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Review Article

Growth and differentiation factors for periodontal regeneration: a review on factors with clinical testing

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Background and Objective: A large body of evidence implies that growth and differentiation factors, based on their ability to regulate various functions of cells originating in the periodontal tissues, may support periodontal wound healing/regeneration, creating an environment conducive to and/or immediately inducing *de novo* tissue formation. This study presents a short systematic overview on growth and differentiation factor technologies evaluated in the clinic for their potential to enhance periodontal wound healing/regeneration.

Material and Methods: Reports on growth and differentiation factor technologies evaluated in the clinic for their potential to enhance periodontal wound healing/regeneration were selected for review.

Results: Growth and differentiation factor technologies intended for periodontal wound healing/regeneration and evaluated clinically included platelet-derived growth factor, insulin-like growth factor-I and -II, basic fibroblast growth factor, bone morphogenetic protein-3 and growth differentiation factor-5; platelet-derived growth factor was the only Food and Drug Administration-approved commercially available growth and differentiation factor technology. In general, enhanced periodontal regeneration was observed in sites receiving growth and differentiation factors compared with control(s). However, improvements of relatively limited clinical magnitude have been shown thus far.

Conclusion: Although growth and differentiation factors project considerable appeal as candidate technologies in support of periodontal wound healing/regeneration, current candidate and commercially available technologies enhance treatment outcomes only to a limited extent in clinical settings.

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Conventional periodontal therapy usually results in healthy periodontal tissues including reduced probing depths and attachment levels that can be preserved for decades provided the patient is maintaining adequate oral hygiene standards (1–3). However, conventional periodontal therapy rarely translates into periodontal regeneration, characterized by cementum formation, insertion of functionally oriented collagen fibers and alveolar bone formation, resulting in the establishment of a periodontal ligament (PDL) of physiologic width and composition (4).

A number of treatment protocols have been introduced with the assumption that they somehow induce/support periodontal regeneration. These comprise various surgical approaches, adjunct root/wound conditioning schemes, implantation of cadaver-sourced or synthetic bone biomaterials

and application of barrier devices, used as stand-alone protocols or in combinations (5–7). In recent years, advances in cell and molecular biology suggest that growth and differentiation factors, which are natural biological mediators critical for the development and growth of tissues and organs, may also support wound healing/regeneration, creating an environment conducive to and/or immediately inducing *de novo* tissue formation. Several growth and differentiation factors associated with periodontal tissues have been evaluated as candidate technologies in periodontal wound healing/regeneration and these include platelet-derived growth factor (PDGF), insulin-like growth factors I and II (IGF-I/-II), acidic and basic fibroblast growth factors (a/bFGF), transforming growth factor-β (TGF-β) and bone morphogenetic proteins (BMPs). Only a few growth and differentiation factor technologies have reached clinical testing. The aim of this report was to provide a short, systematic overview on growth and differentiation factors that have been clinically evaluated for their potential to enhance periodontal wound healing/regeneration.

Material and methods

An electronic PubMed search was performed to identify reports in which the clinical potential of growth and differentiation factors to enhance periodontal wound healing/regeneration had been evaluated. The reference list of identified publications was manually searched to further identify publications reporting on preclinical *in vivo* experimental models in periodontal settings. In addition, publications reporting on the potential of commercially available growth and differentiation factors to enhance periodontal wound healing/regeneration were also included. Furthermore, some general information was included for each factor; for detailed *in vitro* and *in vivo* background please refer to Lee *et al*. (7).

Results and Discussion

Growth and differentiation factors that have been evaluated in the clinic for periodontal indications include PDGF-beta (PDGF-B), IGF-I/-II, bFGF, BMP-3 and growth differentiation factor (GDF)-5 (Table 1). Currently, the only commercially available growth and differentiation factor for periodontal indications is PDGF-B, while BMP-2 and BMP-7 are available for maxillofacial and/or orthopedic indications, respectively.

