J. Periodontol.* 2005, 76, 1778–1784. [CrossRef] [PubMed]

49. Bavariya, A.J.; Andrew Norowski, P.; Mark Anderson, K.; Adatrow, P.C.; Garcia-Godoy, F.; Stein, S.H.; Bumgardner, J.D. Evaluation of biocompatibility and degradation of chitosan nanofiber membrane crosslinked with genipin. *J. Biomed. Mater. Res. B Appl. Biomater.* 2014, 102, 1084–1092. [CrossRef] [PubMed]

50. Mi, F.L.; Tan, Y.C.; Liang, H.C.; Huang, R.N.; Sung, H.W. *In vitro* evaluation of a chitosan membrane cross-linked with genipin. *J. Biomat. Sci. Polym. Ed.* 2001, 12, 835–850. [CrossRef] [PubMed]

51. Norowski, P.A.; Fujiwara, T.; Clem, W.C.; Adatrow, P.C.; Eckstein, E.C.; Haggard, W.O.; Bumgardner, J.D. Novel naturally crosslinked electrospun nanofibrous chitosan mats for guided bone regeneration membranes: Material characterization and cytocompatibility. *J. Tissue Eng. Regen. Med.* 2015, 9, 577–583. [CrossRef] [PubMed]

52. Kaya, M.; Baran, T.; Erdoğan, S.; Mentese, A.; Aşan Özüsgağlam, M.; Çakmak, Y.S. Physicochemical comparison of chitin and chitosan obtained from larvae and adult Colorado potato beetle (*Leptinotarsa decemlineata*). *Mater. Sci. Eng. C Mater. Biol. Appl.* 2014, 45, 72–81. [CrossRef] [PubMed]

53. Soto Barreras, U.; Torres Mendez, F.; Martinez Martinez, R.E.; Valencia, C.S.; Martinez Rodriguez, P.R.; Loyola Rodriguez, J.P. Chitosan nanoparticles enhance the antibacterial activity of chlorhexidine in collagen membranes used for periapical guided tissue regeneration. *Mater. Sci. Eng. C Mater. Biol. Appl.* 2016, 58, 1182–1187. [CrossRef] [PubMed]

54. Mogosanu, G.D.; Grumezescu, A.M. Natural and synthetic polymers for wounds and burns dressing. *Int. J. Pharm.* 2014, 463, 127–136. [CrossRef] [PubMed]

55. Jiang, T.; Carbone, E.J.; Lo, K.W.-H.; Laurencin, C.T. Electrospinning of polymer nanofibers for tissue regeneration. *Prog. Polym. Sci.* 2015, 46, 1–24. [CrossRef]

56. Zhang, S.; Huang, Y.; Yang, X.; Mei, F.; Ma, Q.; Chen, G.; Ryu, S.; Deng, X. Gelatin nanofibrous membrane fabricated by electrospinning of aqueous gelatin solution for guided tissue regeneration. *J. Biomed. Mater. Res. A* 2009, 90, 671–679. [CrossRef] [PubMed]

57. Chou, J.; Komuro, M.; Hao, J.; Kuroda, S.; Hattori, Y.; Ben-Nissan, B.; Mithorpe, B.; Otsuka, M. Bioresorbable zinc hydroxyapatite guided bone regeneration membrane for bone regeneration. *Clin. Oral Implants Res.* 2016, 27, 354–360. [CrossRef] [PubMed]

58. Noritake, K.; Kuroda, S.; Nyan, M.; Ohy, K.; Tabata, Y.; Kasugai, S. Development of a new barrier membrane for guided bone regeneration: An *in vitro* and *in vivo* study. *J. Oral Tissue Eng.* 2011, 9, 53–63.

59. Altman, G.H.; Diaz, F.; Jakuba, C.; Calabro, T.; Horan, R.L.; Chen, J.; Lu, H.; Richmond, J.; Kaplan, D.L. Silk-based biomaterials. *Biomaterials* 2003, 24, 401–416. [CrossRef]

60. Santin, M.; Motta, A.; Freddi, G.; Cannas, M. *In vitro* evaluation of the inflammatory potential of the silk fibroin. *J. Biomed. Mater. Res. 1999*, 46, 382–389. [CrossRef]

