Translation of Antibody-Polysaccharide Conjugates to Treating Burns in the Clinic

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Statement of Purpose: Over 60,000 Americans each year are hospitalized for treatment of burns. Partial-thickness burns can progress to full-thickness burns due to intrinsic inflammatory responses following the primary injury. Strategies for locally controlling inflammation could result in improved healing and reduced need for skin grafts. We demonstrate in a rat burn model that monoclonal antibodies against tumor necrosis factor-α (TNF-α) conjugated to high molecular weight polysaccharides are capable of rescuing viable tissue from burn-induced necrosis. This technology is being commercialized by an NIH-funded spin-off company from Carnegie Mellon University. This presentation will highlight research advances in biomaterial strategies for controlling inflammation and discuss the opportunities and challenges in applying these as a burn treatment.

Methods: Hyaluronic acid derived from Streptococcus equi (~1.6 MDa; Sigma, St. Louis, MO) or sodium alginate (~100 kDa; Sigma) were conjugated to rat anti-mouse anti-TNF-α monoclonal antibody (R&D Systems, Minneapolis, MN) were conjugated using carbodiimide coupling via established protocols.[1] Partial-thickness burns were induced on the backs of shaved, anesthetized Sprague-Dawley rats by pressing a 1 cm brass disk heated to 85 C for 10 s against the skin. One day following injury, animals were re-anesthetized and the eschar was removed. Antibody conjugates or saline controls were applied to the site and an occlusive bandage was placed over the injury. Tissues were recovered at 1, 4, and 7 days following primary injury for histological and biochemical analyses.

Results: Partial-thickness burns that were treated with saline solution showed significant progression toward full-thickness burns in the majority of animals treated. Extensive necrosis was observed in previously viable tissue, as shown in Figure 1.

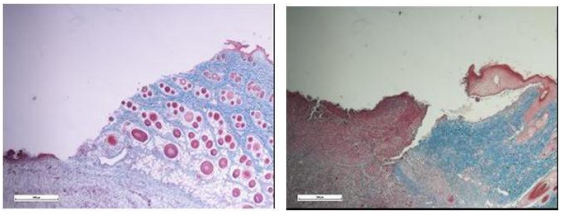

Figure 1. Partial-thickness burn treated with saline solution at day 1 (left) and day 4 (right).

Application of 50 μg anti-TNF-α conjugated to hyaluronic acid resulted in decreases in the extent of necrosis observed in the treated sites, as shown in Figure 2.

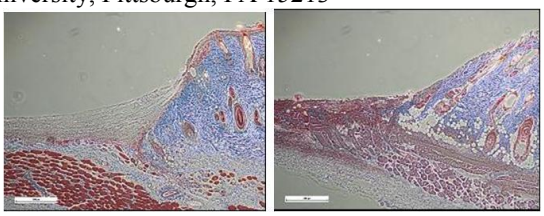

Figure 2. Partial-thickness burn treated with (anti-TNF-α)-HA solution at day 1 (left) and day 4 (right).

Analysis of interleukin-1β concentrations suggests that neutralization of TNF-α is actively reducing the state of inflammation at the injury site, as shown in Figure 3.

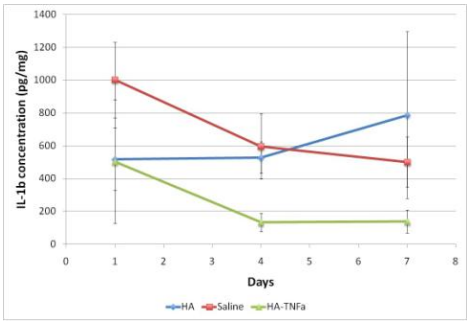

Figure 3. ELISA analysis of IL-1β concentration from burn sites treated with saline, HA, and (anti-TNF-a)-HA conjugates.

Conclusions: We hypothesize that conjugation of cytokine-neutralizing antibodies to high molecular weight polysaccharides localizes the antibodies to the site of application due to the slow polysaccharide diffusion. Local cytokine neutralization could be an important strategy for treating a broad range of conditions with strong underlying inflammatory components, including burns, chronic wounds, and osteoarthritis. This presentation will discuss the biochemical basis for the effects of these biomaterials and discuss efforts at translation of the technology into the clinic, including intellectual property, regulatory approval, fund-raising, and partnering with established producers of anti-TNF-α.

References:

1. Sun, L. T. et al. *Cytokine Binding by Polysaccharide-Antibody Conjugates.* **Wound Rep Regen** 2010;18: 302-10.