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

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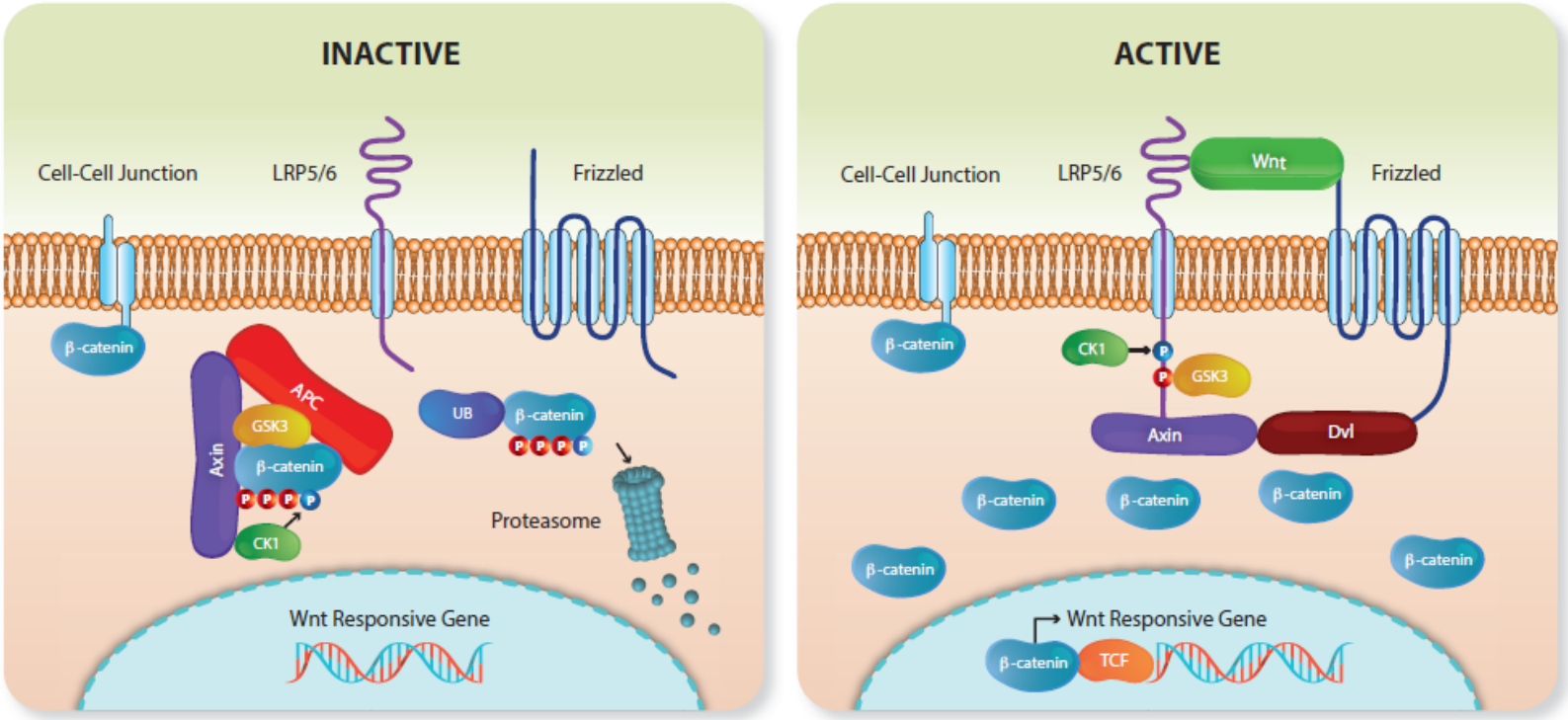
Disclosures

