

DISCOVERY OF A SMALL MOLECULE WNT PATHWAY INHIBITOR (SM04690) AS A POTENTIAL DISEASE MODIFYING TREATMENT FOR KNEE OSTEOARTHRITIS

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Aim:

Wnt signaling affects pathogenesis of osteoarthritis (OA) by regulating stem cell differentiation that results in cartilage thinning and increased subchondral bone. SM04690, a novel, small-molecule Wnt pathway inhibitor was evaluated *in vitro* to determine its ability to augment chondrogenesis and in a preclinical OA model to prevent cartilage deterioration and improve joint health.

Methods:

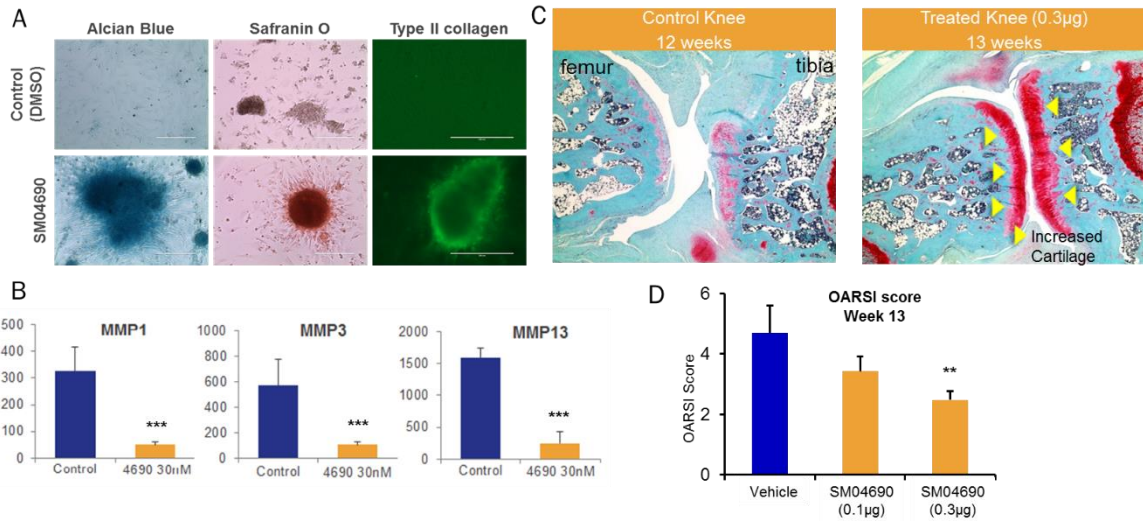
Wnt pathway inhibition was measured using a cell-based reporter assay. Chondrogenesis was histologically evaluated using differentiation of human mesenchymal stem cells (hMSCs) to chondrocytes. Protease release from chondrocytes and cytokine release from synovial fibroblasts was measured by qRT-PCR and ELISA. Pharmacokinetics were evaluated by intra-articular (IA) injection in rats, followed by analysis of SM04690 concentrations in joints and plasma. Safety evaluations included clinical observation and histopathology. *In vivo* efficacy was measured in a rodent model of knee OA by histological evaluation, using Osteoarthritis Research Society International (OARSI) score and biomarker measurement.

Results:

SM04690 was a potent ($EC_{50} \cong 3nM$) inhibitor of Wnt signaling, and significantly increased the differentiation of hMSCs ($EC_{50} \cong 30nM$) into mature and functional chondrocytes (figure 1A). SM04690 inhibited matrix metalloprotease release (figure 1B) from chondrocytes and cytokine release (CAN YOU LIST THE CYTOKINES- $TNF\alpha$, $IL1\beta$, $IL5$, $IL6$, $IL8$ and $IL17$) from synovial fibroblasts. One IA injection of SM04690 resulted in joint concentrations $>EC_{50}$ for >180 days, with no detectable systemic exposure or toxicity up to $>1400X$ the therapeutic dose. This dose also inhibited Wnt signaling *in vivo* and in the rodent model of knee OA, it increased cartilage thickness (figure 1C), resulting in significantly reduced OARSI scores (** $p < 0.01$; figure 1D) and OA biomarkers compared to vehicle.

Conclusions:

In a rodent model of knee OA, an IA injection of the Wnt pathway inhibitor SM04690 induced chondrogenesis, inhibited protease and cytokine production, and improved cartilage health compared to vehicle, with no detectable exposure in plasma or systemic toxicity. SM04690 has potential as a disease modifying therapy for OA.



SM04690 induced chondrogenesis and protected cartilage

(A) hMSCs treated with either DMSO or SM04690 (30nM) for 21 days and stained for various markers of mature chondrocytes. (B) Gene expression of proteases in chondrocytes treated with TNF α (20ng/ml) + Oncostatin M (10ng/ml) and SM04690 (30nM) for 72hrs (n=3, Mean \pm SD, ***p<0.001). (C) Representative images of medial tibial plateau of the knee joint stained with Safranin O-Fast Green from naïve or vehicle treated or SM04690 (0.3µg) treated rats 13 weeks after surgery. (D) The medial tibial plateau joint score in the ACLT+pMMx model, based on the OARSI scoring system (n= 12 rats, Mean \pm SEM, **p<0.01)