SM04690 caused dose-dependent Wnt pathway modulation within a homeostatic range in a rat model of knee osteoarthritis

Vishal Deshmukh[1], Charlene Barroga[1], Sunil KC[1], Rik Lories[2], and Nancy E. Lane[3]

[1]Samumed, LLC, San Diego, CA [2]Skeletal Biology and Engineering Research Center, Leuven, Belgium [3]UC Davis Medical Center, Davis, CA

Poster# P729

Background

- Knee osteoarthritis (OA) is characterized by degradation of articular cartilage, subchondral bone remodeling, and osteophyte formation.[1]
- Wnt signaling affects OA pathogenesis by regulating chondrogenic stem cell differentiation *in vitro* and cartilage catabolism *in vivo*, thereby suggesting a potential role in OA.[2] Absence as well as excessive Wnt pathway activation disturbs homeostasis and triggers OA in *in vivo* models.[3-5] Therefore, potential pharmacological Wnt pathway inhibition cannot be excessive in order to achieve optimal restoration of joint homeostasis and stem cell activity.[6]
- SM04690, a small-molecule Wnt pathway inhibitor, has been shown to prevent or slow cartilage loss in preclinical OA models. Evidence of non-linear SM04690 dose response effects in these models is presented.

Methods

- **Pharmacokinetics:** Single intra-articular (IA) SM04690 injection into rats (0.3 µg, 1 µg, 3 µg, 9 µg) or beagle dogs (3 µg, 30 µg) was performed. Bone and cartilage samples were isolated, and SM04690 levels were measured by HPLC-mass spectrometry.
- **Rat OA model:** SM04690 efficacy was evaluated in a rat instability OA model (anterior cruciate ligament transection + partial medial meniscectomy [ACLT + pMMx]) with IA injection of vehicle or SM04690 (0.1 µg, 0.3 µg, 1 µg) at Week 1. Chondrocyte differentiation markers (collagen type II alpha 1 chain [Col2a1]; cartilage oligomeric matrix protein [COMP]; Aggrecan; collagen type x alpha 1 chain [Col10a]; sex-determining region-Y-box 9 [Sox9]) and protease enzymes (matrix metalloproteinases [MMP1, 3, 13], Aggrecanase [ADAMTS5]) were evaluated in cartilage using qPCR, OA serum biomarkers (COMP; procollagen type IIA N-propeptide [PIIANP]) by ELISA (Week 5), and cartilage pathology using Safranin O-stained sections (Week 13).
- **Statistics:** Data are shown as mean ± SEM. One-way ANOVA was used to evaluate differences between vehicle and treatment groups.

Results

Dose-dependent SM04690 exposure in rat and dog cartilage following single IA injection

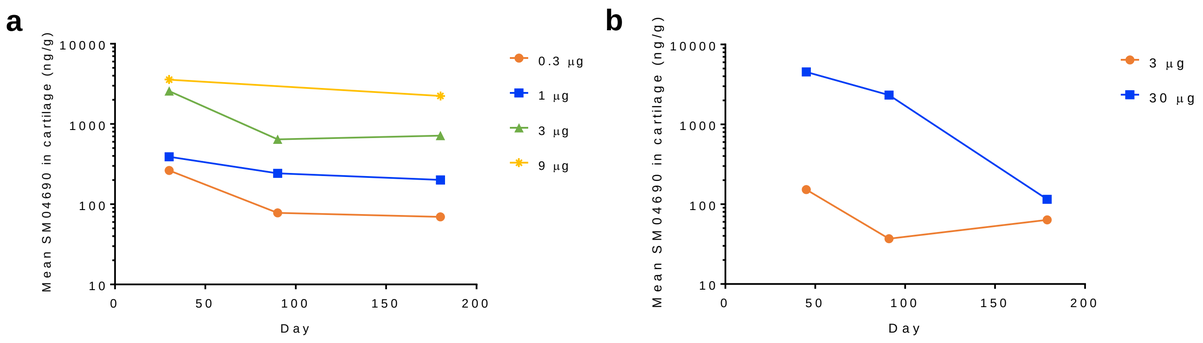

Figure 1. SM04690 showed dose-dependent exposure in cartilage in **a)** naïve rats and **b)** beagle dogs following single IA injection.

