BMPs in Dental Medicine: Promises and Challenges

Ulf M.E. Wikesjö and Cristiano Susin

Abstract Regeneration of bone is critical to the rehabilitation of congenital malformations and defects resulting from trauma or tumor resection in the craniofacial skeleton, as well as defects resulting from periodontal disease or remodeling following tooth extractions. It is the objective of this text to reflect pioneering and significant preclinical and clinical observations, promises, and challenges, of bone morphogenetic proteins (BMPs) with focus on recombinant human BMP-2 (rhBMP-2) but also recombinant human BMP-7 (rhBMP-7) and recombinant human growth/differentiation factor-5 (rhGDF-5) in craniofacial settings to include alveolar bone augmentation for implant dentistry.

Keywords Recombinant human BMP-2 (rhBMP-2) • Recombinant human BMP-7 (rhBMP-7) • Recombinant human growth/differentiation factor-5 (rhGDF-5) • Alveolar augmentation • Sinus augmentation • Alveolar preservation • Osseointegration • Implant dentistry • Dental implants

1 Introduction

Regeneration of bone is vital to the rehabilitation of congenital malformations in the craniofacial skeleton, defects resulting from trauma or tumor resection and defects resulting from periodontal disease or remodeling following tooth extractions. Historically, autogenous bone grafts have been preferred for bone augmentation on craniofacial indications; however, demand for a second surgical site, finite intraoral sources, and associated morbidity has constrained their widespread acceptance and

U.M.E. Wikesjö, DDS, DMD, Dr Odont (✉) • C. Susin, DDS, MSD, Dr Odont
Laboratory for Applied Periodontal and Craniofacial Regeneration – The Dental College of Georgia, Augusta University, 1430 John Wesley Gilbert Drive, Augusta, 30912 GA, United States
e-mail: uwikesjo@augusta.edu; wikesjo@comcast.net

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use [2, 11, 51]. In consequence, the dental profession increasingly has embraced cadaver-sourced allogeneic and xenogeneic (bovine, porcine, equine, coral) or synthetic (polymeric, ceramic) bone biomaterials and in addition resorbable/non-resorbable devices (membranes) for guided tissue/guided bone regeneration (GTR/GBR) as stand-alone therapeutic interventions or in various combinations to meet clinical demands [1, 18, 61]. The global market for dental bone biomaterials and devices for GTR/GBR illustrates this trend, the US/North American market estimated to $363 M, the EU/Middle East/African market to $189 M, the Latin American market to $97 M, and the Asian Pacific market to $125 M in 2015 for a total estimated value of $773 M (iData Research). As the bone-anchored dental implant-based prosthesis progressively has become favored for oral rehabilitation replacing missing and compromised teeth, augmentation of the deficit alveolar ridge has become an even more significant prerequisite. In perspective, it is estimated that in excess of 14 M, dental implants are sold/placed annually worldwide, the US market alone estimated to approach 2.5 M units in 2015 (iData Research).

Intuitive observations of bone formation associated with implanted bone matrices [39, 46, 52] eventually led to the critical discovery of bone morphogenetic proteins (BMPs) [71]. Subsequent purification, characterization, and cloning [10, 30, 31, 53, 60, 72, 79] triggered research and development pursuing purified and recombinant forms of BMPs to induce bone formation in orthopedic, spine, and craniofacial settings [5, 16, 32, 40, 78]. Recombinant human BMP-2 in an absorbable collagen sponge carrier (rhBMP-2/ACS) became the first BMP technology approved for human use by the US Food and Drug Administration, approved for spine fusion in 2002 and in 2004 for open tibia fracture repair [48]. In 2007, rhBMP-2/ACS met approval for bone augmentation in conjunction with tooth extraction sockets and bone augmentation in the maxillary sinus to enable installation of bone-anchored (osseointegrated) dental implants in the rehabilitation of dilapidated dentitions. It is the objective of this text to reflect pioneering and significant preclinical and clinical observations, promises, and challenges of BMPs with focus on rhBMP-2 but also rhBMP-7 and recombinant human growth/differentiation factor-5 (rhGDF-5) in craniofacial settings to include alveolar bone and sinus augmentation for implant dentistry.

2 Setting the Stage

Alveolar augmentation may out of principle be divided into inlay and onlay indications translating to contained (inlay) and non-contained (onlay) defect sites. Tooth extraction sockets, intrabony defects, and maxillary sinus floor sites represent inlay defects, and width and height deficiencies of the alveolar ridge represent onlay defects.

In perspective, it is important to realize elementary biomechanical requirements for any compatible technology, BMP or other, tasked to support alveolar augmentation to challenges and constraints offered in inlay and onlay settings [28]. Whereas particulate or paste formulations may suffice to support/enhance bone formation in contained sites, structural integrity and geometry hardly offered by particulate

technologies become requisite characteristics for technologies considered for augmenting/expanding the width and height of the alveolar envelope. This is also true for compressible carriers such as the ACS which poorly withstands the challenges imposed by intraoral forces. Devices and membranes have long been used to provide containment and space provision for particulate and compressible carriers.

Slowly/non-resorbable biomaterials, which are often used alone or in combination for alveolar ridge augmentation, may actually compromise space-provision obstructing the site for bone formation. In the long-term, slowly/non-resorbable technologies may compromise mechanical properties of bone including dental implant fixation and load-bearing. Nevertheless, combined with successful space-providing delivery technologies or adjunctives, BMPs have shown significant promise to support bone formation in the craniofacial skeleton. A number of studies using rodent screening models, translational inlay and onlay defect models, and canine, porcine, or nonhuman primate platforms including discriminating critical-size defects and clinical modeling illustrate the potential of BMPs to augment alveolar bone in craniofacial settings. We herein separately review alveolar bone augmentation (inlay and onlay defects), maxillary sinus augmentation, and peri-implant defects in preclinical and clinical settings.

3 Alveolar Ridge Augmentation/Preservation

A concerted chain of events occur following tooth extraction leading to remodeling of the alveolar ridge and, ultimately, to the complete resorption of the alveolar bone. Whereas most of the efforts in implant dentistry have been directed at augmenting the resorbed alveolar ridge, alveolar bone preservation following extractions has become increasingly important. To that end, the application of BMPs at the time of tooth extraction – prior to bone loss due to remodeling – represents a compelling treatment option.