Platelet-derived growth factor

PDGFs are secreted primarily from the platelet α-granules, but also from macrophages, fibroblasts, myocytes, and endothelial and bone marrow hematopoietic cells. The PDGF family encompasses four isoforms (A, B, C and D) that always appear in a dimeric form (i.e. -AA, -BB, -AB, etc.); all exert a number of biological activities and play important roles in cell growth, survival and function in connective tissues, including bone, and in wound healing (in particular angiogenesis). PDGF-A, PDGF-B and PDGF-AB have been evaluated for their potential to stimulate periodontal wound healing/regeneration. PDGF-A appears to play a role during the early stages of wound healing, while PDGF-B, appearing somewhat later, seems to be the more effective ligand. *In vitro* and *in vivo* studies suggest that PDGF-B influences various aspects of wound healing and regeneration relevant to periodontal attachment. Application of PDGF-B onto surface-demineralized dentin stimulates human PDL cell proliferation and increases anabolic effects on osteoblasts and osteoclasts. Systemic application of PDGF-B in an osteoporotic animal model increased bone formation, trabecular bone density and biomechanical strength in long and flat bones.

Preclinical studies using canine and nonhuman primate platforms have evaluated surgical application of PDGF in acute and chronic periodontal defects, with variable outcomes. PDGF in a carrier matrix, either alone or combined with guided tissue regeneration (GTR), has been shown to enhance periodontal regeneration compared with control(s) or stand-alone treatments (8–10) but show limited, if any, effect in others (11).

Clinical application of PDGF combined with an allogeneic demineralized freeze-dried bone matrix was evaluated in a limited case series including teeth with deep intrabony and/or furcation defects, some deemed hopeless and scheduled for extraction (12,13). Significant improvements were observed in most sites; a mean probing-depth reduction of 6.4 mm, attachment-level gain of 6.2 mm and radiographic bone-fill of 2.1 mm were recorded for the intrabony defects. Histological evaluation of the hopeless teeth revealed healing characterized by variable amounts of periodontal regeneration.

A product including recombinant human (rh)PDGF-BB combined with a beta-tricalcium phosphate (β-TCP) matrix (GEM 21; Luitpold Pharmaceuticals, Inc., Shirley, NY, USA) recently received Food and Drug Administration approval and became available for clinical use. Only limited (0.5 mm) gains in attachment level were observed for sites receiving the rhPDGF-BB/β-TCP product compared with a β-TCP control at 3 mo postsurgery in a large multicenter pivotal study including 180 subjects who required surgical treatment of deep (≥ 4 mm) intrabony periodontal defects (14). This limited difference between groups was no longer statistically significant at 6 mo, revealing a 3.8 mm vs. 3.5 mm attachment-level gain. Remarkably, radiographic bone gain was significantly greater, averaging 2.6 mm vs. 0.9 mm, respectively. A separate histologic study of intrabony periodontal defects treated with rhPDGF-BB/β-TCP showed limited periodontal regeneration (range: 0.3–1.6 mm) in 12 of 16 defects at 6 mo (15). Bone formation was restricted to the defect walls and never juxtaposed new cementum, while a major portion of the defects was still occupied by residual β-TCP sequestered within connective tissue; bone formation never penetrated the β-TCP mass or contacted the particles. The limited added clinical and histologic improvements observed in these studies cast doubt on the overall clinical relevance of this technology.

