

rhBMP - 2

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* . ** . * . *** . ***

*

**

I. Morales 1988).

가

(Glowacki 1992, Malinin 1992, Mellonig 1996).

(Pinholt 1990, Simion 1994, Brugnami 1999).

rhBMP - 2(recombinant human bone morphogenetic protein - 2)

II.

가

gold standard

가

(Aspenberg 1988, Pinholt 1994, Becker 1994, Caplanis 1997, 1998a,b, Kim 1998a,b).

가

(Weikel Habal 1977, Marx

(Skoglund
1997, Berglundh Lindhe 1997, Young
1999, Merckx 1999). 가

가

가

(Buser 1994). 가,

가 , 가 ,

(Lekholm 1993, Trombelli

1997).

가

(calci-
um - based ceramics), (bioac-
tive glass), (synthetic polymer)

가

가

Karring

(Karring 1993, Buser 1994).

(Guided tissue

regeneration; GTR)

(Guided bone regeneration; GBR)

가

:

GTR/GBR

III. BMP

1. (Historical Perspectives)

Levander(1938) BMP 가

가
 . Levander , 가

Lacroix(1954) ,

Levander
 “Osteogenin” ()

Urist 1956

BMP(Bone Morphogenetic Protein) 가

가
 (Urist 1982,

Mizutani Urist 1982).

BMP 30kD
 (Wang 1988). Wozney
 BMP(BMP

(1988)
 1~BMP 4)

BMP - 5 BMP - 8 BMP가

BMP가 20

2. rhBMP - 2 (rhBMP - 2 and Osteoinduction)

가
 (ectopic site)

BMP 가
 (Urist 1965, Sampath Reddi 1981). BMP

. rhBMP - 2

(undifferentiated mesenchymal cell) rhBMP - 2
 (chondroblast)

(endochondral ossifica - tion)

rhBMP가

가

rhBMP - 2

5

(Li 1996). ,
 rhBMP - 2 (intramembra - nous ossification)

BMP

가 . BMP - 2, 4, 5, 6, 7
 (ectopic model)

(Sampath 1992, BMP - 5
 Gitelman 1994).

BMP

BMP가

GDF7(BMP12 BMP13) , GDF6 가 BMP BMP

(Wolfman 1997).

BMP 4. rhBMP - 2 (Production of rhBMP - 2)

가 rhBMP - 2 , BMP BMP (primitive, uncommitted stem cell)가

(Sampath 1992, Thies 1992). BMP가 BMP

가 BMP (calvarial cells) BMP BMP (1kg

BMP BMP BMP BMP

3. (Synergy with 0.1µg BMP) BMP(recombinant BMP)

Growth Factors) rhBMP - 2 BMP

BMP (cloning) messenger

tumor necrosis factor - (TNF -) ribonucleic acid(mRNA) mRNA가

BMP가 (reverse transcriptase) DNA 가

(Urist 1967). Si (1998) transforming growth factor - (TGF -) rhBMP - 2 DNA(complementary DNA; cDNA) (Figure 1).

rhBMP - 2 (ectopic) Wozney(1992) BMP - 2 5. rhBMP - 2 가 (Safety and Efficacy of rhBMP - 2)

BMP - 2가 BMP 가 BMP가 가

BMP 가 가

rhBMP - 2 가

rhBMP - 2 , (Wikesj 1999a).

rhBMP - 2 (critical - size supraalveolar periodontal defect model) (Wikesj 1994).