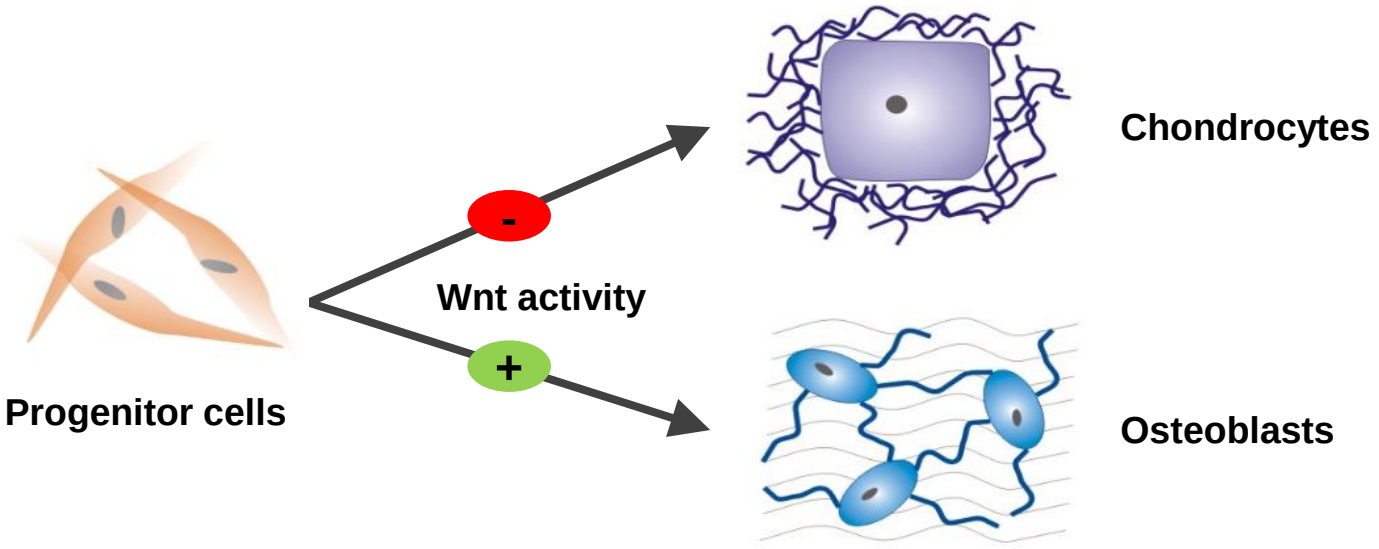
- John D. Hood, Ph.D.
  - Financial disclosure: employee of Samumed, LLC; salary and equity
- Charlene Barroga, Ph.D.
  - Financial disclosure: employee of Samumed, LLC; salary and equity
- Yong Hu, Ph.D.
  - Financial disclosure: former employee of Samumed, LLC; salary and equity
- Vishal Deshmukh, Ph.D.
  - Financial disclosure: employee of Samumed, LLC; salary and equity
- Yusuf Yazici, M.D.
  - Financial disclosure: employee of Samumed, LLC; salary and equity

Wnt Pathway Regulates Homeostasis

- Controls stem cell differentiation and lineage fate
- Implicated in tissue development & regeneration



Wnt Pathway and Osteoarthritis



Progenitor cells reside in subchondral bone and synovium

Increased Wnt signaling contributes to the pathophysiology of OA.[1-5]

Figure adapted from www.york.ac.uk

References:
1. Blom AB, et al. *Arthritis Rheum*. 2009;60(2):501-12.
2. Im GI, et al. *Biotechnol Lett*. 2011;33(5):1061-8.
3. Loughlin J. *Curr Opin Rheumatol*. 2005;17(5):629-33.
4. Rudnicki JA & Brown AM. *Dev Biol.* 1997;185(1):104-18.
5. Thomas RS, et al. *Arthritis Res Ther*. 2011;13(6):R203.