Table 1. Overview of clinical and human histological studies using growth and differentiation factors for periodontal wound healing/regeneration

Factor	Authors	Study design; defect type; groups	Dose; carrier; evaluation time; evaluation type	Major outcomes
PDGF	Camelo *et al.* 2003	Case series of four patients; furcations ≥ 5 mm PD; test	0.5 and 1 mg/mL; DFDBA; 9 mo; clinical and histological	3.6 mm CAL gain Only descriptive histology; periodontal regeneration coronal to root notch in four out of four
	Nevins *et al.* 2003	Case series of nine patients; ≥ 7 mm PD in i.b.: six sites ≥ 5 mm PD in furcations: five sites; test	0.5, 1 or 5 mg/mL; DFDBA; 9 mo; clinical and histological	i.b.: 6.2 mm CAL gain; 2.14 mm radiographic bone fill Furcations: 3.2 mm CAL gain Only descriptive histology; periodontal regeneration coronal to root notch in four out of six i.b., and in four out of four furcations
	Nevins *et al.* 2005	RCT Phase III, 180 patients; ≥ 7 mm PD ≥ 4 mm i.b.; test vs. carrier	0.3 or 1.0 mg/mL; β-TCP; 3 and 6 mo; clinical	Statistically significant larger CAL gain with 0.3 mg/mL vs. carrier only at 3 mo (2.8 mm vs. 2.3 mm) No difference with 1.0 mg/mL vs. control
	Ridgeway *et al.* 2008	Case series of nine patients; ≥ 5 mm PD furcations 18 sites; test	0.3 or 1.0 mg/mL; eight sites each β-TCP; ≥ 6 mo; clinical and histological	CAL gain 3.1 mm (0.3 mg/mL) to 3.2 mm (1.0 mg/mL) Periodontal regeneration coronal to root notch in 12 out of 16 teeth (five out of eight with 0.3 mg/mL; seven out of eight with 1 mg/mL) 0.3 mg/mL: new bone 0.7 mm; new cementum 0.6 mm; new PDL 0.9 mm 1.0 mg/mL: new bone 1.9 mm; new cementum 1.1 mm; new PDL 0.9 mm
	Mellonig *et al.* 2009	Case series of four patients; furcations Class III; test + GTR	0.3 mg/mL; β-TCP; 6 mo; clinical and histological	One furcation changed to Class 2 Periodontal regeneration coronal to calculus notch in three sites New bone 1.1 mm; new cementum 2.45 mm; new PDL 1.1 mm
	Jayakumar *et al.* 2011	RCT of 50 patients; ≥ 7 mm PD ≥ 4 mm i.b.; test vs. carrier	0.3 mg/mL; β-TCP; 3 and 6 mo; clinical	Statistically significantly larger CAL gain in test vs. carrier at 3 mo (3.2 mm vs. 2.6 mm) and 6 mo (3.7 mm vs. 2.8 mm) Statistically significantly larger PD reduction in test vs. carrier at 3 mo (3.9 mm vs. 2.9 mm) and 6 mo (4.3 mm vs. 3.2 mm) Statistically significantly larger linear bone growth at 6 mo vs. carrier (3.7 mm vs. 2.8 mm)
PDGF/IGF	Howell *et al.* 1997	RCT Phase I/II split-mouth 38 patients; i.b. and furcations; test vs. carrier or OFD	50/50 or 150/150 μg/mL; methylcellulose gel; 6–9 mo; clinical	Statistically significant bone formation with 150/150 μg/mLvs. controls at re-entry
FGF	Kitamura *et al.* 2008	RCT Phase II of 74 patients; ≥ 3 mm i.b.; test vs. carrier	0.03, 0.01 or 0.3%: hydroxypropyl cellulose gel; 9 mo; clinical	Statistically significantly larger bone fill with 0.3% vs. carrier (23.9% vs. 58.6%); no difference in CAL gain (2.6 mm vs. 2.2 mm)
	Kitamura *et al.* 2011	RCT of 253 patients; ≥ 3 mm i.b.; test vs. carrier	0.2, 0.3 or 0.4%: hydroxypropyl cellulose gel; 9 and 18 mo; clinical	Statistically significantly larger bone fill with test vs. carrier, with 0.03% being the most effective (52.2% vs. 15.9%) at 72 mo; No differences in clinical parameters at 72 mo (CAL gain: 2.4–2.5 mm vs. 2.1 mm)

Table 1. (Continued)