(Soda 1998). rhBMP - 2가 “ (Wikesj 1999a).

rhBMP - 2 (absorbable collagen sponge carrier; ACS) rhBMP - 2 (critical - size supraalveolar peri - implant defect model)(Figure 2) (Caplanis 1997, Wikesj 1999a).

rhBMP - 2/ACS rhBMP - 2/ACS (Boyne 1997, Howell 1997). 가 가

rhBMP - 2/ACS 가 가

IV. / 가

rhBMP - 2

1. (Role of Preclinical Models) 가 . rhBMP - 2 가

가 가 (Toriumi 1992, Boyne 1996), (Mayer 1996, Boyne 1998), (Steinberg 1999), (Nevins 1996, Hanisch 1997a), (Cochran 1999, Barboza 1999), (Hanisch 1997b) rhBMP - 2

(critical - size defect model) 가

가 가

2. rhBMP - 2 (rhBMP - 2 Delivery Systems) (Schmitz Hollinger 1986).

BMP , rhBMP - 2/DBM, rhBMP - 2/ACS, rhBMP - 2/Bio - Oss, rhBMP - 2/PLA, rhBMP - 2/BEP, DBM ()

BMP가 . 8 가 , 가 , rhBMP - 2 . Bio - Oss 8 가 가 BMP (Figure 3). Bio - Oss (Hanisch 1997a,b, Cochran 1999, Wikesj 1999b), (Gerhart 1993, Giannobile 1998), (Ripamonti 1992, Gerr 1993), calci - umphosphate(Oda 1997), tricalciumphos - phate(Urist 1987), (Watanabe 1990, Asahina 1997), - hydroxy acids (Miyamoto 1993, Miki 1994, Sigurdsson 1995, Mayer 1996), (Kawai 1993, Wang 1993, 1994, Jin 1994, Herr 1996) PLA PLGA 가 가 . PLGA 가 가 . PLA 가 가 (Figure 4). PLA 가 (frag - mentation) BMP DBM/ 가 가 . (Figure 5). DBM Bio - Oss, PLGA, PLA 가 . 6% carboxymethyl cellulose , 6 beagle dog (con - tralateral) ACS

가 . HA

가 .

가 . 3

rhBMP - 2/ACS .

가 .

가 . rhBMP - 2 HA

가 .

가 .

(Figure 6).

가 . Jovanovic (1999) GBR

rhBMP - 2

. 7 (Hound dog)

15 ± 10mm

(1/4

3. (Alveolar Ridge Defects) 2)

rhBMP - 2/ACS , rhBMP - 2/ACS

GBR (rhBMP - 2/GBR; rhBMP - 2

0.2mg/Mℓ) , ACS

가 . , GBR

. GBR ePTFE (WL Gore & Associates)

. 12

rhBMP - 2 section

가 . rh BMP - 2/GBR GBR 16

7

Barboza (1999) (Figure 7). 가

4 3 rhBMP - 2/ACS rhBMP - 2/GBR

101%

rhBMP - 2/ACS rhBMP - 2/ACS (HA; 가 GBR

92%

Osteograft/LD; rhBMP - 2 0.2mg/Mℓ) rhBMP - 2/ACS GBR rhBMP -

12 57% rhBMP - 2/GBR 50 -

rhBMP - 2/ACS 34%

(0.6 ± 0.7mm). , rhBMP - 2/ACS

rhBMP - 2/ACS/HA 가 가

(5.5 ± GBR

1.6mm). , rhBMP - 2/ACS/HA 가

가 HA . rhBMP - 2 GBR 가 가

가 . rhBMP - 2 가

(Sigurdsson 1999). 5 beagle dog . 3 1

5 - 6mm 2

rhBMP - 2/DBM/ .

(rhBMP - 2 0.2mg/Ml) .

8 16 10mm ,

(Straumann/ITI) (Wikesj

(Figure 8). 24 1999a).