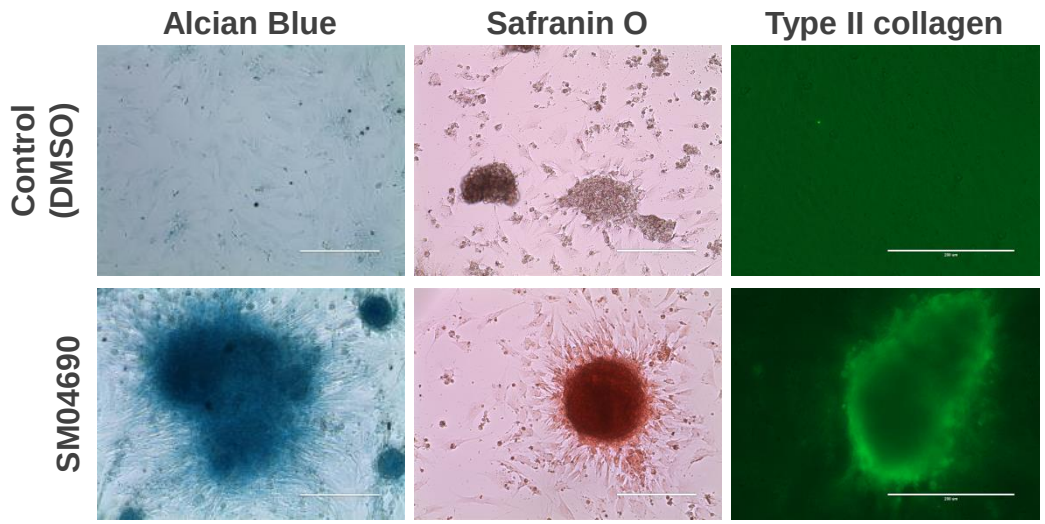
Proposed Therapy: SM04690

- SM04690 drug product has the following properties:
  - Small molecule
  - Inhibitor of the Wnt signaling pathway (EC_{50}=3 nM)
  - Intra-articular injection

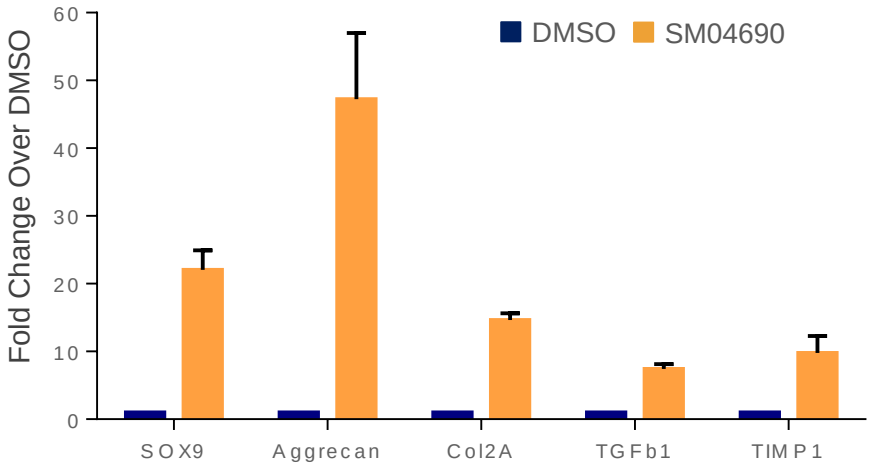
SM04690 Induced a Chondrogenic Lineage Fate

21 Day cellular assay – hMSCs:

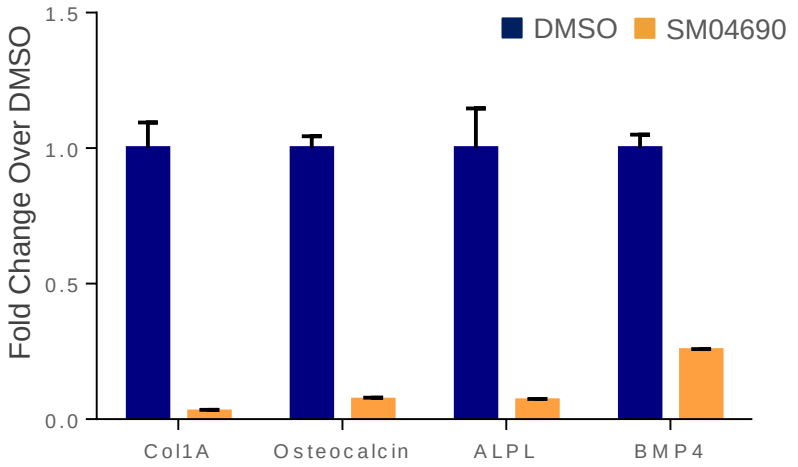
- Treated with 30 nM SM04690 every 7 days
- Stained for biomarkers and gene expression (measured by qPCR)



