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Wnt inhibitor shows potential as a DMOAD

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New research demonstrates that SM04690, a small-molecule inhibitor of the Wnt signalling pathway, has potential as a disease-modifying osteoarthritis (OA) drug (DMOAD). “SM04690 was able to induce chondrocyte differentiation and regenerate and protect cartilage both *in vitro* and in an OA animal model,” reports corresponding author Yusuf Yazici. Following the promising results of the preclinical studies, SM04690 is now being evaluated in human clinical trials.

“The Wnt pathway [has] a prominent role in OA joints, including cartilage catabolism and regeneration,” explains Yazici, “thus it is an attractive target for the development of a DMOAD.” SM04690 was developed as a potent inhibitor of the Wnt pathway that has sustained local residence in the joint.

In bone marrow-derived human mesenchymal stem cells (hMSCs), SM04690 induced chondrocyte differentiation and, under conditions designed to mimic cytokine-induced cartilage degeneration during OA progression, protected chondrocytes from catabolic breakdown.

The *in vivo* effects of SM04690 were then evaluated in rats with OA induced by acute cruciate ligament tear and partial medial meniscectomy (ACLT + pMMx). “The ACLT + pMMx model that we chose is a relatively severe model

for OA in rats and therefore [has] a high bar for success,” says Yazici. In this model, a single intra-articular injection of SM04690 promoted cartilage growth and improved joint morphology. Markers of matrix degradation were also reduced in SM04690-treated rats compared with

vehicle-treated animals, suggesting potential cartilage protective effects. Altered expression of Wnt pathway genes and inhibition of the nuclear localization of β -catenin in cartilage confirmed the functional inhibition of Wnt signalling in the *in vivo* model.

The investigators have further studies planned to evaluate the effects of the drug on chondrocytes derived from patients with OA. In clinical studies, SM04690 was safe and well tolerated in a phase I clinical trial; we now await data from a completed phase II trial.

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Macmillan Publishers Limited

ORIGINAL ARTICLE Deshmukh, V. et al. A small-molecule inhibitor of the Wnt pathway (SM04690) as a potential disease modifying agent for the treatment of osteoarthritis of the knee. *Osteoarthritis Cartilage* <http://dx.doi.org/10.1016/j.joca.2017.08.015> (2017)

FURTHER READING Yazici, Y. et al. A novel Wnt pathway inhibitor, SM04690, for the treatment of moderate to severe osteoarthritis of the knee: results of a 24-week, randomized, controlled, phase 1 study. *Osteoarthritis Cartilage* **25**, 1598–1606 (2017)