. rhBMP - 2 5 beagle dog

90% . 8 16

) . (55% rhBMP - 2가

가 (Sigurdsson 1997). 10mm

5mm 5mm

rhBMP - 2 DBM/ 가 rhBMP -

2/ACS(rhBMP - 2 0.4mg/Ml) buffer/ACS

가 . rhBMP - 2

rhBMP - 2 (0.5

가 ±0.3mm)

가 , 3 가(4.2 ± 1.0mm)

rhBMP - 2

가

rhBMP - 2 Cochran (1999)

GBR rhBMP - 2

GBR . 6

. GBR (4

가 rhBMP - 2 mm) . rhBMP - 2/ACS (rhBMP - 2

(Linde Hedner 1995, 0.2mg/Ml) buffer/ACS

Jovanovic 1999, Cochran 1999). ePTFE GBR

가 . GBR

4. (Alveolar

Peri - implant Defects) 4 12

rhBMP - 2

(47% 34%), -

(32% 16%), (8% 5%) 3 . rhBMP - 2
가 . 4 GBR

12
GBR
가 . GBR
GBR
가
rhBMP - 2
rhBMP - 2
(Figure 9).

6. (Subantral Augmentation)

rhBMP - 2 , GBR
rhBMP - 2

5. (Peri - rhBMP - 2
implantitis Defects) 가
Hanish (1997b) (Hanisch 1997a). (Cynomolgus monkey) 가
rhBMP - 2/ACS Schenk 1991). 4 (Simmons 1967,
. 4 rhBMP - 2/ACS (rhBMP - 2 0.4mg/Ml),
11 , HA buffer/ACS
. 3
()
. 3

1997a). (Hanisch rhBMP - 2
(6.0 ± 0.3mm 2.6 ± 0.3mm).
rhBMP - 2
rhBMP - 2/ACS
1/4 , rhBMP - 2
buffer/ACS . rhBMP - 2
가

(Figure 10).

, Nevins (1996)
 (Alpine - Saanen) 6

rhBMP - 2가
 rhBMP - 2/ACS(rhBMP - 2
 1.7mg), buffer/ACS(
) 4, 8, 12
 .3 CT

rhBMP - 2
 가

rhBMP - 2/ACS

rhBMP - 2가

7. (Congenital and
 Traumatic Bone Gap Defects)

Torium (1994) rhBMP - 2가 3cm
 (segmental defects)

3
 (allogenic
 decalcified bone matrix carrier) rhBMP -
 2, (),

3, 6
 가 rhBMP - 2
 2.5

가

rhBMP - 2가

가

Boyne(1996)

rhBMP - 2 가 . 2.2cm
 orthopaedic mesh

rhBMP - 2/ACS 0.2mg/Mℓ 0.8
 mg/Mℓ

가

Mayer (1996) (Maxillary
 cleft) rhBMP - 2 가 가
 4 rhBMP -
 2/PLGA/ 가 (rhBMP - 2 0.2mg/Mℓ),
 PLGA/ 가 , 가

2 4
 가

가

4 PLGA

Boyne (1988)
 rhBMP - 2 가 (par -
 ticulate marrow cancellous bone; PMCB)
 (Rhesus
 Monkey)

3
 rhBMP - 2/ACS(rhBMP - 2 0.4mg /Mℓ),
 buffer/ACS, PMCB
 3 rhBMP - 2
 PMCB

Buffer/ACS

rhBMP - 2 가

rhBMP - 2, 가 . rhBMP - 2

가 rhBMP - 2 가 16 가 12

가 rhBMP - 2가 가 rhBMP - 2

가 가

V. rhBMP - 2 16

가 (polarized light microscopy)

1. (Current Perspective)

2가 BMP 가 ; rhBMP - 2 (Genetics Institute, Sofamor - Danek Group, Yamanouchi Pharmaceutical) rhOP - 1 (Creative BioMolecules, Stryker Biotech). rhBMP - 2 가, 가

가 rhBMP - 2/ACS

2. (Bone augmentation of the Maxillary Sinus) 2/ACS (Howell 1997). rhBMP - 2/ACS 가 12 6 rhBMP - 2/ACS 6 rhBMP - 2/ACS 0.4mg/Ml rhBMP - 2 rhBMP - 2

가 rhBMP - 2/ACS 가 rhBMP - 2

가 rhBMP - 2 (Fig ure 11). 가 가

rhBMP - 2/ACS

가 CT가 , , 가
 rhBMP - 2/ACS
 가
 가
 . rhBMP - 2/ACS
 rhBMP - 2/ACS
 가 가
 가
 가 . rhBMP - 2

VI.

rhBMP - 2가
 . rhBMP - 2
 (Absorbable collagen sponge; ACS)
 rhBMP - 2 가
 rhBMP - 2

VII.

