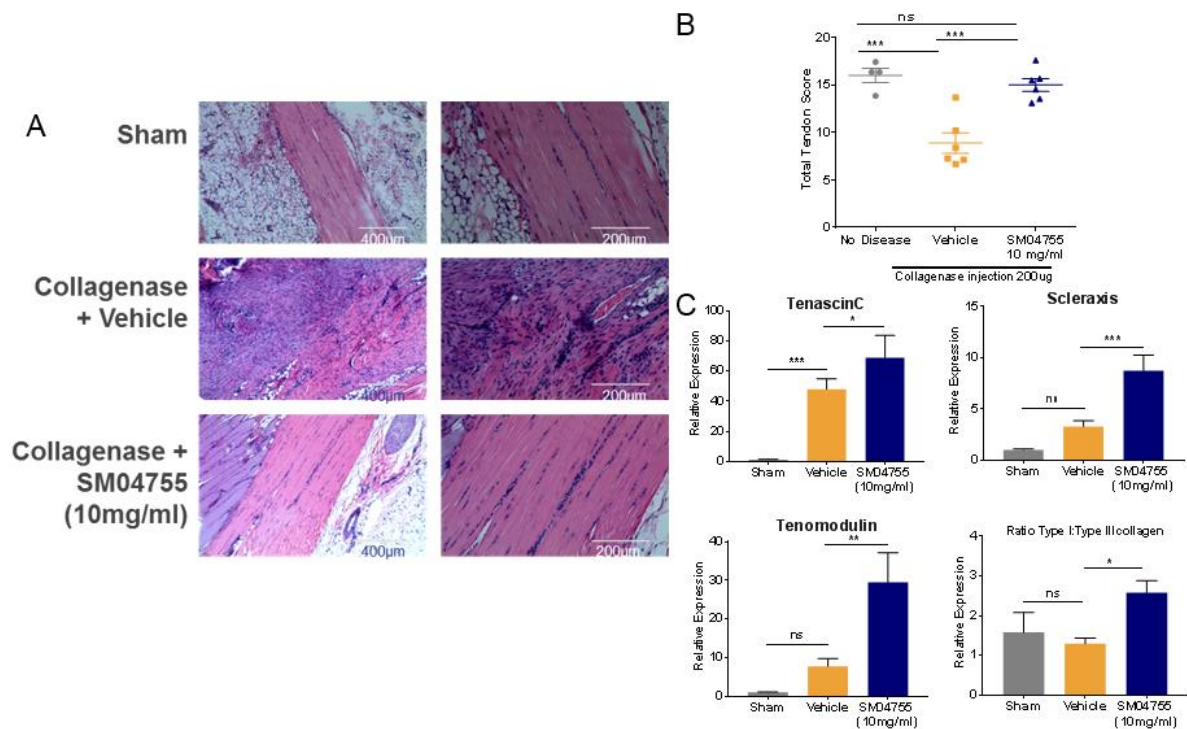


DISCOVERY OF A SMALL MOLECULE WNT PATHWAY INHIBITOR (SM04755) AS A POTENTIAL TOPICAL TREATMENT FOR TENDINOPATHY

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Introduction: Tendinopathy is an inflammatory, degenerative condition with increased Wnt signalling. SM04755, a topical, small-molecule Wnt pathway inhibitor, was evaluated for its potential to inhibit inflammation and induce tenocyte differentiation. **Methods:** *In vitro* SM04755 anti-inflammatory effect on cytokines was measured by ELISA in lipopolysaccharide (LPS)- and anti-CD3/anti-CD28-stimulated peripheral blood mononuclear cells (PBMCs). Differentiation of human mesenchymal stem cells (hMSCs) and rat tendon derived stem cells (rTDSCs) to tenocytes was measured by histology for tenocyte markers scleraxis A, tenomodulin and tenascin C. Pharmacokinetics were evaluated after topical application of product in rats. *In vivo* SM04755 efficacy was evaluated in a collagenase injection rat tendinopathy model by histology, chemokine ligand 1 (CXCL1) plasma levels and inflammatory markers. Tendon regeneration was assessed by tenocyte marker expression and Type I:III collagen ratio using qPCR. **Results:** SM04755 inhibited cytokine secretion in stimulated PBMCs ($EC_{50}=600nM$). SM04755 induced tenocyte marker expression in differentiated hMSCs and rTDSCs ($EC_{50}=200nM$). Topical SM04755 resulted in tendon concentrations $>EC_{50}$ $>24hrs$, with minimal systemic exposure or toxicity. In the collagenase injection model, SM04755 significantly increased tendon health score ($p<0.01$) (fig. 1A/B); decreased plasma CXCL1 ($p<0.05$) and inflammatory marker gene expression ($p<0.05$); increased tenocyte marker expression ($p<0.01$) (fig. 1C) and Type I:III collagen ratio ($p<0.01$) compared to vehicle. **Conclusions:** Topical SM04755 reduced inflammation and showed evidence of tendon regeneration compared to vehicle. SM04755 has potential as a tendinopathy treatment.



SM04755 inhibited inflammation and promoted tendon healing in a rat collagenase-injection tendinopathy model

(A) Images of rat tendons stained with H&E from sham or collagenase-injected and vehicle- or SM04755 (0.3 mg/cm^2) treated rats on day 21. (B) Histological score of inflammation, linearity and density of tendon fibers, shape of tenocytes and hemorrhage for the rat tendons. Mean \pm SEM, $n=4$ sham, $n=6$ vehicle & SM04755, $**p<0.01$. (C) Expression of tenocyte markers and Type I:III collagen ratio in the tendon following sham or collagenase injection and vehicle or SM04755 (10 mg/ml) for 21 days measured by qRT-PCR. $n=12$, Mean \pm SEM, $** p<0.01$.