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Studies of Bone Morphogenetic Protein based Surgical Repair

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Abstract

Over the past several decades, recombinant human bone morphogenetic proteins (rhBMPs) have been the most extensively studied and widely used osteoinductive agents for clinical bone repair. Since rhBMP-2 and rhBMP-7 were approved by the U.S. Food and Drug Administration for certain clinical uses, millions of patients worldwide have been treated with rhBMPs for various musculoskeletal disorders. Current clinical applications include treatment of long bone fracture non-unions, spinal surgeries, and oral maxillofacial surgeries. Considering the growing number of recent publications related to clincal research of rhBMPs, there exists enormous promise for these proteins to be used in bone regenerative medicine. The authors take this opportunity to review the rhBMP literature paying specific attention to the current applications of rhBMPs in bone repair and spine surgery. The prospective future of rhBMPs delivered in combination with tissue engineered scaffolds is also reviewed.

Keywords

rhBMPs; regenerative medicine; spinal surgery; bone fracture; oral surgery; bone tissue engineering; drug delivery

2. Introduction

The repair and replacement of bone is a major clinical problem. The need for functional treatments of fracture non-unions, spinal injuries, and bone loss associated with trauma and cancer has become increasingly common and remains a significant challenge in the field of orthopaedic surgery. In the United States alone, it is estimated that over 10 million fracture-related physician or emergency visits occur every year [1]. These numbers will only continue to grow as human life expentancies increase due to better medical care.

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Bone fractures can be treated with a cast because the broken bone needs to be set to improve the healing. Sometimes, surgery is required for bone fractures associated with small bone voids that can be filled with an appropriate bone void filler. For large bone defects, biological grafts such as autologous bone grafts, allografts and demineralized bone matrix can be used, but each having their own advantages and disadvantages. Autografts have been recognized as the gold standard bone grafts because of their high success rate (as high as ~80–90%) and unlikelihood of being rejected [2]. However, these grafts are often associated with several shortcomings including donor-site morbidity, limited tissue for harvesting, and increased surgical time [3–6]. Allografts and demineralized bone matrix have been introduced into clinical practice to overcome the drawbacks of autografts. Allografts are tissues harvested from one individual and implanted into another. Demineralized bone matrix is allograft bone tissue in which the inorganic mineral has been removed by exposure to acid, leaving behind organic collagenous matrix and non-collagenous proteins including growth factors [7,8] [9]. The advantages of allografts and demineralized bone matrix are that they are readily available in nearly unlimited supply and can be easily processed into a variety of forms for specific applications [9,10]. However, disease transmission, host immune reaction and implant rejection remain significant disadvantages of these grafts [11]. As a result of these limitations, there has been significant recent interest in the development of biomaterials that can augment bone healing to preclude the needs for autografts and allografts [12]. For instance, researchers have actively investigated biodegradable polymeric scaffolds combined with growth factors and/or osteoprogenitor cells as a viable alternative to traditional grafts. [13–17].

Tissue engineering can be described as the combination of biological, chemical and engineering principles toward the repair, restoration and replacement of tissues using cells, scaffolds and biologic factors alone or in combination [18]. An important element of successful bone tissue engineering constructs is osteoinduction, stimulation of osteoprogenitor cells to differentiate into osteoblasts, which is often accomplished through the use of growth factors [19]. Bone growth factors are usually proteins secreted by cells which provide the necessary driving force for osteoblast functions including proliferation and differentiation. Generally, the mechanism of action of bone growth factors is to interact with membrane receptors on target cells. This interaction triggers an intracellular signaling cascade that ultimately induces the expression of bone associated genes in the nucleus and protein production in the cytoplasm [20,21]. Over the past several decades, scientists have actively investigated growth factors for use in bone repair and regeneration preclinically. For instance, bone morphogenetic proteins (BMPs), insulin-like growth factors (IGFs), granulocyte-macrophage colony stimulating factor (GM-CSF), basic fibroblast growth factor (bFGF), and platelet-derived growth factor (PDGF) have all demonstrated significant bone formation and potential for use in bone reparative therapies [21,22]. A review of the literature has shown that BMPs are the most effective growth factors in improving healing of non-unions, fractures, spinal fusions, and dental implants [23–33]. Although PDGF is currently used in clinical practices, the only osteoinductive material commercially available today is BMPs. BMP was discovered by Dr. Marshall Urist when he observed *de novo* bone formation in rats after the implanation of decalcified bone into soft tissue pouches which he later named the proteins responsible for the bone formation-BMPs [34]. To date, more than 20 BMPs have been identified, of which 7 appear capable of initiating bone growth [35,36]. Thanks to notable advances in molecular biology and genomics, human BMP genes have been identified and cloned. rhBMPs can now be produced and purified from *E.coli* and mammailian cell lines for biochemical analysis and clincial trails [37–41]. Different animal models have been used to demonstrate the therapeutic potential of rhBMPs in bone repair and regeneration [22,42,43]. Presently, rhBMPs remain the most important growth factors in bone formation and repair [44,45]. Two rhBMP-based commercial products: INFUSE® (rhBMP-2, Medtronic, Minneapolis, MN) and OP-1™ (rhBMP-7, Stryker Biotech,

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Hopkinton, MA) have received Food and Drug Administration (FDA) approval for several surgical applications (see Table 1). Since the half-life of rhBMP-2 is about 6.7 min in nonhuman primates due to enzymatic degradation and rapid rate of clearance [46–48], to increase its effectiveness of healing nonunion fractures, rhBMPs are combined with biocompatible carriers such as aborbable collagen sponges. Loading rhBMP into an absorbable collagen sponge allows for the gradual rhBMP release over time, which stimulates new bone formation in the implant site. Current clinical applications of rhBMP-based products include long bone non-unions, spinal fusion, and oral surgeries [49–51]. In certain open tibial fractures and non-unions, rhBMPs play an active role to heal broken bones [52]. In spinal surgery, the rhBMP induces new bone formation in the disc space to fuse the vertebrae to reduce back pain, restore function, and strengthen the spine [53]. In oral surgery, rhBMP plays a role in the induction of new bone formation in the edentulous area of a missing tooth in order to support a dental implant [54,55]. Considering the growing number of publications related to the clinical applications of rhBMPs, the purpose of this review is to cover the latest clinical development of rhBMPs including the use of BMP delivery carriers and approved BMP products for surgical repairs.

