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ANTI-INFLAMMATORY PROPERTIES OF SM04690, A SMALL MOLECULE INHIBITOR OF THE WNT PATHWAY AS A POTENTIAL TREATMENT FOR KNEE OSTEOARTHRITIS

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My abstract has been or will be presented at a scientific meeting during a 12 months period prior to EULAR 2017:

Yes

Abstract presented or will be presented at (meeting): Osteoarthritis Research Society International

Is the first author applying for a travel bursary and/or an award for undergraduate medical students?: No

Background: Osteoarthritis (OA) is characterized by pain, deformity, and reduced function in the knee joint. Upregulated Wnt signaling affects the pathogenesis of OA through increased inflammation, increased subchondral bone and thinning cartilage. SM04690, a novel small molecule, was previously shown to inhibit the Wnt pathway and induce chondrogenesis *in vitro* and *in vivo*.¹

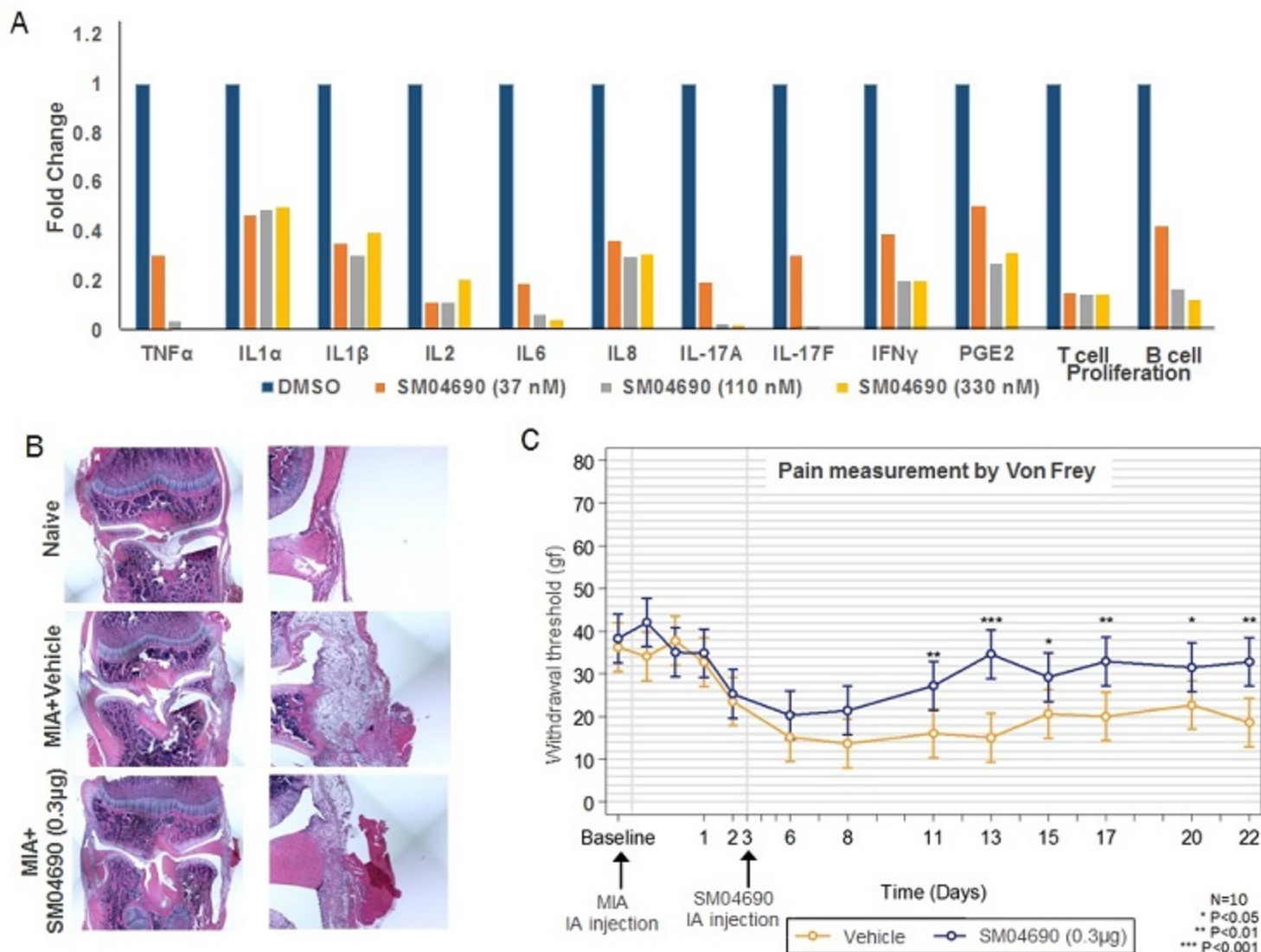
Objectives: SM04690 was evaluated in preclinical studies to determine its capacity to reduce inflammation, and reduce pain in OA.

