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A Small Molecule Inhibitor of the Wnt Pathway (SM04755) as a Potential Topical Treatment for Tendinopathy

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Purpose: Tendinopathy is an inflammatory and degenerative disorder. The Wnt pathway is upregulated in tendinopathy and involved in inflammation, fibrosis, and tenocyte differentiation. The effects of a topical Wnt pathway inhibitor, SM04755, in preclinical experimental tendinopathy are presented.

Methods: Wnt pathway inhibition was measured via cell-based reporter assay. Anti-inflammatory activity was evaluated by measuring TNF- α and IL-6 secretion from THP1 monocytes and peripheral blood mononuclear cells (PBMCs) using ELISA. Histological expression of Scleraxis A (SCXA), tenomodulin, and tenascin C measured human mesenchymal stem cells (hMSCs) to tenocyte differentiation. Skin pharmacokinetics was evaluated in rats, dogs, and mini-pigs. *In vivo* efficacy of 0.3 mg/cm² SM04755 was evaluated with single and multiple collagenase injection rodent tendinopathy models, by scoring tendon health. Inflammation was measured by plasma chemokine ligand 1 (CXCL1) levels and tendon cytokines. Tendon regeneration was evaluated by qPCR-based gene expression of SCXA, tenascin C, Type I and Type III collagen, and Sirius Red staining.

Results: SM04755 demonstrated potent Wnt signaling inhibition, inhibited TNF- α and IL-6 secretion, and induced hMSCs differentiation into SCXA-, tenomodulin-, and tenascin C-expressing tenocytes. Single topical SM04755 application resulted in tendon concentrations >EC₅₀ for up to 24 hours, with minimal systemic exposure. In collagenase injection tendinopathy models, SM04755 treatment improved tendon morphology (Figure A), significantly increased tendon health score (Figure B; p<0.01), decreased plasma CXCL1 levels (Figure C; p<0.05), reduced gene expression of pro-inflammatory cytokines (p<0.05), increased SCXA, tenascin C and Type I collagen expression (p<0.05), and Sirius Red stained collagen fibers in tendon compared to vehicle.

Conclusions: SM04755, a topical small-molecule Wnt pathway inhibitor, reduced tendon inflammation, promoted tendon regeneration, and increased tendon health scores compared to vehicle in a rodent tendinopathy model. SM04755 has potential as a therapeutic intervention for tendinopathy. Clinical studies are planned.

Figure. SM04755 inhibited inflammation and promoted tendon healing in a rat collagenase-induced tendinopathy model

