Dual delivery of Vancomycin & BMP-2 from Polyurethane Implants for Contaminated Bone Wound Healing

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Statement of Purpose: Infection is a significant clinical problem in bone wound healing (1), even in the presence of an osteogenic factor, especially for open fractures with large gaps in the bone which happens frequently in combat-related trauma. Present clinical approaches require a two-step process, in which the infection is first controlled by implantation of non-degradable antibiotic-impregnated PMMA beads, followed by implantation of a bone graft to promote bone healing. To reduce the healing time of the patient, it is desirable to promote bone fracture healing and control infection through one surgical procedure. We have previously shown that sustained delivery of BMP-2 from polyurethane (PUR) was able to promote new bone formation in rat femora (2). We were also able to deliver vancomycin free base (V-FB) from PUR for up to 8 weeks at a concentration well above minimum inhibitory concentration (MIC) which inhibited infection in contaminated rat femoral segmental defect (submitted work). The purpose of the present study is to incorporate both drugs in the same PUR scaffold, and to test the composite's ability of controlling infection and promoting bone wound healing simultaneously.

Methods: rhBMP-2 was purchased from R&D systems. V-FB was obtained by precipitation of vancomycin solution at pH 8. Porous PUR scaffolds incorporating BMP-2 and V-FB were then fabricated using a one-shot two-component reaction between the Lysine triisocyanate (LTI) and polyester triol as described previously (3). *In vitro* release experiment was carried out in PBS, with medium refreshed as indicated. The vancomycin concentration was determined by absorbance at 280 nm, and the BMP-2 concentration was measured by ELISA assay (R&D). The scaffolds were then tested in critical sized rat femoral segmental defects, contaminated or non-contaminated. After 4 or 8 weeks, the defects are harvested, and both the new bone formation and infection control were examined.

Results: Either BMP-2 or V-FB can be released from the composite PUR/BMP-2/V-FB, with profiles similar to reported when incorporating any of them individually in the PUR (Figure 1).

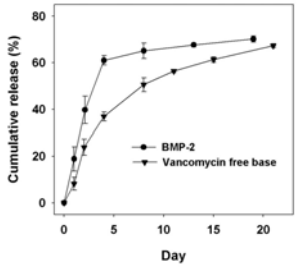

Figure 1, *In vitro* release of BMP-2 and V-FB from PUR.

In order to test whether the presence of V-FB interfere with the osteogenic activity of BMP-2, the composites were first tested in the non-contaminated segmental defect for 4 weeks. Two BMP-2 dosages in PUR were chosen (Low: 2 ug per implant, and High: 20 ug per implant), with or without V-FB. The results showed that the presence of V-FB did not compromise the new bone formation promoted by BMP-2 (data not shown). Then the composites were tested in the contaminated segmental defect for 8 weeks, using collagen sponge soaped with BMP-2 as control. Figure 2 showed that, at both low and high BMP-2 dosages, PUR performed better than collagen sponge due to more sustained release. Furthermore, in the presence of V-FB, the new bone formation was enhanced due to infection control by long-term release of antibiotic.

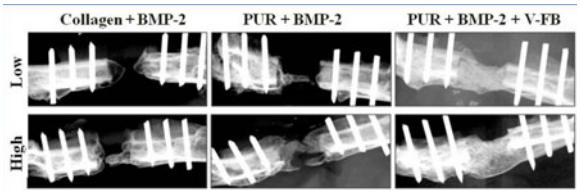

Figure 2, Test of PUR composite in contaminated critical sized rat femoral segmental defect

Interestingly, the trend of new bone formation is consistent with the clinical infection rate observed. As shown in figure 3, when counting the number of rats with infection at the end of the experiment, PUR treatment groups has less infection rate compared with collagen, and the infection decreases when V-FB is present. The PUR treatment group with both high BMP-2 dosage and V-FB showed no clinical signs of infection.

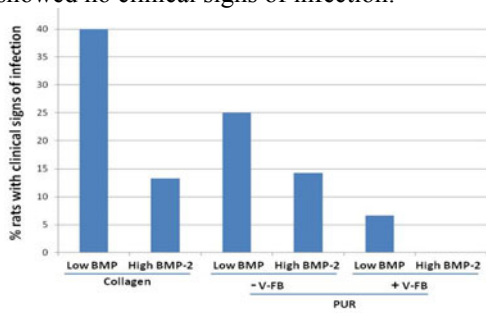

Figure 3, Percentage of rats with signs of infection at week 8 in each treatment group.

Conclusions: In the contaminated segmental defect, both infection control and new bone formation were achieved synergistically through dual release of V-FB and BMP-2 in a sustained manner. The outcome of this study suggests that the biodegradable PUR/BMP-2/V-FB composite may be a potential strategy for the clinical treatment of bone wounds complicated by infection.

References:

[1] Johnson EN et al, Clin Infec Dis 45, 2007, 409-415.
[2] Li B et al, Biomaterials 30, 2009, 6768-6779.
[3] Guelcher SA et al, Tissue Eng 13 (2007) 2321-2333.