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

Vishal Deshmukh, Ph.D., Charlene Barroga, Ph.D., Yong Hu, Ph.D., John Hood, Ph.D., and Yusuf Yazici, M.D.

samumed

DISCLOSURES

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

Pathophysiology of Osteoarthritis

- Mechanical forces and inflammation result in degenerative tissue remodeling in OA.
- Induce cartilage catabolic enzymes - matrix metalloproteinases (MMPs), aggrecanases, etc.
- Cartilage loss and subchondral bone remodeling

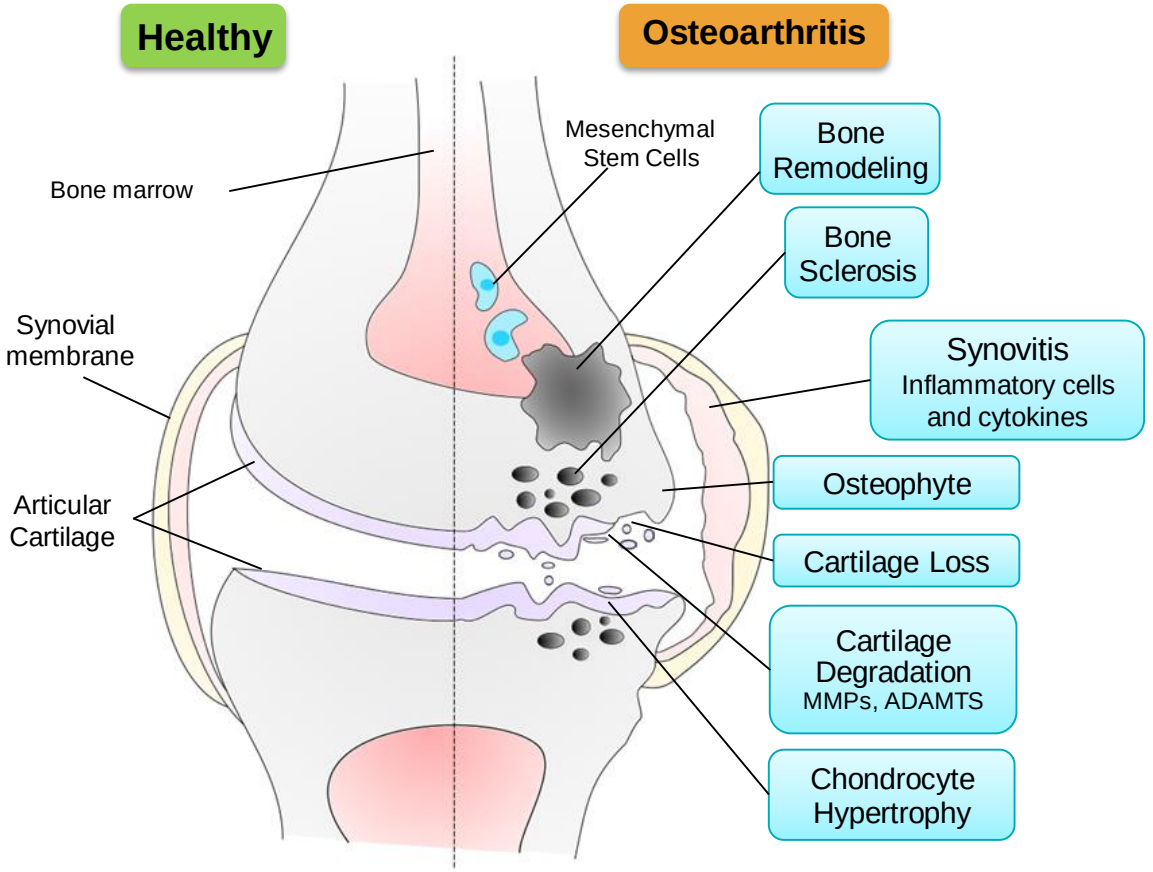
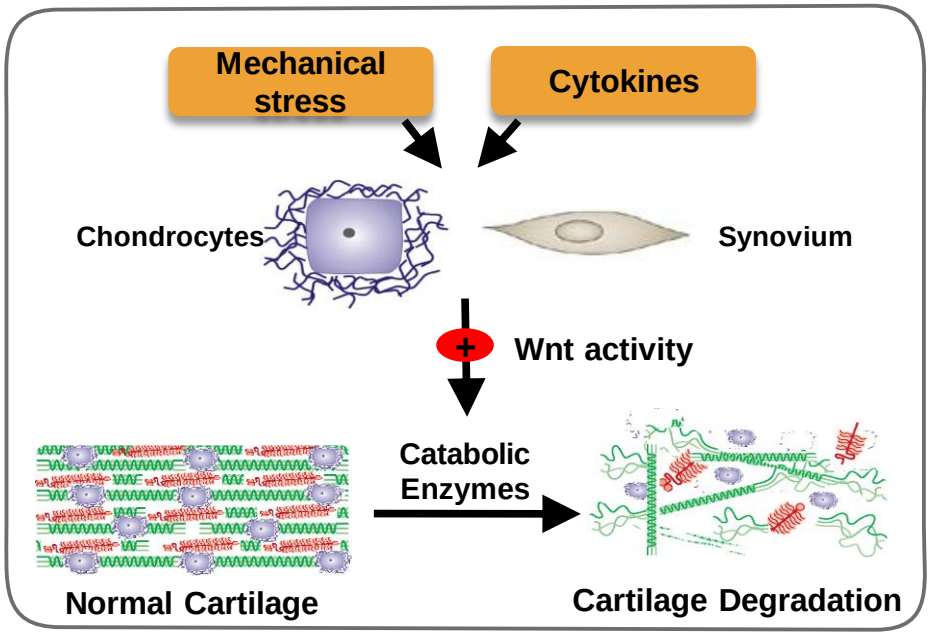
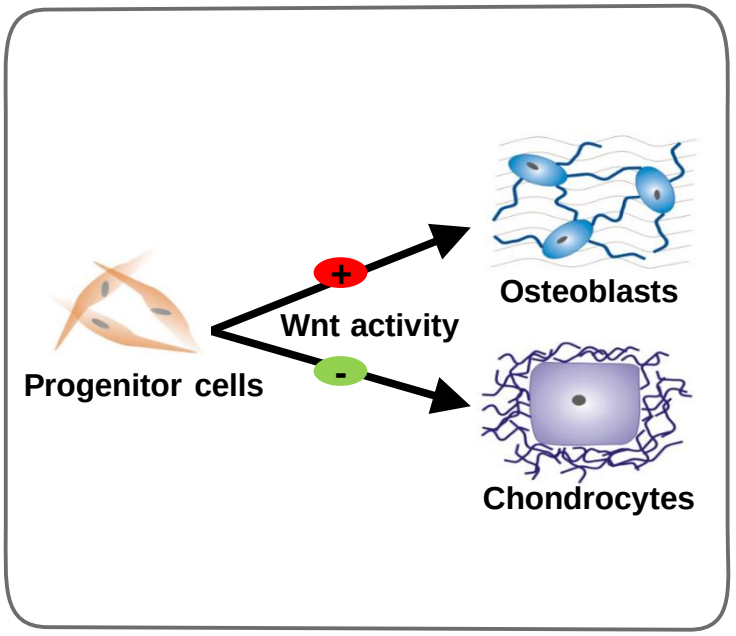