3.1 Observations from Preclinical Inlay Models

Preclinical studies using inlay defect models have evaluated rhBMP-2 and rhGDF-5 for alveolar augmentation. These early studies have primary focus on alternative delivery systems to present BMP to the defect site. Cochran and colleagues applied rhBMP-2/ACS (*rhBMP-2 at 0.2 mg/mL*) and rhBMP-2 in a polylactide/glycolide copolymer carrier (rhBMP-2/PLGA, *rhBMP-2 at 0.2 mg/mL*) to 1.5 × 4-mm (width × depth) gap defects circumscribing dental implants in dogs to evaluate bone formation following 4- and 12-week healing intervals [12, 13, 34]. Defect sites receiving rhBMP-2/ACS and rhBMP-2/PLGA showed significantly enhanced bone fill compared with control at 4 but not at 12 weeks. Comparing the ACS with the PLGA carrier, the ACS supported greater bone fill in this inlay defect model. Notably, sites additionally fitted with an occlusive expanded polytetrafluoroethylene (ePTFE) GBR membrane to exclude soft tissue infiltration showed delayed bone formation.

Commentary This early study points to accelerated bone formation in alveolar sites receiving rhBMP-2, and that tissue resources originating in adjoining mucosal tissues substantially contribute to rhBMP-2-induced bone formation if not blocked by an occlusive membrane.

In parallel studies using clinically advanced (~15 × 10 × 10 mm; length × depth × width) alveolar ridge saddle-type defects in dogs and a 12-week healing interval, Jovanovic and co-workers evaluated suitability of a volume-defining hyaluronan (Hy) sponge vs. the ACS technology to serve as delivery systems for rhBMP-2 (*rhBMP-2 at 0.2 mg/mL*). Both rhBMP-2/ACS- and rhBMP-2/Hy-induced bone formation filled the saddle-type defects to capacity suggesting that Hy may be used interchangeably with ACS in support of rhBMP-2-induced bone formation [33]. In separate studies, rhBMP-2/ACS (*rhBMP-2 at 0.2 mg/mL*) was benchmarked to GBR demonstrating superior bone fill over GBR following a 12-week healing interval [36]. Combining rhBMP-2/ACS with GBR did not offer additional benefits (Figs. 1 and 2). Of note, GBR sites often encountered suture-line dehiscences exposing the ePTFE membrane that readily became infected compromising wound healing/regeneration altogether in contrast to sites receiving rhBMP-2/ACS alone displaying uneventful healing potentially reflecting a beneficial effect of rhBMP-2 also on soft tissue healing. In still other studies, long-term stability of rhBMP-2/ACS-induced bone (*rhBMP-2 at 0.2 mg/mL*) vs. that of the pristine resident bone was compared [35] (Fig. 3). Dental implants were inserted into the rhBMP-2/ACS-induced and adjoining pristine resident bone, osseointegrated, and fitted with a fixed dental prosthesis. The animals were then returned to a solid dog-food diet for functional loading. Crestal bone levels and dental implant fixation evaluated following 12 months of functional loading showed limited, if any, differences between rhBMP-2/ACS-induced and pristine resident bone again substantiating unique properties of rhBMP-2/ACS rarely, if at all, reached using conventional allogeneic/xenogeneic bone derivatives or synthetic biomaterials.

Commentary Significant for this series of studies in addition to key observations of clinically meaningful bone formation for the benefit of fixation of dental implants following surgical implantation of rhBMP-2/ACS is the clinical swelling at the defect sites subsiding within 7–10 days as well as frequently occurring seroma formation, seromas constituted as serum-filled radiolucent vacuoles within the regenerate eventually filling with bone demonstrated in the radiographic and histologic evaluation.

Still other studies evaluated the clinical potential of rhGDF-5 in a resorbable particulate micro-/macroporous ß-tricalcium phosphate carrier (rhGDF-5/ß-TCP, *rhGDF-5 at 0.6 mg/g ß-TCP*) also using alveolar ridge saddle-type defects in dogs, sites receiving the rhGDF-5/ß-TCP technology showing enhanced bone formation compared with the autogenous bone graft control [73]. Studies in rodent screening models further substantiate the superiority of rhGDF-5/ß-TCP (*rhGDF-5 at 0.5 mg/g ß-TCP*) benchmarked to a market leader particulate bovine bone biomaterial [57].

Commentary Adverse events, i.e., local swelling or seroma formation, were not evident or reported with the use of rhGDF-5/ß-TCP.

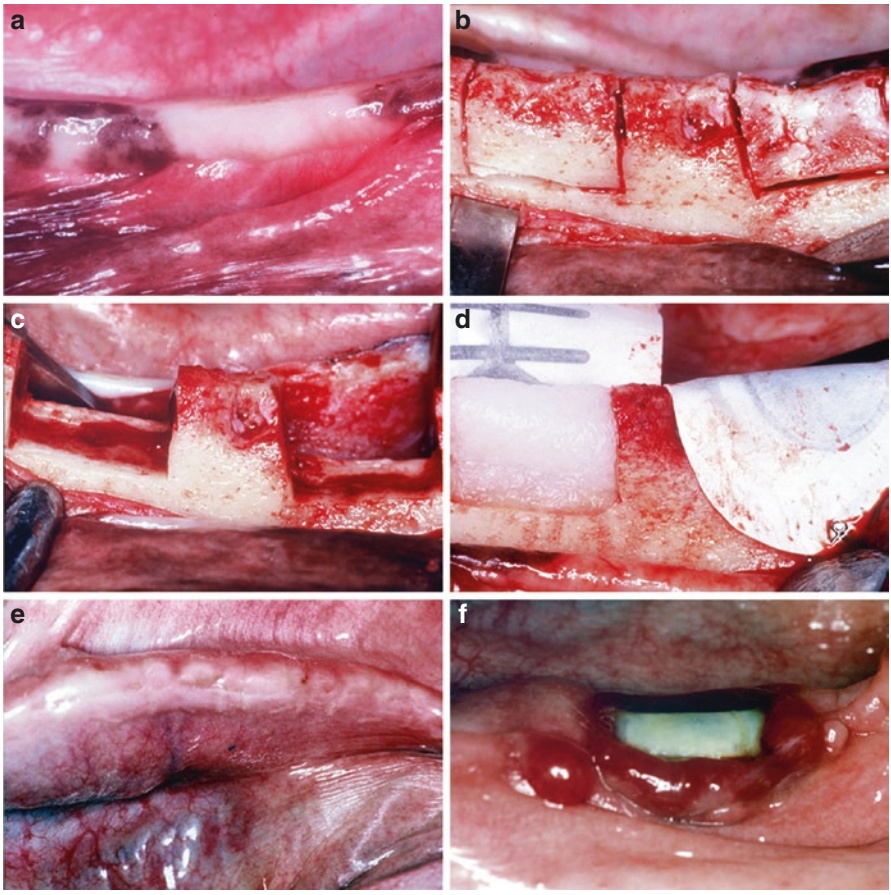

Fig. 1 Mandibular, alveolar ridge, saddle-type defect implanted with rhBMP-2/ACS and guided bone regeneration (GBR): presurgery baseline (**a**); surgical outline of the alveolar ridge defect (**b**); alveolar ridge saddle-type defect (**c**); application of rhBMP-2/ACS and GBR membranes (**d**); and clinical observations of sites implanted with rhBMP-2/ACS (**e**) and GBR (**f**). Note swelling of the site implanted with rhBMP-2/ACS and wound failure at the site receiving GBR (From Jovanovic et al.[36]; Figures copyrighted by and modified with permission from John Wiley & Sons Ltd.)