Factor	Authors	Study design; defect type; groups	Dose; carrier; evaluation time; evaluation type	Major outcomes
BMP-3	Bowers *et al.* 1991	Case series of 14 patients; i.b. 36 submerged 50 nonsubmerged; test, carrier	200 μg/mL; DFDBA; bovine collagen Type I (BC) 6 mo; histological	Statistically significantly more regeneration with DFDBA/BMP-3 vs. DFDBA in submerged sites New bone: 2.0 mm vs. 1.3 mm New cementum: 2.31 mm vs. 1.75 mm New PDL: 1.9 mm vs. 1.3 Statistically significantly more regeneration with DFDBA/BMP-3 and DFDBA vs. BC/BMP-3 and BC in both submerged and nonsubmerged sites No differences between BC/BMP-3 vs. BC
GDF-5	Stavropoulos *et al.* 2011	RCT Phase II of 20 patients; ≥ 7 mm PD, ≥ 4 mm i.b.; test vs. OFD	500 μg/g; β-TCP; 6 mo; clinical and histological	2× more CAL gain with GDF-5 vs. OFD (3.2 mm vs. 1.7 mm) 3× more new bone histologically with GDF-5 vs. OFD (2.19 mm vs. 0.81 mm) 2× more new cementum and PDL histologically with GDF-5 vs. OFD (2.16 mm vs. 1.23 mm) No statistically significant differences between the groups

BC, bone collagen; FGF, fibroblast growth factor; BMP-3, bone morphogenetic protein-3; CAL, clinical attachment level; DFDBA, demineralized freeze-dried bone allograft; GDF-5, growth/differentiation factor-5; i.b., intrabony; IGF, insulin-like growth factor; OFD, open flap debridement; PD, probing depth; PDGF, platelet-derived growth factor; PDL, periodontal ligament; RCT, randomized controlled trial.

Notably, a recent study using surgically created two-wall intrabony defects in dogs evaluated larger β-TCP particles than those included in the commercial product (16). Significantly enhanced periodontal regeneration was observed in the sites receiving the large particles compared with the commercial product. This observation emphasizes the importance of the carrier technology for periodontal wound healing/regeneration. The alternative carrier may not only have differed in size but also influenced PDGF bioavailability and own bioresorption, all representing factors of consideration for optimized technology.

Insulin-like growth factor

Insulin-like growth factors are a family of factors including insulin, relaxin and the polypeptides IGF-I and IGF-II, and are produced by several cells. IGFs exert a variety of biological activities, including chemotaxis, proliferation, differentiation and transformation, and play a critical role in development, stimulating organogenesis and growth during the early stages of embryogenesis and regulating specific tissue and organ functions at later developmental stages. *In vitro*, IGF-I enhances rat and human PDL and gingival fibroblast migration and proliferation in a dose and temporal order, but does not exhibit an apparent effect on Type I collagen synthesis. Moreover, IGF-I stimulates bone formation, inducing osteoblast proliferation, differentiation and Type I collagen synthesis, and inhibits bone collagen degradation by blocking collagenase activity. IGF-I infusion significantly increases cortical and trabecular bone formation, stimulates osteoblastic proliferation and decreases the number of osteoclasts. On the other hand, IGF-I may stimulate osteoclastic resorption through direct or indirect pathways, supporting the generation and activation of osteoclasts.

Based on data from *in vitro* and *in vivo* studies, it was expected that IGF-I would exert a positive influence on periodontal wound healing/regeneration. However, the results of preclinical studies failed to support this assumption. IGF-I in a methylcellulose gel carrier did not support regeneration of the periodontal attachment in monkeys compared with controls (17); comparable observations were made in naturally occurring periodontitis defects treated with IGF-I in dogs (18). Collectively, these results may be interpreted to suggest that IGF-I has limited, if any, appreciable effect on periodontal wound healing/regeneration.