Methods: Anti-inflammatory activity was evaluated by measuring cytokine (IL-6 and TNF- α) secretion using ELISA with IL-1 β stimulated synovial fibroblasts. A panel of pro-inflammatory cytokines (TNF- α , IL-1 α , IL-1 β , IL-2, IL-6, IL-8, IL-17A, IL-17F, IFN- γ and PGE2) was evaluated by ELISA; T and B cell proliferation by flow cytometry in peripheral blood mononuclear cells (PBMCs), and T and B cell co-cultures stimulated with super-antigen (SAg) or lipopolysaccharides (LPS), compared to vehicle or benchmark immunosuppressant or steroid (cyclosporin A and prednisolone). SM04690 effects on LPS-induced expression and phosphorylation of JNK, NF κ B, Erk, cJun, Akt, Stat3 in THP-1 cells were measured by qPCR and Western Blot. *In vivo* SM04690 activity was evaluated in a rat monosodium iodoacetate (MIA) injection-induced OA model, immediately followed by a single intra-articular SM04690 or vehicle injection. Joint inflammation was evaluated by measuring synovial thickness and infiltrating cells histology; inflammatory cytokines (IL-1 α , IL-1 β , IL-2, IL-5, IL-6, IL-8, TNF- α and IFN- γ) by qPCR and ELISA and cartilage protection by qPCR for matrix metalloproteinases (MMPs). Pain was measured as paw withdrawal threshold using Von Frey apparatus.

Results: SM04690 inhibited IL-1 β -induced TNF- α and IL-6 secretion in synovial fibroblasts (EC₅₀@30nM). SM04690 significantly inhibited ($p < 0.01$) SAg and LPS stimulated pro-inflammatory cytokine production (TNF- α , IL-1 α , IL-1 β , IL-2, IL-6, IL-8, IL-17A, IL-17F, IFN- γ , PGE2), T and B cell proliferation in PBMCs and T and B cell co-cultures (Figure A), with activity comparable to or better than cyclosporin A and prednisolone. SM04690 treatment specifically decreased LPS-induced gene expression ($p < 0.01$) and phosphorylation of NF κ B in THP-1 cells with no effect on JNK, Erk, cJun, Akt and Stat3. Compared to vehicle in the rat MIA OA model, SM04690 injection reduced inflammatory cells, decreased synovial thickness ($p < 0.05$, Figure B), inhibited production of pro-inflammatory cytokines and MMPs ($p < 0.05$). SM04690 increased ($p < 0.01$) paw withdrawal threshold in treated rats compared to vehicle at multiple time points (Figure C).

Image/graph:

Figure. SM04690 inhibited inflammatory cytokine production *in vitro* and decreased inflammation and pain in the MIA model of OA



Conclusions: SM04690 demonstrated potent anti-inflammatory properties, comparable to or greater than cyclosporin A and prednisolone. In a rat knee OA model, SM04690 injection reduced inflammation, protease production and pain compared to vehicle. The anti-inflammatory properties of SM04690 may provide beneficial effects in the treatment of OA. Clinical studies are ongoing.

References: ¹ Hood et al. OAC 2016, s187

Disclosure of Interest: V. Deshmukh Shareholder of: Samumed, LLC, Employee of: Samumed, LLC, C. Barroga Shareholder of: Samumed, LLC, Employee of: Samumed, LLC, M. Ibanez Shareholder of: Samumed, LLC, Employee of: Samumed, LLC, T. Seo Shareholder of: Samumed, LLC, Employee of: Samumed, LLC, S. KC Shareholder of: Samumed, LLC, Employee of: Samumed, LLC, Y. Yazici Shareholder of: Samumed, LLC, Employee of: Samumed, LLC