LORECIVIVINT (SM04690), A POTENTIAL DISEASE-MODIFYING TREATMENT FOR KNEE OSTEOARTHRITIS, DEMONSTRATED CARTILAGE-PROTECTIVE EFFECTS ON HUMAN OSTEOARTHRITIC EXPLANTS

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Poster #166

Background

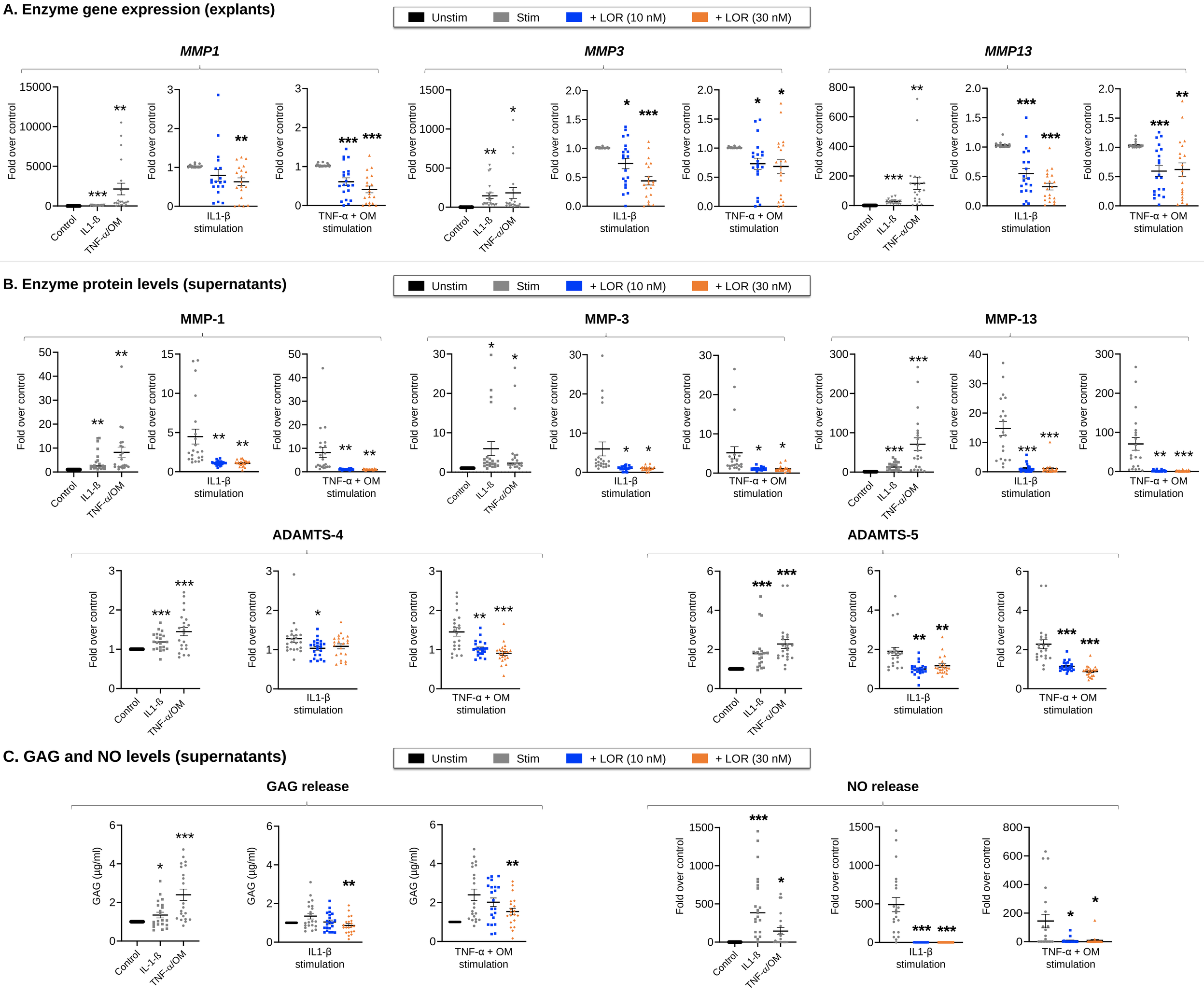
- Excessive Wnt pathway signaling contributes to osteophyte formation, cartilage degeneration, and inflammation[1] in knee osteoarthritis (OA)
- Lorecivivint (LOR) is an intra-articular (IA), small-molecule drug candidate that modulates Wnt pathway activity via CLK/DYRK1A inhibition[2]
- LOR has demonstrated 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 population[3]
- 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

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**

Results

Figure 1. Catabolic gene expression, enzyme secretion, and extracellular levels of catabolic end products in human TKR explants with and without LOR



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

Methods

- After receiving IRB approval from Scripps Health, 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-1β (10 ng/ml) or TNF-α (20 ng/ml) + oncostatin M (OM; 10 ng/ml) per the timeline above
- Effects of LOR on cartilage catabolism (compared with DMSO) in the stimulated cultures were measured by:
  - qRT-PCR for gene expression of matrix metalloproteinases (MMPs) 1, 3, and 13
  - ELISA for release of MMP-1, MMP-3, MMP-13, and the thrombospondin motif-containing disintegrin/metalloproteinases ADAMTS-4 and ADAMTS-5
  - Dimethylmethylene blue and Griess assays for release of the degradation products glycosaminoglycan (GAG) and nitric oxide (NO), respectively
- 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

References

1. Usami Y, et al. *Lab Invest.* 2016.
2. Deshmukh V, et al. *Osteoarthr Cartil.* 2019.
3. Yazici Y, et al. *Osteoarthr Cartil.* 2019.

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