3.2 Observations from Preclinical Onlay Models

Our laboratories first showed that rhBMP-2/ACS (*rhBMP-2 at 0.4 mg/mL*) has potential to support clinically relevant bone formation for implant dentistry expanding the alveolar ridge [63] (Fig. 4). Using the critical-size supraalveolar peri-implant defect model [76], 10-mm dental implants were placed 5 mm into the edentulated mandibular alveolar crest leaving 5 mm of the implant extending above the crest covered with rhBMP-2/ACS or buffer/ACS (control) and submerged under the advanced

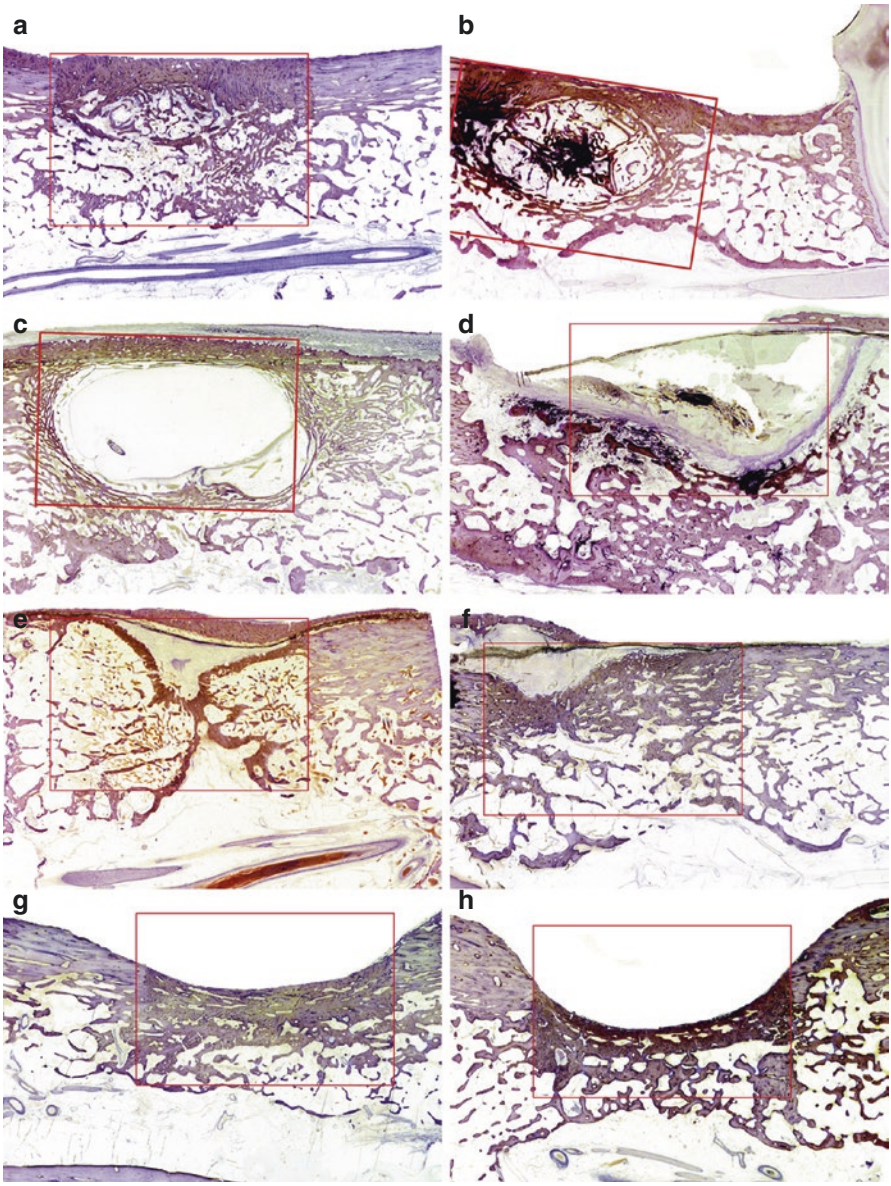

Fig. 2 Representative photomicrographs of defect sites receiving rhBMP-2/ACS (**a** cortex formation and complete trabecular bone fill; **b** cortex formation and resolving seroma filled with trabecular bone); rhBMP-2/GBR (**c** cortex formation and large seroma; **d** wound failure/membrane exposure; note cortex formation over part of the GBR barrier); GBR (**e** cortex formation; **f** limited, late(?) wound failure/membrane exposure; note cortex formation over part of the GBR barrier); and surgery controls with (**g**) or without (**h**) ACS. Red frames approximate the original defect sites. Healing interval 12 weeks (From Jovanovic et al. [36]; Figures copyrighted by and modified with permission from John Wiley & Sons Ltd.)

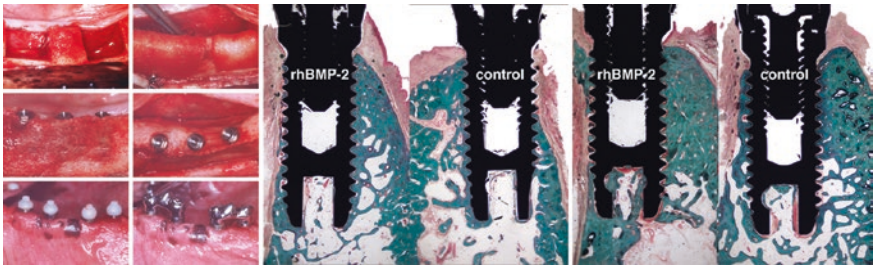

Fig. 3 Evaluation of titanium implants placed into rhBMP-2-induced bone subject to 12 months of functional loading. The clinical panels show surgically induced mandibular, saddle-type (~15 × 10 mm), full-thickness alveolar ridge defects (two per jaw quadrant). The defects were immediately implanted with rhBMP-2/ACS with or without a barrier membrane. Healing progressed for 3 months when endosseous oral implants were installed into the rhBMP-2/ACS-induced bone and adjoining resident bone (control). Following 4 months of osseointegration, the implants received abutments and prosthetic reconstruction. Prosthetic reconstructed implants were then subject to functional loading for 12 months. The photomicrographs show implants placed into rhBMP-2-induced and resident bone following 12 months of functional loading. There is no discernable difference in bone formation and osseointegration between rhBMP-2-induced and resident bone (From Jovanovic et al. [35]; Figures copyrighted by and modified with permission from John Wiley & Sons Ltd.)