Non-linear dose effects of SM04690 on cartilage degradation in the ACLT + pMMx model of OA

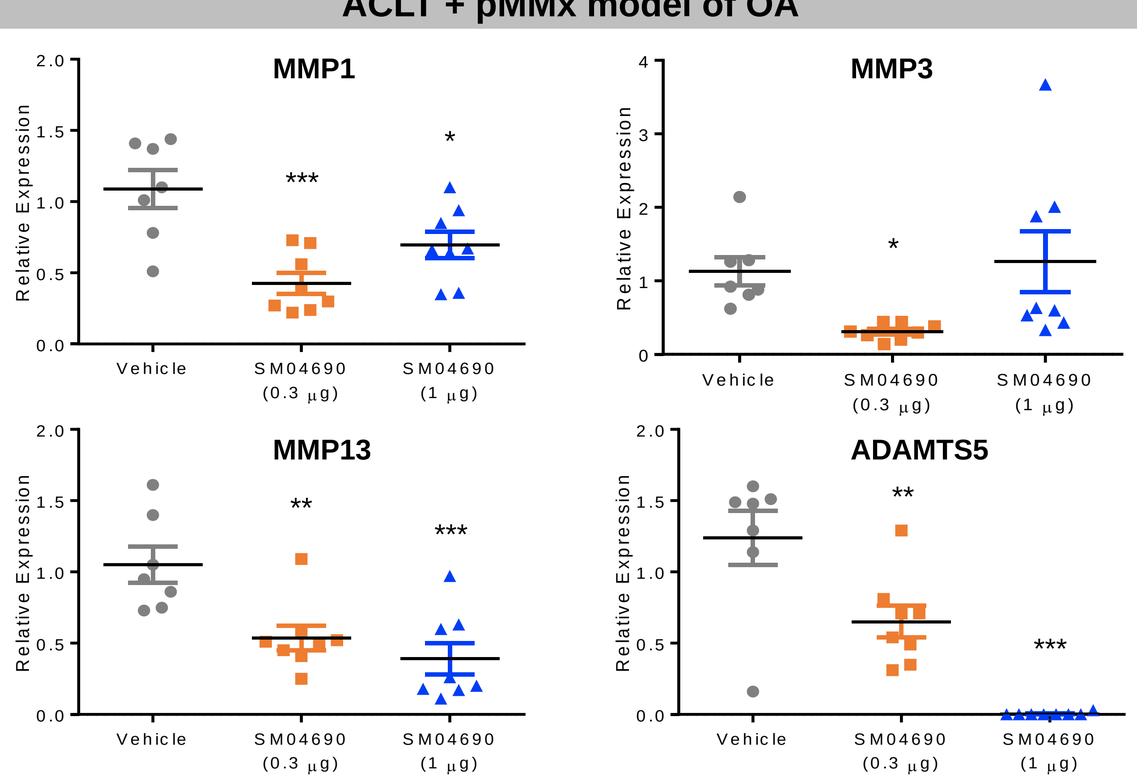

Figure 2. SM04690 dose-dependently decreased expression of MMP13 and ADAMTS5, but not MMP1 or MMP3, compared with vehicle (n=7 for vehicle; n=8 for treatment; *p<0.05; **p<0.01; ***p<0.001).

