Bone Response to New Generation Nanocrystalline Calcium Sulfate Based Materials

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Statement of Purpose: One of the most common surgical repair procedures is bone grafting. This is true in dental, maxillofacial and orthopedic surgery. The simplest bone repair materials represent off-the-shelf bone substitutes that do not require additional surgical sites for bone harvest. Calcium Sulfate (CS) is a highly biocompatible material used in promoting bone regeneration for the last 110 years (*1-2*). Limitations of CS are its low mechanical strength and fast degradation rate. Studies have shown that in most dental defects CS is completely degraded in 4 weeks (*3*). Larger bone defects take much longer to heal and hence need a graft material that undergoes controlled degradation. On the other hand, CS is the only bone graft material that has guided tissue regeneration barrier, angiogenic and hemostatic properties. Hence this project is focused on developing calcium sulfate based bone grafts that undergo controlled degradation. Previously, we successfully developed particles of nanocrystalline calcium sulfate (nCS) and composites of nCS with polymers and showed the effect on degradation rate *in vitro*. The nCS particles and nCS based composites had varying degradation rates.

During the *in vivo* phase of this study bone response to eight different experimental groups was studied, each representing a composite of nCS+4% p(DTE-C), nCS+2% p(DTE-C), nCS+8% PA, nCS+4% PA, nCS+4% PLLA (2 varying granule sizes) and particles of nCS (proprietary technology of Orthogen, LLC, 2 varying granule sizes).

Methods: All materials were made by agglomeration and provided by Orthogen, LLC (Springfield, NJ). Composite materials were mixed with CS at a 65:35% ratio, respectively, in order to produce scaffold implants. Implants were placed in 11mm diameter trephine defects in each of the two parietal skull bones in New Zealand White rabbits. After sacrifice at 4, 8 and 16 weeks, the bone repair sites and surrounding areas were processed for microCT and histopathology. These sites were evaluated to determine the effect of different compositions on bone formation. Histopathologic analysis includes evaluation of bone, marrow, and local soft tissue response to these materials. Histomorphometrical analysis was conducted to quantify the amount of bone formed.

Results: Preliminary 4 and 8-week data (Figures 1 and 2) are based on microCT analysis of bone grown in the trephine defects. Significantly greater amounts of bone grew in trephine defects grafted with particles of nCS and nCS+P(DTE-C) composite compared to those grafted with particles of nCS+PLLA and nCS+PA. There was no significant difference between the amount of bone grown in defects grafted with nCS+P(DTE-C) vs nCS or between composites of nCS+PLLA vs. nCS+PA. Histological analysis showed excellent response to composites of nCS+P(DTE-C) and nCS particles. Figure 3 shows immature bone with osteoid tissue and active osteoblasts in defects grafted with nCS at 8 weeks.

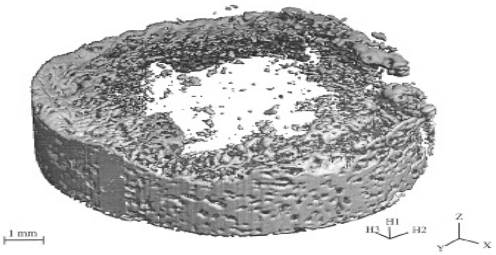

Figure 1: MicroCT analysis of bone ingrowth within the nCS scaffold at 4 weeks.

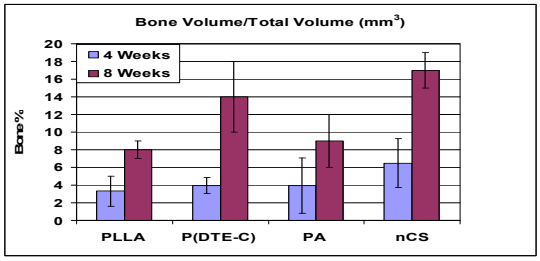

Figure 2: % Bone growth in defects at 4 and 8 weeks.

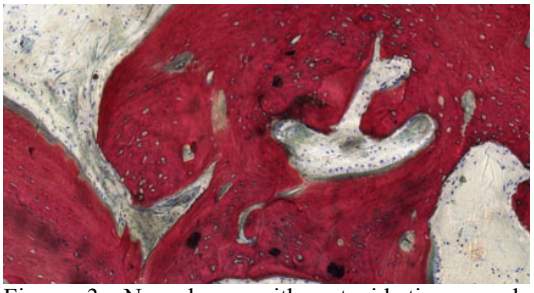

Figure 3: New bone with osteoid tissue and active osteoblasts in defects grafted with nCS at 8 weeks after Stevenel's Blue staining.

Conclusions: From these preliminary results, it can be concluded that all composite materials allowed for a controlled degradation rate, encouraged bone formation, were osteoconductive and did not induce any inflammatory response.

References:

1. M. Orsini, G. Orsini, D. Benlloch, J. J. Aranda, M. Sanz, *J Periodontol* **79**, 1630 (Sep, 2008).
2. M. Paolantonio *et al.*, *J Periodontol* **79**, 1886 (Oct, 2008).
3. S. S. Mamidwar, C. Arena, S. Kelly, H. Alexander, J. Ricci, *J Biomed Mater Res B Appl Biomater* **81**, 57 (Apr, 2007).

Supported by NIH Grant R44DE015703