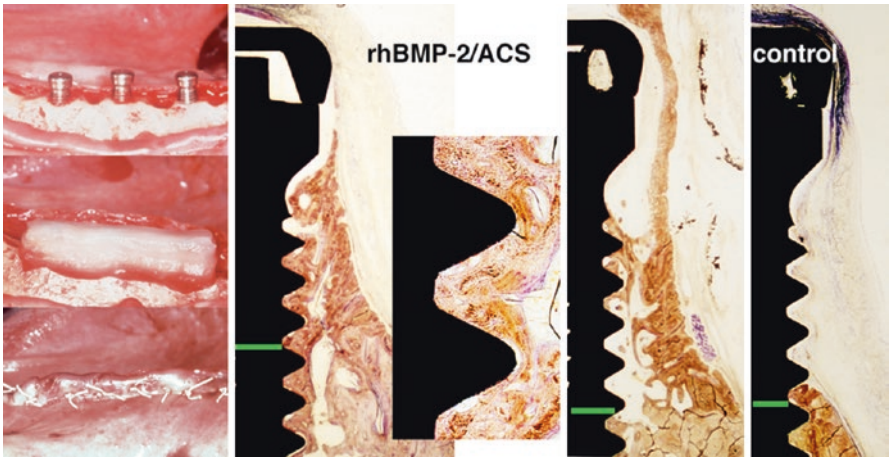

Fig. 4 Critical-size, supraalveolar, peri-implant defect implanted with rhBMP-2/ACS or ACS without rhBMP-2 (control). Clinical panels show the supraalveolar defect with rhBMP-2/ACS before and after wound closure for primary intention healing. The photomicrographs show defect sites implanted with rhBMP-2/ACS exhibiting bone formation reaching or exceeding the implant platform, the newly formed bone showing osseointegration to the titanium implant surface (high magnification insert). Control sites show limited, if any, bone formation. *Green lines* delineate the level of the surgically reduced alveolar crest. Healing interval 16 weeks (From Sigurdsson et al. [63]; Figures copyrighted by and modified with permission from John Wiley & Sons Ltd.)

mucoperiosteal flaps for primary intention healing. The histologic evaluation following a 16-week healing interval showed significant bone formation anchored to the previously naked implant surface reaching the top of the dental implants at sites receiving rhBMP-2/ACS, whereas controls displayed negligible bone formation. In comparison, parallel studies using space-providing membranes for GBR or membranes combined with an allogeneic demineralized bone matrix demonstrate the limited native regenerative potential of this defect model emphasizing the unique potential of rhBMP-2/ACS to stimulate local bone formation in support of implant dentistry [9, 75] (Fig. 5). Nevertheless, rhBMP-2/ACS-induced bone formation expressed considerable variability at times wallpapering the implant threads, at times showing bone formation of clinically relevant volume and geometry adjoining the implant. Apparently, the rhBMP-2/ACS technology appears ineffective to consistently support significant bone formation in onlay settings also shown in other studies using the canine supraalveolar peri-implant defect model, rhBMP-2, evaluated at concentrations of 0.05, 0.1, and 0.2 mg/mL [47, 68, 74] (Figs. 6 and 7).

Commentary Variable bone formation may rest with rhBMP-2 dose and/or bioavailability but also ACS structural integrity, biodegradation, soak-load, or any combination thereof.

Several routines have been considered to safeguard rhBMP-2/ACS performance for alveolar augmentation for implant dentistry. They include above mentioned rhBMP-2 dose variation ([68]; *rhBMP-2 at 0.05*, *0.1*, *and 0.2 mg/mL*) (Fig. 6), as well as the use of purpose-designed space-providing macroporous membranes/devices ([41, 74, 75]; *rhBMP-2 at 0.2 mg/mL*) (Fig. 7). Bulking agents including

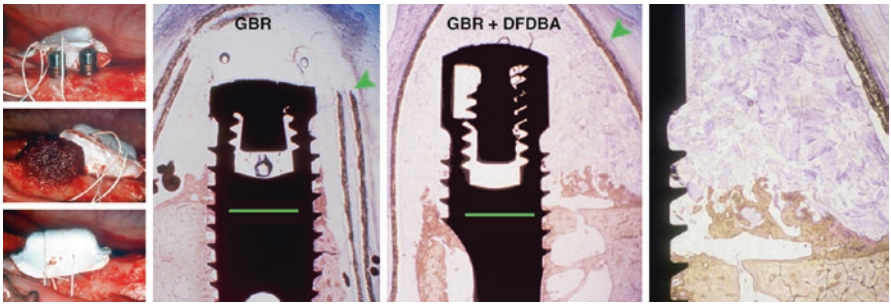

Fig. 5 Critical-size, supraalveolar, peri-implant defect treated with guided bone regeneration (*GBR*) using an occlusive space-providing ePTFE membrane (*green arrowheads*), with or without an allogeneic demineralized bone matrix (DBM). Clinical panels show the supraalveolar defect with the ePTFE membrane, with DBM rehydrated in autologous blood, and with the membrane in place prior to wound closure for primary intention healing. Note limited regeneration of alveolar bone in the absence and presence of DBM suggesting that the innate regenerative potential of alveolar bone is limited and that the DBM biomaterial has limited, if any, osteoinductive and/or osteoconductive properties to support bone regeneration. *Green lines* delineate the level of the surgically reduced alveolar crest. Healing interval 16 weeks (From Caplanis et al. [9]; Figures copyrighted by and modified with permission from Quintessence Publishing)