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(1)

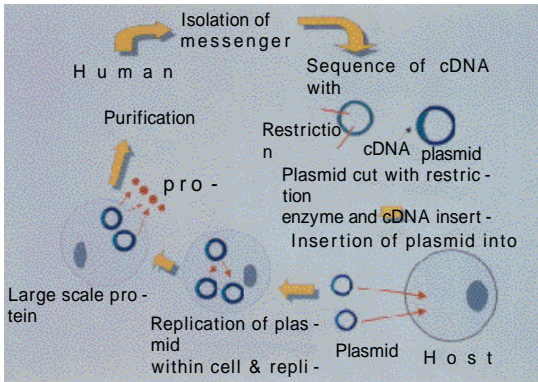


Figure 1

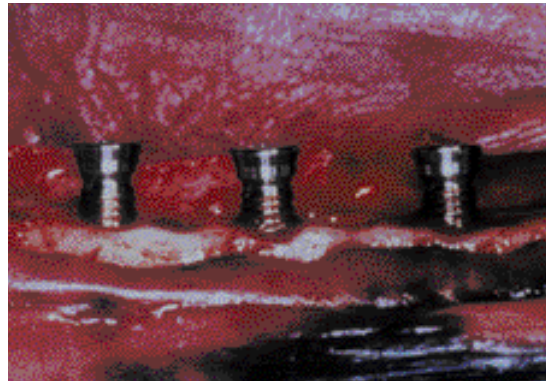


Figure 2

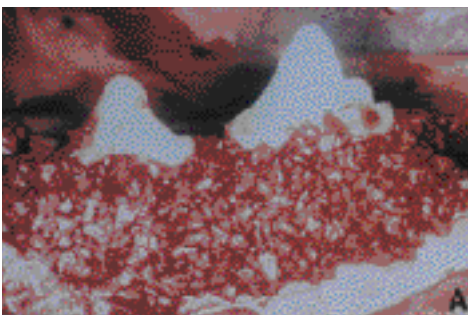


Figure 3

(II)

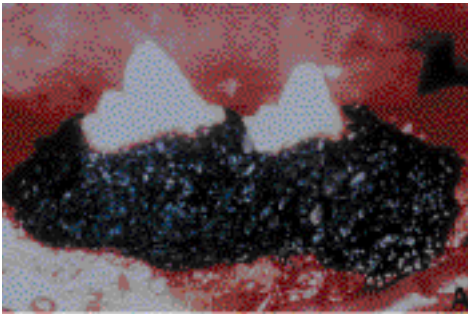


Figure 4

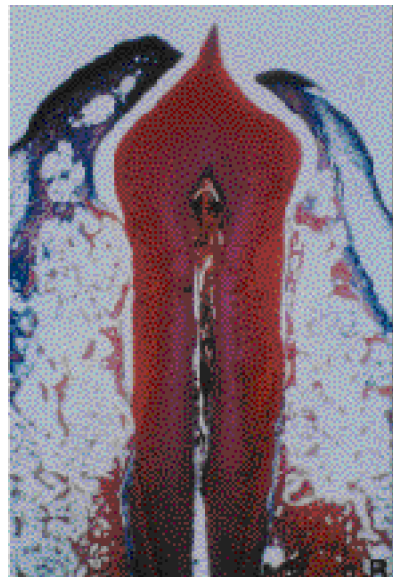
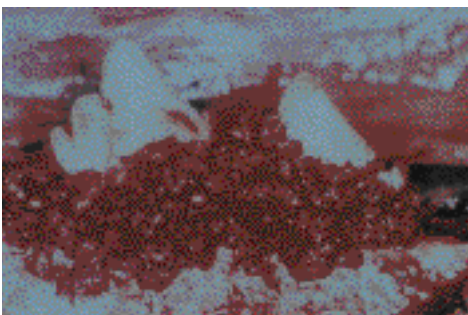


