In vivo Performance of Resorbable Polymer Scaffolds with Calcium Phosphate Coatings Tested in a Rabbit Critical-Sized Calvaria Model

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Statement of Purpose: For the repair of large bone defects, the use of autografts and allografts has serious clinical limitations. Consequently, tissue engineering-based bone graft substitutes (BGS) have been developed and approved by the US FDA.[1,2] Tyrosine-derived polycarbonates (TyrPCs) represent a library of over 10,000 polymers. Several of these polymers, in particular E1001(1k), have provided promising results in previous studies when bone regeneration scaffolds made of E1001(1k) were tested in vivo.[3] The purpose of this study was to compare the *in vivo* performance of E1001(1k) scaffolds in combination with a calcium phosphate (CP) coating or a coating containing bone matrix minerals (BMM). These coatings were deposited onto the scaffold and throughout its pores. To assess the value of these new compositions, we included ChronOS, a commercially available bone graft substitute (BGS) as a positive control. The study was conducted in a rabbit critical-size calvaria model.

Methods: E1001(1k)+CP scaffolds were prepared as described previously.[3] Using the same procedure, scaffolds were produced with a coating containing bone matrix minerals (BMM). E1001(1k) scaffolds were immersed in 1 M $CaCl_2$ solution containing 0.03mM magnesium chloride and 0.01mM zinc chloride. This was followed by exposure to 0.96 M K_2HPO_4 solution containing 0.01 mM of sodium fluoride. These scaffolds were identified as *E1001(1k)+BMM*. ChronOS was obtained from a commercial vendor.
The scaffolds were implanted in a rabbit calvaria critical-size defect (CSD) model. The model is a unilateral craniotomy (15 mm diameter) in the parietal bones. A single scaffold was implanted into each rabbit calvaria CSD. Bone regeneration was determined at 2, 4, 6, 8, and 12 weeks post-implantation using micro-computed tomography (μCT), histology and histomorphometry. Each of the 3 treatment groups BGS (ChronOS), E1001(1k)+CP, and E1001(1k)+BMM) had 5 time points with 4 replicates in each cohort (n=4).

Results: The key results of this study are summarized in Figure 1. The μCT data are presented as % bone volume over the total volume of the region of interest (BV/TV%). At all time points, there was a trend for *E1001(1k)+CP* to be superior over the other treatment groups. However, because of the large variability observed for the laboratory specimens of *E1001(1k)+CP* and *E1001(1k)+BMM* relative to the commercially manufactured BGS, this trend reached statistical significance only at the 6-week time point. We were surprised to find that the scaffolds with *BMM* performed worse than any of the other test groups. This finding requires further study. ChronOS provided very consistent results but did not generate significant amounts of bone in this model. This result is in line with clinical reports indicating that synthetic BGSs require some biological components (bone marrow aspirate, cells, or BMP) to perform well.
The general trend of the μCT data was confirmed by histology and histomorphometry. All of the test specimens were well tolerated and were biocompatible. In the implant sites treated with ChronOS, beta-TCP fragments persisted throughout all time points. Only in implant sites treated with *E1001(1k)+CP* bone regeneration was observed within the inner section of the defect, while the other treatment groups produced new bone only along the periphery where the scaffold was in contact with the surrounding bone.

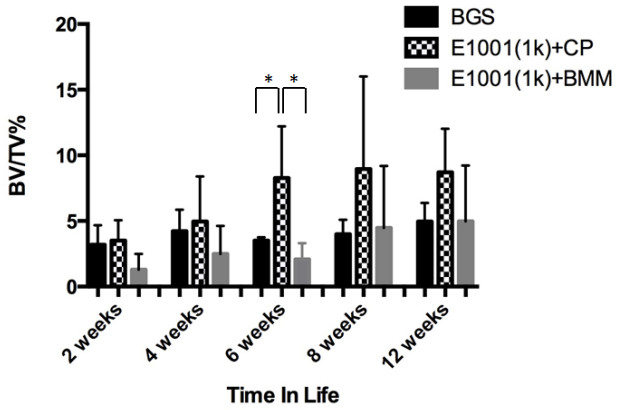

Figure 1. μCT data for all three treatment groups in the rabbit calvarial critical-size defect model at 2, 4, 6, 8 and 12 weeks.

Conclusions: This was the first time, the experimental E1001(1k) scaffolds with CP or BMM coatings were directly compared with each other and with a clinically used BGS. The results suggest (1) Scaffolds containing bone matrix minerals (i.e., Mg, Zn, and F) appeared to produce the least new bone formation; (2) Osteoconduction in the *E1001(1k)+CP* group progressed durally and resulted in some bone regeneration throughout the entire defect; (3) the total amount of bone regenerated by all three treatment groups was rather low, indicating the need for further optimization of synthetic BGSs. The results for *E1001(1k)+CP* scaffolds are promising, however, significant additional studies must be completed to validate clinical opportunities.

References:

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