

Lorecivivint (SM04690), a Potential Disease-Modifying Treatment For Knee Osteoarthritis, Demonstrated Cartilage-Protective Effects on Human Osteoarthritic Explants

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Background

- Excessive Wnt pathway signaling contributes to osteophyte formation, cartilage degeneration, and inflammation¹ in knee osteoarthritis (OA)
- Lorecivivint (LOR; SM04690) is an intra-articular, small-molecule drug candidate that modulates Wnt pathway activity via CLK/DYRK1A inhibition²
- LOR has demonstrated potential as a treatment for knee OA in randomized controlled trials, with improvements seen in pain and function as well as maintenance of radiographic medial joint space width in a target population³
- The cartilage-protective effects of LOR in knee OA were measured by assessing catabolic enzyme expression and activity in cartilage explants from human total knee replacement (TKR) donors

1. Usami Y, et al. *Lab Invest.* 2016.

2. Deshmukh V, et al. *Osteoarthr Cartil.* 2019.

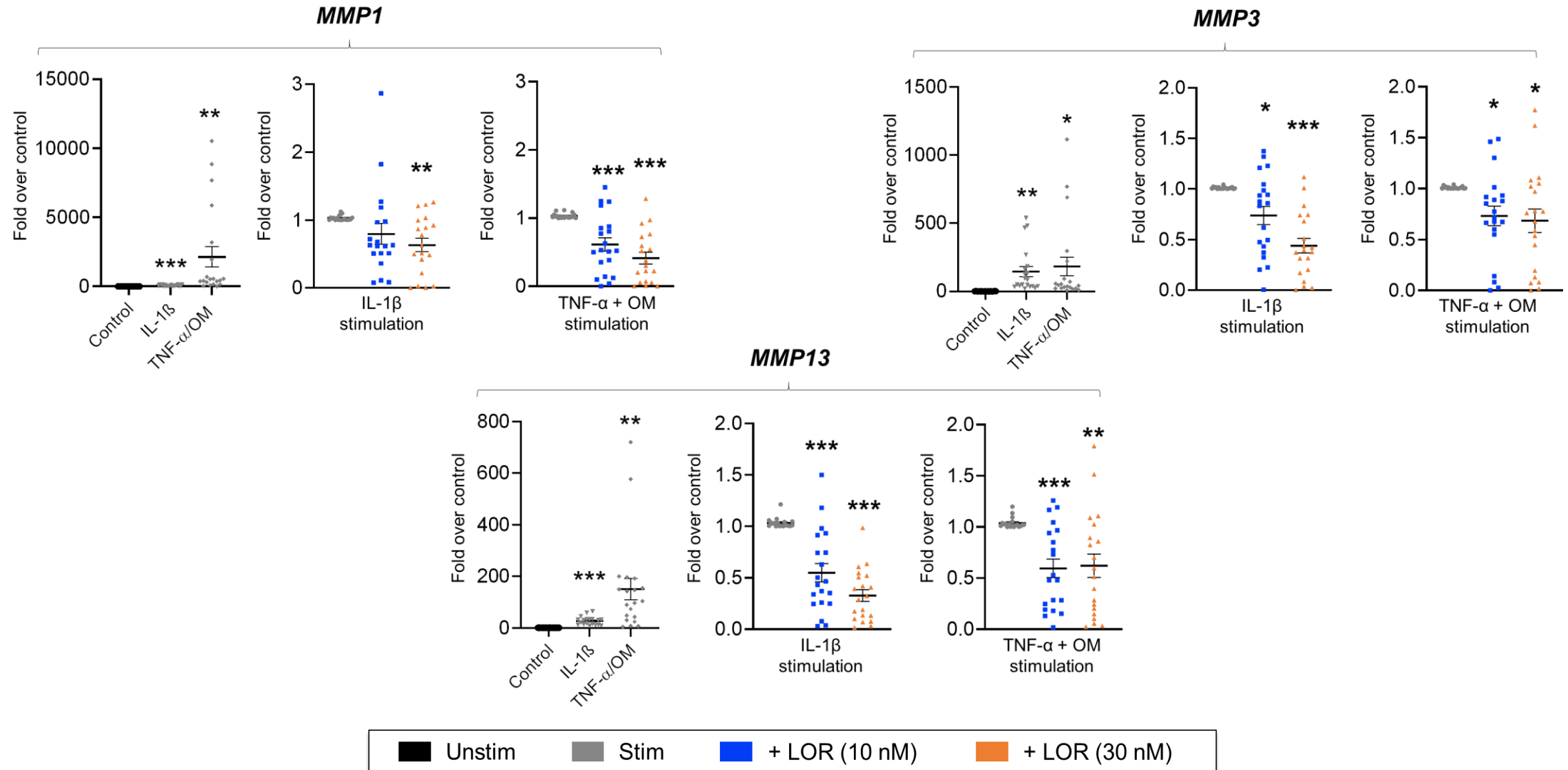
3. Yazici Y, et al. *Osteoarthr Cartil.* 2019.