3. Clinical applications of BMPs

3.1 Long Bone Fractures

Long bone fractures make up a large portion of clinically reported fractures[1]. While many long bone fractures can be repaired without surgery, a significant portion of fractures are considered critical-size defects meaning they commonly form non-unions without surgical intervention. It should be noted the term critical-size is contraversial since a recent study found that the excepted critical-size for human long bones (fracture gap greater than 1 cm and affect at least 50% of the cortical diameter) showed only a 53% non-union rate [56]. Also, the definition is highly dependent on the species and location of the fracture. Regardless, many long bone fractures require surgical intervention with a bone graft to assist repair and regeneration. Autografts or allografts are often used, but recently BMP-loaded tissue engineering constructs has become more frequently utilized. In 2002, the BMP-2 Evaluation in Surgery for Tibial Trauma Study Group (BESTT) published the results from a 450 patient global clinical study showing that rhBMP-2 loaded collagen sponges greatly benefited patients undergoing severe, open tibial fracture repair surgeries with intramedullary nail fixation [57]. This study showed that not only were the rhBMP-2 loaded sponges safe to use clinically, but that they reduced the risk of failure, lowered the need for invasive interventions, and accelerated fracture healing with statistical significance over fracture repairs conducted with nail fixation alone. A 60 patient study in the United States was conducted concurrently with the same treatment groups and yielded similar positive results [58]. These results lead to the FDA approval of Medtronic's INFUSE® (rhBMP-2/collagen implant) for the treatment of acute, open tibial fractures in April 2004 [59] Interestingly, a follow-up economical analysis on the BESTT study in the United Kingdom, Germany, and France found that the medical cost-savings of the BMP-2 loaded sponges (€7,911 – €9,291) greatly outweighed their product cost (€2,260 – €2,970) [60]. A recent clinical study found that the advantages of INFUSE® reported in the BESTT study were confined to repairs using unreamed nails whereas repairs using reamed nails saw no statistically significant differences between patients receiving no scaffold and those receiving INFUSE® [61]. INFUSE® is currently being investigated by the Capital District Health Authority, Canada in a Phase IV clinical trial for its capacity to expedite healing of fractures in the clavicle, tibia, femur, humerus, radius, and ulna [62]. Medtronic has recently started a Phase III clinical trial investigating the potential for INFUSE® to be coupled with MASTERGRAFT®, a biphasic calcium phosphate composite, as a regenerative device for tibial delayed healing defects [63]. Collagen sponges loaded with rhBMP-2 placed in

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allografts are currently being investigated by the Major Extremity Trauma Research Consortia for their capacity to enhance open tibial fracture healing in Phase IV trials [64].

Pfizer has investigated the potential for rhBMP-2/calcium phosphate matrix (rhBMP-2/CPM) for a variety of long bone defect applications. rhBMP-2/CPM has been studied in a Phase I trial for radial fractures [65], a Phase II trial for humeral fractures [66], a Phase II trial for femoral fractures [67], and Phase II/III trials for tibial fractures [68]. While promising, the published results from the Phase II studies for humeral and femoral fractures showed little enhancement over traditional treatments [69,70]. A positive risk/benefit ratio for these treatments was not demonstrated leading to Pfizer no longer pursuing the clinical development of rhBMP-2/CPM for these applications.

Like rhBMP-2, rhBMP-7 has shown tremendous clinical promise in promoting long bone fracture healing. In fact, clinical trials using rhBMP-7 for fracture repair started nearly 20 years ago [71]. In 2001, rhBMP-7 was approved by the FDA under the Humanitarian Device Exemption (HDE) for the use in long bone non-unions. The first study showed that collagen sponges with rhBMP-7 have the same effectiveness in healing tibial fracture non-unions as autografts. Another early study showed rhBMP-7 loaded collagen sponges were able to induce bone healing in critical-size fibular defects similar to demineralized bone matrix as determined by bone mineral density measurements [72]. These promising initial results have been supported by the more recent use of rhBMP-7 in the enhancement of treatments for diaphyseal humeral non-unions [73] and externally fixated distal tibial fractures [74]. From 2005 to 2007, a 120 patient study was conducted to investigate the potential for rhBMP-7/collagen constructs to guide repair of a wide-range of non-unions (tibial, femoral, humeral, ulnar, and radial) [75]. Clinical and radiological union was found in 86.7% of all cases. Follow-up long-term, multi-center, observational analyses have shown overwhelming clinical safety and success with the use of rhBMP-7 to treat tibial and femoral non-union [28,76]. Non-union fracture healing was found to occur in 89.7% and 86.7% of patients undergoing fixation revision surgery for tibial and femoral non-unions, respectively. Radiographic evidence of the enhanced healing effects of rhBMP-7 is provided in Figure 1. After unsuccessful repair of a femoral fracture by intramedullary nail alone, revision surgery with nail repositioning and the use of Osigraft® (Stryker Biotech), a rhBMP-7/collagen mixture, lead to complete fusion and healing of the defect. A Phase II clinical trial [77] and a Phase IV clinical trial [78] for the use of rhBMP-7 based devices to treat tibial fracture are currently underway.

3.2 Spinal Fusion

BMP-based therapies have also greatly enhanced the outcomes of spinal fusion surgery. This procedure is typically conducted in order to reduce pain associated with abnormal vertebrae motion or to treat spinal deformities. The gold standard graft for spinal fusion surgery has been harvested tissue from the iliac crest of the pelvis which unfortunately can often lead to significant pain and morbidity at the donor site [79]. Synthetic grafts coupled with BMPs have been shown to be clinically viable alternatives. Originally, INFUSE® was added to cortical allografts and shown to induce similar interior lumbar interbody fusion results when compared to ileac crest autografts leading to its FDA approval for this application in 2002 [80–82]. More recently utilizing INFUSE® without an allograft has shown promise in “off-label” use for posterolateral spinal fusion [83]. Specifically, two follow-up studies have shown that patients over 60 years of age that received INFUSE® for posterolateral fusion had less complications, decreased need for additional treatment or revision surgery and cost less to treat ($2,316 – $2,443 on average) than patients who received an ileac crest bone graft [84,85]. A Phase II clinical trial is currently being conducted by the Capital District Health Authority, Canada to determine the capacity for INFUSE® to promote spinal fusion [86]. In addition to collagen-based scaffolds, calcium phosphate scaffolds have shown

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promise for use in spinal fusion surgery [87]. Since calcium phosphates can provide structural support and osteoinductivity, composite scaffolds composed of BMP-2 loaded collagen and calcium phosphate have been studied and shown tremendous potential [88–91]. All of these studies showed similar or enhanced clinical outcomes for patients receiving composite scaffolds compared to patients receiving ileac crest autografts. Figure 2 provides radiographic evidence of the osteoinductive promise of rhBMP-2/collagen/ceramic composite materials. Ceramic granules in synergy with rhBMP-2 induced considerable new bone formation between vertebrae 24 month postoperatively. rhBMP-2 delivery and subsequent spinal fusion has also been mediated by biocompatible polymers like poly(lactide-*co*-glycolide) (PLGA) [92,93] and poly(ether ether ketone) (PEEK) [94,95]. Specfically, CD-Horizon®, a PEEK-based material made by Medtronic, has been supplemented with rhBMP-2 and a compression resistant matrix composed of calcium phosphate and collagen and shown to enhance spinal fusion in a Phase III clinical trial [96].

Similar to rhBMP-2, significant research has shown rhBMP-7 has the capacity to mediate enhanced spinal fusion. To date, research evaluating rhBMP-7 as an osteoinductive protein for spinal applications focuses on the use of OP-1®, a collagen/rhBMP-7 putty, which is produced by Olympus Biotech. This product has been shown to be relatively safe and effective for the treatment of posterolateral lumbar fusion [97,98] [99–101] and cervical non-unions [102,103]. In 2004, the FDA gave HDE approval for the use of OP-1® as an alternative to autografts in patients requiring posterolateral spinal fusion. Phase I/II/II clinical trials investigating OP-1® have shown promise for spinal fusion in patients suffering from vertebra displacement [104–106]. A new Phase II clinical trial is investigating the potential for OP-1® to be combined with a PEEK crush-resistant spacer to better facilitate fusion while limiting pain [107]. Unfortunately, some research has shown issues with the use of BMP-7 for spinal fusion. In one study, only 57.1% of patients treated with OP-1® to assist posterolateral lumbar fusion actually had complete spinal fusion one year after surgery [23]. Similarly to rhBMP-2 loaded devices, OP-1® also caused increased soft tissue swelling that was linked to some patients experiencing transient pain at the fusion site [103]. Further research must be conducted before OP-1® or other rhBMP-7 products become commonly used in spinal fusion surgeries.