61. Kim, K.H.; Jeong, L.; Park, H.N.; Shin, S.Y.; Park, W.H.; Lee, S.C.; Kim, T.I.; Park, Y.J.; Seol, Y.J.; Lee, Y.M.; et al. Biological efficacy of silk fibroin nanofiber membranes for guided bone regeneration. *J. Biotechnol.* 2005, 120, 327–339. [CrossRef] [PubMed]

62. Ha, Y.-Y.; Park, Y.-W.; Kweon, H.; Jo, Y.-Y.; Kim, S.-G. Comparison of the physical properties and *in vivo* bioactivities of silkworm-cocoon-derived silk membrane, collagen membrane, and polytetrafluoroethylene membrane for guided bone regeneration. *Macromol. Res.* 2014, 22, 1018–1023. [CrossRef]

63. Von Arx, T.; Cochran, D.L.; Schenk, R.K.; Buser, D. Evaluation of a prototype trilayer membrane (PTLM) for lateral ridge augmentation: An experimental study in the canine mandible. *Int. J. Oral Maxillofac. Surg.* 2002, 31, 190–199. [CrossRef] [PubMed]

64. Simion, M.; Misitano, U.; Gionso, L.; Salvato, A. Treatment of dehiscences and fenestrations around dental implants using resorbable and nonresorbable membranes associated with bone autografts: A comparative clinical study. *Int. J. Oral Maxillofac.* *Implants* 1997, 12, 159–167. [PubMed]

