

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

Vishal Deshmukh, Timothy Seo, Maureen Ibanez, Josh Stewart and Yusuf Yazici
Samumed, LLC, San Diego, CA, USA

Corresponding Author- Yusuf Yazici,
Samumed, LLC, San Diego, CA, USA
yusuf@samumed.com

Aim:

Tendinopathy is an inflammatory, degenerative condition caused by injuries or overuse. The Wnt pathway, upregulated in tendinopathy, plays an important role in tenocyte differentiation. SM04755, a novel, small-molecule Wnt pathway inhibitor, was evaluated in preclinical studies to determine its potential to inhibit inflammation and induce tenocyte differentiation, thereby promoting tendon healing.

Methods:

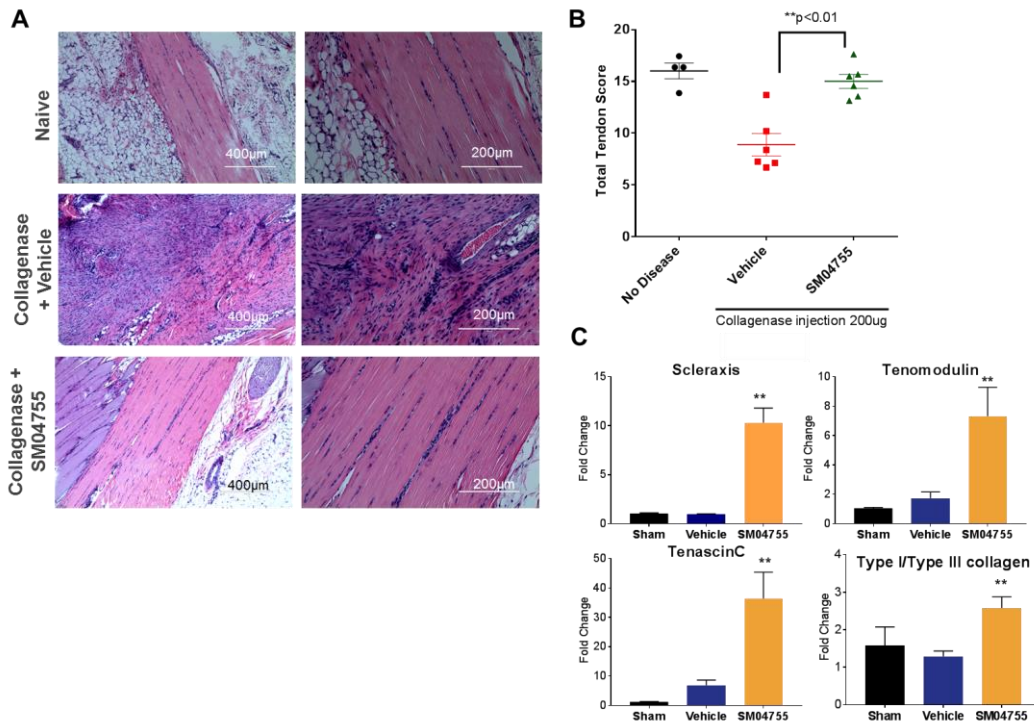
Wnt pathway inhibition was measured via cell-based reporter assay. Anti-inflammatory activity was evaluated by cytokine secretion using ELISA in lipopolysaccharides (LPS)- and anti-CD3/anti-CD28-stimulated peripheral blood mononuclear cells (PBMCs). Differentiation of human mesenchymal stem cells (hMSCs) and rat tendon derived stem cells (rTDSCs) to tenocytes was measured by immunocytochemistry for tenocyte markers scleraxis A, tenomodulin and tenascin C. Pharmacokinetics were evaluated following topical application in rats. *In vivo* efficacy of topical SM04755 was evaluated in an intra-tendon collagenase-induced rodent tendinopathy model by tendon histology, chemokine ligand 1 (CXCL1) plasma levels, tendon inflammatory markers, and tendon regeneration, by expression of tenocyte markers and Type I/Type III collagen ratio using qPCR.

Results:

SM04755 was a potent ($EC_{50}=152\text{nM}$) inhibitor of Wnt signaling in hMSCs, and cytokine secretion in LPS and anti-CD3/anti-CD28 stimulated PBMCs ($EC_{50}=500\text{nM}$). SM04755 induced expression of tenocyte markers in differentiated hMSCs and rTDSCs ($EC_{50}=200\text{nM}$). Single topical application of SM04755 resulted in tendon concentrations $>EC_{50}$ for up to 24hrs, with minimal systemic exposure or toxicity. In the intra-tendon collagenase injection-induced model, SM04755 treatment significantly increased tendon health score ($p<0.01$) (figure 1A, 1B), decreased plasma CXCL1 ($p<0.05$), reduced gene expression of pro-inflammatory markers (IL-6, TNF- α , IL-1 β , INF- γ , IL-8) ($p<0.05$), increased expression of tenocyte markers ($p<0.01$) (figure 1C) and improved Type I/Type III collagen ratio ($p<0.01$) in tendon compared to vehicle.

Conclusions:

Topical SM04755 reduced inflammation and showed evidence of tendon regeneration compared to vehicle. SM04755 has potential as a therapeutic intervention for tendinopathy. Clinical studies are planned.



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

(A) Images of rat tendons stained with H&E from sham or collagenase-injected and vehicle- or SM04755 (0.3 mg/cm²) 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 treatment with either vehicle or SM04755 (0.3 mg/cm²) for 21 days as measured by qRT-PCR. n=12, Mean \pm SEM, ** p<0.01.