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

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Background
- Knee osteoarthritis (OA) is characterized by degradation of articular cartilage, subchondral bone remodelling, synovitis, and inflammation.
- Increased Wnt signaling has been linked to inflammation and OA pathogenesis.12
- Samumed is developing a small molecule Wnt pathway inhibitor, SM04690, as a potential therapeutic administered as an intra-articular (IA) treatment for knee OA.
- In previous preclinical studies, SM04690 inhibited inflammation, decreased cartilage degradation, regenerated cartilage, and demonstrated sustained local exposure with no observed systemic toxicity.3
- The current studies characterize SM04690 anti-inflammatory effects in vitro and in an in vivo OA model.

Methods
- **Experiment 1: Primary anti-inflammatory activity:** Evaluated by measuring TNF-α and IL-6 secretion using ELISA in primary PMCs. A panel of pro- and anti-inflammatory cytokines (TNF-α, IL-1β, IL-1, IL-2, IL-4, IL-8, IL-17A, IL-17F, IFN-γ, PGE2) was evaluated for IL-6, IL-8, IL-17A, IL-17F, and PGE2 by ELISA. IL-1α and IL-1β cell proliferation by flow cytometry in PMCs, and T and B cell co-cultures stimulated with super-antigens (αβ or lipopolysaccharides (LPS), compared with vehicle (DiscoverBioMapMM platforms).
- **Experiment 2: Mechanism of action:** SM04690 effects on LPS-induced expression and phosphorylation of NFκB in THP-1 cells were evaluated by qPCR and Western Blot.
- **Experiment 3: OA model (a vive):** SM04690 activity was evaluated in a rat monoarthritis oedema (MIA) injection-induced model of OA, followed by single IA SM04690 or vehicle injection at Day 3.
- Joint inflammation was evaluated by H&E staining, synovial thickness measurement, and qPCR for pro-inflammatory markers (TNF-α, IL-1β, IL-16). Cartilage protection was measured by qPCR for MMPs and ADAMTS at Day 11. Cartilage appearance was evaluated by Safranin-O staining and Osteoarthritis Research Society International (OARSI) scoring at Day 28.4
- Pain was measured as paw withdrawal threshold using Von Frey apparatus.

Results
- **Experiment 1: SM04690 suppressed inflammatory cytokines compared with vehicle**
- **Experiment 2: SM04690 inhibited NFκB phosphorylation and expression in human monocytes stimulated with LPS**
- **Experiment 3: SM04690 attenuated acute inflammation in a rat MIA knee OA model compared with vehicle**
- **Experiment 3: SM04690 protected cartilage in a rat MIA knee OA model compared with vehicle**

Conclusions
- In vitro, SM04690 demonstrated potent anti-inflammatory effects across a broad range of cytokines.
- In an MIA knee OA model, SM04690 attenuated inflammation, improved pain, and protected cartilage.
- Studies to further investigate the anti-inflammatory mechanism of action for SM04690 are ongoing.
- A phase IIb clinical trial is in progress (clinicaltrials.gov identifier NCT01322865).

References

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