Injectable, Biodegradable, Porous Polyurethane Scaffolds for Tissue Regeneration

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Statement of Purpose: Numerous synthetic and biological scaffolds show promise for wound repair and tissue regeneration, but few have the capacity to polymerize *in situ*. An injectable formulation should facilitate minimally invasive surgical procedures. In addition, injectability could allow customization at the time of implantation, including conforming to irregular wound dimensions and delivering biologicals to enhance the wound repair response.

We have developed highly porous, biodegradable polyurethane (PUR) scaffolds that support cellular infiltration, new tissue formation in skin and bone, and degrade to non-cytotoxic products with a limited local inflammatory response [1]. Their elastomeric, resilient properties may promote thorough contact with wound boundaries. Compositional alterations were required to optimize the injectability, addressing cure time, material-tissue adhesion, reaction temperature profile, and limiting possible monomer toxicity. These scaffolds would ideally support regeneration of both form and function of wounds in a range of tissues, including bone and skin.

Methods: Injectable PUR scaffolds were synthesized by syringe-mixing of two phases: a prepolymer of lysine triisocyanate (LTI) and 200-MW PEG, and a hardener consisting of a polyester triol, water, catalyst, and pore opener. Hyaluronic acid (HA) particles were added to the prepolymer at 15-wt% to absorb excess moisture in the wound area and perhaps enhance healing. The reactive liquid mixture was applied directly into 8-mm excisional dermal wounds or 3-mm femoral plug defects, both in male Sprague-Dawley rats, and expanded by gas foaming to fill the respective defects. The adherence and permeability of the scaffolds were evaluated after injecting and curing *in situ*, and the water, catalyst, pore opener concentrations were adjusted to achieve curing times practical for clinical applications. The scaffolds were assessed for biocompatibility, biodegradation, cellular infiltration, and tissue regeneration. Ongoing experiments include assessment of long-term biocompatibility and regenerative capacities of the injected scaffolds. Mechanical properties were also ascertained by dynamic mechanical analysis (DMA).

Results: After a mixing time of 2 min, the formulation allowed 5 min of working time. The scaffolds had an average rise time 8 – 10 minutes, with an internal reaction temperature maximum of 41 ºC. At 87% porosity, the elastomeric scaffolds exhibit a Young's modulus of 75 kPa & compressive stress of 46 kPa, which can be increased with higher HA content.

Gomori's trichrome histology showed rapid material biodegradation resulting in a high level of mononuclear cell infiltration in early granulation tissue by day 4 (Fig. 1). Collagen deposition and new tissue organization proceeded by day 11 with material remnants engulfed by giant cells. Mature granulation tissue was visible by day 18, accompanied by evidence of folliculogenesis in the neoepidermis, which might suggest regeneration and limited scarring.

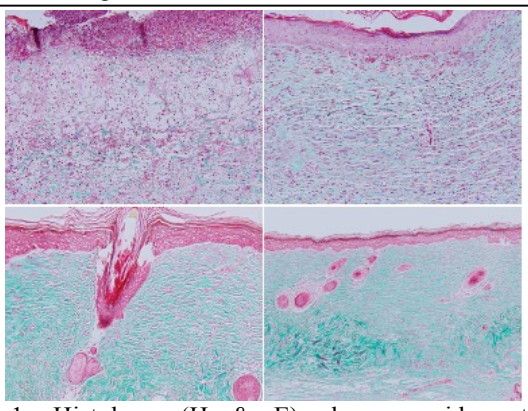

Fig 1. Histology (H & E) shows rapid material degradation, cellular infiltration, & mature granulation tissue at days 4 (top left), 11 (top right), & 18 (bottom).

H & E-stained histological sections taken just after scaffold injection & curing show its porous structure and thorough adhesion of the material to the surrounding bone, as well as immediate infiltration of blood into the scaffold pores (Fig. 2). MicroCT images at 2, 4, & 6 weeks show progressive bone formation within the defect site, although material degradation cannot be discerned from these images. Further histological evaluation is currently underway to assess the rate of material degradation & bone mineralization in the bone defects.

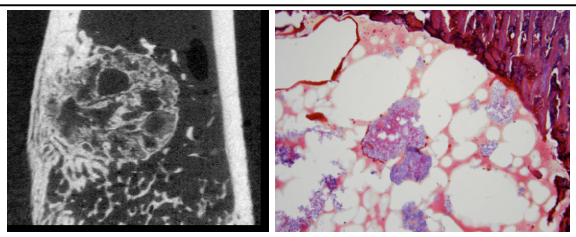

Fig 2. μCT shows new bone formation at 6 weeks (left). Histology shows thorough material-bone apposition (right).

Conclusions: These biodegradable PUR materials demonstrate potential as a template for regeneration of both skin and bone, with strength and material properties tunable for a specific application. To optimize the injectability, the isocyanate was re-formulated as an LTI-PEG prepolymer in order to avoid any possible monomeric isocyanate toxicity. In addition to providing a template for tissue regeneration, biologicals—including growth factors, antibiotics, small-molecule drugs—also may be incorporated in the scaffolds to enhance healing.

References: 1. Hafeman AE. *Pharm Res* 2008; 25: 2387.

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