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

Author Block: V. Deshmukh, T. Seo, M. Ibanez, B. Hofilena, S. KC, L. Dellamary, J. Stewart, J. Hood, Y. Yazici; Samumed, San Diego, CA

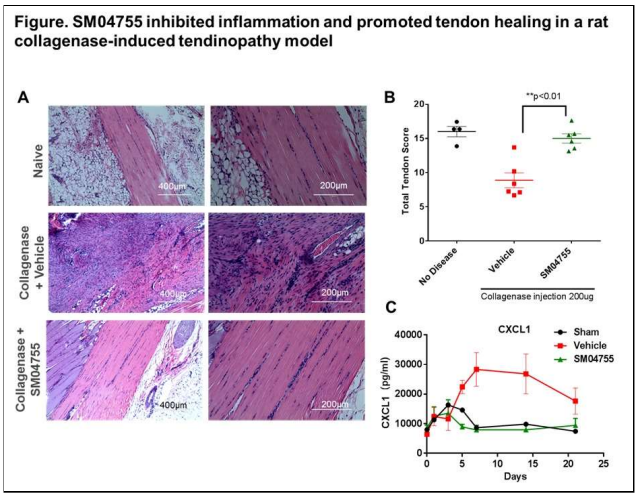
Abstract:

Purpose: Tendinopathy is an inflammatory and degenerative disorder caused by injuries or overuse. Tendinopathy can progress to a chronic condition with tendon fibrosis and micro-tears that lead to pain and sometimes rupture. Current therapeutic options focus on pain alleviation. Stem cell and growth factor treatments are under investigation, but have not established safety or efficacy. No agent currently induces tendon healing and prevents fibrosis. The Wnt pathway is upregulated in tendinopathy and plays an important role in inflammation, fibrosis and tenocyte differentiation. SM04755, a novel, topical, small molecule 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: Wnt pathway inhibition was measured via cell-based reporter assay and qPCR. Anti-inflammatory activity was evaluated by measuring TNF-α and IL-6 secretion using ELISA in lipopolysaccharides (LPS) stimulated THP1 monocytes and antiCD3/antiCD28 stimulated peripheral blood mononuclear cells (PBMCs). Histological expression of scleraxis A (SCXA), tenomodulin, and tenascin C were measured using high-content imaging to evaluate differentiation of human mesenchymal stem cells (hMSCs) to tenocytes. Pharmacokinetics were evaluated by topical application in rats, dogs and mini-pigs, followed by analysis of compound concentrations in tendon and plasma. *In vivo* efficacy of topical SM04755 was evaluated in an intra-tendon collagenase-induced rodent tendinopathy model, using both single and multiple collagenase injection conditions, by scoring (range 5-20) several histological indicators of tendon health. Inflammation in the rodent model was measured by chemokine ligand 1 (CXCL1) levels in plasma by ELISA and pro-inflammatory markers (IL-6, TNF-α, IL-1β, IFN-γ, IL-8) in the tendon by qPCR. Tendon regeneration was evaluated by qPCR based gene expression of tenocyte differentiation markers SCXA and tenascin C. Tendon healing was evaluated by measuring the ratio of Type I to Type III collagen by qPCR as well as polarized light microscopy using Sirus Red staining.

Results: SM04755 demonstrated potent (EC50~152nM) and selective inhibition of Wnt signaling. SM04755 inhibited both LPS and antiCD3/antiCD28 induced TNFα and IL6 secretion (EC50~500nM) in THP1 cells and PBMCs, respectively. SM04755 induced differentiation of hMSCs into SCXA, tenomodulin, and tenascin C expressing tenocytes (EC50~200nM). A single topical application of SM04755 resulted in tendon concentrations >EC50 for up to 24hrs, with minimal systemic drug exposure or toxicity. In both the single and multiple injection collagenase-induced tendinopathy models, SM04755 treatment improved tendon morphology (Figure A), significantly increased mean tendon health score (Figure B; n=6, $p<0.01$), decreased plasma levels of CXCL1 (Figure C; $p<0.05$), reduced gene expression of pro-inflammatory markers ($p<0.05$), and increased expression of SCXA and tenascin C in tendon compared to vehicle ($p<0.05$). Additionally, SM04755 treatment increased the gene expression of Type I collagen ($p<0.01$) and Sirus Red stained collagen fibers compared to vehicle.

Conclusions: Upregulated Wnt signaling has been implicated in tendon inflammation and fibrosis in tendinopathy. Topically applied small-molecule Wnt inhibitor, SM04755 reduced tendon inflammation, showed evidence of tendon regeneration, and increased tendon health scores compared to vehicle in a rodent tendinopathy model. Plasma exposure was minimal, with no systemic toxicity. These data suggested that SM04755 has potential as a therapeutic intervention for tendinopathy. Clinical studies are in progress.



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Osteoarthritis Research Society International
1120 Rt. 73, Ste. 200
Mt. Laurel, NJ 08054, USA
vconverse@oarsi.org

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