Experimental design



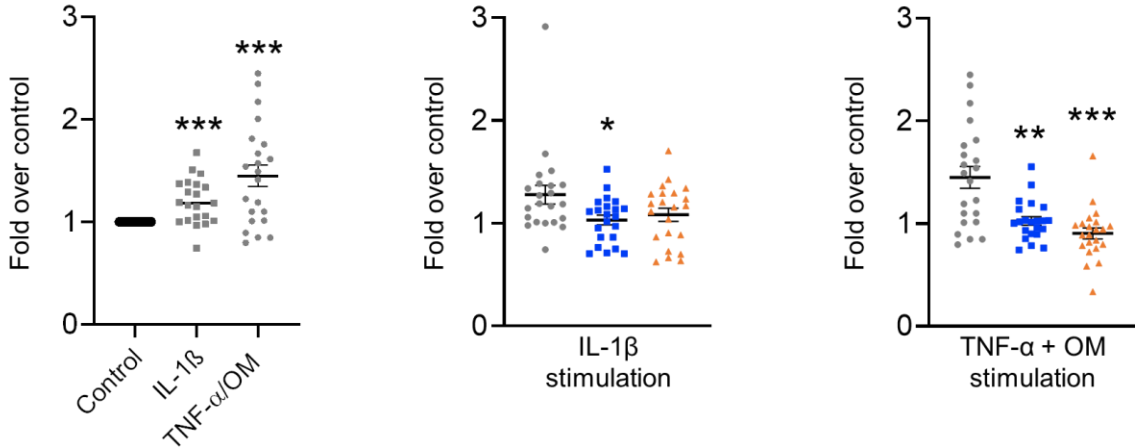
- Knee joint tissue was obtained from 22 TKR donors through Scripps Clinic*
- Cartilage was assessed on the Outerbridge scale by gross appearance and graded from 1 (least damage) to 4 (most damage)
- Grade 2–3 explants (4 mm diameter) were harvested and cultured for 48 hours
- Explant cultures were either untreated and unstimulated (stimulated-catabolism controls) or treated with DMSO (control) or LOR (10 or 30 nM) and then stimulated with IL-1 β (10 ng/ml) or TNF- α (20 ng/ml) + oncostatin M (OM; 10 ng/ml) per the timeline above
- Data analyzed via mixed-effects, one-way ANOVA. Outliers identified using extreme studentized deviate test (Grubb's test, $\alpha < 0.001$). Type 1 error controlled at $\alpha < 0.05$ using Dunnett's multiple comparison test, comparing both treatment dose groups independently with untreated group

