Effect of Local Alendronate Delivery on *In Vivo* Osteogenesis From PCL Coated 3D Printed TCP Scaffolds

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Introduction: Ever increasing rate of musculoskeletal diseases and disorders caused by bone tumors, trauma, disease, birth defects and war or traffic injuries often times require treatment with an appropriate drug for accelerated healing or preventing post-operative infections. The shortcomings of systemic drug delivery such as low bioavailability and low efficacy can cause unwanted potential side effects. However, reduced side effects, improved bioavailability and efficacy can be achieved by local drug delivery (1). Alendronate (AD), a member of the bisphosphonate family, is the most commonly used for osteoporosis because of its potent inhibition of bone resorption (2). Calcium phosphates (CaPs) are widely used and preferred choice for hard tissues such as teeth or bone repair, replacement, augmentation, and regeneration due to their excellent bioactivity and compositional similarities to bone mineral (1). Drug delivery from CaPs in most cases ends up with an initial burst release. Sustained and controlled release of any drug over desired period of time from the implant material is an important factor for effective treatment. **Objective** of this research is to understand the effect of polycaprolactone (PCL) coating on alendronate (AD) coated 3D printed macro porous tricalcium phosphate (TCP) scaffolds on *in vivo* osteogenesis. Our **hypothesis** is that *PCL coating will be beneficial for sustained and controlled release of AD by preventing the burst release, which will reduce the healing time by enhancing bone ingrowth inside the 3D macroporous network.*

Methods: Scaffolds were fabricated using commercially available β-TCP powder (Berkeley Advanced Biomaterials Inc., Berkeley, CA). Scaffolds [3.4 mm (ϕ) and 5.2 mm (h)] with 350 µm designed interconnected pore size were fabricated using a 3D printer (ProMetal®, ExOne LLC). Scaffolds sintered at 1250°C in a conventional muffle furnace for 2 h were coated with PCL (M_w=14000) (Sigma, St. Louis, MO, USA) and Alendronate (AD). Scaffolds were coated by 1 wt. % PCL solution in acetone. Six different scaffold compositions namely, (i) TCP (bare TCP), (ii) TCP+AD (AD coated TCP), (iii) TCP+PCL (PCL coated TCP), (iv) TCP+PCL+AD, (v) TCP+AD+PCL and (vi) TCP+AD+PCL+AD were tested in distal femoral defect model of Sprague-Dawley rats. Effect of PCL and AD were examined on new bone formation and tartrate resistant acid phosphatase (TRAP) positive cells activity by histomorphology and histomorphometric analysis after 6 and 10 weeks post implantation.

Results: PCL coating resulted a thin flake like layer on the strut of the scaffold as shown in **Figure 1**.scaffolds with single AD coating were loaded with 2 µg AD except TCP+AD+PCL+AD, which was loaded with 4 µg due to two AD coating layer. Histomorphology of the scaffolds showed an excellent bone formation inside the micro and macro pores of the scaffolds. Histomorphometric analysis revealed maximum amount new bone formation in

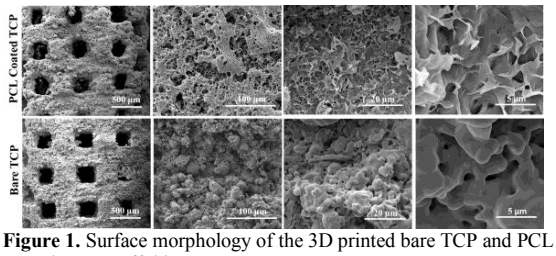

Figure 1. Surface morphology of the 3D printed bare TCP and PCL coated TCP scaffolds.

TCP+AD+PCL scaffolds after 6 weeks as shown in **Figure 2**. No adverse effect of PCL on *in vivo* bone formation was observed. Bare TCP scaffolds showed the highest TRAP positive cells activity followed by TCP+PCL scaffolds. TCP+AD scaffolds showed the lowest TRAP activity followed by TCP+AD+PCL

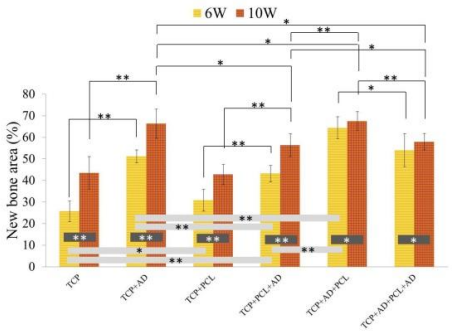

Figure 2. Histomorphometric analysis showing total new percent bone formation comparison between the treatments (**$p < 0.05$, *$p > 0.05$, n = 3 tissue sections of 800 µm width and 800 µm height each).

Higher TRAP positive cells activity in TCP+AD+PCL compared to TCP+AD after 6 weeks indicates controlled release of AD inhibited osteoclasts activity gradually maintaining higher bone formation at the same time.

Conclusions: Both histomorphology and histomorphometric analysis revealed maximum bone formation after 6 weeks when TCP+AD scaffolds were coated with PCL. This is probably caused by a gradual release AD as a result of inhibition of initial burst release by PCL coating. These results suggest that PCL coating can effectively be used for local AD delivery from TCP scaffolds for enhanced osteogenesis for early wound healing. Thus, PCL coating has the excellent potential in bone tissue engineering applications for local *in vivo* drug delivery for early implant fixation with host tissue and early wound healing.

Authors like to acknowledge the financial support from the NIH (grant # R01 EB 007351) for this work.

References:(1). Bose S, Tarafder S. Acta Biomater 2012; 8:1401–1421. **(2).** Liberman et al. N Engl J Med 1995; 333:1437–1444.