Figure adapted from Bush J & Beier F. *Nature Med*. 2013;19(6):667-9.

Wnt Pathway and Osteoarthritis





- The Wnt signaling pathway is involved in stem cell control and regeneration of tissues
- Increased Wnt signaling contributes to the pathophysiology of OA[1-2]
- Wnt signaling is involved in increased bone formation and cartilage breakdown
- Progenitor cells reside in the synovium and subchondral bone[3-5]

Hypothesis: Inhibiting the Wnt Pathway protects and regenerates cartilage

1. Rudnicki JA & Brown AM. *Dev Biol.* 1997;185(1):104-18.
2. Thomas RS, et al. *Arthritis Res Ther*. 2011;13(6):R203.
3. Blom AB, et al. *Arthritis Rheum*. 2009;60(2):501-12.
4. Im GI, et al. *Biotechnol Lett.* 2011;33(5):1061-8.
5. Loughlin J. *Curr Opin Rheumatol*. 2005;17(5):629-33.
Figure adaptations: www.york.ac.uk and Bush J & Beier F. *Nature Med*. 2013;19(6):667-9.

Proposed Therapy: SM04690

- SM04690 is a small molecule Wnt inhibitor in development for the treatment of OA

- SM04690 demonstrated the following properties in pre-clinical studies:
  - Decreased inflammation
  - Decreased cartilage degradation
  - Regenerated cartilage
  - Sustained local exposure and no observable systemic toxicity

In vitro Efficacy- SM04690

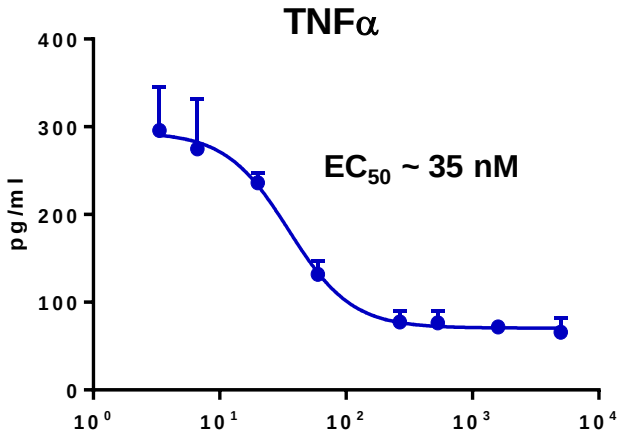
Decreased inflammation: SM04690 suppressed inflammatory cytokines

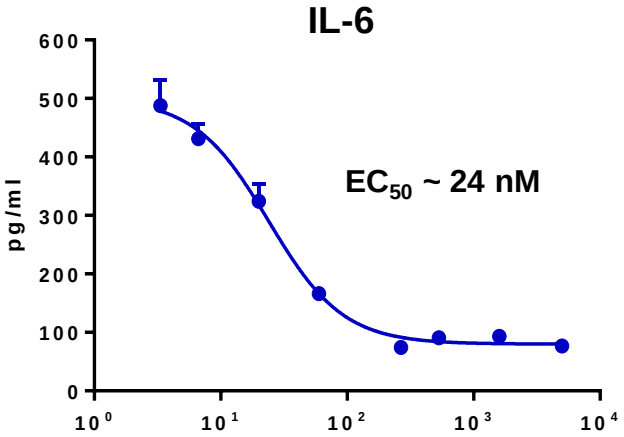
- IL1β, TNFα and IL-6 are associated with the pathophysiology of OA[1]

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
- Dose dependent inhibition of both TNFα and IL-6 production demonstrated in both cell types

Synovial fibroblasts



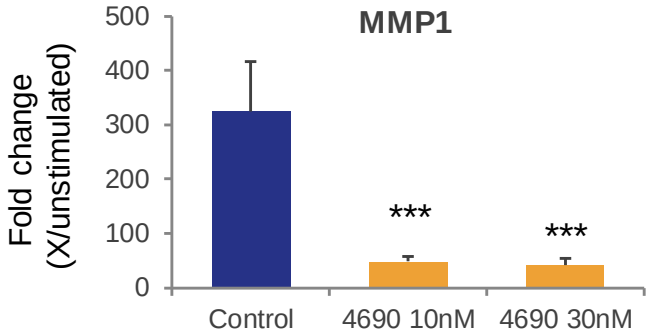


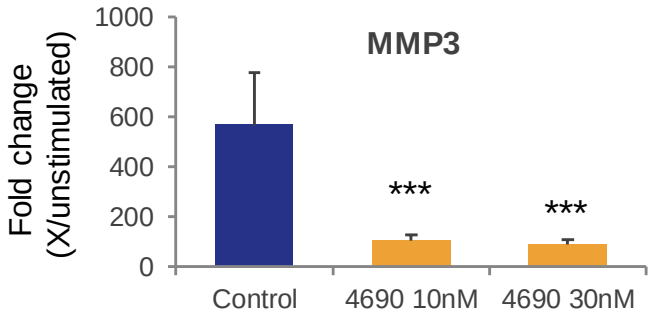
1. Glyn-Jones S, et al. *Lancet.* 2015;386(9991)376-387.

