Lorecivivint (SM04690), an Intra-articular, Small-Molecule CLK/DYRK1A Inhibitor That Modulates the Wnt Pathway, as a Potential Treatment for Meniscal Injuries

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Background

- Meniscal injuries, linked with pain, stiffness, and localized swelling, are the most common pathology of the knee and are associated with the progression of knee osteoarthritis (OA).[1]
- Efforts to repair meniscal damage have been largely unsuccessful and do not prevent the progression of degenerative changes that lead to knee OA.[2]
- The Wnt pathway is regulated during meniscal development.[3] Modulation of this pathway may influence meniscal regeneration.

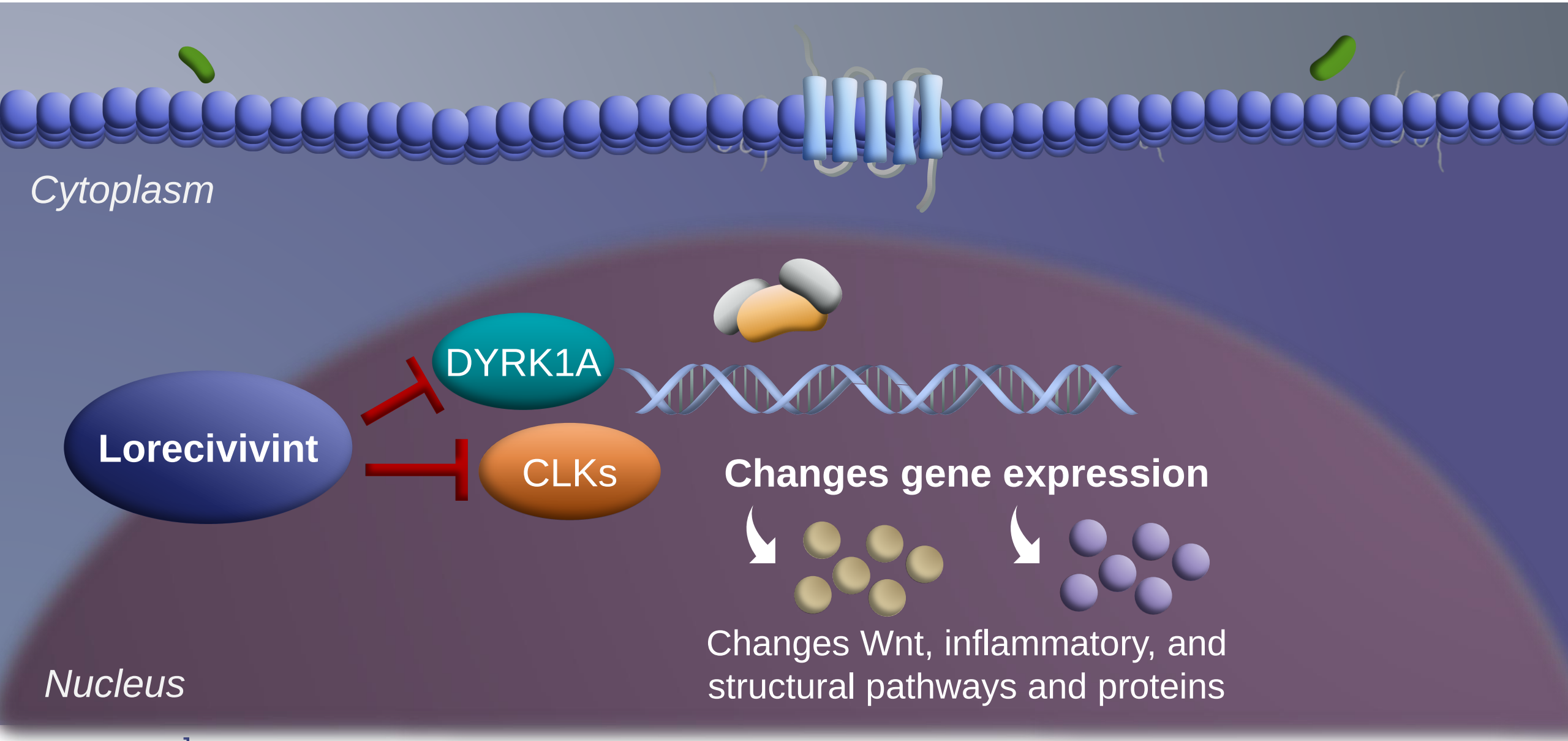
1. Englund M, et al. *Rheum Dis Clin North Am*. 2009.
2. Collins JE, et al. *Arthritis Care Res (Hoboken)*. 2019.
3. Pazin DE, et al. *Dev Dyn*. 2012.

