Dynamic Biomaterials for Healing Chronic Wounds

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Statement of Purpose: Chronic wounds are largely a complication of the compromised, in that they are rarely observed in healthy individuals. (1) One in four diabetics will develop at least one chronic foot ulcer during their lifetime, although multiple wounds are common due to a staggering 70% rate of reoccurrence. (2) These wounds carry a significant economic burden, with an estimated $9 billion spent on diabetic wound treatment in 2001, and over $25 billion spent annually on chronic wound care in general.(1)

These wounds generally arise from a heterogeneous combination of intrinsic and extrinsic factors.(3) One causative factor has been shown to be disruption of the highly synchronized cytokine signaling normally associated with acute wound healing. This results in an over- and underexpression of a wide variety of molecules, along with disruption of the temporal signaling sequence.(4, 5) Here, we explore the use of electrostatically assembled layer-by-layer (LbL) films to temporally control the release of multiple wound healing growth factors, which we hypothesize will enhance healing compared to single, bolus released therapeutics.

Methods: Therapeutic LbL films were assembled on woven nylon wound dressings using a programmable slide stainer. Poly- β -amino ester, poly(acrylic acid), platelet derived growth factor (PDGF), vascular endothelial growth factor (VEGF), and heparan sulfate were used during construction. Growth factor release kinetics were determined by degradation in 37°C PBS and quantified using sandwich ELISA. *In vitro* activity was determined using cell migration assays of human dermal fibroblasts and microvascular endothelial cells. Dressings were subsequently tested *in vivo* using full thickness skin wounds on db/db mice. Histological sections were taken to determine the impact of the therapeutic dressings compared to control dressings.

Results: LbL wound dressings display the ability to control the release kinetics of two therapeutic growth factors over the course of two weeks (Figure 1).

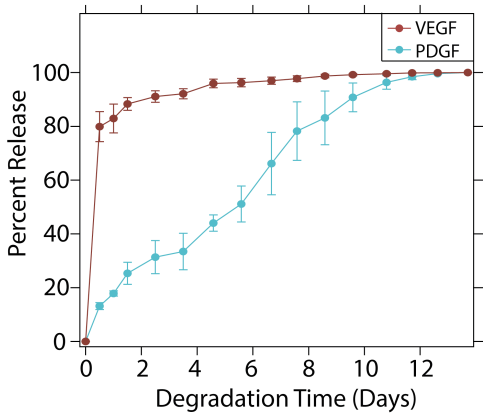

Figure 1. Release behavior of electrostatically assembled wound dressings.

The encapsulated growth factors remain active throughout the release process, with *in vitro* results showing the ability to promote cell migration compared to PBS controls (P>0.05). Growth factors released at 12 hours, 7 days, and 11 days show no significant difference in the degree of stimulated migration.

Genetically diabetic mice with impaired wound healing were subsequently tested to determine the *in vivo* impact of the therapeutic dressings compared to control dressings. Histological measurements indicate a significant increase in angiogenesis for treated wounds compared to controls (Figure 2). In addition, treated mice display increases in the amount of granulation tissue filling the wound at both 7 days (P>0.1) and 14 days (P>0.001).

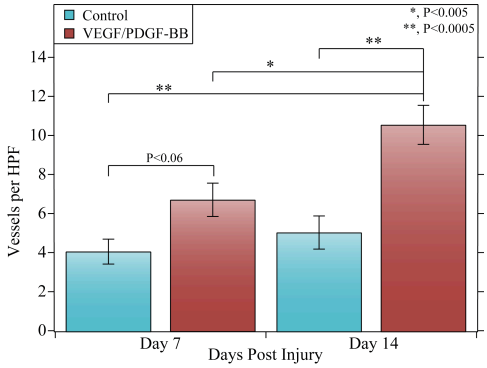

Figure 2. Impact of therapeutic wound dressings on angiogenesis in the wound bed.

Conclusions: We have demonstrated the ability to create therapeutic wound dressings that display temporal modulation of VEGF and PDGF release. These dressings begin to recreate the dynamic healing process observed in acute wound healing. In db/db mice, the therapeutic dressings display increases in vessel formation and granulation tissue. Ongoing work is determining the impact of the temporal release sequence, along with synergistic benefits of modulated growth factor delivery.

References:

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