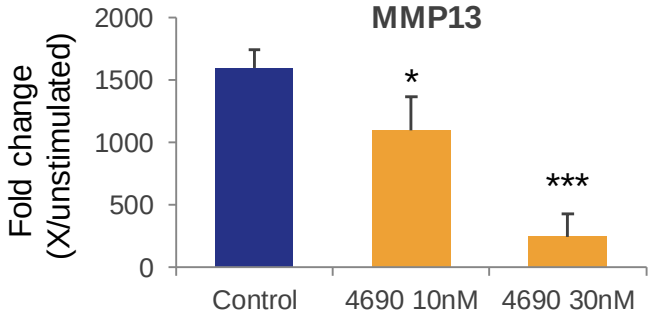
Decreased cartilage degradation: SM04690 inhibited protease production

- In OA, cytokines induce cartilage catabolic enzymes
- Increased Wnt signaling increases protease expression[1]
- Dose dependent inhibition of protease expression demonstrated

Cellular assay – human chondrocytes:







* p<0.05 *** p<0.001

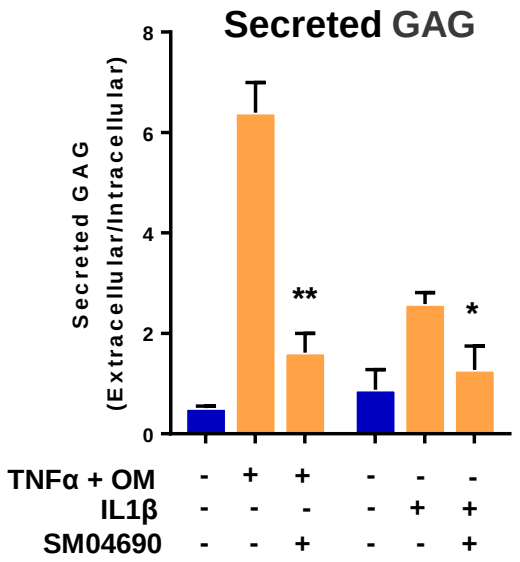
1. Enochson L, et al. *OA Cart.* 2014;22(4):566-77.

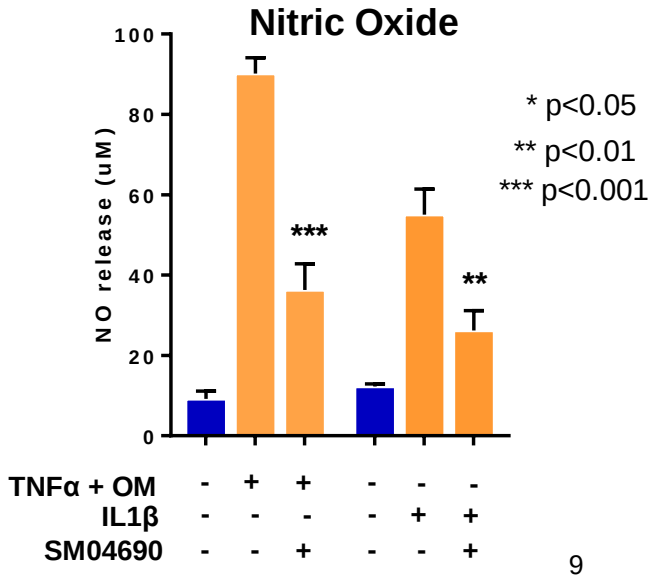
Decreased cartilage degradation: SM04690 inhibited GAG and Nitric Oxide release

- Glycosaminoglycan (GAG) are components of cartilage matrix
- Secreted/extracellular GAG = cartilage breakdown
- Inhibition of GAG and Nitric Oxide (NO) release demonstrated

Cellular assay – human chondrocytes:

