**ABSTRACT NUMBER: 1655**

# Peroxisome Proliferator-Activated Receptor α Is a Disease-Modifying Target for Osteoarthritis

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## SESSION INFORMATION

**Date:** Sunday, November 17, 2024

**Session Type:** Abstract Session

**Title:** Abstracts: Osteoarthritis & Joint Biology – Basic Science

**Session Time:** 1:00PM-2:30PM

**Background/Purpose:** Disease-modifying drugs (DMOADs) to prevent Osteoarthritis (OA) are an urgent clinical need. Recent advances demonstrated that targeting senescence and autophagy in chondrocytes might be a useful strategy to prevent joint damage. Fenofibrate (FN), a PPARα agonist employed in clinic for dyslipidemias show senolytic and pro-autophagy chondroprotective properties. Here, we aimed to evaluate the efficacy of FN as a DMOAD for knee OA and to investigate the relevance of PPARα on joint homeostasis.

**Methods:** FN was administered by oral (O-FN) and by intra-articular delivery (IA-FN) in preclinical models of OA in mice. The IA-FN in microspheres was developed to 1) to extend FN delivery, which is insoluble in water 2) to provide direct access to the joint enhancing FN bioavailability, and 3) to diminish the effects of systemic administration. Evaluation of pain and histopathological changes were determined. The relevance of PPARα for joint homeostasis was investigated through regulation of circadian rhythm (CR) in human chondrocytes.

**Results:** In a preclinical model of OA in mice, the treatment with O-FN did not induce changes in body weight and no liver toxicity occurred after the treatment. The histopathological changes in joint cartilage were significantly reduced in the FN treated group ( $P < 0.05$ ). In addition, the histological evaluation showed a significant decrease in synovitis after O-FN ( $P < 0.05$ ). This protective effect was correlated with increased expression of PPARα in mouse knee joints after O-FN treatment ( $P < 0.001$ ). The IA-FN was prepared and comprehensively characterized. IA-FN comprises a PLGA matrix in an optimized ratio, adequate size, appropriate molecular weight, and exhibits a 3-month extended-

release profile in human synovial fluid. The preclinical results showed a reduction of joint pain after a single intra-articular injection of FN (
*P < 0.01*
). Moreover, IA-FN improved joint function (
*P < 0.01*
) compared to vehicle condition, suggesting that IA-FN
is a disease-modifying therapy for OA
. Mechanistically,
BMAL1 and CRY1 mRNA expression were altered at baseline and upon proinflammatory IL-1β challenge in chondrocytes with PPARα knock-down, suggesting
a role of PPARα on the regulation of CR
. Interestingly, protein studies showed a reduction in BMAL1 expression at baseline and under treatment with IL-1β, suggesting that BMAL1 might be an interesting checkpoint. Moreover, this reduction was correlated with chondrocyte senescence by increasing p21 expression suggesting that PPARα is essential for maintaining chondrocyte homeostasis.

**Conclusion:** These findings support further non-clinical regulatory studies to develop IA-FN formulation as a candidate therapy for OA might be related to
regulation of circadian synchronicity in chondrocyte homeostasis.
A GMP manufactured formulation could be used to test the safety of this treatment in patients with OA of the Knee in a Phase 1 clinical trial.

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