65. Lorenzoni, M.; Pertl, C.; Keil, C.; Wegscheider, W.A. Treatment of peri-implant defects with guided bone regeneration: A comparative clinical study with various membranes and bone grafts. *Int. J. Oral Maxillofac. Implants* 1998, 13, 639–646. [PubMed]
66. Haidar, Z.S. Bio-inspired-/functional colloidal core-shell polymeric-based nanosystems: Technology promise in tissue engineering, bioimaging and nanomedicine. *Polymers* 2010, 2, 323–352. [CrossRef]  
67. Donos, N.; Kostopoulos, L.; Karring, T. Alveolar ridge augmentation using a resorbable copolymer membrane and autogenous bone grafts. An experimental study in the rat. *Clin. Oral Implants Res.* 2002, 13, 203–213. [CrossRef] [PubMed]  
68. Stavropoulos, F.; Dahlín, C.; Ruskin, J.D.; Johansson, C. A comparative study of barrier membranes as graft protectors in the treatment of localized bone defects. An experimental study in a canine model. *Clin. Oral Implants Res.* 2004, 15, 435–442. [CrossRef] [PubMed]  
69. Lundgren, D.; Mathisen, T.; Gottlow, J. The development of a bioresorbable barrier for guided tissue regeneration. *Swed. Dent. J.* 1994, 86, 741–756.  
70. Hua, N.; Ti, V.L.; Xu, Y. Biodegradable effect of PLGA membrane in alveolar bone regeneration on beagle dog. *Cell Biochem. Biophys.* 2014, 70, 1051–1055. [CrossRef] [PubMed]  
71. Wadhawan, A.; Gowdā, T.M.; Mehta, D.S. Gore-tex® versus resolut adapt® GTR membranes with perioglas® in periodontal regeneration. *Contemp. Clin. Dent.* 2012, 3, 406–411. [CrossRef] [PubMed]  
72. Schneider, D.; Weber, F.E.; Grunder, U.; Andreoni, C.; Burkhardt, R.; Jung, R.E. A randomized controlled clinical multicenter trial comparing the clinical and histological performance of a new, modified polylactide-co-glycolide acid membrane to an expanded polytetrafluorethylene membrane in guided bone regeneration procedures. *Clin. Oral Implants Res.* 2014, 25, 150–158. [CrossRef] [PubMed]  
73. Jung, R.E.; Kokovics, V.; Jurisic, M.; Yaman, D.; Subramani, K.; Weber, F.E. Guided bone regeneration with a synthetic biodegradable membrane: A comparative study in dogs. *Clin. Oral Implants Res.* 2009, 20, 1084–1091. [CrossRef] [PubMed]  
74. Miguel, B.S.; Ghayor, C.; Ehrbar, M.; Jung, R.E.; Zwahlen, R.A.; Hortschansky, P.; Schmoekel, H.G.; Weber, F.E. N-methyl pyrrolidone as a potent bone morphogenetic protein enhancer for bone tissue engineering. *Tissue Eng. Part A* 2009, 15, 2955–2963. [CrossRef] [PubMed]  
75. Zwahlen, R.A.; Cheung, L.K.; Zheng, L.-W.; Chow, R.L.K.; Li, T.; Schuknecht, B.; Gratz, K.W.; Weber, F.E. Comparison of two resorbable membrane systems in bone regeneration after removal of wisdom teeth: A randomized-controlled clinical pilot study. *Clin. Oral Implants Res.* 2009, 20, 1084–1091. [CrossRef] [PubMed]  
76. Karfeld-Sulzer, L.S.; Ghayor, C.; Siegenthaler, B.; Gjoksi, B.; Pohjonen, T.H.; Weber, F.E. Comparative study of NMP-preloaded and dip-loaded membranes for guided bone regeneration of rabbit cranial defects. *J. Tissue Eng. Regen. Med.* 2014. [CrossRef] [PubMed]  
77. Jamuna-Thevi, K.; Saarani, N.N.; Abdul Kadir, M.R.; Hermawan, H. Triple-layered PLGA/nanoapatite/lauric acid graded composite membrane for periodontal guided bone regeneration. *Mater. Sci. Eng. C Mater. Biol. Appl.* 2014, 43, 253–263. [CrossRef] [PubMed]  
78. Van Leeuwen, A.C.; Huddleston Slater, J.J.R.; Gielkens, P.F.M.; de Jong, J.R.; Grijpma, D.W.; Bos, R.R.M. Guided bone regeneration in rat mandibular defects using resorbable poly(trimethylene carbonate) barrier membranes. *Acta Biomater.* 2012, 8, 1422–1429. [CrossRef] [PubMed]  
79. Zhou, H.; Lawrence, J.G.; Bhaduri, S.B. Fabrication aspects of PLA-CaP/PLGA-CaP composites for orthopedic applications: A review. *Acta Biomater.* 2012, 8, 1999–2016. [CrossRef] [PubMed]  
80. De Santis, R.; Gloria, A.; Russo, T.; D’Amora, U.; D’Antò, V.; Bollino, F.; Catauro, M.; Mollica, F.; Rengo, S.; Ambrosio, L. Advanced composites for hard-tissue engineering based on PCL/organic-inorganic hybrid fillers: From the design of 2D substrates to 3D rapid prototyped scaffolds. *Polym. Compos.* 2013, 34, 1413–1417. [CrossRef]  
81. Domingos, M.; Intranuovo, F.; Russo, T.; Santis, R.D.; Gloria, A.; Ambrosio, L.; Ciurana, J.; Bartolo, P. The first systematic analysis of 3D rapid prototyped poly(ε-caprolactone) scaffolds manufactured through BioCell printing: The effect of pore size and geometry on compressive mechanical behaviour and in vitro hMSC viability. *Biofabrication* 2013, 5, 045004. [CrossRef] [PubMed]  
82. De Santis, R.; Russo, A.; Gloria, A.; D’Amora, U.; Russo, T.; Panseri, S.; Sandri, M.; Tampieri, A.; Marcacci, M.; Dediu, V.A.; et al. Towards the design of 3D fiber-deposited poly(ε-caprolactone)/iron-doped hydroxyapatite nanocomposite magnetic scaffolds for bone regeneration. *J. Biomed. Nanotechnol.* 2015, 11, 1236–1246. [CrossRef] [PubMed]  
83. Yang, F.; Both, S.K.; Yang, X.; Walboomers, X.F.; Jansen, J.A. Development of an electrospun nano-apatite/PCL composite membrane for GTR/GBR application. *Acta Biomater.* 2009, 5, 3295–3304. [CrossRef] [PubMed]
84. Fujihara, K.; Kotaki, M.; Ramakrishna, S. Guided bone regeneration membrane made of polycaprolactone/calcium carbonate composite nano-fibers. *Biomaterials* **2005**, *26*, 4139–4147. [CrossRef] [PubMed]

85. Thoma, D.S.; Hälg, G.-A.; Dard, M.M.; Seibl, R.; Hammerle, C.H.F.; Jung, R.E. Evaluation of a new biodegradable membrane to prevent gingival ingrowth into mandibular bone defects in minipigs. *Clin. Oral Implants Res.* **2009**, *20*, 7–16. [CrossRef] [PubMed]