SM04690 protected chondrocytes from catabolic breakdown

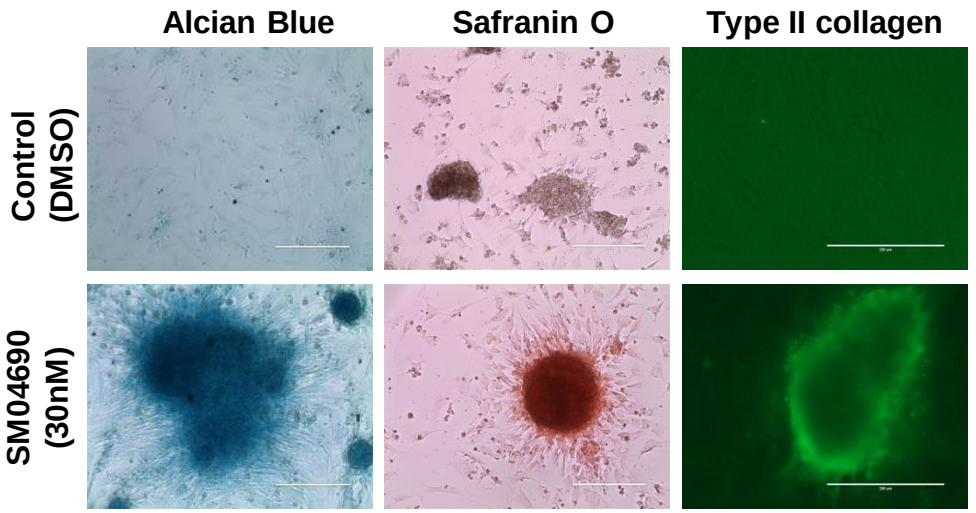


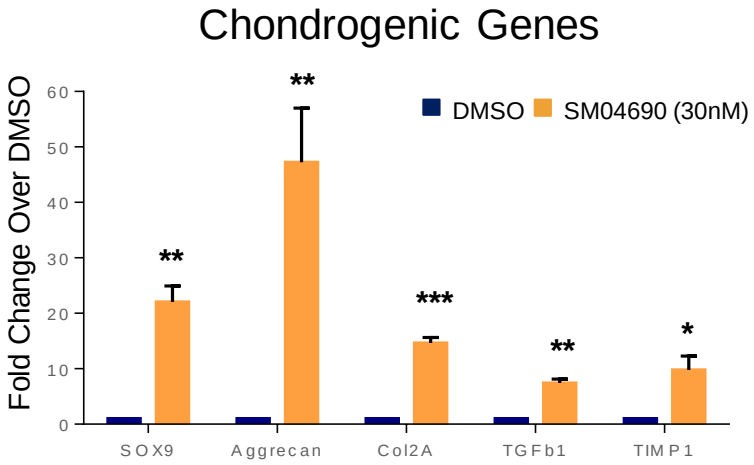


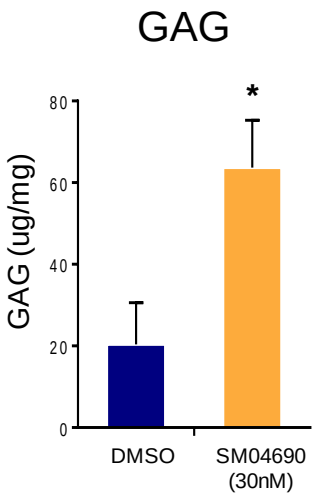
Regenerated cartilage: SM04690 induced functional chondrogenesis

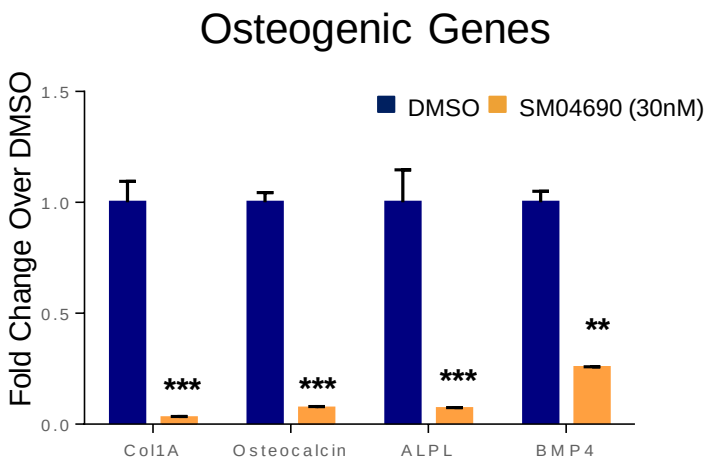
21 day cellular assay – hMSCs:

- Treated with SM04690 every 7 days
- Cells stained for biomarkers and gene expression measured by qPCR
- Increased sulfated glycosaminoglycans (sGAG) with SM04690 treatment
- Functional chondrocytes-cartilage matrix synthesis









