Title: Wnt signaling inhibition promotes wound healing and inhibits fibrosis in chronic wounds

Wnt signaling is activated following acute cutaneous injury and promotes fibrotic wound healing. Topical application of Wnt signaling inhibitors promotes regenerative cutaneous repair following acute injury. However, there is a gap in our understanding of Wnt signaling activation in chronic non-healing human wounds. This work is focused on delineating the impact of canonical Wnt signaling modulation in chronic wounds. Preliminary studies in our lab have shown that full-thickness excisional wounds in Streptozotocin (STZ)-induced type I diabetic mice activated Wnt signaling in both dermal and epidermal layers, as identified by β-catenin immunostaining and **AXIN2** transcript levels. Treatment with Wnt signaling inhibitors promoted regenerative repair following excisional wounds. Analysis of a panel of human chronic wound pathologies by immunofluorescence staining demonstrated that β-catenin is highly expressed in human chronic wounds, including decubitus ulcers and diabetic wounds. β-catenin protein was co-localized with **αSMA**-expressing myofibroblasts but was not present in endothelial or immune cells. To understand the cellular mechanism of Wnt signaling modulation in Wnt-responsive chronic wounds, we treated human diabetic fibroblasts with Wnt signaling inhibitors and performed Western blot analysis for active β-catenin protein. Wnt signaling inhibitors **ICG-001** and **XAV-939** inhibited the expression of a pro-fibrotic protein, **Collagen 1a1**, along with active β-catenin. **ICG-001** and XAV-939 also inhibited diabetic fibroblast proliferation while marginally affecting normal fibroblasts. These results suggest that Wnt signaling inhibitors could be utilized for the treatment of Wnt-responsive chronic wounds. Our future work will focus on identifying the cellular and molecular players of fibrotic wound healing in chronic wounds that can be modulated by Wnt signaling inhibitors. Our studies will pave the way for the use of Wnt signaling inhibitors in selective, personalized therapy for chronic wounds.