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SM04690, a Wnt Pathway Inhibitor: Anti-Inflammatory and Cartilage Protective Effects in Preclinical OA Models

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Purpose: Osteoarthritis (OA) is characterized by pain, swelling, and reduced function in the knee joint. Upregulated Wnt signaling drives OA through synovial inflammation, increased subchondral bone, and thinning cartilage. SM04690, a small molecule Wnt pathway inhibitor that demonstrated chondrogenic and anti-inflammatory properties preclinically,[1] was further evaluated to determine its potential to reduce inflammation, protect cartilage, improve joint health, and modify pain in OA.

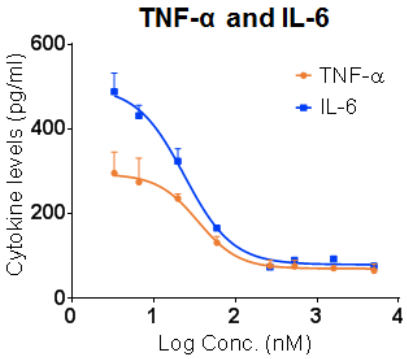
Methods: Cytokine secretion (IL-6 and TNF-α) from IL-1β-stimulated and SM04690-treated synovial fibroblasts was measured by ELISA. A single intra-articular injection of SM04690 or vehicle was evaluated in an *in vivo* rat knee monosodium iodoacetate (MIA) OA model. Joint inflammation was evaluated by H&E staining, inflammatory cytokines (IL-1α, IL-1β, IL-6, TNF-α, and IFN-γ) by qPCR, and cartilage protection by qPCR for matrix metalloproteinases (MMPs). Histological evaluation of cartilage health was performed using OARSI score and thickness by Safranin-O staining. Pain was measured as paw withdrawal threshold using Von Frey apparatus and weight distribution using incapacitance meter and analyzed using generalized estimating equation regression.

Results: SM04690 dose-dependently inhibited IL-1β-induced cytokine secretion in synovial fibroblasts (EC_{50} ~ 30 nM; Fig.1). In the rat MIA OA model, compared to vehicle, SM04690 injection reduced visible knee swelling, inflammatory cells, and proinflammatory cytokine and MMP production ($p<0.05$). SM04690 increased ($p<0.01$) paw withdrawal threshold from Day 6 and improved weight distribution to the affected limb in treated rats, at multiple timepoints, compared to vehicle. SM04690 increased Safranin-O stained cartilage thickness and decreased OARSI score ($p<0.05$) compared to vehicle (Fig. 2).

Conclusion: In a rat MIA OA model, SM04690 injection reduced inflammation, protease production, and pain, with improved cartilage and joint health, compared to vehicle. Previously demonstrated regenerative effects in nonclinical studies[1], along with anti-inflammatory properties, show SM04690 may improve symptoms and potentially provide disease modification in OA. Clinical studies are ongoing.

[1]Deshmukh et al. *OAC* 2017

Figure 1. SM04690 inhibited inflammatory cytokine production in synovial fibroblasts *in vitro*



IL-6 EC_{50}= 24nM; TNF-α EC_{50}= 35nM

0.3 µg

Figure 2. SM04690 inhibited inflammatory cytokine production and decreased inflammation and pain in the MIA model of OA