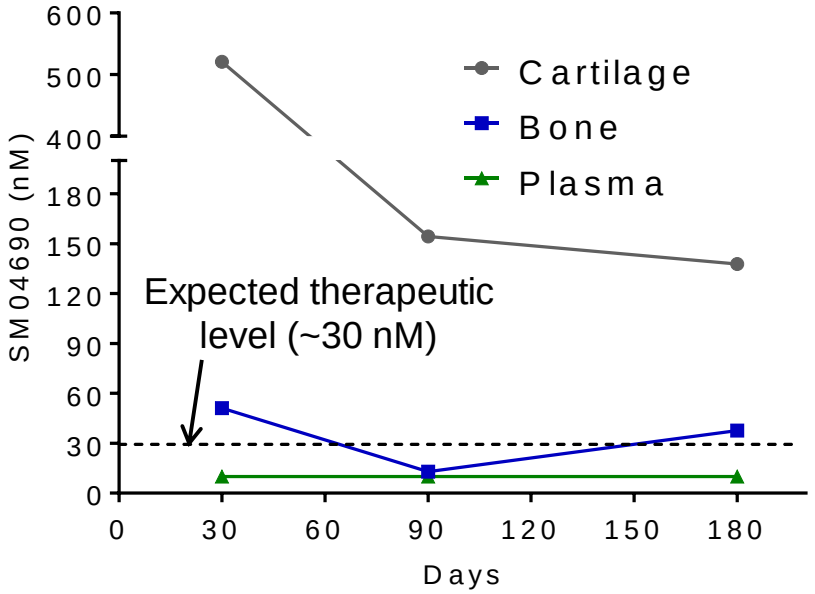
*p<0.05
**p<0.01
***p<0.001

In vivo Efficacy

SM04690 had sustained local exposure and no systemic toxicity

Rats (Sprague Dawley):

- Single intra-articular injection (0.3ug)
- Compound is retained in joint above the target concentration level (~30 nM) for >6 months
- Compound is undetectable in plasma at all time points



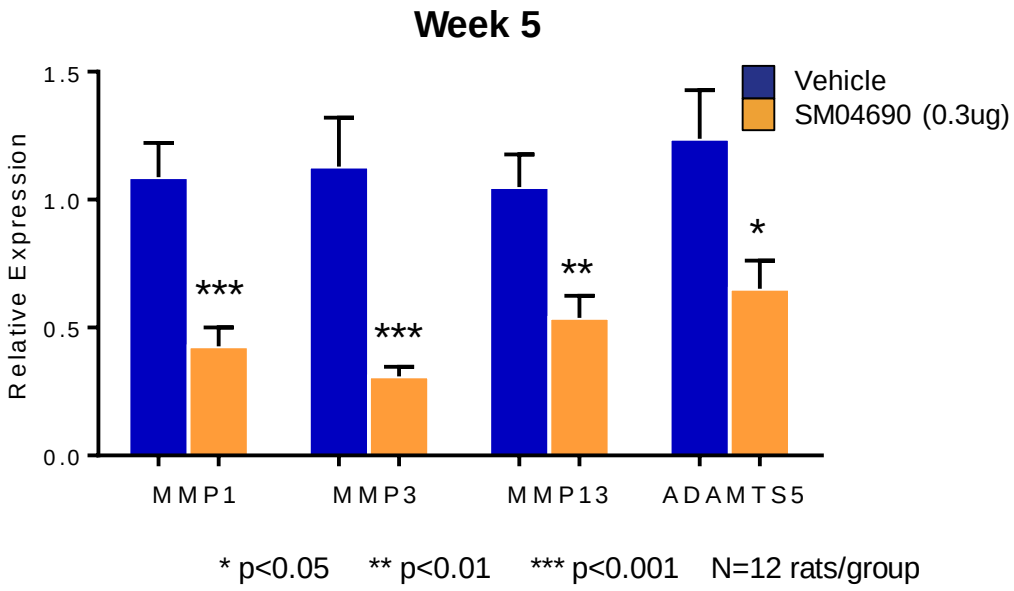
Intra-articular (IA) injection in Rats (Sprague Dawley) and Dogs (Beagle):

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

Decreased cartilage degradation: ACLT + pMMx model of OA

- Rat ACLT + pMMx model- anterior cruciate ligament transection (ACLT) combined with partial medial meniscectomy (pMMx)
- Inject SM04690 single dose, intra-articular after 1 week
- Rat knee analyzed 5 and 13 weeks post-surgery for OA cartilage pathology

- qPCR evaluation of protease enzymes in cartilage
- Decreased protease expression in cartilage with SM04690 treatment