86. Herten, M.; Jung, R.E.; Ferrari, D.; Rothamel, C.F.; Hämmerle, C.H.F.; Becker, J.; Schwarz, F. Biodegradation of different synthetic hydrogels made of polyethylene glycol hydrogel/RGD-peptide modifications: An immunohistochemical study in rats. *Clin. Oral Implants Res.* **2009**, *20*, 116–125. [CrossRef] [PubMed]

87. Jung, R.E.; Hälg, G.A.; Thoma, D.S.; Hämmerle, C.H.F. A randomized, controlled clinical trial to evaluate a new membrane for guided bone regeneration around dental implants. *Clin. Oral Implants Res.* **2009**, *20*, 162–168. [CrossRef] [PubMed]

88. Schwarz, F.; Mihatovic, I.; Golubovic, V.; Hegewald, A.; Becker, J. Influence of two barrier membranes on staged guided bone regeneration and osseointegration of titanium implants in dogs: Part 1. Augmentation using bone graft substitutes and autogenous bone. *Clin. Oral Implants Res.* **2012**, *23*, 83–89. [CrossRef] [PubMed]

89. Mihatovic, I.; Becker, J.; Golubovic, V.; Hegewald, A.; Schwarz, F. Influence of two barrier membranes on staged guided bone regeneration and osseointegration of titanium implants in dogs. Part 2: Augmentation using bone graft substitutes. *Clin. Oral Implants Res.* **2012**, *23*, 308–315. [CrossRef] [PubMed]

90. Owen, G.R.; Jackson, J.K.; Chehroudi, B.; Brunette, D.M.; Burt, H.M. An in vitro study of plasticized poly(lactic-co-glycolic acid) films as possible guided tissue regeneration membranes: Material properties and drug release kinetics. *J. Biomed. Mater. Res. A* **2010**, *95*, 857–869. [CrossRef] [PubMed]

91. Vaquette, C.; Cooper-White, J. A simple method for fabricating 3-D multilayered composite scaffolds. *Acta Biomater.* **2013**, *9*, 4599–4608. [CrossRef] [PubMed]
102. Xue, J.; Feng, B.; Zheng, R.; Lu, Y.; Zhou, G.; Liu, W.; Cao, Y.; Zhang, Y.; Zhang, W.J. Engineering ear-shaped cartilage using electrospun fibrous membranes of gelatin/polycaprolactone. *Biomaterials* 2013, 34, 2624–2631. [CrossRef] [PubMed]

103. Zheng, R.; Duan, H.; Xue, J.; Liu, Y.; Feng, B.; Zhao, S.; Zhu, Y.; Liu, Y.; He, A.; Zhang, W.; et al. The influence of Gelatin/PCL ratio and 3-D construct shape of electrospun membranes on cartilage regeneration. *Biomaterials* 2014, 35, 152–164. [CrossRef] [PubMed]

104. Ji, W.; Yang, F.; Ma, J.; Bouma, M.J.; Boerman, O.C.; Chen, Z.; van den Beucken, J.J.P.; Jansen, J.A. Incorporation of stromal cell-derived factor-1α in PCL/gelatin electrospun membranes for guided bone regeneration. *Biomaterials* 2013, 34, 735–745. [CrossRef] [PubMed]

105. Bottino, M.C.; Thomas, V.; Schmidt, G.; Vohra, Y.K.; Chu, T.-M.G.; Kowolik, M.J.; Janowski, G.M. A novel spatially designed and functionally graded electrospun PCL-PEG nanofibers into porous chitosan scaffolds improved the orientation of collagen fibers in regenereated periodontium. *Acta Biomater.* 2015, 3, 4063–4073. [CrossRef] [PubMed]

106. Xue, J.; He, M.; Liu, H.; Niu, Y.; Crawford, A.; Coates, P.D.; Chen, D.; Shi, R.; Zhang, L. Drug loaded homogeneous electrospun PCL/gelatin hybrid nanofiber structures for anti-infective tissue regeneration membranes. *Biomaterials* 2014, 35, 9395–9405. [CrossRef] [PubMed]

107. Feng, B.; Tu, H.; Yuan, H.; Peng, H.; Zhang, Y. Acetic-acid-mediated miscibility toward electrospinning homogeneous composite nanofibers of GT/PCL. *Biomacromolecules* 2012, 13, 3917–3925. [CrossRef] [PubMed]

108. Chen, S.; Hao, Y.; Cui, W.; Chang, J.; Zhou, Y. Biodegradable electrospun PLLA/chitosan membrane as guided tissue regeneration membrane for treating periodontitis. *J. Mater. Sci.* 2013, 48, 6567–6577. [CrossRef]

