

## Electrospun polyurethane scaffolds: A biomimetic approach to preventing pathologic scarring

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Over 2.4 million Americans and tens of millions of patients worldwide suffer from hypertrophic scar contraction (HSc) following car accidents, house fires, military conflicts, and from cooking over open flames. HSc is a debilitating condition that results in disfigurement and decreased range of motion in affected joints. The current standard of care involves skin grafting with or without the placement of a collagen based, biodegradable, bioengineered skin equivalent (BSE). Present BSEs assist in tissue regeneration, but do not focus on mitigating the debilitating effects of HSc. To overcome this significant unmet medical need, we have created a biomimetic, polyurethane (PU) based BSE that will last throughout the remodeling phase of repair. In unwounded skin, native collagen is arranged randomly, elastin fibers are abundant, myofibroblasts are absent, and matrix stiffness is low. Conversely, in scar contractures, collagen is arranged in linear arrays and elastin fibers are few, while myofibroblast density and matrix stiffness are high. The electrospinning process allowed us to create scaffolds with randomly-oriented fibers that will promote random collagen deposition and prevent myofibroblast formation, and subsequent contracture. Electrospun PU scaffolds were generated, characterized for their mechanical properties, and then tested *in vitro* and *in vivo*. *In vitro* fibroblast ingrowth and scar contraction were compared between the scaffold and a fibroblast populated collagen lattice (FPCL; the FPCL is a 3-dimensional *in vitro* model of wound healing that is the progenitor for present-day BSEs). The scaffolds supported fibroblast ingrowth and proliferation analogous to the FPCL. Fibroblasts in the scaffold displayed random nuclear alignment; conversely, fibroblasts in FPCLs became aligned during over several days in culture. After seven days of culture, the scaffold contracted only 8% whereas the FPCL contracted 66%. Furthermore, there were significantly fewer myofibroblasts present in the scaffold as compared to the FPCL. To provide proof-of-concept that the BSE reduces HSc *in vivo*, we surgically inserted scaffolds beneath skin grafts in a validated immune competent murine HSc model. The BSE was found to limit HSc to 6 +/- 0.2%, whereas wounds treated with the clinical standard (Integra™) contracted 65 +/- 5%, and control scars contracted 68 +/- 4%. Skin grafts were healthy and the BSE was found to promote fibroblast invasion, angiogenesis, and macrophage recruitment. Together our *in vivo* and *in vitro* data suggest that biomimetic electrospun scaffolds provide mechanical support to prevent wound bed contraction during healing, and can prevent fibroblast alignment and myofibroblast activation associated with HSc. Our long-term goal is to develop a rationally designed, translational medical therapy to inhibit HSc.

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