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

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Background: Tendinopathy is an inflammatory and degenerative disorder caused by injuries or overuse. It can progress to a chronic condition with failed healing, tendon fibrosis and micro-tears that lead to pain and sometimes rupture. Current therapeutic options focus mainly on pain relief rather than treatment of underlying disease. The Wnt pathway is upregulated in tendinopathy and has an important role in inflammation, fibrosis and tenocyte differentiation.

Objectives: SM04755, a novel, topical Wnt pathway inhibitor, was evaluated in preclinical studies to determine its potential to inhibit inflammation, reduce fibrosis and increase tenocyte differentiation, thereby promoting tendon healing.

Methods: Anti-inflammatory activity was measured by TNF-α and IL-6 secretion using ELISA in lipopolysaccharides (LPS) or anti-CD3/anti-CD28 stimulated peripheral blood mononuclear cells (PBMCs). Differentiation of human mesenchymal stem cells (hMSCs) and rat tendon derived stem cells (rTDSCs) into tenocytes was measured by high-content imaging for tenocyte markers scleraxis A (SCXA), tenomodulin and tenascin C. Pharmacokinetics were evaluated following topical application in rats. In vivo efficacy of SM04755 was evaluated in a single injection, collagenase-induced acute rodent tendinopathy model and a chronic, multiple injection, failed healing model, by scoring histological indicators of tendon health. Inflammation was measured by chemokine ligand 1 (CXCL1) levels in plasma by ELISA and pro-inflammatory markers (IL-6, TNF-α, IL-1β, INF-γ, IL-8) in the tendon by qPCR. Tendon regeneration and healing were evaluated by qPCR based gene expression of tenocyte differentiation markers SCXA, tenomodulin and tenasin C, Type I/Type III collagen ratio and polarized light microscopy using Sirus Red staining. Pain in the rodent model was evaluated by measuring weight distribution with an incapacitance meter.

Results: SM04755 potently inhibited cytokine secretion in LPS and anti-CD3/anti-CD28 stimulated PBMCs (EC_{50}=500nM). SM04755 induced expression of tenocyte markers in differentiated hMSCs and rTDSCs (EC_{50}=200nM). A single topical application of SM04755 resulted in tendon concentrations >EC_{50} for up to 24hrs, with minimal systemic exposure or toxicity. In both the acute and failed healing tendinopathy models, SM04755 (10mg/ml) treatment improved tendon morphology (Figure A), significantly increased mean tendon health score (p<0.01), decreased plasma levels of CXCL1 (p<0.05) and reduced gene expression of pro-inflammatory markers (IL-6, TNF-α, IL-1b, INF-g, IL-8; p<0.05) compared to vehicle. SM04755 treatment promoted tendon regeneration measured as increased expression of tenocyte markers (p<0.05), increased Type I/Type III collagen ratio (Figure B; p<0.01) and Sirus Red stained collagen fibers in tendon compared to vehicle. SM04755 treatment increased % total weight bearing on the affected limb (p<0.01), at multiple time points (Figure C), indicating reduced pain in the rodent model.
Conclusions: Topical SM04755, a Wnt pathway inhibitor, reduced inflammation, promoted tendon regeneration and healing, and reduced pain compared to vehicle in rodent tendinopathy models. SM04755 is a potential treatment for tendinopathy. Clinical studies are in progress.