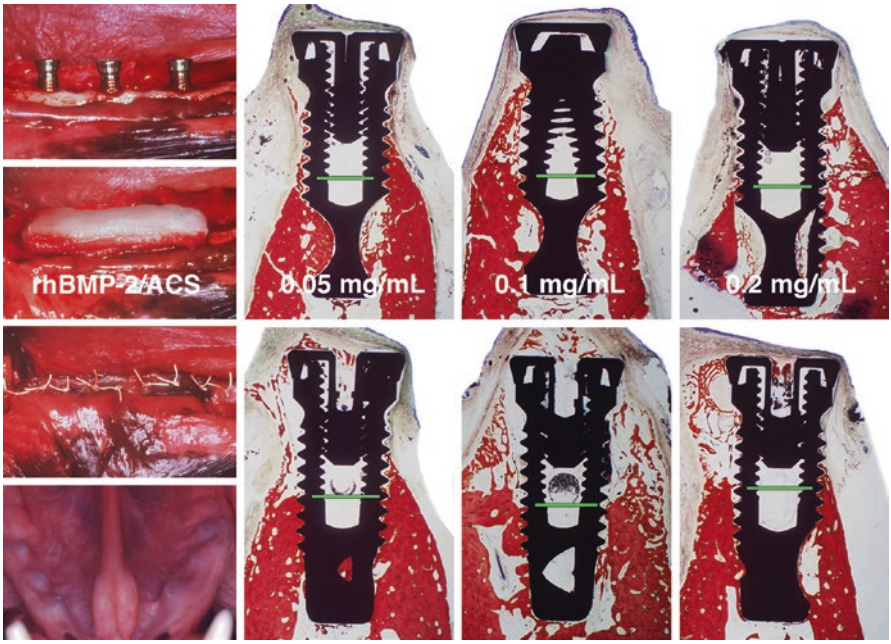

Fig. 6 Critical-size, supraalveolar, peri-implant defects treated with rhBMP-2/ACS; rhBMP-2 at *0.05*, *0.1*, and *0.2 mg/mL*. Clinical panels show a supraalveolar defect implanted with rhBMP-2/ACS before and after wound closure for primary intention healing, and clinical appearance at week 6 postsurgery; the right and left mandibular jaw quadrants of this animal received rhBMP-2 at 0.05 and 0.2 mg/mL, respectively. Representative photomicrographs show defect sites implanted with rhBMP-2/ACS exhibiting bone formation reaching or exceeding the implant platform. The newly formed, sparsely trabecular bone shows osseointegration to the machined titanium implant surface. The top photomicrographs show sites with the poorest bone induction for the various rhBMP-2 concentrations evaluated. The lower photomicrographs show corresponding sites with the best response. The *green lines* delineate the level of the surgically reduced alveolar crest. Healing interval 8 weeks (From Tatakis et al. [68]; Figures copyrighted by and modified with permission from John Wiley & Sons Ltd.)

granular hydroxyapatite, biphasic calcium phosphate, ß-tricalcium phosphate technologies, and others have likewise been considered to counter compressive forces onto the rhBMP-2/ACS as well as outlining desired bone volume and geometry. However, bulking agents may also introduce compromises related to their biodegradation; slowly or non-resorbable technologies may compromise the structural integrity of the newly formed bone including dental implant osseointegration ([3, 4, 47, 49]; *rhBMP-2 at 0.2 and 0.4 mg/mL*), while for bioresorbable conduits, the resorption process per se may solicit inflammatory reactions compromising bone formation and/or maintenance ([62]; *rhBMP-2 at 0.2 mg/mL*).

Commentary Whereas dose variation failed to influence rhBMP-2/ACS-induced bone formation, the use of macroporous space-providing devices allowed directed

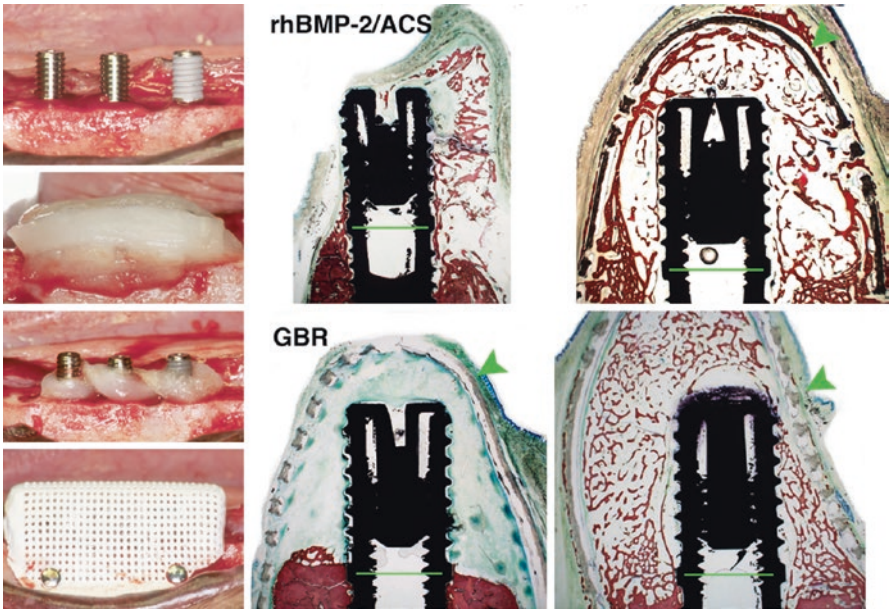

Fig. 7 Critical-size, supraalveolar, peri-implant defects treated with rhBMP-2/ACS, a porous, space-providing ePTFE membrane for guided bone regeneration (*GBR*), or rhBMP-2/ACS combined with the porous ePTFE membrane. The clinical panels show the supraalveolar defect with rhBMP-2/ACS and with the porous ePTFE membrane. Note how rhBMP-2-induced bone fills the space provided by the membrane (*green arrowheads*), whereas rhBMP-2/ACS alone provides very irregular bone formation (*top left*). The ePTFE membrane alone (*bottom left*) provides limited, if any, regeneration of alveolar bone. *Green lines* delineate the level of the surgically reduced alveolar crest. Healing interval 8 weeks (From Wikesjö et al. [74, 75]; Figures copyrighted by and modified with permission from John Wiley & Sons Ltd.)

rhBMP-2/ACS-induced bone formation/alveolar augmentation supporting the principle that the volume/geometry of new bone formation can be ascertained in the design of a space-providing device/matrix.

