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Background: Bioactive glasses enhance bone implant integration by increased osteogenesis. Additionally, factors affecting cell migration could prove useful during healing, since successful implant integration is dependent on the cells arriving at the implantation site.

Purpose: The aim was to assess the migration cues of bioglasses S53P4 and 45S5 to pre-osteoblastic cells (MC3T3-E1) when compared to more common implant materials hydroxyapatite (HAP) and carbonate hydroxyapatite (CAP) or alumina (Al_2O_3) control.

Methods: The Boyden chamber migration assay was used to test the chemotactic attraction of materials towards MC3T3-E1 cl.4 cells *in vitro*. After 6, 12, 24, and 48 hours the migrated cells were counted. The experiment was repeated in the presence of a calcium sensing receptor (CaSR) blocker (NPS2143) to assess the receptor's role in migration. Gene expression in response to S53P4, alumina, and 10 mM $CaCl_2$ was studied with quantitative PCR.

Results: Both bioglasses (S53P4 and 45S5) significantly increased cell migration compared to control at 12 hours ($p=0.01$ and $p=0.03$, respectively), and the positive effect continued after 48 hours. The initial migratory effect of HAP at 24 hours ($p<0.001$) diminished after 48 hours. Alumina had a minor effect on cell migration compared to control. Interestingly, CAP had a negative effect on cell migration. The blocking of CaSR had no uniform effect. The expression of osteopontin encoding gene *Spp1* was significantly increased by S53P4 ($p=0.05$) and $CaCl_2$ ($p=0.02$) after 24 hours.

Conclusions: We found that bioglasses induced a greater chemotactic effect to pre-osteoblastic cells compared to more conventional implant materials. Alumina had a minor effect on cell migration even though it is considered chemically inert. The discovered migratory effects are unlikely conveyed through CaSR, but might be indirectly influenced by osteopontin. All these data provide new knowledge of the initial phases of implant integration, which is relevant for the overall implant ossification.

Keywords: Bioglass; Cell migration; Implant; Osteopontin

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P020

Anabolic effects of rhPTH and novel PTH analog on titanium osseointegration and bone regeneration in ovariectomized beagle model

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Introduction: Recently, there have been concerns in the osseointegration of titanium dental implants and the integrity of bone grafts in osteoporotic patients. Little is known for the anabolic effect of PTH on titanium osseointegration in large ovariectomized animals such as beagle.

Purpose: To investigate the effect of rhPTH and PTH analog on titanium osseointegration and bone regeneration.

Methods: The beagles received ovariectomy to mimic post-menopausal osteoporosis. After teeth extraction (P1-P4) and titanium implant, all the animals received three titanium implants in the right lower jaw. Animals were divided into three groups ($n=4$ for each group): Normal saline injected-control group, injected with 40ug/day PTH (Forsteo) group, and 40ug/day PTH analog-injected group. Each animal was injected subcutaneously for 10 weeks and was sacrificed for evaluation of osseointegration and bone regeneration.

Results: The values of bone volume, bone mineral density, trabecular number, thickness, and separation by morphometric analysis with uCT were highest in the rhPTH-treated group. Each parameter in the PTH analog-treated group was lower than that in the rhPTH-treated group but increased than the control group. Based on Goldner's trichrome staining for histologic evaluation of bone formation, the bone area was the widest in the rhPTH-treated group, and extensive bone was observed on the titanium implant. The staining patterns in the PTH analog and control groups were similar to the uCT results. To determine bone turnover, TRAP staining is performed, and the number of Trap-positive cells was counted. The most TRAP-positive cells were detected in the rhPTH-treated group. There is a greater number of TRAP-positive cells in the PTH analog-treated group than control group.

Conclusions: The rhPTH and PTH analog can enhance osseointegrated implants in bone remodeling and increase osteoanabolic effects. Also, Pharmacological intervention of PTH analog to osteoporotic patients may provide a way to promote osseointegration after dental implant placement.

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P021

Repair of a critical-size defect in estrogen-deficient mice treated with bisphosphonates

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Background/Introduction: Bisphosphonates (BP), a class of anti-resorptive drugs, are the therapy of choice to prevent bone loss in post-menopausal osteoporosis. Since the inhibition of bone resorption by BP will cause, through coupling, a decrease in bone formation, extended treatment protocols may impair bone healing.

Purpose: In this study, β-tri-calcium-phosphate (βTCP) ceramics, coated with the growth factor Bone Morphogenetic Protein-2 (BMP2) and an engineered BMP2 analogue (L51P) that inactivates BMP-antagonists, were inserted into critical-size long bone defects in estrogen-deficient mice to assess bone formation and implant turnover.

Methods: Eleven-week-old mice were ovariectomized (*OVX*) or *sham* operated. Eight weeks later, bone mass was assessed in all animals and BP therapy was started. After five weeks, a femoral critical-size defect was generated, filled with βTCP cylinders loaded with 0.25μg or 2.5μg BMP2, 2.5μg L51P, 0.25μg BMP2/2.5μg L51P or empty control cylinders and rigidly fixed. Femora were collected 12 weeks post-op.