Figure 5

(III)

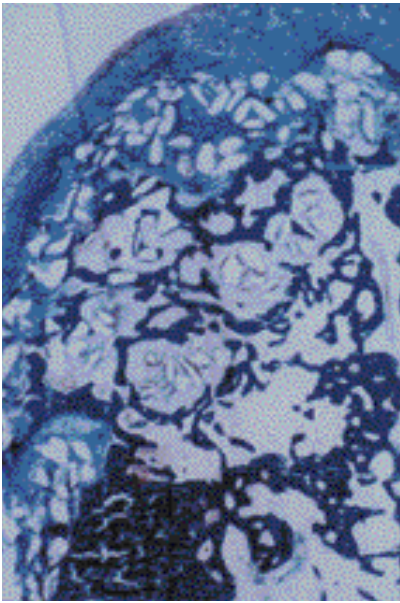


Figure 6

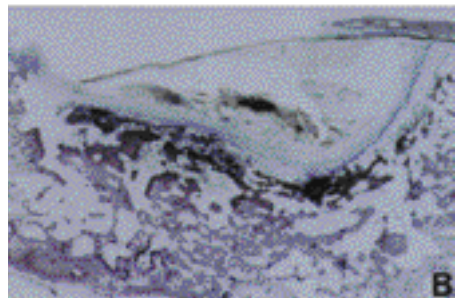
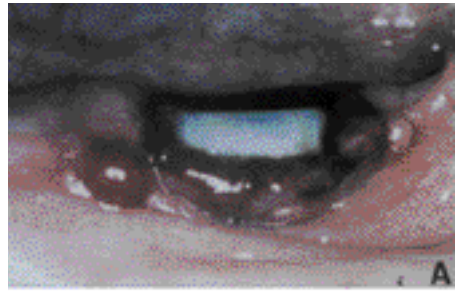


Figure 7

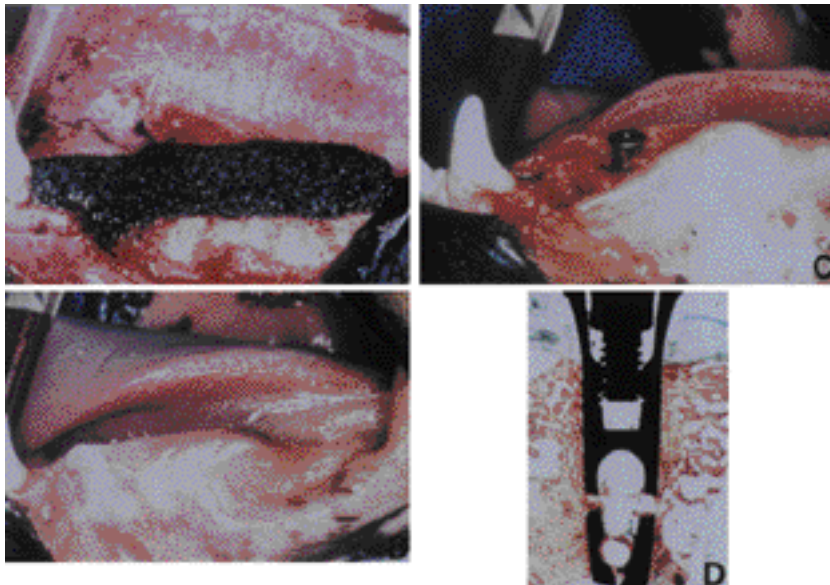


Figure 8

(IV)

