Title

Discovery of a Small Molecule Inhibitor of the Wnt Pathway (SM04690) as a Potential Disease Modifying Treatment for Knee Osteoarthritis

Authors

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Purpose:

Wnt signaling affects the pathogenesis of osteoarthritis (OA) by regulating stem cell differentiation in joints, resulting in thinning cartilage and increased subchondral bone. SM04690, a novel, small-molecule Wnt pathway inhibitor was evaluated in a series of preclinical studies to determine its potential to induce chondrogenesis and improve joint health.

Materials and 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 were measured by qRT-PCR and ELISA. Pharmacokinetics were evaluated by intra-articular (IA) injection in rats and dogs, followed by analysis of compound 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 demonstrated potent (EC_{50}=3nM) and selective inhibition of Wnt signaling, and induced robust differentiation of hMSCs (EC_{50}=30nM) into mature and functional chondrocytes (**Figure-1**). SM04690 inhibited protease release from chondrocytes and cytokine release from synovial fibroblasts. Single IA injection of SM04690 (0.3µg) resulted in joint concentrations >EC_{50} for >180 days, with no detectable systemic exposure or toxicity up to >400X the expected clinical dose. This dose also inhibited the Wnt pathway *in vivo*, and was efficacious in the rodent model of knee OA, with increased cartilage thickness (**Figure-2**), evidence for regeneration and protection from cartilage catabolism observed, resulting in significantly reduced OARSI score and OA biomarkers ($p<0.01$) as compared to vehicle.

Conclusion:

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

Figure 1. SM04690 induces chondrogenesis in human mesenchymal stem cells

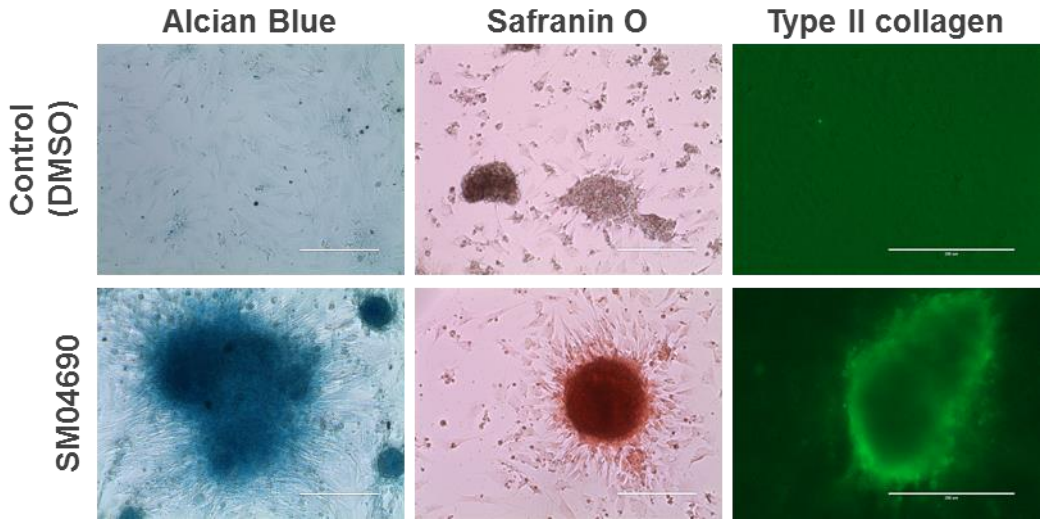

Figure 2. SM04690 increases cartilage thickness relative to control in rat instability model