Nevertheless, synergistic effects of PDGF and IGF-I observed *in vitro* and *in vivo* in skin wound models were also observed using canine and nonhuman primate platforms for periodontal wound healing/regeneration (17–19). Clinical evaluation of an rhPDGF-BB/IGF candidate technology, including 38 patients with bilateral intrabony and furcation defects, showed statistically significant increased bone fill compared with the control (2.1 mm vs. 0.8 mm vertical gain and 42% vs. 19% bone fill, respectively). Despite clinical promise, further evaluation of the rhPDGF-BB/IGF technology has not been presented.

Fibroblast growth factor

FGFs represent a large polypeptide family encompassing more than 20 members sharing structural characteristics. FGFs exert a range of biological effects on cells of endodermal, ectodermal and mesodermal origin, are

considered potent growth and differentiation regulators and angiogenic factors, and play important roles in embryonic development and wound healing. bFGF (also known as FGF-2) appears to be the most recognized form of FGF. bFGF stimulates wound healing and tissue repair by promoting angiogenesis, cell proliferation and noncollagenous protein synthesis. bFGF appears to be produced primarily by PDL fibroblasts and endothelial cells, while bFGF levels appear to be decreased in chronic periodontal lesions. *In vitro*, bFGF promotes the growth and proliferation of human PDL cells and exerts a dose-dependent effect on PDL and gingival fibroblast migration. bFGF has also been shown to enhance human PDL and endothelial cell chemotaxis, attachment and proliferation on dentin blocks. In human calvarial osteoblastic cell cultures, bFGF slightly stimulated cell growth and reduced the expression of osteoblast markers in less-mature cells, whereas it induced osteocalcin production and matrix mineralization in more mature cells. Other studies suggest that bFGF has a profound effect on bone growth and development, while local application of bFGF enhances fracture healing.

The potential of bFGF to stimulate periodontal wound healing/regeneration has been evaluated using large-animal platforms. Surgically created three-wall intrabony periodontal defects and mandibular premolar and molar Class II furcation defects in the Beagle dog and mandibular molar Class II furcation defects in the Cynomolgus monkey were treated with various concentrations of bFGF, while control sites received the carrier matrix alone or sham-surgery (20). Sites treated with bFGF showed significantly greater periodontal regeneration compared with controls at 6 wk in dogs and at 8 wk in monkeys. None of the bFGF sites exhibited epithelial downgrowth or root resorption/ankylosis. Almost identical results were presented in subsequent publications from the same investigators (21,22). Another study evaluated bFGF as an adjunct to GTR in surgically induced chronic mandibular premolar Class III furcation defects in dogs (23). The experimental protocol included root conditioning with tetracycline HCl and application of bFGF in combination with GTR. Control sites received tetracycline HCl + GTR. Sites receiving bFGF showed increased regeneration compared with controls following a 90-d healing interval. Root resorption/ankylosis was not observed.

Clinical evaluation of bFGF encompasses a 24-center 253-patient pivotal study, evaluating various concentrations of bFGF in a hydroxypropylcellulose carrier in two/three-wall intrabony defects of ≥ 3 mm (24,25). Radiographic evaluation at 36 wk showed a statistically significant increased bone fill in bFGF-treated sites compared with the carrier control (51% vs. 15% of the original intrabony component for the 0.3% concentration). Notably, no differences in clinical parameters were observed between groups. Average attachment-level gain was 2.1 mm and 2.4–2.5 mm in the carrier control and growth-factor groups, respectively, at 72 wk. Based on the limited clinical and radiographic improvements observed in this pivotal study, the relevance of this particular bFGF technology for periodontal wound healing/regeneration appears questionable.

Bone morphogenetic proteins

BMPs, members of the TGF-β superfamily, play fundamental roles in skeletal modeling, cell determination, tissue morphogenesis and organogenesis during embryonic development and in postfetal life, in vertebrates and invertebrates, and in diverse tissues and organs such as kidney, eye, nervous system, lung, teeth, skin and heart. At present, the BMP family consists of more than 20 homodimeric or heterodimeric structurally related proteins that have been identified in a large variety of species, including humans.