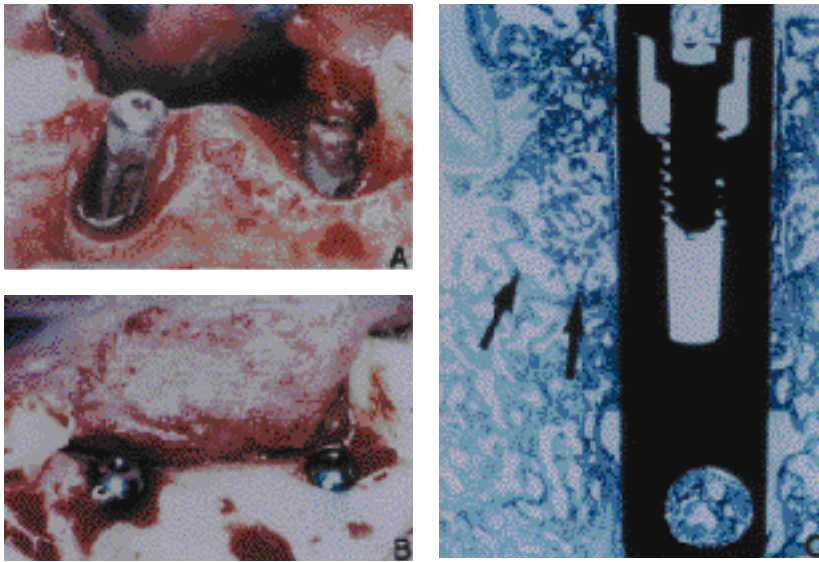


Figure 9

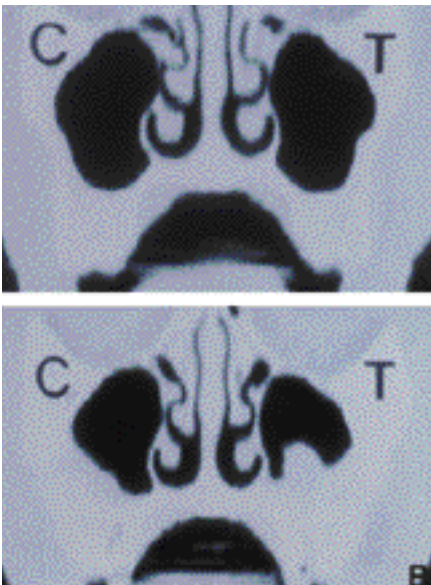


Figure 10

Effect of rhBMP-2 Dose on Mean Change in Alveolar Bone Height

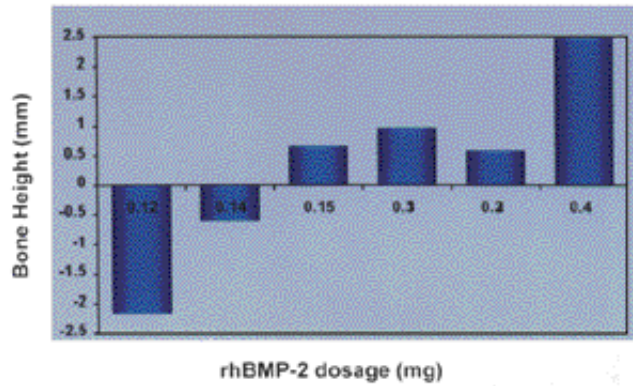


Figure 11

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Figure 1.

Summary of processes involved in the production of rhBMP - 2.

Figure 2.

The critical - size supraalveolar peri - implant defect model in the Beagle dog.

Figure 3.

Intrasurgery view of a critical - size supraalveolar periodontal defect treated with rhBMP - 2/Bio - Oss (A). Photomicrograph from 8 weeks postsurgery. The Bio - Oss particles are poorly resorbed and relatively little new alveolar bone formation can be seen in the region of the Bio - Oss material (B).

