

Medical or Research Professionals/Clinicians

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DISCOVERY OF A SMALL MOLECULE INHIBITOR OF THE WNT PATHWAY (SM04690) AS A POTENTIAL DISEASE MODIFYING 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 2016:

No

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

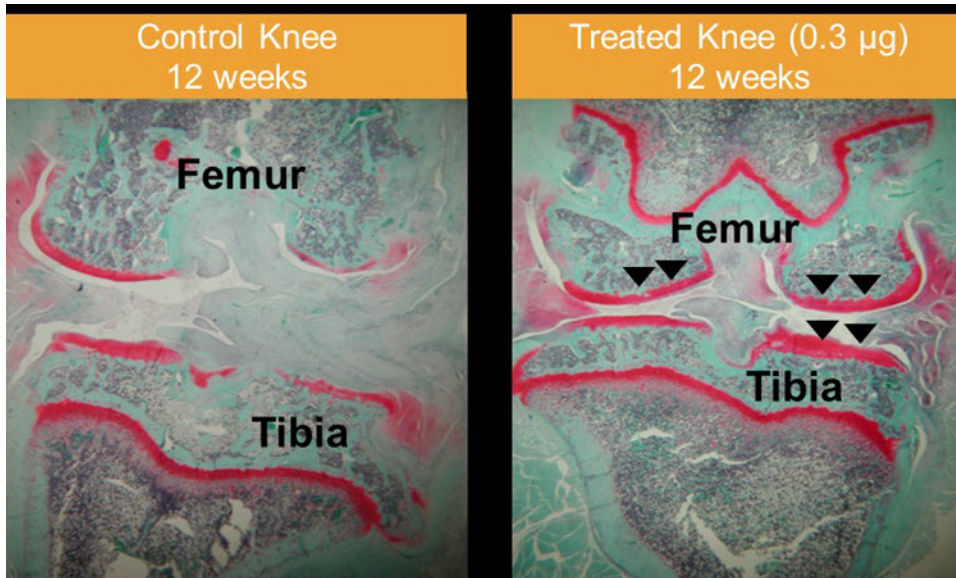
Background: Osteoarthritis (OA) is characterized by increased subchondral bone and thinning cartilage. The Wnt signaling pathway has the capacity to regulate both of these processes. Increased Wnt signaling induces stem cells in the joint to become osteoblasts while decreased Wnt signaling induces chondrogenesis¹. Wnt signaling is increased in the joints of OA patients and polymorphisms in genes involved in Wnt signaling are associated with an increased susceptibility to development of OA².

Objectives: SM04690, a novel, small molecule inhibitor of the Wnt pathway, was evaluated in a series of preclinical studies to determine its capacity to induce chondrogenesis and improve joint health.

Methods: Inhibition of the Wnt pathway was determined with a cellular screen utilizing a luciferase reporter controlled by a Wnt-responsive promoter. Chondrogenesis was evaluated by histology using differentiation of mesenchymal stem cells (MSCs) to chondrocytes. Protease release from human chondrocytes was measured by ELISA. Pharmacokinetics of SM04690 were evaluated by intra-articular (IA) injection in rats and dogs followed by analysis of compound concentration in the joints and plasma. Safety of SM04690 was assessed by IA injection in rats and dogs followed by evaluation of clinical signs and histology. *In vivo* activity of SM04690 was evaluated in the rat instability model combining anterior cruciate ligament transection with medial meniscal tear. SM04690 was injected into the IA space of the damaged knee, followed by histological evaluation using OARSI scoring and measurement of biomarkers.

Results: *In vitro*, SM04690 reduced TCF7 expression leading to selective inhibition of Wnt pathway activation with an EC₅₀=3 nM. Consistent with Wnt's role in chondrogenesis, SM04690 induced MSCs to express chondrogenic genes and differentiate into chondrocytes. SM04690 inhibited production of proteases from human chondrocytes, while increasing expression of GAG suggesting it has the capacity to block cartilage degradation and stimulate matrix generation. *In vivo*, a single IA injection of SM04690 resulted in a joint concentration above the target EC₅₀ with no detectable systemic exposure. No systemic toxicity was observed after single or 9 monthly IA injections of doses >1400X the therapeutic dose in rats and dogs. In the rat instability model, a single IA injection of SM04690 2 weeks post-injury improved cartilage health in a dose-dependent manner relative to vehicle control. Representative histology showed increased cartilage thickness in SM04690-treated animals relative to vehicle control (**Figure 1**). At the optimal IA dose in rats (0.3 mg/knee) OARSI scores decreased significantly, p=0.006.

Image/graph:



Conclusions: SM04690 has been shown in these experiments to inhibit the Wnt pathway, induce chondrogenesis, inhibit protease production and improve cartilage health in rodent models of OA after a single IA injection. SM04690 was maintained in the joint space with no detectable exposure in the plasma, indicative of a low potential for systemic toxicity. These data suggest that locally injected SM04690 has potential as a disease modifying therapy for OA.

References: 1. Gelse, K. *Osteoarthr Cartil.* 2012; 20:162.
2. Wu, L. *Curr Pharm Des* 2012; 18:3293

Disclosure of Interest: J. Hood Employee of: Samumed, C. Barroga Employee of: Samumed, Y. Hu Employee of: Samumed, V. Deshmukh Employee of: Samumed