Several BMPs have been evaluated for their potential to enhance periodontal wound healing/regeneration, with focus on BMP-2, BMP-3 (also known as osteogenin), BMP-7 (also known as osteogenic protein-1) and GDF-5 (also known as cartilage derived morphogenetic protein 1). Evaluation of root development in mice shows that BMP-3 and BMP-7 localized to alveolar bone, cementum and PDL, while BMP-2 localized strictly to alveolar bone. All three BMPs were present in predentin, dentin, odontoblasts, osteoblasts, osteocytes, osteoid, cartilage and chondrocytes, BMP-7 also localized to ameloblasts. Studies in rats show that GDF-5 is expressed during development of the PDL, within the ligament itself, and also in cells residing along the alveolar bone and root cementum, especially in sites where the PDL fibers were inserting in the cementum during root development; GDF-5 expression was down-regulated upon completion of root development. Moreover, GDF-5 and its receptors are also shown in human PDL cells, and GDF-5 increases mitogenesis of this type of cells.

Bone morphogenetic protein-2

The potential of BMP-2 to stimulate periodontal wound healing/regeneration has been evaluated in the supra-alveolar periodontal-defect model in dogs in a number of studies. Defects receiving rhBMP-2 in a bioresorbable poly(D,L-lactide-co-glycolide) microparticle carrier mixed with autologous blood induced significantly greater alveolar bone and cementum formation compared with the carrier control at 8 wk (26). While limited root resorption/ankylosis was observed, the fibrovascular tissue interposing a cementum-like mineralized tissue formed on the root and the new bone only infrequently resembled a functionally oriented PDL. A long-term study using the same experimental platform and a 24-wk observation interval showed that this fibrovascular tissue eventually matured into bone and fatty marrow, resulting in extensive root resorption/ankylosis (27).

Bone morphogenetic protein-3 (osteogenin)

The potential of BMP-3 to enhance periodontal wound healing/regeneration has been evaluated in nonhuman

primates and in clinical studies. In a clinical case series, BMP-3 isolated from human long bones was combined with an allogeneic demineralized freeze-dried bone matrix or a bovine collagen matrix and implanted into intrabony periodontal defects (28). Control sites received the allogeneic demineralized freeze-dried bone matrix or the collagen carrier matrix alone. Some teeth were submerged. Histological evaluation at 6 mo showed that, in submerged sites, BMP-3 significantly enhanced periodontal regeneration compared with controls; limited regeneration was observed in control sites. This first indication that BMP-3 may stimulate periodontal wound healing/regeneration was corroborated in nonhuman primates (29). A construct, predominantly containing BMP-3 (but also BMP-2 and BMP-7) in a collagenous matrix was implanted into surgically created mandibular molar Class II furcation defects in baboons. Histologic evaluation following an 8-wk healing interval showed significant periodontal regeneration in sites receiving the BMP-3 construct compared with controls. The newly formed PDL exhibited Sharpey's fibers inserting into newly deposited cementoid, which showed foci of nascent mineralization. Despite promising observations, further clinical evaluation of BMP-3 has not been reported.

BMP-7 (osteogenic protein-1)

BMP-7 in a collagen carrier was implanted into surgically induced mandibular molar Class II furcation defects in baboons (30). Following an 8-wk healing interval, sites implanted with BMP-7 showed significant cementogenesis, including insertion of Sharpey's fibers, while limited regeneration was observed in the controls. Thus, unlike that observed regarding BMP-2, the cementum-like tissue and the alveolar bone were separated by fibrovascular tissue resembling PDL. Significantly greater periodontal regeneration in supraalveolar defects after BMP-7 application compared with carrier or sham-operated controls was also observed in dogs (31). However, defects showing extensive regeneration were compromised by root resorption/ankylosis. In separate studies, based on the observation of synchronous but spatially different localization of BMP-2 and BMP-7 in periodontal tissue development, the combination of BMP-2 and BMP-7 was evaluated in nonhuman primate furcation defects (32). However, no added effect compared with single-factor application was observed.