Figure 4.

Intrasurgery view of a critical - size supraalveolar periodontal defect treated with a rhBMP - 2/DL - Polylactic Acid (DL - PLA) (A). Photomicrograph from 8 weeks postsurgery. Note the relative lack of newly formed bone adjacent to the teeth. Numerous foamy macrophages are associated with the fragmenting PLA biomaterial (B).

Figure 5.

Intrasurgery view of a critical - size supraalveolar periodontal defect treated with rhBMP - 2 in an allogeneic, freeze - dried demineralized bone matrix (DBM) carrier (A). Photomicrograph from 8 weeks postsurgery. New alveolar bone is observed interposed between few residual DBM particles (B).

Figure 6.

Photomicrograph from 8 weeks postsurgery following placement of rhBMP - 2/HA only in Class III alveolar ridge defects. Poor quality and quantity of newly formed alveolar bone is apparent within the defect area. Illustration courtesy of Dr. Eliane Porto Barboza.

Figure 7.

Clinical view of an exposed ePTFE membrane following treatment of a large saddle - type alveolar ridge defect with rhBMP - 2/ACS and GBR (A). Photomicrograph showing exposure of the membrane with inflammation and necrosis underneath (B). . Illustrations courtesy of Dr. Sascha J. Jovanovic.

Figure 8.

Intrasurgery view of a rhBMP - 2/DBM only in the edentulous posterior mandible (A). Postsurgery view at 8 weeks showing the extent of the ridge augmentation (B). Implant placement into the newly formed ridge at 8 weeks postsurgery. Note a significant vertical and horizontal gain of alveolar bone (C). Photomicrograph from 12 weeks following implant placement. The implant is mainly implanted into rhBMP - 2 induced bone. Only the most apical aspect contacts old resident bone (D). . Illustrations courtesy of Dr. Thorarinn J. Sigurdsson.

Figure 9.

Clinical view following surgical exposure and debridement of peri - implant lesions (A). Four months following the placement of rhBMP - 2/ACS into the peri - implant defects in A. Note the substantial fill of the circumferential defects (B). Photomicrograph from 4 months following implantation of rhBMP - 2/ACS into the peri - implant defects in A. Note extensive new bone formation coronal to the base of the defect (indicated by the arrows) approaching the top surface of the implant. Also note evidence of re - osseointegration with the previously pathologically exposed implant surface (C).

Figure 10.

Presurgery CT scan of the maxillary sinuses in a Cynomolgus monkey. T and C delineates

sites to be treated with rhBMP - 2/ACS or ACS alone, respectively (A). Postsurgery (3 months) CT scan following sinus augmentation using a lateral wall approach. Bone formation is increased in the rhBMP - 2/ACS implanted site compared to the site receiving ACS alone (B).

Figure 11.

Graph showing the relationship between rhBMP - 2 dose in rhBMP - 2/ACS constructs and gain in bone height. This clinical study involved the use of rhBMP - 2/ACS for ridge preservation following tooth extraction.

- Abstract -

Tissue Engineering with rhBMP - 2: Bone Reconstruction in Implant Dentistry

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The preclinical and clinical studies reviewed herein show that rhBMP - 2 induces normal physiologic bone in relevant defects in the craniofacial skeleton. The newly formed bone assumes characteristics of the adjacent resident bone, and allows placement and osseointegration of dental implants. Clearly, the bone inducing capacity of rhBMP - 2 is carrier and site dependent. rhBMP - 2 in an absorbable collagen sponge carrier induces relevant bone formation in space providing defects. Space providing carries extends this possibility to non - space providing sites. Notably, some ceramic and polymeric biomaterials may substantially interfere with rhBMP - 2 induced osteogenesis.

Key words: Tissue Engineering, rhBMP - 2,
Bone Reconstruction, Implant Dentistry,
absorbable collagen sponge, carrier