Catabolic gene expression in human TKR explants treated with LOR

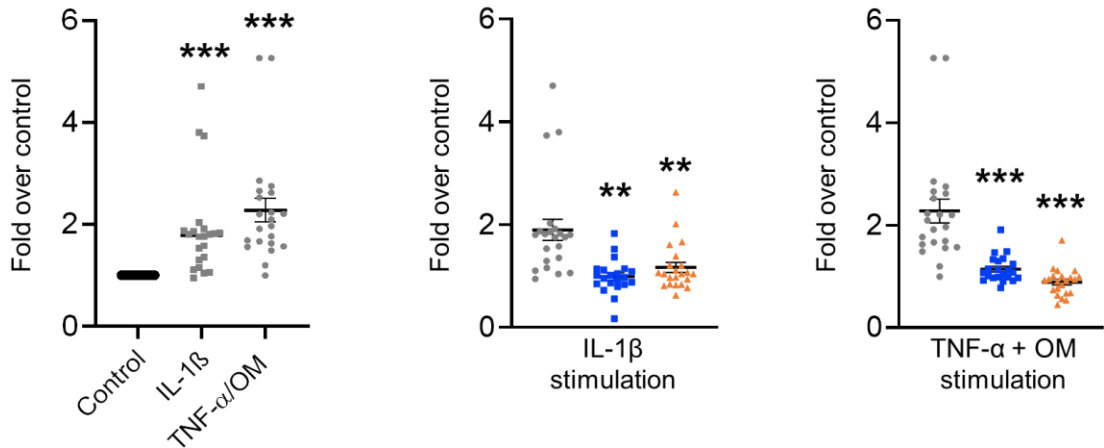


Enzyme secretion in human TKR explants treated with LOR

ADAMTS-4



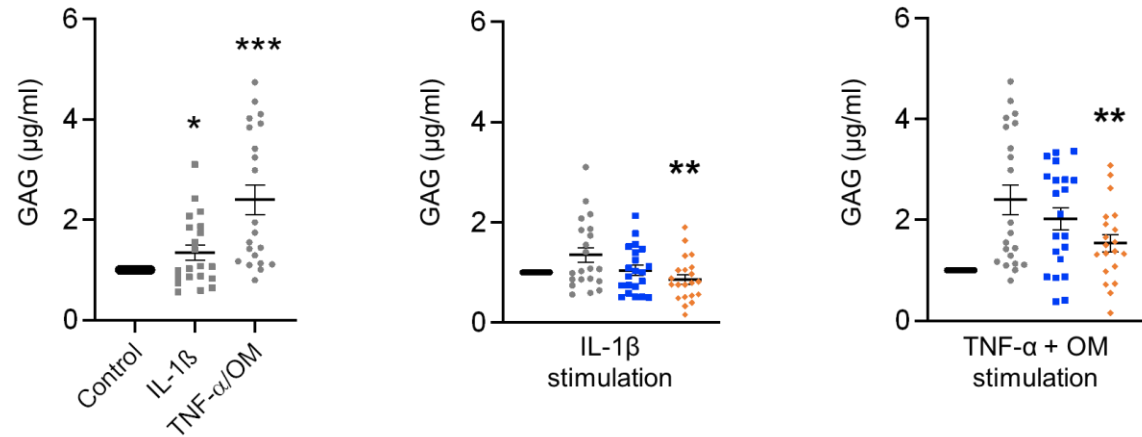
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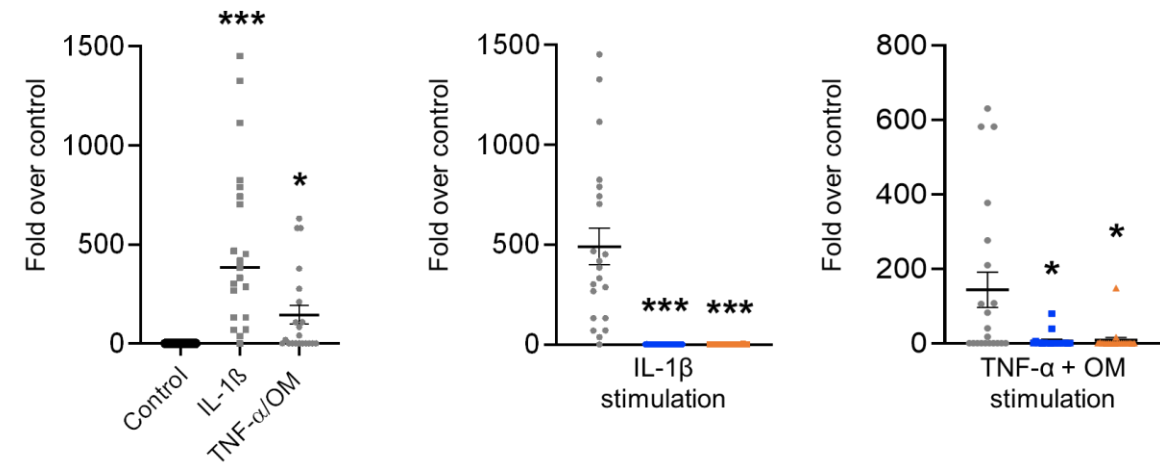
N=22; Mean \pm SEM; * P <0.05, ** P <0.01, *** P <0.001 vs. DMSO, one-way ANOVA

Extracellular levels of catabolic end products in human TKR explants treated with LOR

GAG release



NO release



■ Unstim ■ Stim ■ + LOR (10 nM) ■ + LOR (30 nM)

Conclusions

- LOR impaired pro-inflammatory cytokine-stimulated cartilage catabolism in human knee explant cultures compared with controls, as shown by suppression of
 - Gene expression of *MMP1*, *MMP3*, and *MMP13*
 - Stimulated secretion of all tested catabolic enzymes
 - Release of the cartilage catabolism byproducts GAG and NO
- These data indicate that LOR exerted protective effects on knee cartilage *ex vivo* despite previous OA-related joint damage
- The results support the development of LOR as a potential disease-modifying treatment for knee OA. Phase 3 trials are ongoing

Thank you