Such findings of aberrant healing events (i.e. root resorption/ankylosis) has resulted in that BMP-2 and BMP-7 have not been pursued for periodontal indications. However, BMP-2 and BMP-7 have received Food and Drug Administration approval primarily for orthopedic indications; BMP-2 has also received Food and Drug Administration approval for alveolar ridge augmentation and sinus augmentation.

GDF-5 (cartilage derived morphogenetic protein 1)

GDF-5 has been shown to enhance local bone formation in cranial and craniofacial settings, in small and large animal models (33–36) and in initial clinical studies, including sinus augmentation and dental implant osseointegration (37). Recent preclinical studies using canine platforms have shown that rhGDF-5 adsorbed onto an absorbable collagen sponge carrier (rhGDF-5/ACS) or onto micro/macroporous β-TCP particles (rhGDF-5/β-TCP) significantly enhances periodontal wound healing/regeneration compared with sham-surgery, carrier controls and the commercially available rhPDGF-B/β-TCP (11,38,39). Similarly, larger amounts of periodontal regeneration were observed to occur, in a dose-dependent manner, in rhGDF-5/β-TCP implanted intrabony defects in monkeys compared with sites receiving only β-TCP (40). Importantly, only limited, if any, adverse reactions were observed.

A randomized, controlled, clinical and histological study evaluated periodontal wound healing/regeneration following surgical implantation of rhGDF-5/β-TCP compared with standard flap surgery (41). The study included chronic periodontitis patients, each exhibiting at least one tooth with a probing depth exceeding 6 mm and an associated intrabony defect of > 4 mm after basic therapy and scheduled for extraction (Fig. 1). Block biopsies of the treated defect sites were collected at 6 mo. Treatment with rhGDF-5/β-TCP resulted in greater probing-depth reduction (3.7 mm vs. 3.1 mm), less gingival recession (0.5 mm vs. 1.4 mm) and an attachment-level gain that was almost twofold greater (3.2 mm vs. 1.7 mm) than in the control. Histologic mean bone regeneration was increased almost threefold for the rhGDF-5/β-TCP technology compared with the control (2.2 mm vs. 0.8 mm). Regeneration of a functionally oriented PDL and cementum averaged 2.2 mm vs. 1.2 mm (Fig. 2). Root resorption/ankylosis was not observed. The above animal experiments and pilot clinical and histological study provide evidence that rhGDF-5/β-TCP may substantially support periodontal wound healing/regeneration. Thus, further

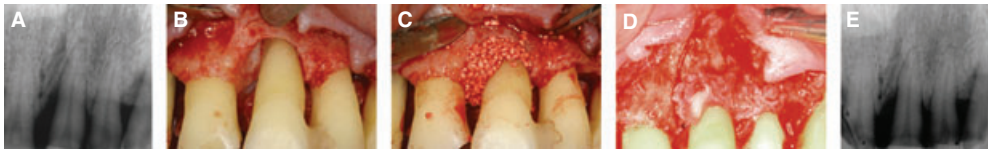

Fig. 1. Pre-operative X-ray (A) and intrasurgical view (B) of an intrabony defect implanted with recombinant human growth differentiation factor-5/beta-tricalcium phosphate (rhGDF-5/β-TCP) (C). Re-entry view (D) and X-ray (E) prior to biopsy 6-mo postoperatively.