Results

Effects of SM04690 on chondrocyte markers in the ACLT + pMMx model of OA

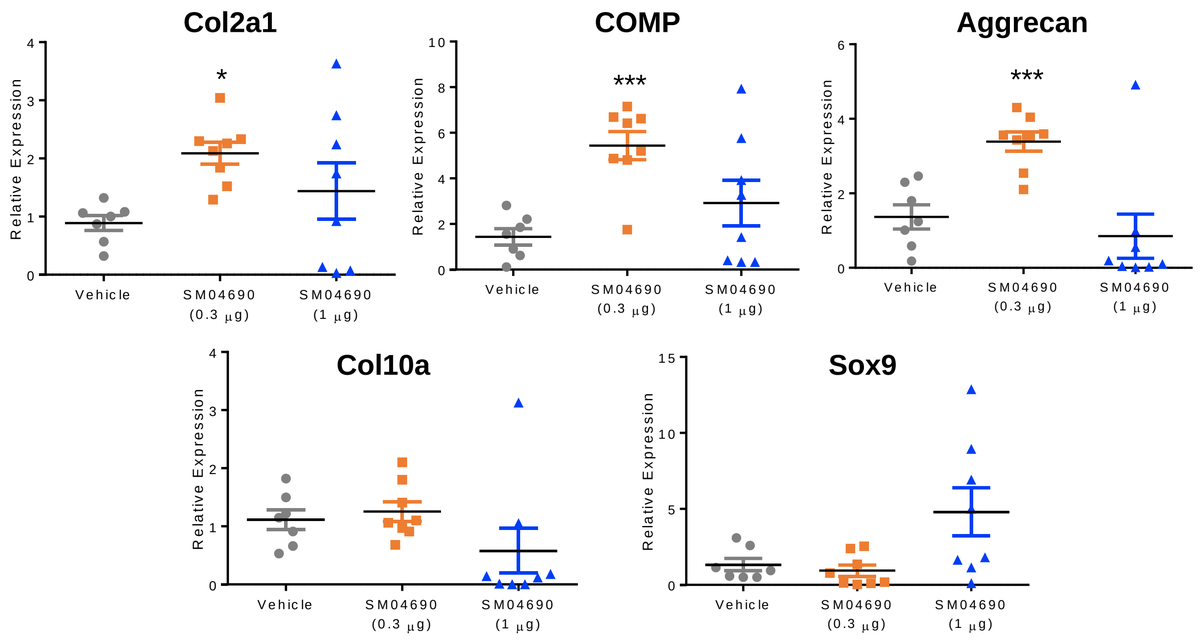

Figure 3. SM04690 (0.3 µg but not 1 µg) increased expression of Col2a1, COMP, and Aggrecan with no effects on Col10a (hypertrophy marker) or Sox9 compared with vehicle (n=7 vehicle; n=8 treatment; *p<0.05; ***p<0.001).

Effects of SM04690 on OA serum biomarkers in the ACLT + pMMx model of OA

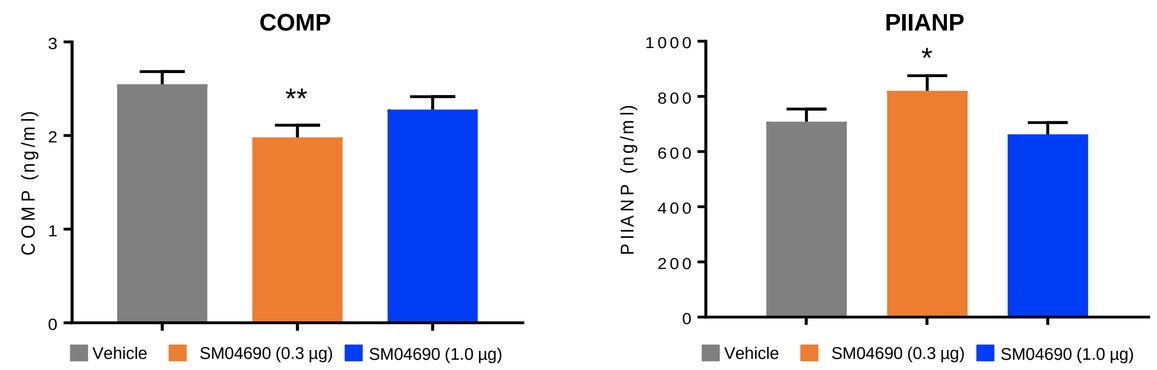

Figure 4. SM04690 (0.3 µg but not 1 µg) decreased COMP and increased PIIANP compared with vehicle (n=12; *p<0.05; **p<0.01).

Effects of SM04690 on knee joint pathology

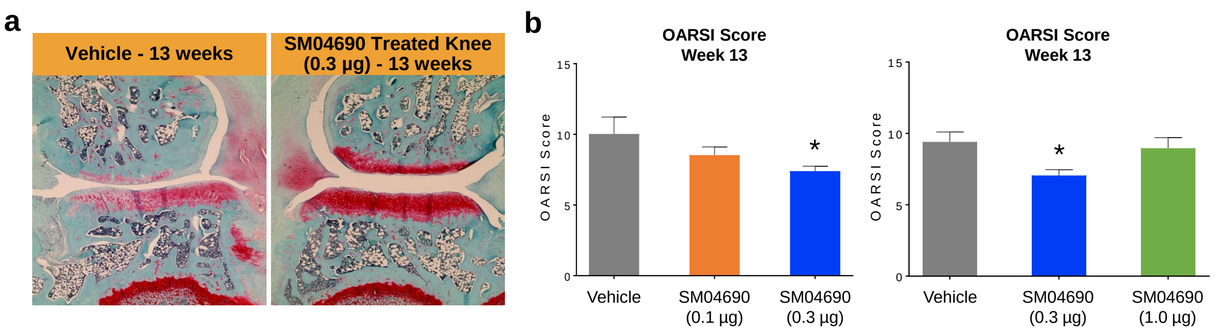

Figure 5. **(a)** SM04690 increased cartilage thickness compared with vehicle. **(b)** SM04690 (0.3 µg but not 0.1 µg or 1 µg) decreased OARSI scores compared with vehicle in two independent experiments (n=9-12/group; *p<0.05).

Discussion and Conclusions

- Linear pharmacokinetics with dose-dependent exposures were observed for SM04690 in rat and dog cartilage following single IA injection.
- SM04690 was well-tolerated in naïve animals at doses up to 58-fold higher than those tested for efficacy in the ACLT + pMMx model (**Poster# P728**).
- In this rat knee OA model, data suggested that SM04690 demonstrated generally non-linear dose-responses.

References

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9381 Judicial Drive ● San Diego, CA 92121 ● Email: info@samumed.com