Release of antibiotic from injectable, biodegradable polyurethane scaffolds for enhanced bone fracture healing

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INTRODUCTION: Infections often accompany open fractures, resulting in compromised fracture healing even in the presence of growth factors such as BMP-2 [1]. Infected fractures are treated in the clinic with tobramycin-PMMA beads, but these are not resorbable and release only a small fraction of the embedded antibiotic [2]. We are developing an alternative approach using injectable, biodegradable polyurethane (PUR) scaffolds. These materials support osteoblast migration and proliferation, and degrade to non-cytotoxic products [3]. PUR scaffolds also support osteoblast migration and proliferation, and degrade to non-cytotoxic products [3]. PUR scaffolds have also been shown to promote ingrowth of new cancellous bone when implanted in sheep tibia models [4]. In this study, we have developed PUR scaffolds to release antibiotics using two approaches: (1) incorporation as a labile powder, and (2) encapsulation in PLGA microspheres. These biomaterials present potential clinical opportunities for treatment of osteomyelitis.

MATERIALS AND METHODS: PUR foams were synthesized by reactive liquid molding of hexamethylene diisocyanate trimer and hardener consisting of a polyester triol, 600-MW PEG, water, catalyst, and pore opener using previously reported techniques [3]. Lyophilized antibiotic (tobramycin or colistin) and glycerol, 600-MW PEG, water, catalyst, and stabilizer were mixed thoroughly with the hardener component at 8 wt-% before foam synthesis. Tobramycin-encapsulated PLGA microspheres were likewise included at 25 wt-% in some of the foams [5]. In vitro release of tobramycin in PBS at 37°C was measured from 0.5 to 28 days and quantified using a CIBCA Protein Quantitation assay. The activity of the antibiotics released from the foam was evaluated using a Kirby-Bauer test. In these experiments, 6x2 mm tobramycin foam discs were placed on agar plates streaked with methicillin-susceptible S. aureus, while colistin foams were plated on multi-drug-resistant A. baumannii. The zone of inhibition (ZI) was measured in comparison with standard 10-μg antibiotic discs after 24 hrs. The in vitro behavior of the scaffolds was evaluated for biocompatibility, biodegradation, cellular infiltration, and tissue regeneration. 8x2 mm foam discs were implanted into excisional dermal wounds in adult SD rats, and splinted with washers to prevent wound contraction and allow normal granulation tissue infiltration. The osteoconductivity of the scaffolds is currently being evaluated in a rat tibia model.

RESULTS: 60-70% of the labile tobramycin eluted after 24 hrs, with 90% released by 5 days (Fig. 1). The foams with microspheres showed slower release: 25% after 24 hrs. The release curve was still increasing after 26 days, suggesting extended release of tobramycin from the microspheres.

DISCUSSION: This biocompatible and biodegradable PUR foam shows promise as an effective scaffold for bone fracture healing. Its injectability and resilience promote thorough contact with the surrounding bone. Its material properties can be tuned for varied strength and elasticity (manuscript in preparation). In vivo studies show extensive cellular infiltration and new tissue formation in both bone and soft tissue with minimal inflammation. Furthermore, we can release biologically active antibiotics from these foams in a controlled manner. In vitro release profiles show nearly complete release of antibiotic embedded in the foam by 4 days, plus extended release from PLGA-tobramycin microspheres. Kirby-Bauer tests illustrate that the released antibiotic effectively inhibits bacteria growth. This scaffold therefore provides both a structural support for bone fractures and a matrix from which antibiotic can be released locally to enhance healing of infected fractures.

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Fig. 1. Tobramycin release from foams with 8% powder (circles) & 20% microspheres (triangles).

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