ROS Degradable Polythioketal Urethane Foam Dressings Promote Porcine Ischemic Wound Repair

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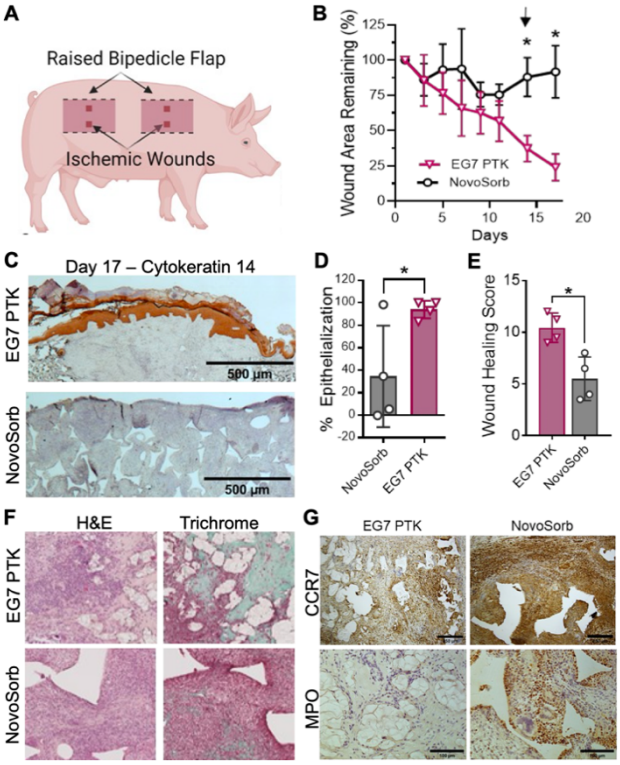
Statement of Purpose: We previously developed a class of reactive oxygen species (ROS) responsive polythioketal urethane (PTK-UR) foam dressings capable of promoting wound healing. These foams overcome the limitations associated with hydrolytically-degradable wound dressings, which are susceptible to autocatalytic degradation and biomaterial-associated inflammation[1,2,3,4]. Recently, we studied the effects of PTK-UR scaffold hydrophilicity by varying the ethylene glycol (EG) content within the polymer backbone. This library of foams was screened in a non-ischemic porcine wound model, identifying the most hydrophilic scaffold (EG7) as the lead candidate[4]. This work aims to evaluate EG7 PTK-UR foams in a chronic wound environment while comparing our lead material against a clinical dermal substitute. We hypothesize that utilizing hydrophilic EG7 PTK-UR foam dressings in ischemic excisional wounds will promote favorable scaffold resorption by scavenging ROS while simultaneously minimizing the material-associated inflammatory response ultimately promoting improved tissue repair in a challenged wound model.

Methods: A PTK diol was synthesized containing a ROS responsive thioketal group flanked by seven ethylene glycol repeat units (EG7). Foams were fabricated through a liquid reactive molding technique in which EG7 was reacted with lysine triisocyanate to yield a porous foam-like scaffold. EG7 PTK-UR scaffolds were evaluated in vivo in an ischemic full-thickness porcine wound model. Briefly, four bipedicle ischemic flaps were raised on the dorsum of Yorkshire pigs in which 1 cm^2 full-thickness excisional wounds were placed and treated with either EG7 PTK-UR or a clinical dermal substitute to assess the quality of tissue repair in an impaired healing model (Fig. A)[1]. EG7 PTK-UR foams were compared against NovoSorb BTM, an FDA-approved polyurethane dermal substitute[5]. Wound area was tracked throughout the study, and the quality of wound healing (inflammation, granulation tissue, vascularization, epithelialization, and collagen deposition) was evaluated blindly by a pathologist using H&E and Masons Trichrome. The individual scores associated with each of the five categories of wound grading were summed into a total wound healing score. In addition, immunohistochemistry was conducted to evaluate re-epithelialization (Cytokeratin 14) as well as the presence of macrophages (CCR7) and neutrophils (Myeloperoxidase - MPO) associated with the biomaterial 17 days post-implantation.

Results: Following 17 days, the ischemic wounds treated with EG7 PTK-UR demonstrated significantly faster closure rates than NovoSorb. EG7 PTK-UR treated wounds resulted in an average of 76.1% closure, while NovoSorb only achieved 8.3% closure (Fig. B). In addition



to accelerated wound closure, EG7 PTK-UR treated wounds also achieved nearly complete re-epithelialization, while NovoSorb treated wounds achieved an average of less than 40% re-epithelialization (Fig. C and D). Histological analysis of the treated wounds at day 17 illustrated decreased inflammation and improved collagen deposition associated with EG7 PTK-UR relative to NovoSorb, ultimately resulting in an improved composite wound healing score (Fig. E and F). Further analysis of the inflammatory response associated with EG7 and NovoSorb via IHC indicated an increased density of both macrophages (CCR7) and neutrophils (MPO) associated with NovoSorb treated ischemic wounds as compared to EG7 PTK-UR treated wounds (Fig. G), demonstrating the less inflammatory nature of the EG7 versus traditional, hydrolytically-degradable wound dressings.

Conclusion: ROS responsive EG7 PTK-UR foam dressings have improved wound healing compared to the clinical dermal substitute NovoSorb in a challenged ischemic wound model, ultimately decreasing the material associated inflammatory response while promoting granulation tissue formation and restoration of the epithelium.

References: [1] Patil P. Tissue Eng Part C Methods. 2017;23(11):654-762 [2] Martin JR. Adv Healthc Mater. 2016;5(21):2751-2757 [3] Martin JR. Biomaterials. 2014;35(12):3766-76 [4] Patil P. bioRxiv. 2021 [5] Greenwood JE. J Burn Care Res. 2012;33(1):7-19