Results: Micro-computed-tomography (MicroCT) revealed low bone formation and osseointegration of implants that were either empty or loaded with 2.5μg L51P and 0.25μg BMP2 in *sham* and *OVX* mice +/- BP therapy. In contrast, insertion of cylinders loaded with 0.25μg BMP2/2.5μg L51P and 2.5μg BMP2 induced bone formation and high biomaterial turnover in *sham* and *OVX* animals, this result was even more pronounced in BP treated animals. After 12 weeks, no significant differences in levels of transcripts encoding bone and cartilage markers were detected by PCR among the experimental groups. Relative expression levels of transcripts encoding collagen I

were 150 times higher than those for collagen II and around 5000 times higher than those for collagen X.

Conclusion(s): MicroCT results demonstrated the potential of L51P to increase the osteogenic efficiency of BMP2 in the healing of ceramic filled critical size bone defects. The relative expression profile of the different collagens suggests intramembranous bone formation in the rigidly fixed defects.

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P023

Comparison of efficacy of rhBMP2 and rhBMP6 delivered within autologous blood coagulum with synthetic ceramics in rat subcutaneous assay

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Introduction: Majority of bone morphogenetic proteins (BMPs) posess osteoinductive properties, but only rhBMP2 is commercialy available for bone regeneration in clinical practice. However, it has been shown that BMP6 is more potent in promoting osteoblasts *in vitro* as compared to the BMP2 and BMP7 due to BMP6 resistance to noggin inhibition. Osteogrow C is a novel osteogenic device consisting of rhBMP6 in autologous blood coagulum (ABC) with synthetic calcium phosphate ceramic particles. The aim of this study was to compare osteogenic potential of rhBMP2 and rhBMP6 in this novel device conducting rat subcutaneous assay.

Materials and methods: Osteoinductive implants were prepared by mixing rhBMP2 or rhBMP6 in three different doses (5, 20 and 50 μg) with 500 μL of blood and 100 mg of synthetic ceramics (500-1700μm, TCP/HA 80/20). Following blood coagulation, osteogenic device was implanted subcutaneously in the axillary region of Sprague Dawley rats. Animals were terminated 14 days after implantation and implants were analysed by microCT and on histology sections stained by Goldner stain.

Results: MicroCT analyses revealed that rhBMP2 and rhBMP6 possess similar osteoinductive potential in low-dose range (5-20 μg,) while rhBMP6 was superior to rhBMP2 when higher dose (50 μg) was applied. Histological analyses demonstrated that all tested formulations induced formation of bone at the surfaces and between the ceramic particles. However, the most extensive amount of bone was observed on histological sections of implants containing 50 μg of rhBMP6 confirming the findings of microCT analysis.

Discussion: We demonstrated herein that rhBMP6 is superior to rhBMP2 when higher BMP doses are used. Higher efficacy of rhBMP6 might arise from resistance to noggin inhibition and affinity across the BMP type I receptors in comparison to BMP2 and BMP7.

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P024

rhBMP6 in autologous blood coagulum with ceramics induces rapid spinal fusion in sheep

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Introduction: Osteogrow, an autologous bone graft substitute (ABGS) containing recombinant human Bone Morphogenetic Protein 6 (rhBMP6) within autologous blood coagulum (ABC) as a BMP carrier is a novel therapeutic solution for bone regeneration. Calcium phosphate ceramic particles might be added to Osteogrow to improve the biomechanical properties of implants.

Purpose: This study aimed to evaluate Osteogrow with synthetic ceramic particles (Osteogrow C) in the sheep posterolateral spinal fusion (PLF) model.

Methods: Osteogrow C implants containing 74-420 μm (n=6) or 500-1700 μm (n=6) ceramic particles were prepared as follow: lyophilized rhBMP6 (0,5 mg per implant) was dissolved in water and added to 8 mL of autologous blood withdrawn from the jugular vein and mixed with ceramic particles. Osteoinductive implants were placed between L4-L5 transverse processes of sheep (Ovis Aries, Merinolaandschaf breed, aged 4-5 years). Spinal fusion was assessed 9 weeks after surgery by *in vivo* CT scanning. Animals were terminated 14 weeks following implantation to further evaluate the spinal fusion outcome by microCT, biomechanical testing, and histology. The study was approved by the Institutional and National Ethics Committees

Results: Osteogrow C implants with both 74-420 and 500-1700 μm ceramic particles induced formation of bone and fusion with transverse processes 9 weeks following implantation as evidenced by *in vivo* CT scans. *Ex vivo* microCT, histological and biomechanical analyses confirmed these findings and revealed that newly formed bone was completely integrated with native transverse processes providing biomechanically competent fusion.

Conclusions: Osteogrow C implants induce rapid spinal fusion in the sheep PLF model and provide a possible therapeutic solution for patients with degenerative disease of the spine.

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P029

Risk factors for developing sacral insufficiency fractures

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Background/Introduction: Fragility fractures of the pelvis have been detected with increasing frequency in recent times, whereby their incidence will increase further as a result of the increase in life expectancy.

Purpose: The objective of the present retrospective investigation on women suffering from sacral insufficiency fractures was to determine the extent of a possible vitamin-D deficiency and existing osteoporosis.

Methods: In 276 female patients aged from 58 - 99 (Ø 81.3) years with sacral insufficiency fractures, the fractures were classified