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

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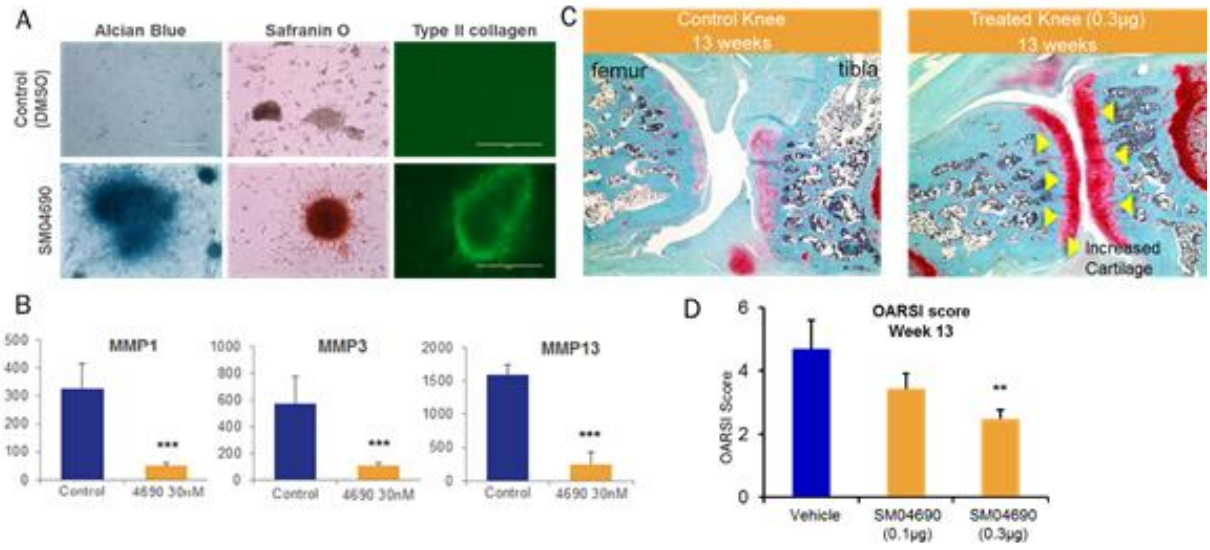
Introduction: Increased Wnt signaling in osteoarthritis (OA) affects differentiation of stem cells leading to cartilage thinning and osteophyte formation. SM04690, a small-molecule Wnt pathway inhibitor, was evaluated to determine its potential to induce stem cell chondrogenesis and improve joint health. **Methods:** SM04690 induced chondrogenesis from human mesenchymal stem cells (hMSCs) was evaluated by gene expression and histological staining. Release of proteases from chondrocytes and cytokines from synovial fibroblasts were measured by qRT-PCR and ELISA. Pharmacokinetics were evaluated by drug concentration analysis in rat knee joints and plasma after intraarticular (IA) injection. *In vivo* efficacy was measured in a rat knee OA model by histology using Osteoarthritis Research Society International (OARSI) score, and biomarker measurements. **Results:** *In vitro* SM04690 induced differentiation of hMSCs ($EC_{50}\cong$30nM) into mature functional chondrocytes (fig. 1A).SM04690 inhibited release of matrix metalloproteases (figure 1B) from chondrocytes and cytokines from synovial fibroblasts. Single IA injection of SM04690 resulted in joint concentrations >EC_{50} for >180 days, with no detectable systemic exposure or toxicity. *In vivo* SM04690 increased cartilage thickness (figure 1C), with evidence for cartilage regeneration and reduced catabolism, leading to significantly reduced OARSI scores ($p<0.01$; fig. 1D) and OA biomarkers compared to vehicle. **Conclusions:** In a rat knee OA model, SM04690 induced chondrogenesis, inhibited protease and cytokine release, 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 DMSO or SM04690 (30nM) for 21 days and stained for markers of mature chondrocytes. (B) Gene expression of proteases in chondrocytes treated with TNFα (20ng/ml) + Oncostatin M (10ng/ml) and SM04690 (30nM) for 72hrs (n=3, Mean ± 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 (12 weeks post treatment). (D) The medial tibial plateau joint score in the ACLT+pMMx model, based on the OARSI scoring system (n= 12 rats, Mean ± SEM, **p<0.01)*