Cartilage regeneration in a rat model of knee OA by SM04690, a potential disease modifying Wnt pathway inhibitor

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Introduction: Increased Wnt signaling in osteoarthritis (OA) leads to cartilage thinning and bone remodeling. SM04690, a small-molecule Wnt pathway inhibitor, was evaluated for potential to induce chondrogenesis, protect cartilage, limit inflammation, and improve joint health.

Methods: SM04690-induced chondrogenesis from human mesenchymal stem cells (hMSCs) was evaluated by qPCR and histology. *In vivo* efficacy was measured in a rat knee surgical OA model by histology (OARSI score) and biomarkers, and in the rat monosodium iodoacetate (MIA) injection-induced OA model by histology, ELISA for pro-inflammatory cytokines, and pain by paw withdrawal threshold using Von Frey apparatus.

Results: *In vitro,* SM04690 induced differentiation of hMSCs into mature, functional chondrocytes. In rat OA models, a single SM04690 intra-articular injection resulted in therapeutic concentrations >180 days, without detectable systemic exposure or toxicity. Compared to vehicle, SM04690 regenerated cartilage, decreased OARSI score ($p<0.05$), inhibited proteases ($p<0.05$) and improved OA biomarkers ($p<0.05$). In the MIA model, SM04690 inhibited inflammatory cytokine production ($p<0.05$) and increased paw withdrawal threshold ($p<0.05$).

Conclusions: Preclinically, SM04690 induced chondrogenesis, regenerated cartilage, inhibited protease release, improved cartilage health, and reduced inflammation and pain compared to vehicle. SM04690 has potential as a disease modifying therapy for OA.