3.3 Oral and maxillofacial surgeries

Bone grafts are also performed to repair mandibular defects [112]. These defects usually arise as a result of traumatic injuries, congenital defects, or surgeries for tumor removal. Bone grafts are also sometimes required to create a base for dental implant so they can strengthen and thicken dental sites [113]. Nowadays, bone grafts harvested from other parts of the patient such as the tibia, ilium or chin, are the gold standard for oral surgical procedures [114]. However, if large amounts of bone are required, rhBMP products are usually recommended by surgeons as an alternative to autogenous bone grafts [115]. INFUSE® was approved by the FDA in 2009 for certain oral and maxillofacial surgical procedures. It is used when more bone is needed in the sinus region, i.e. sinus lift to place endosseous dental implants in the upper mandible [116,117]. It is also used to increase bone formation in extraction sites prior to dental implant placement [33].

The first clinical studies were conducted by the Nummikoski group on 12 patients who underwent maxillary sinus augmentation. These patients received rhBMP-2 delivered on an absorbable collagen sponge, where the total delivered dose of rhBMP-2 implanted varied from 1.77 to 3.40 mg per patient [116]. Significant bone growth was evidenced in all evaluable patients (11/12) using computerized tomographic scans and the overall mean height response for the maxillary sinus floor augmentation was 8.51 mm [116]. Triplett and colleagues reported a prospective study of the safety and effectiveness of rhBMP-2 on an absorbable collagen sponge [118]. In this study, a total of 160 patients with maxillary sinus

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floor augmentation were randomized into either a control group (autograft) or a rhBMP-2 treatment group (1.5 mg/ml). The outcomes were measured based on the bone height and density using computed tomography scans in the 5-year study period. The data demonstrate the effectiveness and safety of rhBMP-2 compared with autograft for sinus floor augmentation. No adverse events were found related to the rhBMP-2 treatment and there was no statistically significant difference in outcome between the 2 groups. The authors concluded that rhBMP-2 and autograft groups performed similarly [118]. Cochran and colleagues evaluated the use of rhBMP-2 loaded in an absorbable collagen sponge in human extraction sites or in sites that required alveolar ridge augmentation in 12 patients followed for up to 3 years [119]. During the study period, no serious adverse effects occurred. Human bone biopsies were used to confirm bone formation in areas treated with rhBMP-2. Endosseous implants (4 augmentations and 6 extraction sockets) placed in these areas were all clinically stable and all sites were functionally restored [119]. Compared to spinal fusion and non-union fractures, there are limited cases of clinical studies involving oral and maxillofacial surgeries using BMPs. Nevertheless, it is reasonable for us to anticipate that the uses of BMP for oral and maxillofacial surgeries will continue to expand.

4. Design Metrics for BMP Delivery Devices

While current clinical treatments have been shown to be effective in treating bone and spinal defects or injuries, the research community is actively seeking alternative drug delivery vehicles in order to improve current therapies. The overall aim is to develop an osteoinductive, osteogenic, and osteoconductive scaffold that accelerates bone formation at a similar rate to autologous treatment. To reach this aim, significant research has focused on the local, controlled delivery of rhBMPs because such controlled spatiotemporal release can stimulate endogenous repair mechanisms by recruiting and programming the patient's own progenitor cells. However, the controlled delivery of rhBMPs to sites of damaged, injured, or otherwise impaired bone tissue continues to be a challenging task due to the variable release profiles of rhBMPs from carriers [120]. For instance, rhBMPs are well documented for exhibiting a burst release pharmokinectic profile from their most typical carrier, the absorbable collagen sponge (ACS) [121]. This rapid release requires supraphysiological protein loading of carrier devices to maintain local rhBMP biological activity. As a result, concentrations of rhBMPs required for acceleration of fracture healing range from 0.01 mg/ml in rodents to 1.5 mg/ml in non-human primate models, and even higher concentrations have been used for spine fusion applications in human clinical trials. Using dosages approximately 1 million times concentrations found endogenously have made clinically used rhBMP therapies very expensive at a cost of $5,000 or more [72,76,116,122]. Furthermore, while rhBMPs generally act only on nearby cells to promote bone formation and are confined to the geometry of their polymeric, ceramic, or composite carrier, at high doses rhBMPs can increase diffusion to nearby tissues such that bone formation extends beyond the carrier material [123]. The diffusion of this pleiotropic protein can result in unwanted ectopic bone formation, native bone resorption, soft tissue swelling, and osteolysis [124]. The pleiotropic nature of BMPs is evidenced by their role in developmental biology as well as their ability to trans-differentiate already committed cells like mesothelial and tenosynovial cells [125,126]. Thus, it is important to note that one of the most critical characteristics of a delivery system is its ability to maintain physiologic levels of rhBMP within a confined space for a sufficient time to stimulate bone formation [48]. Additionally, an ideal delivery system should:

- Protect the rhBMPs from degradation and maintain its bioactivity
- Be biodegradable to allow for the formation of an interface with the surrounding biological tissue or complete biodegradability for complete invasion of healed tissues

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- Present adequate porosity to allow the infiltration of cells and formation of blood vessels
- Be conveniently sterilizable, easy to handle, stable over time with well-defined storage procedures
- Be suitable for commercial manufacturing, allowing for scale-up production and approval by regulatory agencies[127]

Growth factors are typically adsorbed to, immobilized onto, entrapped, or encapsulated within delivery vehicles to accomplish spatiotemporal delivery at the implantation site. While adsorbing rhBMPs to the surface of the implant is the easiest way to deliver the growth factor, the protein may undergo conformational changes once adsorbed and is typically released rapidly and in an uncontrolled manner when exposed to a physiological environment. Immobilization of rhBMPs to implant surfaces typically results in a more sustained presence; however, due to covalent bonds the protein cannot freely diffuse within the microenvironment to interact with its receptor. Entrapment and encapsulation of rhBMPs circumvents the issues of rapid release and immobilization, and are the most popular way to deliver rhBMPs. However, it is important to note that many of these methods involve exposing rhBMPs to harsh solvents and acidic environments that may disrupt the conformational structure and thus bioactivity of the protein. Methods such as binding proteins to charged polymers such as chitosan, alginate, hyaluronans also have shown great efficacy in sustained protein delivery.

There are several types of carriers that have been investigated for rhBMP delivery [128]. In general, the five groups are: natural (Table 2a) and synthetic polymers (Table 2b), natural and synthetic ceramics (Table 2c), and composites of these four groups (Table 2d). This section will cover in detail the documented uses of these carriers in conjuction with rhBMP-2 and rhBMP-7 in pre-clinical cases for fracture non-unions, spinal fusion, and fracture repair.