Pilot observations from rodent screening models suggest that a considerably lowered rhBMP-2 dose may effectively support bone formation/maturation [29, 54]. Using the critical-size supraalveolar peri-implant defect model, we evaluated the effect of rhBMP-2, rhBMP-7, and rhGDF-5 coated immediately onto dental implants on alveolar bone formation using a dose range protocol [43–45, 58, 66, 77]. Compared with control, BMP-coated implants yielded clinically relevant vertical bone gain (Fig. 8). Notably, rhBMP-2-coated implants displayed an inverse relationship between rhBMP-2 dose and induced bone formation/maturation [43, 77]. Whereas the low rhBMP-2 dose supported clinically relevant vertical/horizontal alveolar augmentation, in contrast, the high dose delayed bone maturation and in addition showed considerable clinical swelling and radiographic seroma formations.

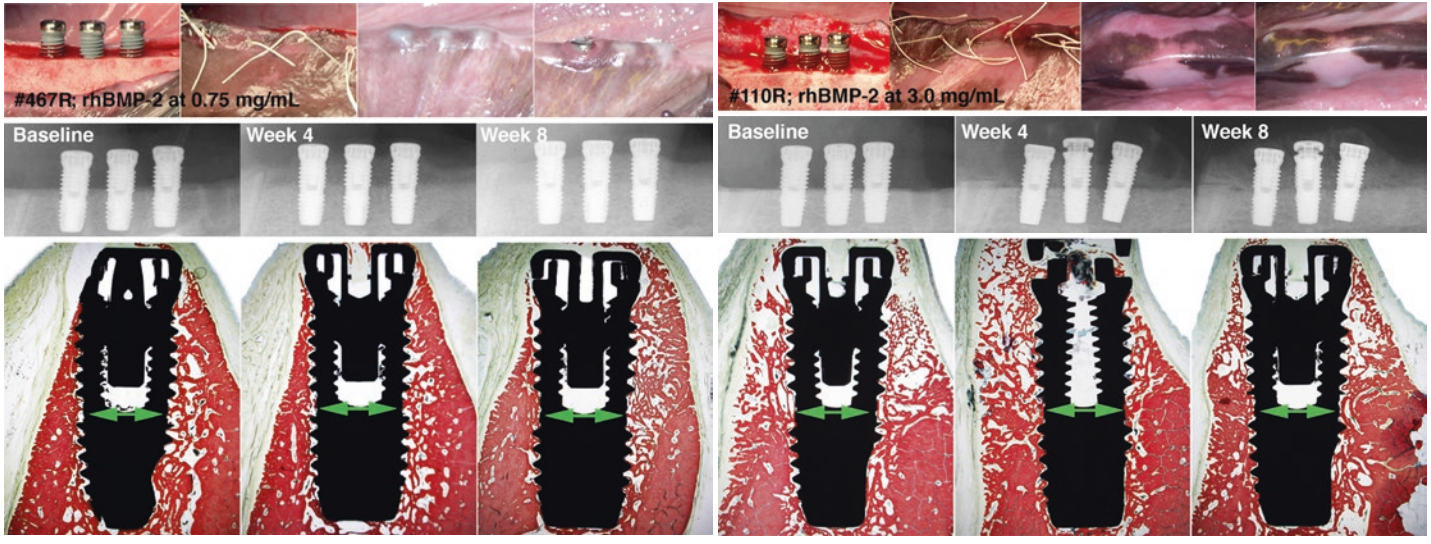

Fig. 8 Clinical panels showing ø4.0 × 10-mm dental implants coated with rhBMP-2 at *0.75 mg/mL* (*left*) and *3.0 mg/mL* (*right*) following placement and wound closure and healing at week 4 and 8. For implants coated with rhBMP-2 at *0.75 mg/mL* (*left*) the implant platforms (*cover screws*) can be visualized through the mucosa at week 4 and 8 when one implant becomes exposed. Radiographs show bone formation reaching the implant platform at week 4 and 8. Photomicrographs show bone formation with an established cortex reaching or exceeding the implant platform. Implants coated with rhBMP-2 at *3.0 mg/mL* (*right*) show significant swelling at week 4 somewhat resolving week 8. Radiographs show significant peri-implant radiolucencies (seromas) at week 4 apparently resolving week 8. Note the partial loosening of a cover screw within the tissues and implant displacements. The photomicrographs show immature bone formation exceeding the implant platform without an established cortex. Again note the partial loosening of the cover screw within the tissues at the central implant. *Green arrows* delineate the 5-mm notch placed level with the resident alveolar bone. Healing interval 8 weeks (From Wikesjö et al. [77]; Figures copyrighted by and modified with permission from John Wiley & Sons Ltd.)

Commentary Comparing bone formation/maturation at rhBMP-2/ACS ([47]; [68]; [74]) and rhBMP-2-coated dental implants suggests that the rhBMP-2-coated implant provides a more effective outcome than rhBMP-2/ACS and at a low dose. Such observations provide a rationale for developing novel delivery technologies with release kinetics profiling that of the rhBMP-2-coated implant for next generation BMP technologies for craniofacial indications and beyond.

3.3 Observations from Clinical Trials

A randomized controlled clinical trial evaluating rhBMP-2/ACS (*rhBMP-2 at 0.75 and 1.5 mg/mL*) for alveolar ridge augmentation following tooth extraction demonstrates that extraction socket sites receiving rhBMP-2/ACS (mean rhBMP-2 dose 1.9 mg/site) critically maintained alveolar crestal height, whereas control sites without this treatment projected a mean 1.2 mm crestal loss [20]. A recent randomized clinical trial expanded these findings by testing rhBMP-2/ACS (*rhBMP-2 at 1.5 mg/mL*) at extraction sites with large bone fenestrations. rhBMP-2/ACS yielded greater bone formation than ACS alone, rendering the resulting alveolar ridge more suitable to receive a dental implant [14].

rhBMP-2/ACS has also been evaluated in a randomized controlled clinical trial as alternative to autogenous bone grafts for alveolar augmentation and dental implant installation in the atrophic anterior maxilla [15]. Participating subjects either received rhBMP-2/ACS (*rhBMP-2 at 1.5 mg/mL*) or the "gold standard" particulated autogenous bone harvested from the mandibular retromolar region. A titanium mesh was used to define the regenerative space and provide wound stability. rhBMP-2/ACS yielded significantly greater radiographic horizontal bone gain compared with the autogenous bone graft at the critical immediate subcrestal level averaging 1.5 vs. 0.5 mm. No other significant differences in clinical/radiographic horizontal bone gain between rhBMP-2/ACS and autogenous bone graft were observed at 6 months allowing placement and osseointegration of dental implants.

Commentary The observations from this randomized clinical trial document and broaden the potential use of rhBMP-2/ACS in support bone augmentation beyond approved maxillary sinus and extraction socket augmentation indications.