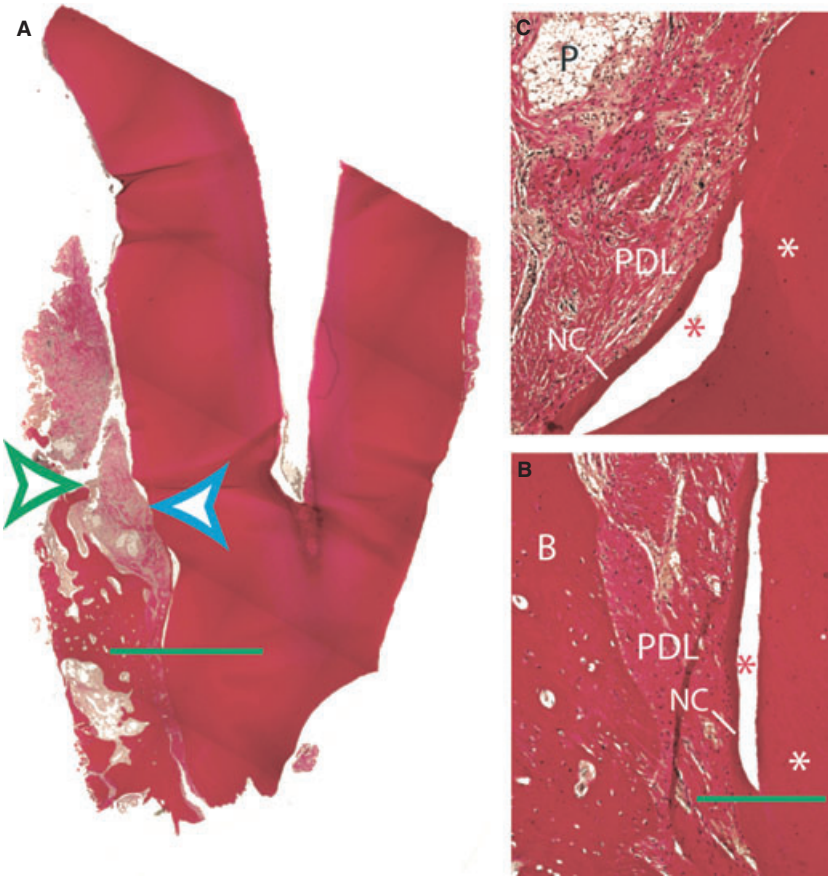

Fig. 2. Photomicrograph of a defect site treated with recombinant human growth differentiation factor-5/beta-tricalcium phosphate (rhGDF-5/β-TCP) [overview (A) and 90× magnification of the apical (B) and coronal (C) aspects of the defect site] showing a thin new cellular cementum (NC) throughout the biopsy and β-TCP particles (P) without apparent association with bone formation. The green line indicates the apical termination of root instrumentation; arrowheads indicate the coronal extension of new cementum (blue) and bone (green) formation. The white asterisk (*) indicates the root; the red asterisk (*) indicates an artefactual split between the new cementum and the root; and B indicates resident bone (van Giesons' picro fuchsin).

clinical evaluation in randomized controlled clinical trials, as well as controlled comparisons with clinical benchmarks should be pursued.

Summary

Several growth and differentiation factors have been identified as potential therapeutic candidates to enhance periodontal wound healing/regeneration. Only a few have received clinical scrutiny. While a PDGF-BB/β-TCP product has met Food and Drug Administration approval for periodontal indications, the pivotal clinical evaluation and observations from human histology indicate that it may only provide a limited added effect on periodontal wound healing/regeneration. Despite preclinical evidence suggesting that bFGF has potential to enhance periodontal regeneration, limited clinical effects have been observed also for this factor. Application of BMP-2 and BMP-7 in periodontal sites resulted in extensive bone formation but also in root resorption/ankylosis and therefore these factors are currently only indicated for sinus and alveolar augmentation. In perspective, preclinical and clinical evidence, including human histology, suggest that GDF-5 may have substantial potential to enhance periodontal wound healing/regeneration without significant aberrant events. Large clinical studies to confirm this promise have yet to be conducted.

In conclusion, further adjustment of carrier technologies and dose optimization, and larger-scale clinical studies seem important necessary steps for elucidating any clinically meaningful use of growth and differentiation factors for periodontal indications.

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