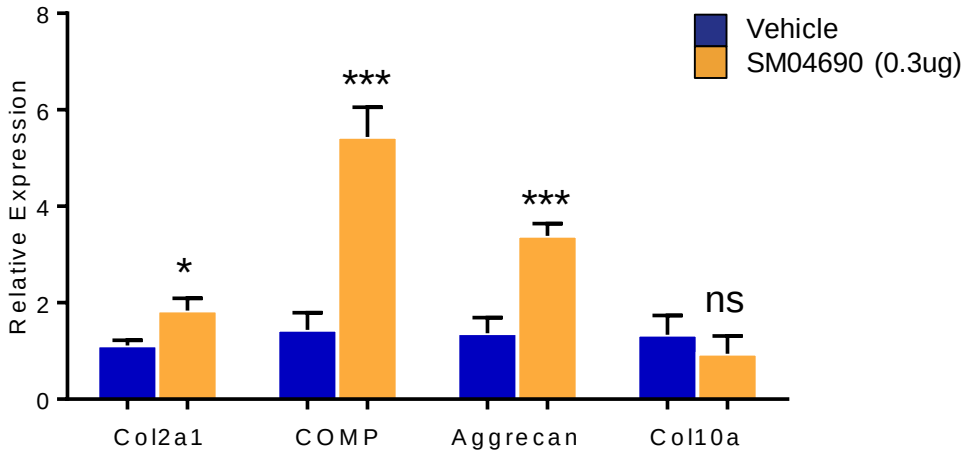
* p<0.05 ** p<0.01 *** p<0.001 N=12 rats/group

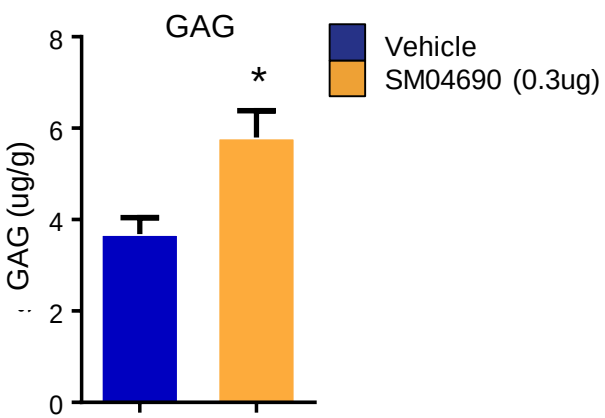
SM04690 protected cartilage from catabolic breakdown

SM04690 regenerated cartilage: ACLT + pMMx model of OA

- qPCR evaluation of cartilage production markers
- Increased expression of cartilage markers with SM04690 treatment
- Increased sulfated glycosaminoglycans (sGAG) - cartilage matrix
- No change in Col10a (hypertrophic marker)