4 Maxillary Sinus Augmentation

Prosthetic rehabilitation of the edentulated posterior maxilla presents considerable challenge. Remodeling following tooth loss not only produces decreased alveolar ridge width and height but also increased pneumatization significantly reducing potential housing for dental implant anchors. Modified Caldwell-Luc and transalveolar surgical approaches have thus been developed to access the subantral space with the intent to

increase the vertical dimension of the alveolar ridge through implantation of autogenous bone or bone biomaterials [6, 65]. Systematic reviews confirm the clinical efficacy of these approaches to fixation of dental implants [1, 19, 56, 67]. However, efficacious, present BMP technologies offer to expand the clinical protocol beyond autogenous bone grafting or the use of off-the-shelf cadaver-sourced or synthetic biomaterials.

4.1 Observations from Preclinical Studies

Hanisch and co-workers first evaluated rhBMP-2/ACS (*rhBMP-2 at 0.4 mg/mL*) for maxillary sinus augmentation and dental implant osseointegration using the modified Caldwell-Luc approach in nonhuman primates [24]. Dental implants were placed 3 months following implantation of rhBMP-2/ACS and allowed osseointegration over 3 months. The histometric evaluation showed sites receiving rhBMP-2/ACS exhibiting a clinically relevant two-fold increase in vertical bone augmentation compared with the ACS control (6.0 *vs.* 2.6 mm), newly formed bone exhibiting the same density and osseointegration as the adjoining native resident bone.

Commentary This first study provided the evidence for clinically relevant bone augmentation by rhBMP-2/ACS in maxillary sinus serving as a baseline for subsequent clinical evaluations and regulatory approval.

As autogenous cancellous bone maintains recognition as the "gold standard" for bone grafting, we compared local bone formation/osseointegration following sinus augmentation using rhBMP-2/ACS (*rhBMP-2 at 0.4 mg/mL*) vs. a particulated fresh autogenous cancellous bone graft harvested from the iliac crest in mini-pigs [42]. Dental implants were installed in conjunction with the augmentation procedure rather than using the staged protocol from our previous nonhuman primate study. Histologic evaluation at 8 weeks post-implantation revealed significant augmentation of the maxillary sinus following implantation of rhBMP-2/ACS approximating most of the dental implant bone-anchoring surfaces compared with irregular bone formation/active resorption in sites receiving autogenous bone grafting, rhBMP-2/ACS-induced bone exhibiting significantly greater density compared with the autogenous bone grafted sites (52 % *vs.* 33 %).

Commentary The observations in this study imply significant clinical time-savings using rhBMP-2/ACS due to the augmentation protocol that can be used in parallel with implant placement without need to access a donor site and associated morbidity; greater bone density of predicable volume and geometry without evidence of osteoclastic resorption overall suggests that rhBMP-2/ACS appears a realistic effective alternative to autogenous bone grafts for maxillary sinus augmentation and should thus be considered the new standard for this indication.

In similar evaluations, also using the mini-pig model, the Terheyden group applied rhBMP-7 (0.4 mg rhBMP-7 in 0.6 mL acetate buffer) with 1080 mg (3 mL) of a non-resorbable bovine bone mineral matrix vs. bovine bone mineral matrix with buffer only (control). Osseointegration at 6 months postsurgery averaged 80 %

for the rhBMP-7 sites vs. 39 % for the control [69]. In following, they compared the rhBMP-7 construct with a bovine bone mineral/autologous bone/platelet-rich plasma (PRP) composite. Osseointegration following a 6-week healing interval at sites receiving rhBMP-7 amounted to 46 % compared with 6 % for the PRP composite, whereas vertical bone gain averaged 8.3 *vs.* 3.6 mm, respectively [59].

rhGDF-5/ß-TCP (*rhGDF-5 at 0.4 mg/g ß-TCP or 0.8 mg/g ß-TCP*) has also successfully been considered in support of sinus augmentation using the mini-pig model. Control treatments included ß-TCP [22] or ß-TCP mixed with autogenous cortical bone chips (1:1) [23]. Healing intervals ranged up to 12 weeks. The authors concluded that rhGDF-5/ß-TCP significantly enhanced local bone formation (volume, density and osseointegration) compared with ß-TCP alone or combined with autogenous bone. Notably, there were no remarkable differences between rhGDF-5 concentrations.

Commentary Observations in the studies evaluating rhBMP-7 and rhGDF-5 suggest that both technologies present as viable alternatives to rhBMP-2 and should be considered as such. In comparison, the use of resorbable in front of non-resorbable technologies appears preferable relative to bone formation and osseointegration.

4.2 Observations from Clinical Trials

rhBMP-2/ACS has been scrutinized for sinus augmentation to meet regulatory approval [7, 8, 70]. Summarized in a systematic review (16) "rhBMP-2/ACS yielded clinically meaningful new bone formation for maxillary sinus augmentation – new bone height ranging between 7.8 and 10.2 mm" well meeting clinical requirements for dental implant installation although the statistical analysis showed average new bone height for the autogenous/allogeneic bone graft control exceeding the rhBMP-2/ACS by 1.6 mm. These studies used rhBMP-2 at 0.43, 0.75, and 1.5 mg/mL without consistent differences in bone formation, actual rhBMP-2 dose ranging between 2.9 and 20.8 mg/site.

Commentary It may be surprising that large rhBMP-2 dose differences do not reflect significant differences in bone formation, volume, or density; however, considering the maxillary sinus volume and geometry and rhBMP-2/ACS weak structural integrity vs. that of the autogenous bone graft, space provision and structural integrity become naturally limiting factors. Also lengthy observation intervals in these studies would allow considerable remodeling deflating any discernable differences in bone formation.

In separate studies, rhBMP-2/ACS was combined with particulate allogeneic mineralized bone or a commercial bovine bone preparation for maxillary sinus augmentation [21, 37]. Using core biopsies for a qualitative histologic analysis, sites receiving rhBMP-2/ACS (*rhBMP-2 at 1.5 mg/mL*) for a total of 4.2 or 8.4 mg/sinus combined with the allogeneic bone matrix could not demonstrate bone formation exceeding that of the allogeneic bone matrix as a stand-alone treatment [21]. Core biopsies featuring the rhBMP-2/ACS (*rhBMP-2 at 1.5 mg/mL*) bovine bone combination showed less bone formation than the bovine bone control prompting the authors to conclude "that the addition of rhBMP-2/ACS to Bio-Oss has a negative effect on bone formation" [37].