4.1 Natural Polymers

Collagen—As a natural polymer, collagen is a popular choice for bone tissue regeneration applications due to its biocompatibility, ease of degradation, and interaction with other bioactive molecules. As previously reviewed [129], ACS have been used extensively for bone regeneration. In fact, the only rhBMP-2 containing FDA-approved product for clinical use in spinal fusions, tibial shaft fractures, and oral surgeries is comprised of an ACS. In the rhBMP-2 INFUSE® products, aqueous rhBMP-2 is physically adsorbed to an ACS prior to implantation and placed into a titanium fusion device to aid in spinal fusion [83,89] in several animal [130–132] and human cases [51,82] with the overall outcome of high fusion rates without significant side effects. However, when delivered on the ACS the FDA-approved concentration of rhBMP-2 for interbody spinal fusion (1.5 mg/mL) has failed to induce clinically relevant amounts of bone formation in a posterolateral spine fusion model in animals [131,133] and humans [83], warranting further investigation into this area. In osteogenic protein [OP]-1TM products, rhBMP-7 is contained within a putty of bovine collagen matrix and carboxymethylcellulose sodium [134] and used for long bone non-union and revision posterolateral lumbar fusion [50,99,101].

Despite the proven clinical efficacy of collagen carriers, it is known that delivery of rhBMPs from these matrices have a number of disadvantages. Of the existing problems, the most prominent include the lack of mechanical strength and unpredictable biodegradability of the collagen matrix. Specifically, since the collagen sponge lacks mechanical integrity, the local concentration of rhBMPs can increase to undesirably high levels as the sponge is compressed by overlying muscles and other tissue. Furthermore, since rhBMPs are

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physically entrapped in the collagen matrices and depend on matrix degradation for release, their release kinetics are unpredictable and difficult to control [134]. In fact, reports indicate that due to initial burst release, less than 5% of rhBMP remains within the collagen sponge at 2 weeks *in vivo* [135].

4.2 Other natural polymers

As summarized in Table 2a, in addition to collagen there are a number of other natural polymers such as gelatin, hyaluronans, alginate, chitosan, silk, and fibrin that have been combined with ceramics and/or synthetic polymers (Table 2d) to increase osteoconductivity and mechanical strength. Although these potential therapies have not been approved for clinical use, pre-clinical results indicate promising future applications.

Gelatin is a commercially available denatured collagen that has been used extensively for medical purposes. The controlled release of growth factors from biodegradable gelatin hydrogels can be modulated by gelatin percentage since gelatin-immobilized growth factors are released when water-soluble hydrogels undergo degradation. It has been shown that gelatin hydrogels containing rhBMP-2 releases the osteogenic agent in a controlled manner such that the osteoinductive activity of the bioactive hydrogel is significantly enhanced in a rabbit ulnar segmental defect (20mm) in comparison to rhBMP-2-free hydrogels [136].

Hyaluronic acid (HA) is a naturally occurring hydrophilic, non-immunogenic glycosaminoglycan that has been shown to support bone growth in combination with rhBMP-2 in dog alveolar ridge defects [137], rabbit mid-tibial non-unions [138], and rat calvarial defects when mesenchymal stem cells (MSCs) are added [139]. The degradation of HA hydrogels can be modified via crosslinking strategies and additional incorporation of degradable sites. Since cationic rhBMP-2 interacts with HA hydrogels based on electrostatic interactions, the rate of hydrogel degradation is directly proportional to growth factor release. When crosslinked rhBMP-2/HA hydrogels degraded at fast, intermediate, and slow rates, it was shown that in a rat calvarial bone critical size defect model, the fastest and slowest degrading scaffolds induced the most organized bone formation [140]. In addition, studies have recently demonstrated that an injectable HA/rhBMP-2 hydrogel stimulates bone formation, as indicated by a high expression of osteocalcin and osteopontin [141], as well as x-ray, microcomputed tomographical, and histological analysis [142].

Alginate is a polysaccharide that is generally used in cartilage tissue engineering [143]. However, Simmons and colleagues demonstrated that in mice, RGD-functionalized alginate hydrogels co-delivered with rhBMP-2, transforming growth factor (TGF)-β3 and bone marrow stromal cells (BMSCs) successfully enhance bone formation [144,145]. Also, in combination with alginate loaded MSCs, a low dose of rhBMP-2 (2.5 μg) enhanced bone formation and spinal fusion in a rabbit posterolateral intertransverse fusion model. In more recent reports, Kolambkar showed that the injection of a RGD-functionalized alginate hydrogel containing a low dose of rhBMP-2 into a nanofiber mesh tube allows for the sustained spatiotemporal release of the growth factor for effective bone regeneration [146]. Furthermore, the addition of nanohydroxyapatite/collagen (nHAp/C) particles into an alginate hydrogel rhBMP-2 carrier results in the successful bone formation in a critical size rat calvarial defect [147].

Chitosan, a biocompatible and bioresorbable polymer of N-acetylglucosamine and glucosamine, is obtained from chitin through deacetylation. This natural polymer is biocompatible, bioresorbable, and bioactive and thus extremely attractive for tissue engineering applications. Abarrategi *et al.* first investigated the delivery properties of chitosan films in vivo and found that rhBMP-2 not only diffused slowly from the film, but also remained active as the film itself degraded at a slow kinetic rate [148]. Further reports

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indicated that porous ceramic scaffolds coated with rhBMP-2 carrier chitosan films stimulate bone formation at an earlier timepoint in comparison to ceramics without the coating [149], and promote the most extensive bone formation in a rat calvarial defect model [150]. Injectable forms of chitosan with rhBMP-2 and MSCs enhanced rat calvarial critical sized defects [151], but failed to regenerate bone in a rabbit 15mm critical sized radius defect, even with the addition of β-TCP [152]. However, chitosan combined with heparin enhanced rhBMP-2 induced bone formation and showed superior osteoinductive effects as compared to rhBMP-2/collagen implants [153].

The use of natural silkworm cocoon silk, or silk fibroin (SF), in bone regenerative applications has increased in recent years due to their excellent biocompatibility, degradability, and mechanical properties. After rhBMP-2 immobilization on SF films first resulted in increased osteogenesis of hBMSCs [154], investigators have since adsorbed the osteogenic protein to electrospun SF scaffolds [155], encapsulated it within microparticles [156], and injected protein-loaded silk hydrogels [157] into various critical defect and ectopic animal models. These studies overall resulted in increased bone infiltration and formation, indicating the potential use of SF as a biodegradable carrier vehicle for rhBMP-2.

Fibrin is a material that can be rapidly invaded, remodeled, and replaced by cell-associated proteolytic activity [158]. Although there are conflicting results concerning the use of fibrin gel for *in vivo* bone regeneration applications [159], it has been shown that in combination with heparin-functionalized nanoparticles and rhBMP-2, fibrin gel promotes significant improvement and effective bone regeneration in a rat calvarial critical size defect [160]. Further, covalently conjugating heparin to fibrin has been shown to significantly enhance bone formation in comparison to rhBMP-2 and free heparin loaded in fibrin matrices [161]. With the addition of adipose stem cells (ASCs), rhBMP-2 in a fibrin matrix was able to significantly reduce callus size in a non-critically sized femur transcortical drill hole within 2 weeks, as compared to rhBMP-2 alone [162].