Chondrogenic Genes



Osteogenic Genes

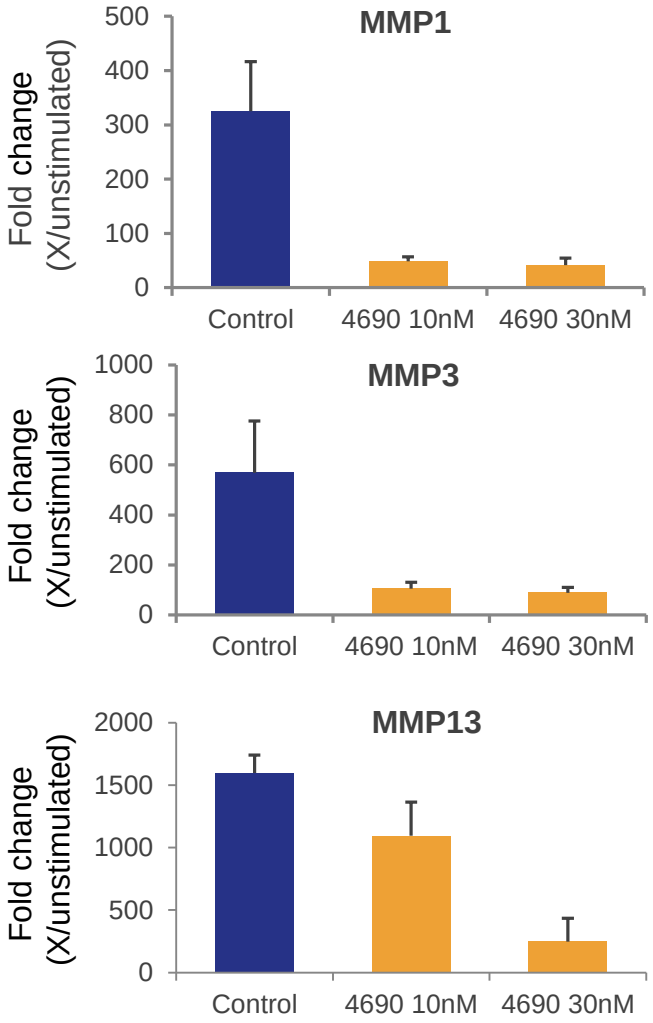


SM04690 Inhibited Protease Production

In OA, cytokines induce cartilage catabolic enzymes

Cellular assay – human chondrocytes:

- Dose dependent inhibition of protease expression was demonstrated

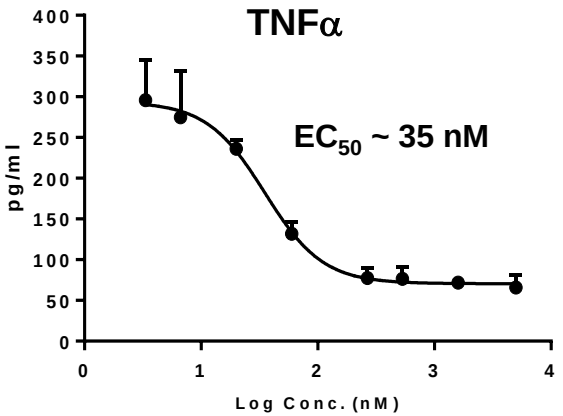


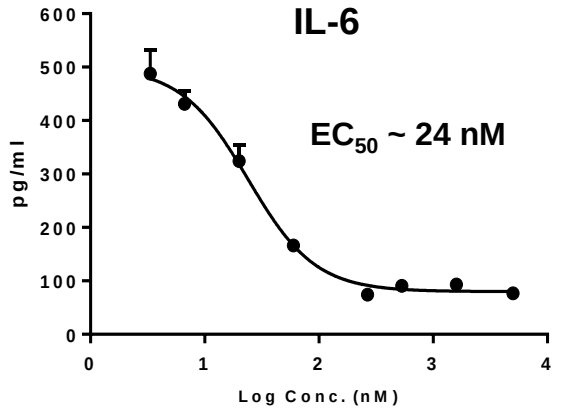
SM04690 Suppressed Inflammatory Cytokines

