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

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My abstract has been or will be presented at a scientific meeting during a 12 months period prior to EULAR 2017: Yes

Abstract presented or will be presented at (meeting): American College of Rheumatology

Is the first author applying for a travel bursary and/or an award for undergraduate medical students?: No

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.

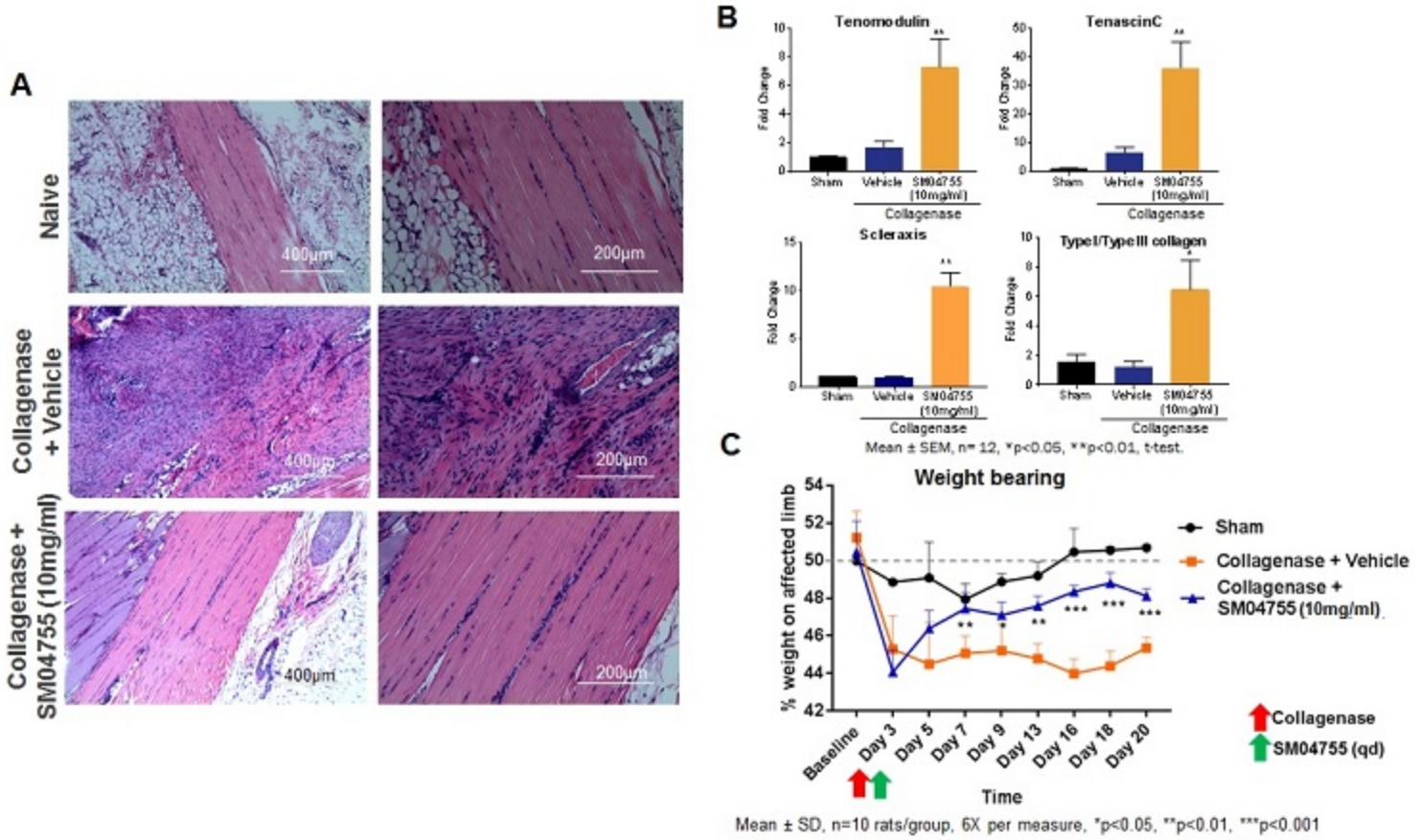
Objectives: SM04755, a novel, topical Wnt pathway inhibitor, was evaluated in preclinical studies to determine its potential to inhibit inflammation, reduce fibrosis and increase tenocyte differentiation, thereby promoting tendon healing.

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, IFN-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 tenascin 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-a, 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.

Image/graph:

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

Disclosure of Interest: V. Deshmukh Shareholder of: Samumed, LLC, Employee of: Samumed, LLC, T. Seo Shareholder of: Samumed, LLC, Employee of: Samumed, LLC, M. Ibanez Shareholder of: Samumed, LLC, Employee of: Samumed, LLC, J. Stewart Shareholder of: Samumed, LLC, Employee of: Samumed, LLC, B. Hofilena Shareholder of: Samumed, LLC, Employee of: Samumed, LLC, Y. Yazici Shareholder of: Samumed, LLC, Employee of: Samumed, LLC