4.3 Calcium Phosphate

Calcium phosphates have been extensively reviewed for their osteoconductive properties [163–165] due to their marked similarity in mineral composition, properties, and microarchitecture to human cancellous bone. Thus it is no surprise that in recent years significant research has focused on the development of calcium phosphates for bone repair and regeneration. Calcium phosphate materials have been grouped into three main categories based on their chemical composition: hydroxyapatite (HAp), β-tricalcium phosphate (β-TCP), and biphasic calcium phosphate (combination of β-TCP and HAp). While these various ceramics differ in mechanical strength, bioresorbabilty, and osteoconductivity, all of these compositions have a high affinity for binding proteins, and thus serve as potential candidates for rhBMP delivery in pre-clinical animal spinal fusion and bone repair models (Table 2c).

HAp is a commercially available biomaterial for bone replacement that is derived from coral exoskeletons. While this porous scaffold is similar to the inorganic phase of bone and exhibits osteoconductive properties, it is brittle, not readily resorbable, and carries minimal mechanical strength until bone ingrowth. Due to these characteristics, HAp is typically incorporated into other protein carriers to enhance bone-forming properties. However, there are a few instances when HAp has been exclusively used as a rhBMP delivery vehicle for bone formation [166]. For instance, Morisue *et al.* fabricated HAp into a fibrous rhBMP-2 loaded mesh to enhance bone union in a rat posterolateral fusion model. The resulting 80% fusion rate of the loaded mesh, as compared to the 20% fusion rate of the control, suggested that the HAp mesh is an efficient rhBMP-2 carrier [167]. In a weight-bearing model, the implantation of nHAp/rhBMP-2 composites to a bone defect on the unilateral radii of rabbits

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stimulated significantly more bone formation than a similar nHAp artificial bone without the growth factor [168]. HAp/rhBMP-7 composites have also demonstrated success in solid spinal fusion as compared to HAp without rhBMP-7 and autograft in a sheep model [169], as well as success in baboon orthotopic calvarial defects in relatively low dosages [170]. However, as recently revealed by Tazaki *et al.*, β-TCP may make a more effective rhBMP carrier due to its slower release rate as compared to HAp [171].

β-TCP is one of the most common used synthetic bone graft substitute due to its chemical similarily with normal bone [165]. Furthermore, TCP does not evoke immunological or toxic reactions, has good biocompatibiltity, and degrades as it is replaced by bone [172]. Given the osteogenic nature of rhBMP-2, the addition of the growth factor may enable β-TCP to act as an osteoconductive and osteoinductive bone graft substitute in future clinical spine surgeries. In fact, Ohyama *et al.* demonstrated that β-TCP combined with rhBMP-2 (200 μg) could serve as a substitute for autografts in the packing of interbody fusion cages in the canine lumbar spine model. In comparison to autograft cages and β-TCP without rhBMP-2, the β-TCP/rhBMP-2 substitute induces more fusion and produces a greater mean percentage of trabecular bone formation and mechanical stiffness [173]. Later studies confirmed this occurrence in bovine trepanation defects filled with a β-TCP/rhBMP-2 composite. Results indicated that β-TCP/rhBMP-2 composites induce a similar amount of calcified structures as compared to an autologous graft [174]. In contrast, recent reports indicate that in 5 mm calvarial critical size defects, the osteoconductive properties of β-TCP are not only superior to those of autografts, but that rhBMP-2 (5 μg) supplementation may not be necessary [175].

The differing restorability characteristics of HAp and β-TCP have led to the investigation of biphasic ceramics - scaffolds made from mixtures of the two ceramics. These composites provide osteoconduction for bone production as well as long-term stability since the stable tertiary structure of the HAp does not resorb quickly, thus providing structural rigidity to the implant as β-TCP degrades at the rate of bone formation [176]. Clearly, the ratio of HAp to β-TCP is an important parameter when designing osteoinductive rhBMP delivery vehicles for the modulation of bone formation. Previous reports suggest that a high concentration of HAp is necessary to observe bone formation [177], but such concentrations lead to slow biphasic graft resorption. To overcome this issue, Boden and colleagues demonstrated that in a non-human primate lumbar intertransverse process, increasing the dosage of rhBMP-2 in a 60:40 HAp/β-TCP carrier could enhance the amount and quality of bone through the ceramic block [178]. Even at lower HAp concentrations (20:80 HAp:β-TCP), rhBMP-2 incorporation enhanced bone formation in a rat calvarial defect model, although the ideal protein dosage was not clearly determined [179].

4.4 Natural Polymers and Ceramics

To account for the distinct disadvantages of polymeric carriers alone, as well as to replicate the chemical structure of bone to an even greater degree, natural polymers, namely collagen, have been combined with ceramic constructs to enhance mechanical properties of implantable scaffolds and establish more controlled release kinetics in animal models (Table 2d). Recently, Majid and colleagues incorporated rhBMP-2 within a calcium phosphate coating on a type I bovine collagen sponge to evaluate the orthotopic application of localized protein delivery in a rabbit posterolateral spinal fusion model. Their findings suggest that the biomimetic calcium phosphate coatings are effective as rhBMP-2 delivery systems as indicated by radiograph, manual palpation, computed tomography, and histological analysis [180]. In the same rabbit spinal fusion model, previous studies have also indicated that rhBMPs are retained [181] and can be successfully delivered from a compression-resistant 5:95 biphasic calcium phosphate/collagen sponge matrix resulting in bone that is biomechanically stiffer than the autograft control [182]. The use of a biphasic

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osteoinductive bulking agent not only induces bone formation [183], but also has been shown to reduce the required rhBMP-2 dose for posterolateral spinal fusions in rhesus monkeys to the FDA-approved 1.5 mg/mL concentration for interbody spinal fusions [133]. Porous hydroxyapatite and collagen scaffolds have likewise shown to induce bone formation ectopically [184] and in bone defects. For instance, Itoh *et al.* demonstrated that hydroxyapatite/type I collagen composites are efficient rhBMP-2 carriers and induce new bone formation for dog radius, ulna [185] and tibia [186] repair in these weight-bearing sites. In a rabbit lumber intertransverse fusion model, nHAp/collagen combined with rhBMP-2 showed similar fusion ratio and mechanical strength as the autogenous bone alone [187].

In addition to collagen, other natural polymers have been combined with ceramics to increase scaffold osteoconductivity. For example, Matsumoto et al. combined rhBMP-2 gelatin hydrogels with bioactive β-TCP and observed the enhanced regeneration of critical-sized (5mm) bone defects in rats [188]. However, the incorporation of β-TCP did not improve the biomechanical properties of the regenerated bone resulting from these composite gels, as determined by the three-point bending test [123]. In another study, a gelatin/nHAp scaffold was fabricated and combined with a fibrin glue/rhBMP-2 solution to create a hybrid scaffold with sustained and slow protein release kinetics, which resulted in the repair of a critical-size rabbit segmental bone defect after 12 weeks [189]. Furthermore, in a sheep anterior lumbar interbody fusion model, an injectable calcium phosphate cement/SF/rhBMP-2 scaffold resulted in comparable stiffness and bone formation to autografts at 12 months [190].