Commentary It must be noted that core biopsies only provide partial appreciation of rhBMP-2/ACS-induced bone formation. Observed from preclinical histology, rhBMP-2/ACS yields significant bone formation for dental implant osseointegration equal to if not surpassing autogenous bone grafts following sinus augmentation [42]. Moreover, non-resorbable matrices such as the bovine bone preparation have repeatedly been shown to displace/obstruct rhBMP-2/ACS-induced local bone formation ([3]; [4]; [47]; [49]) in part explaining the unexpected observations above.

A parallel group randomized clinical trial was used to evaluate rhGDF-5/ß-TCP for maxillary sinus augmentation [38, 64]. Using a staged protocol, the patients either received rhGDF-5/ß-TCP (rhGDF-5 at 500 mg/g ß-TCP) or an autogenous bone/ß-TCP (1:1) composite (control) using a modified Caldwell-Luc approach and a 16-week healing interval followed by installation of dental implants. The radiographic evaluation favored the rhGDF-5/ß-TCP construct; the histometric evaluation of trephine core biopsies showed similar fractions of bone formation at sites receiving rhGDF-5/ß-TCP (28 %) compared with sites receiving the autogenous bone/ß-TCP composite (32 %). In other words, the rhGDF-5/ß-TCP construct was as effective as the benchmark autogenous bone/ß-TCP composite, even though the rhGDF-5/ß-TCP construct does not provide viable bone cells at implantation, whereas the ß-TCP/autogenous bone composite does.

Commentary The observations herein suggest that the rhGDF-5/ß-TCP construct is worthy second-generation BMP candidate for regeneration of bone in the craniofacial skeleton, the ß-TCP structural integrity, and timely biodegradation presenting as advantages over present ACS technology.

5 Peri-implant Defect Repair

Peri-implantitis is defined as a biofilm-induced inflammatory lesion around a dental implant, which progressively causes alveolar bone resorption. The array of pathogens found at implants affected by peri-implantitis closely resembles the microbiota associated with periodontitis. The prevalence of peri-implantitis seems to be in the order of 10 % of the implants and 20 % of the patients within 5–10 years following implant placement though reported estimates are rather disperse [17, 50]. Even if favorable short-term treatment outcomes have been reported, failing disease resolution, disease progression or recurrence, and implant loss despite treatment have also been reported [27]. Importantly, predictable re-osseointegration of the exposed implant surface has not been achieved with current treatments [55].

Hanisch and co-workers used ligature-enhanced plaque accumulation to provoke peri-implantitis at hydroxyapatite-coated titanium dental implants in the posterior maxilla and mandible in four *Macaca mulatta* monkeys over 11 months [25]. Submucosal microbial samples revealed a large proportion of G-anaerobic rods, predominantly *Porphyromonas gingivalis*, *Bacteroides forsythus*, and *Fusobacterium* species as well as beta-hemolytic streptococci following ligature removal, microbiota associated with destructive periodontal disease and peri-implantitis in humans.

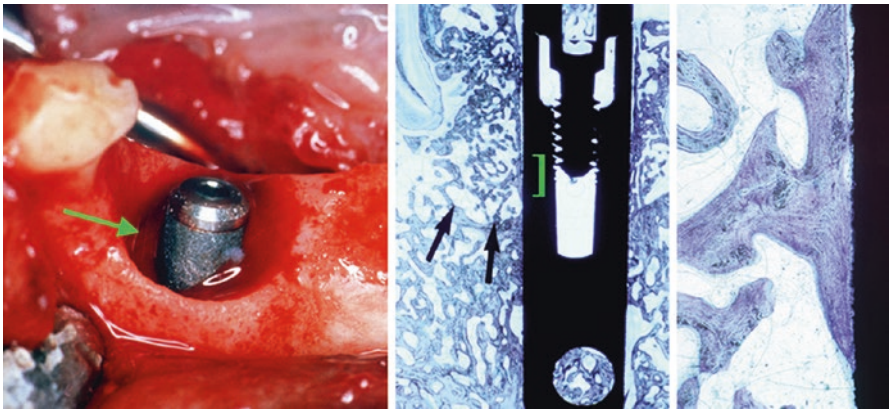

Fig. 9 Re-osseointegration following treatment of chronic peri-implantitis defect with rhBMP-2/ACS. The clinical panel shows the debrided peri-implantitis defect prior to treatment with rhBMP-2/ACS; the *green arrow* points to the aspect of the implant shown in the photomicrographs. *Black arrows* delineate the apical aspect of the peri-implantitis defect; the green bracket depicts a high magnification area (*right*) showing re-osseointegration. Note that the rhBMP-2-induced bone exhibits qualities of the contiguous resident bone. Healing interval 16 weeks (From Hanisch et al. [26]; Figures copyrighted by and modified with permission from Quintessence Publishing)

Resulting advanced inlay/onlay defects exhibited a mean depth of 3.3 ± 1.3 mm and width of 2.0 ± 0.5 mm. Subsequently the investigators implanted rhBMP-2/ACS (*rhBMP-2 at 0.4 mg/mL*) as a stand-alone therapy following defect soft tissue debridement and cleansing of the biofilm-contaminated denuded implant surfaces to resolve the peri-implantitis defects [26] (Fig. 9). rhBMP-2/ACS supported significant resolution of the advanced chronic peri-implantitis defects, defect fill averaging 77 % of the defect depth vs. 24 % for the sham surgery control following the 16-week healing interval. Importantly, the newly formed bone osseointegrated to a hydroxyapatite-coated titanium dental implant surface that had been exposed to a biofilm-induced inflammatory lesion over 11 months, osseointegration reaching clinically relevant 40 %.

Commentary The singularly unique observations gained in this "first" proof-of-concept study become even more critically important considering the increasing awareness of peri-implantitis and the up till now, almost two decades later, absence of effective clinical solutions.

6 Concluding Remarks

Bone regeneration has become a major objective of implant dentistry, dictated by functional and esthetic demands. rhBMP-2, rhBMP-7, and rhGDF-5 have been evaluated in independent- and industry-sponsored preclinical and clinical studies focused on craniofacial indications. Whereas rhBMP-2 is the only approved BMP

for craniofacial use, other members of the BMP family show clinical relevance and should be pursued. Clinically relevant bone augmentation for inlay defects including extraction sockets and the maxillary sinus has been demonstrated for rhBMP-2; however, dose optimization remains poorly understood. For onlay defects, there is a clear need for the development of BMP carrier technologies with easy-to-handle characteristics, structural integrity, and that allow timely replacement by bone.

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