Sustaining the Release of Vancomycin from Polyurethane Scaffold for Infection Control

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Statement of Purpose: Infection is a common complication in open fractures that compromises the healing of bone and can result in loss of limb or life. Currently, the clinical standard of care for treating contaminated open fractures comprises a staged approach, wherein the wound is first treated with non-biodegradable antibiotic-laden PMMA beads to control the infection followed by bone grafting. Considering that tissue regeneration is associated with new blood vessel formation, which takes up to 6 weeks in segmental defects, a biodegradable bone graft with sustained release of an antibiotic is desired to prevent the implant from becoming infected, thus allowing the processes of both vascularization and new bone formation to occur unimpeded. The main objective of the present study was to synthesize polyurethane (PUR) scaffolds incorporating vancomycin with tunable release kinetics, where the release of vancomycin was extended to 6 – 8 weeks. The biological activity of released vancomycin was verified in contaminated critical-sized rat femoral segmental defects.

Methods: Commercially available vancomycin hydrochloride (V-HCl, 200 mg/ml solubility) was dissolved followed by increasing the pH to 8 (where vancomycin has no net charge and the lowest solubility [1]). The precipitated vancomycin free base (V-FB, solubility < 20 mg/ml) was filtered, washed, and lyophilized overnight. Porous PUR scaffolds incorporating V-HCl or V-FB were then fabricated using a one-shot two-component reaction between the lysine triisocyanate (LTI) and polyester triol as described previously [2]. *In vitro* release experiment were carried out in PBS, with medium refreshed as indicated. The vancomycin concentration was determined by absorbance at 280 nm, and activity was measured by the Kirby-Bauer test. The scaffolds were then tested in contaminated critical-sized rat femoral segmental defects for 4 weeks, and the presence of bacteria within both the soft tissue and bone tissue were analyzed by photon measurement and colony forming units (CFUs) counting, respectively.

Results: As shown in Figure 1A, the vancomycin release from PUR/V-HCl showed a burst release of 42% and 28% on days 1 and 2, respectively, and the cumulative release was 90% at day 8. The release on day 1 of PUR/V-FB was only about 11%. Furthermore, the V-FB exhibited a more sustained release profile from day 8 to day 56, which was 3-fold greater than that for V-HCl, and the released vancomycin concentration remained well above the MIC (0.75~2 μg/ml) for at least 8 weeks. In contrast, PMMA beads exhibited a burst release of 10% on day 1 followed by a small sustained release on days 8 – 56. As shown in Figure 1B, the released vancomycin from each treatment group at each time period was verified to be bioactive through the Kirby-Bauer anti-bacterial assay.

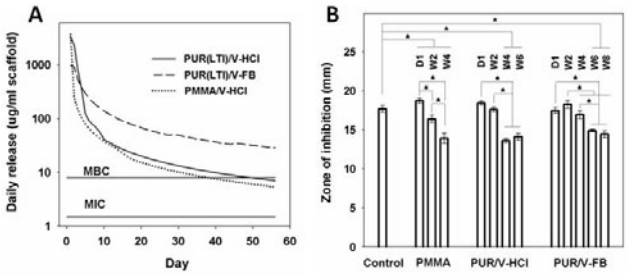

Figure 1, *in vitro* release (A) and Bioactivity (B)

PUR(LTI)/V-HCl, PUR(LTI)/V-FB and PMMA/V-HCl beads were implanted in contaminated rat femoral segmental defects and the femurs harvested after 4 weeks. Both PUR treatment groups performed better than the PMMA beads, although no significant differences were observed between any treatment groups for the soft tissue bacteria counts (Figure 2). The CFU data (Figure 2) suggest that all the vancomycin treatment groups inhibited bacteria growth in bone tissue, but only PUR(LTI)/V-FB and PMMA/V-HCl showed significant inhibition effects.

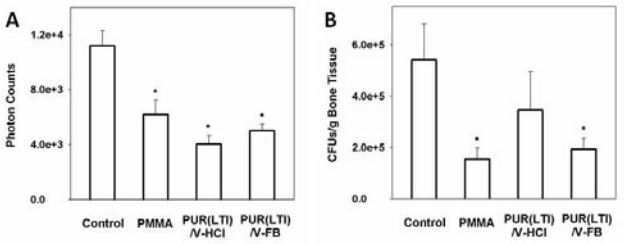

Figure 2, Infection control of vancomycin implants in both soft tissue (A) and bone tissue (B).

Conclusions: Porous biodegradable polyurethane scaffolds have been shown to support tunable, sustained release of vancomycin *in vitro*. When implanted in infected segmental defects in rats, PUR/vancomycin scaffolds significantly reduced the infection relative to the untreated control and performed comparably to PMMA bone cements after 4 weeks. The release profile of vancomycin from PUR was extended to at least 8 weeks when hydrophilic V-HCl was converted to hydrophobic V-FB, and the extended release profile translated to better performance *in vivo*. Therefore, PUR scaffolds incorporating V-FB could be a potential clinical therapy for treatment of contaminated bone defects.

References:

[1] Takacsnovak K et al, International Journal of Pharmaceutics 89 (1993) 261-263.

[2] Guelcher SA et al, Tissue Engineering 13 (2007) 2321-2333.