4.5 Biodegradable synthetic polymers

Biodegradable synthetic polymers are used extensively in bone tissue engineering due to their biocompatibility, hydrolytic biodegradability, formability, and ease of use [191,192]. For these reasons, these polymers are often considered ideal substrates for growth factor delivery and subsequent tissue formation. There are a number of ways to deliver growth factors from biodegradable polymers, but proteins are generally either physically encapsulated within the polymeric matrix or immobilized to the surface. Proteins also may experience ionic, hydrophobic, and/or hydrogen bonding interactions with the polymer. These mechanisms of encapsulation, chemical conjugation, and bonding can be greatly advantageous over purely physical methods of entrapment, as demonstrated by many natural polymers, due to the ability to control release rates for prolonged presence of rhBMPs locally. Of the several types of biodegradable polymers available, poly-α-hydroxy acids, such as polylactic acid (PLA), polyglycolic acid (PGA), and their copolymer poly(DL-lactide-co-glycolide) (PLGA), have emerged as popular choices. Synthetic grafting materials are now routinely combined with various active biologic substances to enhance their osteogenic potential. Poly-α-hydroxy acid polymers have been formed into microspheres, nanospheres, nanofibers, and coated on titanium surfaces alone and in combination with the aforementioned biomaterials—natural polymers and calcium phosphates. In particular, much research has focused on polymeric and ceramic composites since bone is a combination of organic and inorganic elements. Given the reviews previously published [127,191], described below are more recent advancements in rhBMP delivery in pre-clinical biodegradable synthetic polymer systems used for spinal and bone repair (Table 2b).

PLA was first investigated as a rhBMP-2 carrier nearly 20 years ago [193]. It has since undergone modifications such as the addition of polyethylene glycol (PEG) [194], the formation of plastic PEG [195,196], and the synthesis of PLA-p-dioxanone-PEG (PLA-DX-PEG) [197] to decrease the degradation rate, acid byproducts and increase the bone forming capabilities of pristine PLA/rhBMP-2 in ectopic mouse models [193,195,197], rat cranial defects [198], canine [192,199,200] and sheep [201] spinal fusion models, and long bone

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defects in rabbits [202] and dogs [203]. Furthermore, PLA incorporated with nHAp, collagen, and rhBMP-2 increased the lumbar spinal fusion ratio in a rabbit model compared to autografts [204], which is similar to rabbit posterolateral spine fusion results with PLA-DX-PEG/β-TCP/rhBMP-2 scaffolds [205]. More recently, Eguchi *et al*. incorporated an optimal dose of etanercept (ETN), an antitumor necrotic factor, with PLA-DX-PEG discs to enhance rhBMP-2 (5 μg) facilitated bone induction in a mouse ectopic model [206].

To a lesser extent, PGA has also been investigated as an rhBMP-2 carrier. Park and colleagues applied PGA/rhBMP-2 scaffolds combined with modified platelet rich plasma (mPRP) to a rat critical-sized calvarial defect model. In comparison with the control group, the experimental group showed significantly more blood vessels and bone healing at 8 weeks as evaluated with histology, bone mineral density and bone mineral content, and microCT[207]. In another study, PGA combined with poly-L-lysine (PLL), rhBMP-2 and transforming growth factor-beta 1 (TGF-β1) in a multilayered film successfully differentiated embryonic stem cells to osteoblasts *in vitro* [208].

The most recent and extensive work pertaining to rhBMP delivery centers around biodegradable and biocompatible PLGA scaffolds. Originally used as growth factor carrier in the mid-90s [209], the use of PLGA in *in vivo* models has since grown tremendously. PLGA is used alone or in combination with several other biomaterials, such as calcium phosphates, natural polymers, and other synthetic polymers, to release encapsulated rhBMP and facilitate bone formation. Of the several types of delivery vehicles, microspheres have been used the most extensively due to ease of fabrication, tunable degradation rates, and structure versatility [210–212]. However, in recent years the use of nanoparticles has increased because of the enhanced cell-biomaterial interaction at the nano-scale. For instance, Fu *et al*. encapsulated rhBMP-2 in PLGA/HAp composite fibers via electrospinning to not only observe good morphology and mechanical strength of the nanofibers, but also *in vivo* rhBMP-2 release and bioactivity [213]. In another study, PLGA/HAp/rhBMP-2 scaffolds seeded with human cord blood mesenchymal stem cells and implanted subcutaneously in mice resulted in increased bone formation, as evidenced by the presence of osteoblastic markers [214]. rhBMP-7 has also been encapsulated in polymeric systems. As Wei *et al*. detailed, rhBMP-7 incorporated in PLGA nanospheres and immobilized on PLLA nanoscaffolds led to successful bone formation in a rodent dorsal subcutaneous model as indicated by radiodensity and histological results [215], while rhBMP-7 loaded PLGA/nHAp composites resulted in long-term release of the osteogenic protein [216].

Despite the benefits of PLGA/calcium phosphate systems, rhBMPs often releases too rapidly from implanted scaffolds and exhibits decreased bioactivity. Thus, Ruhé *et al*. showed that high molecular weight PLGA/calcium phosphate composites release rhBMP-2 at a slower rate than using composites with low molecular weight PLGA [217]. In a more recent study, apatite-coated PLGA/nHAp suspended in fibrin gel showed a decrease protein release rate and an increase in bone formation in a critical-size rat calvarial defect [218]. rhBMP-2/PLGA has also been combined with natural polymers such as alginate hydrogels to increase osteoblastic gene expression [219] and increase femoral healing in a rat model [220], as well as collagen and rat autologous bone to preserve the *in vivo* activity of rhBMP-2 [221]. The combination of PLGA with synthetic polymers has been shown to decrease rhBMP-2 release rate *in vivo*. For instance, Liu *et al*. used PEG to tether rhBMP-2 to a PLGA scaffold to further delay protein release. After the scaffold was seeded with MSCs and implanted in a rabbit cranial defect model, PEG-tethered rhBMP-2 *de novo* bone formation was enhanced [222]. Furthermore, Kempen *et al*. encapsulated rhBMP-2 within PLGA microspheres and embedded the microspheres in a porous poly(propylene fumarate) (PPF) scaffold. Histology confirmed bone formation after the composite was seeded with

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BMSCs and implanted ectopically in a goat [223]. In a later study, Kempen and colleagues utilized the same carrier vehicle, but incorporated vascular endothelial growth factor (VEGF) to observe enhanced bone formation in a dorsal thoracolumbar goal model [224].

In addition to VEGF and TGF-β1 incorporated constructs, rhBMPs have been delivered with other molecules to enhance *in vivo* rhBMP-2 release and ectopic bone formation. Yu *et al.* detailed a 102% increase in ectopic bone formation upon rhBMP-7/PLGA bioactivity augmentation with a low dose of an anti-catabolic agent, bisphosphonate pamidronate. Heparin is another molecule that has been investigated for its bioactivity augmentation qualities. Jeon and colleagues first demonstrated that rhBMP-2 loaded heparin conjugated PLGA (HC-PLGA) scaffolds induced a 9-fold increase in bone formation area and 4-fold increase in calcium content as compared to rhBMP-2 loaded PLGA or unloaded HC-PLGA scaffolds [225]. In follow-up studies, Kang *et al.* showed that undifferentiated BMSCs on rhBMP-2 loaded HC-PLGA scaffolds induce more extensive bone formation than undifferentiated cells alone or osteogencially differentiated cells on the bioactive scaffold [226], while Kim *et al.* demonstrated the feasibility of using rhBMP-2/HC-PLGA nanoparticles for undifferentiated BMSCs delivery and subsequent bone formation [227]. Further, suspending these rhBMP-2/HC-PLGA nanoparticles in fibrin gel reduced the concentration of rhBMP-2 necessary to facilitate bone formation in mouse calvarial defects [228].