109. Jiang, W.; Li, L.; Zhang, D.; Huang, S.; Jing, Z.; Wu, Y.; Zhao, Z.; Zhao, L.; Zhou, S. Incorporation of aligned PCL-PEG nanofibers into porous chitosan scaffolds improved the orientation of collagen fibers in regenerated periodontium. *Acta Biomater.* 2015, 25, 240–252. [CrossRef] [PubMed]

110. Ku, Y.; Shim, I.K.; Lee, J.Y.; Park, Y.J.; Rhee, S.-H.; Nam, S.H.; Park, J.B.; Chung, C.P.; Lee, S.J. Chitosan/polylactic acid) multilayered membrane for guided tissue regeneration. *J. Biomed. Mater. Res. A* 2009, 90, 766–772. [CrossRef] [PubMed]

111. Bottino, M.C.; Thomas, V.; Schmidt, G.; Vohra, Y.K.; Chu, T.-M.G.; Kowolik, M.J.; Janowski, G.M. Recent advances in the development of GTR/GBR membranes for periodontal regeneration—A materials perspective. *Dent. Mater.* 2012, 28, 703–721. [CrossRef] [PubMed]

112. Bottino, M.C.; Thomas, V.; Janowski, G.M. A novel spatially designed and functionally graded electrospun membrane for periodontal regeneration. *Acta Biomater.* 2011, 7, 216–224. [CrossRef] [PubMed]

113. Liao, S.; Wang, W.; Uo, M.; Ohkawa, S.; Akasaka, T.; Tamura, K.; Cui, F.; Watari, F. A three-layered nano-carbonated hydroxyapatite/collagen/PLGA composite membrane for guided tissue regeneration. *Biomaterials* 2006, 27, 7564–7571. [CrossRef] [PubMed]

114. Rowe, M.J.; Kamoki, K.; Pankajakshn, D.; Li, D.; Bruzzaniti, A.; Thomas, V.; Blanchard, S.B.; Bottino, M.C. Dimensionally stable and bioactive membrane for guided bone regeneration: An in vitro study. *J. Biomed. Mater. Res. B Appl. Biomater.* 2015, 594–605. [CrossRef]

115. Shim, J.-H.; Yoon, M.-C.; Jeong, C.-M.; Jang, J.; Jeong, S.-I.; Cho, D.-W.; Huh, J.-B. Efficacy of rhBMP-2 loaded PCL/PLGA/β-TCP guided bone regeneration membrane fabricated by 3D printing technology for reconstruction of calvaria defects in rabbit. *Biomater. Mater.* 2014, 9, 065006. [CrossRef] [PubMed]

116. Shim, J.-H.; Huh, J.-B.; Park, J.Y.; Jeon, Y.-C.; Kang, S.S.; Kim, J.Y.; Rhie, J.-W.; Cho, D.-W. Fabrication of blended polycaprolactone/poly(lactic-co-glycolic acid)/β-tricalcium phosphate thin membrane using solid freeform fabrication technology for guided bone regeneration. *Tissue Eng. Part A* 2013, 19, 317–328. [CrossRef] [PubMed]

117. Hongjian Zhou, J.L. Nanoscale hydroxyapatite particles for bone tissue engineering. *Acta Biomater.* 2011, 7, 2769–2781. [CrossRef] [PubMed]

118. Jones, J.R. Review of bioactive glass: From hench to hybrids. *Acta Biomater.* 2013, 9, 4457–4486. [CrossRef] [PubMed]

119. Hench, L.L. Opening paper 2015—Some comments on bioglass: Four eras of discovery and development. *Biomed. Glasses.* 2015, 1, 1–11. [CrossRef]

120. Miguez-Pacheco, V.; Hench, L.L.; Boccaccini, A.R. Bioactive glasses beyond bone and teeth: Emerging applications in contact with soft tissues. *Acta Biomater.* 2015, 13, 1–15. [CrossRef] [PubMed]
Polymers 2016, 8, 115

121. Leal, A.I.; Caridade, S.G.; Ma, J.; Yu, N.; Gomes, M.E.; Reis, R.L.; Jansen, J.A.; Walboomers, X.F.; Mano, J.F. Asymmetric PDLLA membranes containing Bioglass® for guided tissue regeneration: Characterization and in vitro biological behavior. Dent. Mater. 2013, 29, 427–436. [CrossRef] [PubMed]