- TNFα and IL-6 play a major role in the pathogenesis of OA, as well as signs and symptoms

Cellular assay:

- Synovial fibroblasts stimulated with IL1β and THP-1 monocytes stimulated with LPS to induce cytokine production
- Then treated with SM04690
- Cytokine production quantified by ELISA

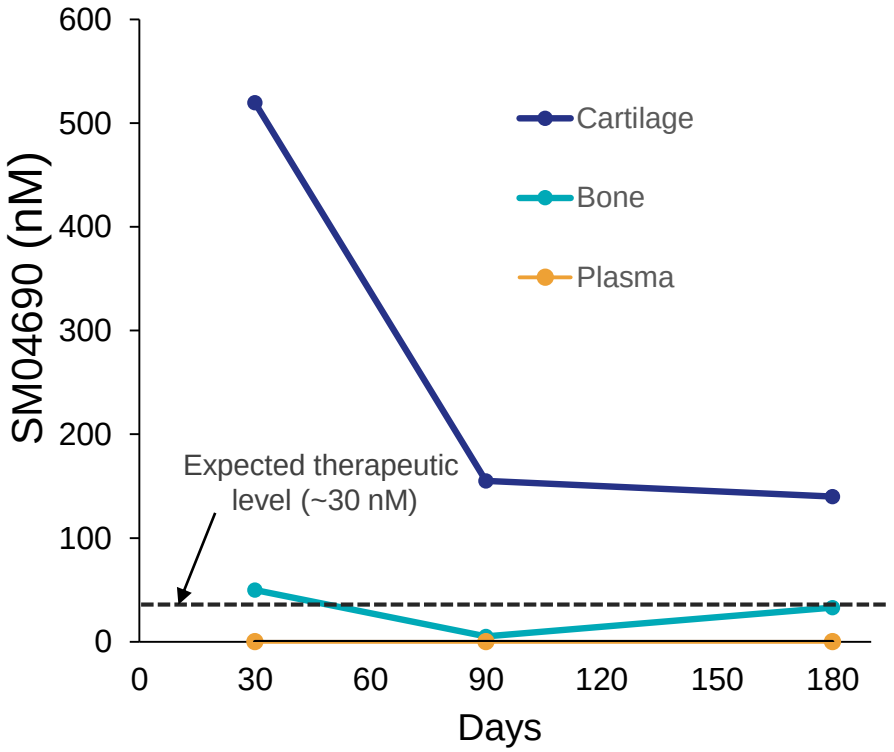




Sustained Local Exposure and Undetectable Systemic Exposure

Rats (Sprague Dawley):

- Single intra-articular injection
- 3 rats (2 knees/rat) at each 30, 90, 180 day time points.
- Compound was retained in joint above the target concentration level (~30 nM)
- Compound was undetectable in plasma at all time points



SM04690 Showed No Observable Systemic Toxicity After IA Injection

Intra-articular (IA) injection in Rats (Sprague Dawley) and Dogs (Beagle):

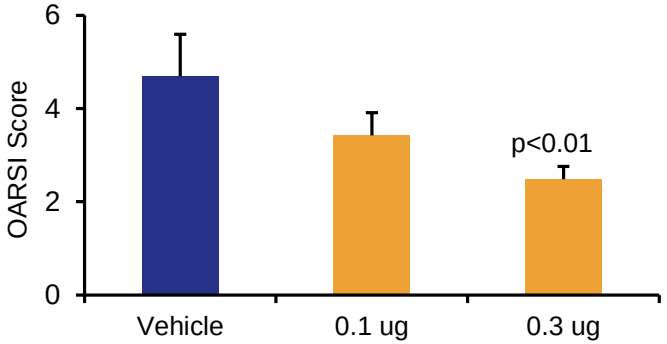
- **No systemic toxicity** - body weight, target or non-target organ effects, ECG and clinical pathology at doses up to 400X the expected clinical dose
- Local inflammation (at the injection site) at doses >1,400X the expected clinical dose
- Single or multiple (6 or 9 once-monthly) IA injections