Poly(epsilon-capralactone) (PCL) is another popular, commercially available polymer used in tissue engineering applications because it is soluble in a number of organic solvents, can form miscible blends with several polymers, and is hydrolytically degradable (2–3 years) [229]. In combination with collagen, PCL/β-TCP scaffolds loaded with rhBMP-2 (5 μg) showed complete healing of a rat calvarial critical-sized defect at 15 weeks as determined by microCT, histology/histomorphometry, and mechanical assessments [230]. Furthermore, filling rat femoral defects with PCL, collagen matrix and rhBMP-2/heparin complexes resulted in new bone formation with mechanical properties similar to those of intact bone [231]. The architecture of the PCL scaffold also plays a significant role in bone formation. For instance, the bone formation, as assessed by radiography, microCT, and histology, in a 15mm rabbit ulna defect model was enhanced in comparison to experimental controls by a three-dimensional rhBMP-2/PCL scaffold with honeycomb-like porous structures [232]. PCL has also been applied in pre-clinical spinal surgeries. As shown in a pig anterior lumber interbody fusion model, bone formation induced by PCL/β-TCP scaffolds with a low dose of rhBMP-2 (0.6 mg) was comparable to the positive control as determined by histology, micro-CT and biomechanical evaluation [233]. These results, combined with the aforementioned, reveal the potential use of natural polymers, ceramics, and synthetic polymers for bone tissue repair and regeneration.

5. Critical Outlook

Applications of BMPs in long bone repairs, spinal fusions, and oral surgeries are becoming increasingly common. While current results and outcomes have shown promise, significant issues with BMP-based therapies remain. One major concern has been the off-label use of BMPs. Over the past decade, at least 85% of the principal procedures using BMPs were off-label applications [235]. rhBMP-2 may lead to early bone resorption around PEEK implants, which can cause loosening and pain [108]. Also, the use of rhBMP-2 in spinal fusion has been shown to cause increased swelling and significant ectopic bone formation in the spinal canal which can lead to significant pain and possibly limit limb function [109,110]. In 2008, the FDA issued a public health notification highlighting at least 38 reports of complications related to off-label use of BMP products in spinal fusion surgery including compression of the airway and/or neurological structures of the neck [234]. A recent review of rhBMP-2 used in spinal surgeries shows that the risk of adverse side effects associated with rhBMP-2

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is 10 – 50 times the original estimates reported in peer-review publications [111]. In 2011, the special issue of the Spine Journal (Volume 11, Issue 6) took the unprecedented step of devoting an entire special issue to the numerous problems associated with using rhBMP-2 in spinal surgery applications for which FDA clearance does not exist. Specifically, Medtronic is alleged to have been illegally promoting off-label uses of their INFUSE graft [236] and doing so with falsified data [237]. Medtronic is currently being sued by both patients disabled by the off-label use of INFUSE [238] and by their own share holders [239]. In response to this and other related cases, a bill has been introduced in the United States Senate to enhance the FDA's ability to monitor medical devices after they have cleared the agency [240].

Another significant and related issue is the demonstrated need for supraphysiological BMP dosages from delivery matrices to achieve clinically desired osteoinductive effects. Many therapies require the delivery of milligram quantities of BMPs when natural localized endogenous BMP production is typically at the nanogram level [241]. The reason for this discrepancy in generating new bone is unknown, but this use of exogenous dosages exceeding one million times normal levels is believed to be at least partially responsible for many of the complications currently seen with BMP-based treatments [242]. With these issues, more research must be conducted in order to understand bone biology with BMPs and improve site-directed BMP delivery before BMP-loaded constructs might become the new gold standard replacing ileac crest bone grafts.

Tissue engineered products comprising biodegradable polymeric scaffolds hold tremendous promise for delivering therapeutic amounts of rhBMPs. Specifically, new systems must protect rhBMP from degradation while maintaining its bioactivity, contain sufficient porosity to facilitate cell infiltration and induce angiogenesis, undergo programmed degradation as new tissue forms, and remain suitable for commercial manufacturing and sterilization. Selecting one or a combination of degradable polymers outlined above; engineers, scientists, and clinicians are working together to synthesize new clinically relevant scaffolds that meet these specifications. In the future, scaffolds possessing osteoinductive small molecules capable of inducing local endogenous production of BMPs will be used in concert with exogenous rhBMPs to better induce osteogenesis. For instance, members of the statin family including cerivastatin, fluvastatin, lovastatin, and simvastatin induce osteogenesis in vitro and in vivo by increasing the expression of BMP-2 through the Smad/BMP signaling mechanism [243–251]. Statins are FDA-cleared drugs for the treatment of cardiovascular disease and have been safely administrated to patients for more than a decade [252]. Research into other potential uses of statins led to their discovery as new therapeutics for treating bone disorders [253]. Similar to statins, several other small molecules have been found to possess osteoinductive activity through the BMP/Smad signaling mechanism. These small molecules include icariin [254–256], tacrolimus hydrate (FK506) [257–261], rapamycin [262,263], helioxanthin-derivative (TH) [264], and phenamil [265]. Lastly, the authors' stimulation of the protein kinase A signaling pathway by a cyclic AMP analog, N6-benzoyladenosine-3',5'-cyclic monophosphate (6-Bnz-cAMP), caused *in vitro* osteogenesis in several cell types such as mouse osteoblast-like MC3T3-E1 cells [266] and human mesenchymal stem cells (unpublished data). Materials-only approaches also hold promise to induce endogenous BMP expression. Ceramics like calcium phosphate have long been found to possess intrinsic osteoinductive properties [267] and these could be further engineered for certain applications. Specifically, the authors have recently demonstrated that polymer-ceramic composite sintered microsphere scaffolds can induce osteogenic differentiation of human adipose-derived stem cells (unpublished data). Taken together, these novel scaffolds hold promise to facilitate the expansion of BMP-loaded systems beyond maxillofacial and spinal surgeries to long bone fracture and skeletal repair where cost and efficacy of current systems have limited their widespread use.

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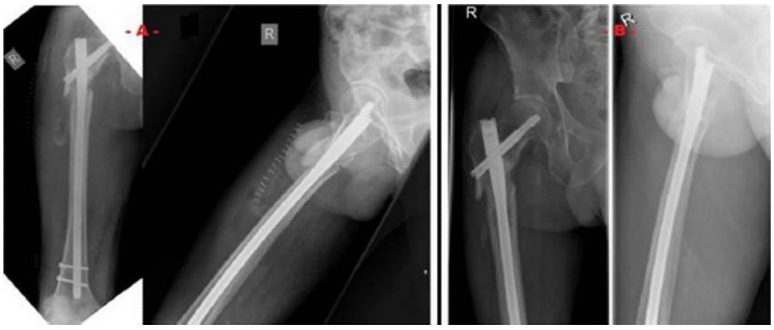

Figure 1.
A 62-year-old man fell and experienced a subtrochanteric right femur fracture that was unsuccessfully repaired by intramedullary nail fixation alone. Radiographs show revision surgery with nail repositioning and application of Osigraft® immediately after surgery (A) and 6 months later (B). Radiologically and clinically evident healing is present. (Reproduced from [30] with permission granted by Elsevier.)