122. Zhao, X.; Wu, Y.; Du, Y.; Chen, X.; Lei, B.; Xue, Y.; Ma, P.X. A highly bioactive and biodegradable poly(glycerol sebacate)-silica glass hybrid elastomer with tailored mechanical properties for bone tissue regeneration. J. Mater. Chem. B 2015, 3, 3222–3233. [CrossRef]

123. Li, W.; Ding, Y.; Yu, S.; Yao, Q.; Boccaccini, A.R. Multifunctional chitosan–45S5 bioactive glass-poly(3-hydroxybutyrate-co-3-hydroxyvalerate) microsphere composite membranes for guided tissue/bone regeneration. ACS Appl. Mater. Interfaces 2015, 7, 20845–20854. [CrossRef] [PubMed]

124. Peter, M.; Binulal, N.S.; Nair, S.V.; Selvamurugan, N.; Tamura, H.; Jayakumar, R. Novel biodegradable chitosan–gelatin/nano-bioactive glass ceramic composite scaffolds for alveolar bone tissue engineering. Chem. Eng. J. 2010, 158, 353–361. [CrossRef]

125. Khan, A.S.; Ahmed, Z.; Edirisinghe, M.J.; Wong, F.S.L.; Rehman, I.U. Preparation and characterization of a novel bioactive restorative composite based on covalently coupled polyurethane–nanohydroxyapatite fibres. Acta Biomater. 2008, 4, 1275–1287. [CrossRef] [PubMed]

126. Seo, H.-J.; Cho, Y.-E.; Kim, T.; Shin, H.-I.; Kwun, I.-S. Zinc may increase bone formation through stimulating cell proliferation, alkaline phosphatase activity and collagen synthesis in osteoblastic MC3T3-E1 cells. Nutr. Res. Pract. 2010, 4, 356–361. [CrossRef] [PubMed]

127. Góes, J.C.; Figueiró, S.D.; Oliveira, A.M.; Macedo, A.A.M.; Silva, C.C.; Ricardo, N.M.P.; Sombra, A.S.B. Apatite coating on anionic and native collagen films by an alternate soaking process. Acta Biomater. 2007, 3, 773–778. [CrossRef] [PubMed]

128. Xia, Z.; Wei, M. Biomimetic fabrication of collagen-apatite scaffolds for bone tissue regeneration. J. Biomater. Tissue Eng. 2013, 3, 369–384. [CrossRef]

129. Arafat, M.T.; Tronci, G.; Yin, J.; Wood, D.J.; Russell, S.J. Biomimetic wet-stable fibres via wet spinning and diacid-based crosslinking of collagen triple helices. Polymer 2015, 77, 102–112. [CrossRef]

130. Xia, Z.; Villa, M.M.; Wei, M. A biomimetic collagen-apatite scaffold with a multi-level lamellar structure for bone tissue engineering. J. Mater. Chem. B Mater. Biol. Med. 2014, 2, 1998–2007. [CrossRef] [PubMed]

131. Campoccia, D.; Montanaro, L.; Arciola, C.R. A review of the clinical implications of anti-infective biomaterials and infection-resistant surfaces. Biomaterials 2013, 34, 8018–8029. [CrossRef] [PubMed]

132. He, M.; Xue, J.; Geng, H.; Gu, H.; Chen, D.; Shi, R.; Zhang, L. Fibrous guided tissue regeneration membrane loaded with anti-inflammatory agent prepared by coaxial electrospinning for the purpose of controlled release. Appl. Surf. Sci. 2015, 335, 121–129. [CrossRef]

133. Münchow, E.A.; Albuquerque, M.T.P.; Zero, B.; Kamocki, K.; Piva, E.; Gregory, R.L.; Bottino, M.C. Development and characterization of novel ZnO-loaded electrospun membranes for periodontal regeneration. Dent. Mater. 2015, 31, 1038–1051. [CrossRef] [PubMed]

134. Spicer, P.P.; Shah, S.R.; Henslee, A.M.; Watson, B.M.; Kinard, L.A.; Kretlow, J.D.; Bevil, K.; Kattchee, L.; Bennett, G.N.; Demian, N.; et al. Evaluation of antibiotic releasing porous polymethylmethacrylate space maintainers in an infected composite tissue defect model. Acta Biomater. 2013, 9, 8832–8839. [CrossRef] [PubMed]