Week 5



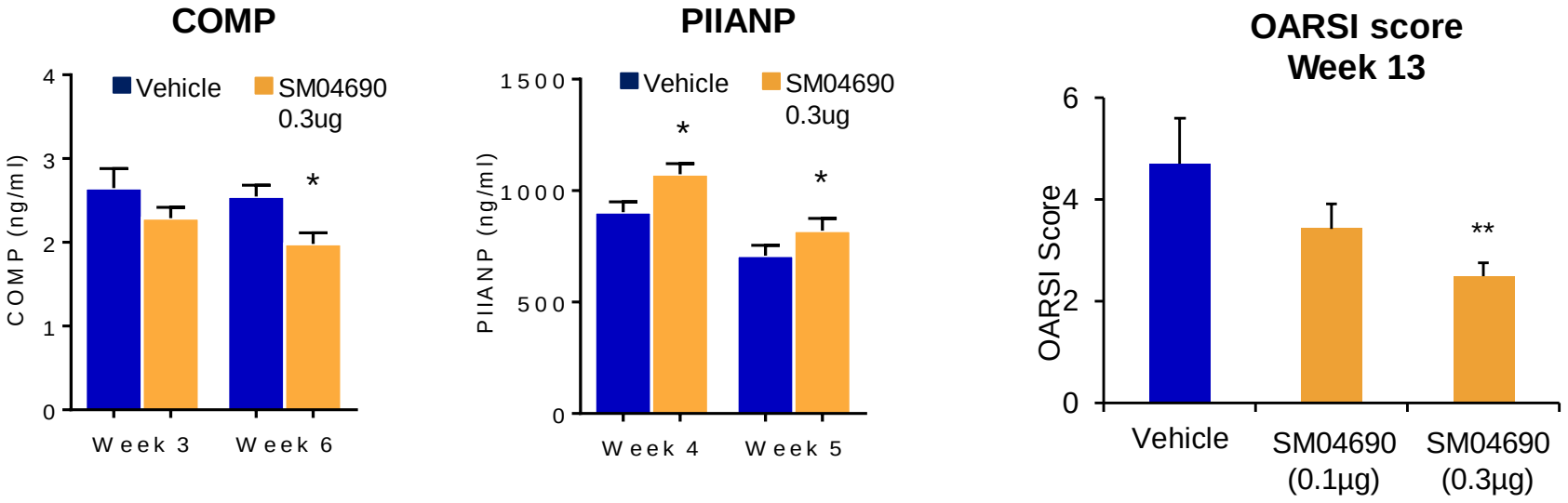


* p<0.05 *** p<0.001 ns- not significant N=12 rats/group

SM04690 induced chondrocyte and cartilage matrix production

SM04690 regenerated cartilage: Improved OA biomarkers and OARSI scores

- Decreased serum COMP and increased serum PIIANP observed with SM04690 treatment
- Safranin O-stained sections from the rat knee scored (blinded) using OARSI system
- OARSI cartilage pathology score measures cartilage matrix loss, fissures and subchondral bone remodeling, based on stage and grade of cartilage damage



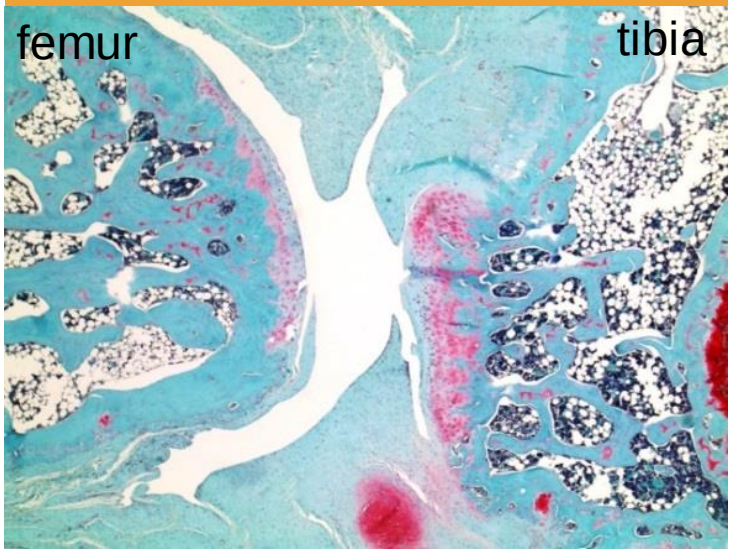
*p<0.05 **p<0.01
N=12 rats/group

SM04690 improved joint health

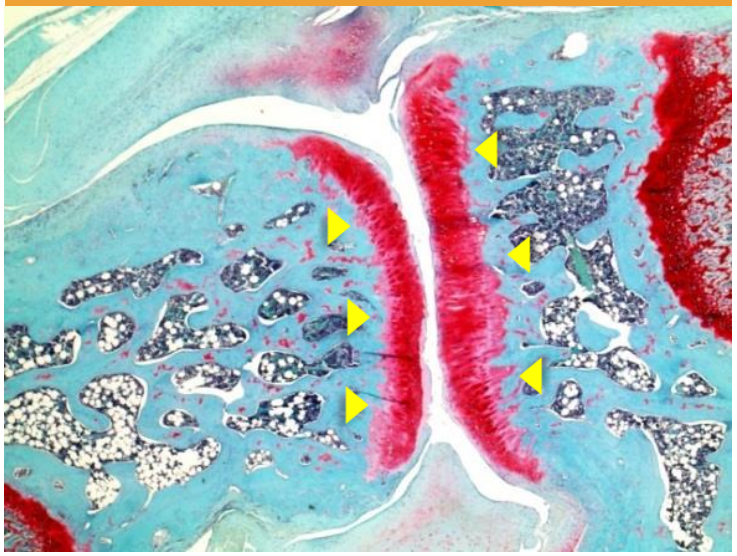
SM04690 regenerated cartilage

- Safranin O-stained sections from the rat knee analyzed 13 weeks post-surgery for OA cartilage pathology
- Increased cartilage thickness and decreased fissures observed with a single intra-articular injection of SM04690

Control Knee
12 weeks



Treated Knee (0.3µg)
13 weeks



Increased Cartilage

SM04690 increased cartilage thickness

Summary

- Wnt signaling is a critical pathway in osteoarthritis
- In preclinical models, SM04690:
  - Inhibited inflammatory cytokine and protease production
  - Induced chondrogenesis
  - Had sustained local availability and no systemic exposure
  - Had no observable systemic toxicity
- Phase 1 clinical data
  - Poster SAT0428, Saturday June 11th, 10:15-11:45

Thank you

samumed