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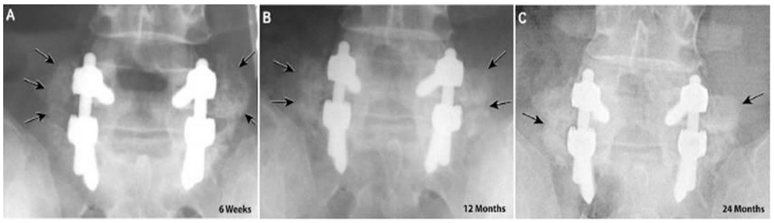

Figure 2.

Radiographs of the fusion mass at 6 weeks (A), 12 months (b), and 24 months after posterolateral arthrodesis spinal surgery using a ceramic-granule bulking agent with rhBMP-2 loaded collagen sponge to mediate joint ossification. Radiographs show the initial presence of ceramic granules (arrows in A) which are later resorbed and replaced with new bone formation (arrows in B & C). (Reproduced from [91] with permission pending from Rockwater Inc.)

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Table 1

FDA-approved clinical applications of recombinant BMP-2 and BMP-7.

Recombinant BMP isoforms	**rhBMP-2**	**rhBMP-7**
FDA approval	Spinal fusion (anterior lumbar interbody fusion)	*Spinal fusion (posterolateral lumbar fusion)
	Open tibial fractures	*Long bone nonunion
	Sinus lift	
	Alveolar ridge augmentation	

* Under a humanitarian device exemption (HDE)

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Table 2a

Summary of animal studies involving rhBMP-2 incorporated with natural polymers

Natural Polymers & rhBMP-2				
Polymer	**Carrier**	**Animal Model**	**Defect Model**	**Ref.**
Collagen	Sponge	Nonhuman primate	Anterior interbody fusion	[130]
		Rabbit	Posterolateral lumbar spinal fusion	[131]
		Canine	Lumbar spinal fusion	[132]
Gelatin	Hydrogel	Rabbit	Ulnar segment defect	[136]
Hyaluronic Acid	Hydrogel	Canine	Alveolar ridge defect	[137]
		Rabbit	Mid-tibial non-union	[138]
		Rat	Calvarial bone defect	[139–141]
Alginate	Hydrogel	Mouse	Ectopic bone formation	[144]
		Rabbit	Posterolateral intertransverse fusion	[145]
		Rat	Femoral bone defect	[146]
Chitosan	Hydrogel	Rat	Calvarial bone defect	[150,151]
		Rat	Ectopic bone formation	[153]
Silk Fibroin	Electrospun scaffold	Mouse	Calvarial bone defect	[155]
	Microparticles	Rat	Ectopic bone formation	[156]
	Hydrogel (injectable)	Rabbit	Maxillary sinus floor augmentation	[157]
Fibrin	Hydrogel (injectable)	Rat	Calvarial bone defect	[160]

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Table 2b

Summary of animal studies involving rhBMP-2 incorporated with synthetic polymers such as polylactic acid (PLA), polyglycolic acid (PGA), poly(DL-lactide-co-glycolide) (PLGA), poly(propylene fumarate) (PPF), and poly(epsilon-capralactone) (PCL) alone, with a natural polymer, or modified with polyethylene glycol (PEG) and dioxanone (DX).

Synthetic Polymers & rhBMP-2				
Polymer	**Carrier**	**Animal Model**	**Defect Model**	**Ref.**
PLA-PEG	Pellet	Mouse	Ectopic bone formation	[193,195,197]
	Injected; Polymeric Strip	Canine	Anterior thoracic spinal fusion; Lumbar intertransverse fusion	[199,200]
PLA-DX-PEG	Pellet	Rat	Cranial bone defect	[198]
	Implant coating	Canine	Femoral bone defect	[203]
PDLLA	Titanium cage coating	Sheep	Anterior cervical discectomy and fusion	[201]
PGA	Mesh	Rat	Calvarial bone defect	[207]
PLGA	Microsphere	Rat	Calvarial bone defect	[210,211]
PLGA; alginate	Cylindrical scaffold	Rat	Femoral bone defect	[220]
PLGA-PEG	Disk	Rabbit	Cranial bone defect	[222]
PLGA/PPF	Embedded microspheres	Goat	Ectopic bone formation	[223]
PCL; collagen	Disk	Rat	Femoral bone defect	[231]
PCL	Honeycomb porous scaffold	Rabbit	Ulna bone defect	[232]

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Table 2c

Summary of animal studies involving rhBMP-2 incorporated with ceramics such as hydroxyapatite (HAp), β-tricalcium phosphate (β-TCP), and bisphasic calcium phosphate (BCP).

Ceramics & rhBMP-2				
Ceramic	**Carrier**	**Animal Model**	**Defect Model**	**Ref.**
HAp	Disk	Rat	Ectopic bone formation	[166]
	Mesh	Rat	Postereolateral spinal fusion	[167]
	Block	Rabbit	Unilaterial radii defect	[168]
β-TCP	Particulate	Canine	Postereolateral lumbar interbody fusion	[173]
	Cement	Sheep	Trepanation defect	[174]
BCP	Block	Nonhuman primate	Posterolateral lumbar intertransverse fusion	[178]
	Disk	Rat	Calvarial bone defect	[179]

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Table 2d

Summary of animal studies involving rhBMP-2 incorporated with polymeric and ceramic composites.

Polymeric & Ceramic rhBMP-2 Composites					
Natural Polymers					
Polymer	**Ceramic**	**Carrier**	**Animal Model**	**Defect Model**	**Ref.**
Collagen	HAp	Coated sponge	Rabbit	Posterolateral spinal fusion	[180–182]
		Disk	Mouse	Ectopic bone formation	[184]
		Disk	Canine	Radius and ulna defect	[185]
		Block	Canine	Tibial bone defect	[186]
Collagen	nHAp	Graft	Rabbit	Posterolateral lumbar intertransverse fusion	[187]
		Sponge & granules	Nonhuman primate	Posterolateral lumbar intertransverse fusion	[183]
		Stacked sheets	Rhesus monkey	Posterolateral spinal fusion	[133]
Gelatin	β-TCP	Sponge	Rat	Mandible bone defect	[188]
Gelatin	nHAp	Porous scaffold	Rabbit	Radial bone defect	[189]
Silk Fibroin	CaP	Injectable cement	Sheep	Anterior lumbar interbody fusion	[190]
Synthetic Polymers					
PLA; collagen	nHAp	Porous scaffold	Rabbit	Lumbar intertransverse fusion	[204]
PLA-DX-PEG	β-TCP	Porous rod	Rabbit	Posterolateral lumbar intertransverse fusion	[205]
		Coated porous cylinder	Rabbit	Femoral bone defect	[202]
PLGA	HAp	Electrospun fibers	Mouse	Tibial bone defect	[213]
		Disk	Mouse	Ectopic bone formation	[214]
PLGA	CaP	Cement Disk	Rat	Ectopic bone formation	[217]
PLGA; fibrin	nHAp	Gel suspended particulates	Rat	Calvarial bone defect	[218]
PLGA; collagen	Bone particles	Microspheres	Rat	Ectopic bone formation	[221]
PCL; collagen	β-TCP	Disk	Rat	Calvarial bone defect	[230]
PCL	β-TCP	Mesh	Pig	Anterior lumbar interbody fusion	[233]