135. Qi, R.; Guo, R.; Zheng, F.; Liu, H.; Yu, J.; Shi, X. Controlled release and antibacterial activity of antibiotic-loaded electrospin halloysite/poly(lactic-co-glycolic acid) composite nanofibers. Colloids Surf. B Biointerfaces 2013, 110, 148–155. [CrossRef] [PubMed]

136. Castillo-Dali, G.; Velázquez-Cayón, R.; Serrera-Figallo, M.A.; Rodríguez-González-Elipe, A.; Gutierrez-Pérez, J.-L.; Torres-Lagares, D. Importance of poly(lactic-co-glycolic acid) in scaffolds for guided bone regeneration: A focused review. J. Oral Implantol. 2015, 41, e152–e157. [CrossRef] [PubMed]

137. Lee, K.; Silva, E.A.; Mooney, D.J. Growth factor delivery-based tissue engineering: General approaches and a review of recent developments. J. R. Soc. Interface 2011, 8, 153–170. [CrossRef] [PubMed]

138. Spiller, K.L.; Vunjak-Novakovic, G. Clinical translation of controlled protein delivery systems for tissue engineering. Drug Deliv. Transl. Res. 2013, 3, 101–115. [CrossRef] [PubMed]

139. Haidar, Z.S.; Hamdy, R.C.; Tabrizian, M. Delivery of recombinant bone morphogenetic proteins for bone regeneration and repair. Part A: Current challenges in BMP delivery. Biotechnol. Lett. 2009, 31, 1817–1824. [CrossRef] [PubMed]
140. Shalumon, K.T.; Lai, G.-J.; Chen, C.-H.; Chen, J.-P. Modulation of bone-specific tissue regeneration by incorporating bone morphogenetic protein and controlling the shell thickness of silk fibroin/chitosan/nanohydroxyapatite core-shell nanofibrous Membranes. ACS Appl. Mater. Interfaces 2015, 7, 21170–21181. [CrossRef] [PubMed]

141. Wynn, R.F.; Hart, C.A.; Corradi-Perini, C.; O’Neill, L.; Evans, C.A.; Wraith, J.E.; Fairbairn, I.J.; Bellantuono, I. A small proportion of mesenchymal stem cells strongly expresses functionally active CXCR4 receptor capable of promoting migration to bone marrow. Blood 2004, 104, 2643–2645. [CrossRef] [PubMed]

142. Gassling, V.; Purcz, N.; Braesen, J.-H.; Will, M.; Gierloff, M.; Behrens, E.; Açil, Y.; Wiltfang, J. Comparison of two different absorbable membranes for the coverage of lateral osteotomy sites in maxillary sinus augmentation: A preliminary study. J. Craniomaxillofac. Surg. 2013, 41, 76–82. [CrossRef] [PubMed]

143. Kawase, T.; Kamiya, M.; Kobayashi, M.; Tanaka, T.; Okuda, K.; Wolff, L.F.; Yoshie, H. The heat-compression technique for the conversion of platelet-rich fibrin preparation to a barrier membrane with a reduced rate of biodegradation. J. Biomed. Mater. Res. B Appl. Biomater. 2015, 103, 825–831. [CrossRef] [PubMed]

144. Wada, K.; Yu, W.; Elazizi, M.; Barakat, S.; Ouimet, M.A.; Rosario-Meléndez, R.; Fiorellini, J.P.; Graves, D.T.; Uhrich, K.E. Locally delivered salicylic acid from a poly(anhydride-ester): Impact on diabetic bone regeneration. J. Control. Release 2013, 171, 33–37. [CrossRef] [PubMed]

145. Erdmann, L.; Uhrich, K.E. Synthesis and degradation characteristics of salicylic acid-derived poly(anhydride-esters). Biomaterials 2000, 21, 1941–1946. [CrossRef]

146. Subramanian, S.; Mitchell, A.; Yu, W.; Snyder, S.; Uhrich, K.; O’Connor, J.P. Salicylic acid-based polymers for guided bone regeneration using bone morphogenetic protein-2. Tissue Eng. Part A 2015, 21, 2013–2024. [CrossRef] [PubMed]

© 2016 by the authors; licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons by Attribution (CC-BY) license (http://creativecommons.org/licenses/by/4.0/).