SM04690 Increased Cartilage Thickness

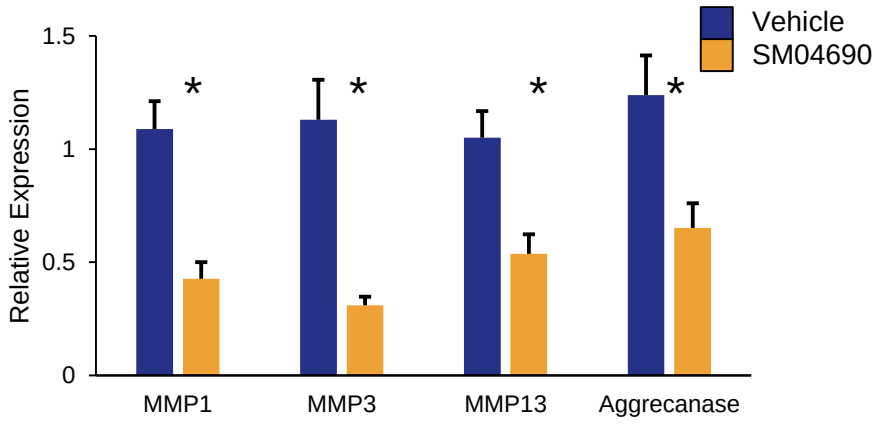
- Anterior cruciate ligament transection combined with medial meniscectomy in rat model
- Allowed cartilage degeneration for 2 weeks, injected SM04690 (0.3 µg) intra-articularly, and evaluated joints by histology after 12 weeks
- Safranin O-stained sections from the rat knee analyzed 3 months post-surgery for OA cartilage pathology using the OARSI scoring system
- Increased cartilage thickness, decreased fissures and subchondral bone remodeling observed with a single intra-articular injection of SM04690

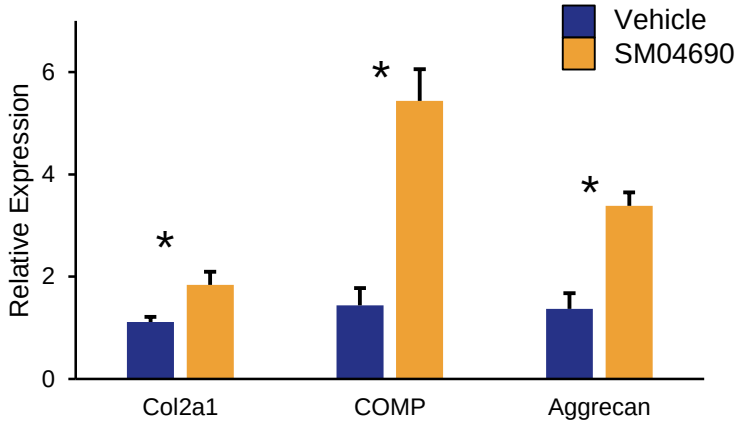
SM04690 Improved Joint Health

- OARSI cartilage pathology score measures cartilage matrix loss, fissures, subchondral bone remodeling, and bone cyst formation
- Safranin O-stained sections from the rat knee scored (blinded) using the OARSI system



- qPCR evaluation of protease and cartilage production markers





* p < 0.05

Summary

- SM04690 - a potent inhibitor of the Wnt pathway
  - Induced chondrogenesis
  - Inhibited protease production and inflammatory cytokine production
  - Had sustained local availability and no systemic exposure
  - No observable systemic toxicity
  - Potential to treat signs and symptoms and regenerate cartilage in knee OA
- Next Steps
  - Completed Phase 1 study (N=61)
  - Phase 2 study (N=445) is on-going

Thank you