Lorecivivint

- Lorecivivint (LOR; SM04690), an intra-articular (IA), small-molecule CLK/DYRK1A inhibitor that modulates the Wnt pathway, is in development as a potential treatment for knee OA.[1]
  - Clinical trials suggest that a single IA injection of LOR appears to be well tolerated and has potential to improve pain and function and maintain medial joint space width in subjects with knee OA.[2,3]
- This study sought to determine if the effects of LOR seen in preclinical models of OA could be extended to affect the meniscus.

1. Deshmukh V, et al. *Osteoarthr Cartil.* 2019.
2. Yazici Y, et al. *Arthritis Rheumatol*. 2020.
3. Yazici Y, et al. *EULAR.* 2019. Poster #THU0458.

LOR modifies inflammation and Wnt signaling



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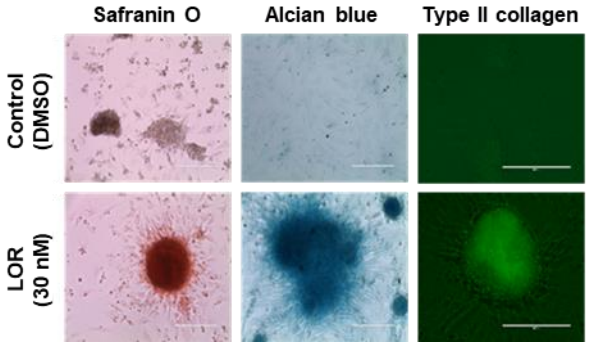
CLK: CDC-like kinase, DYRK1A: Dual-specificity tyrosine phosphorylation-regulated kinase 1A

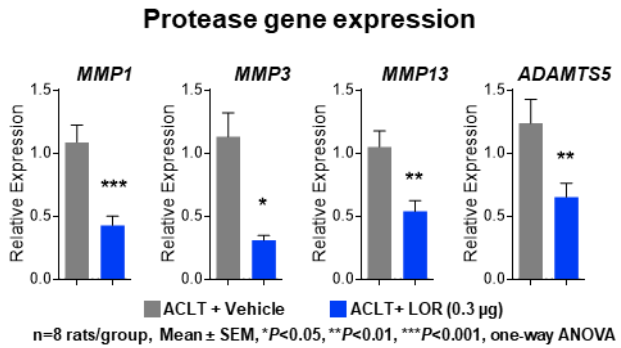
LOR preclinical development in OA

In vitro assays and animal models of OA

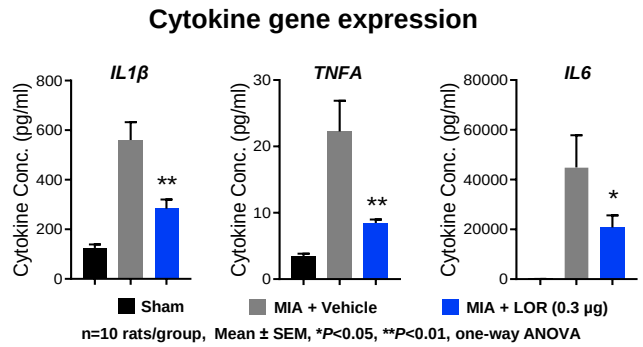
hMSC assays → **Chondrocyte Regeneration**



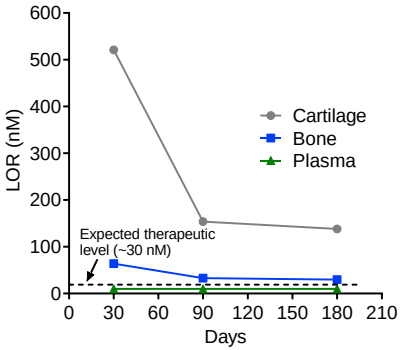
Protease assays → **Cartilage Protection**

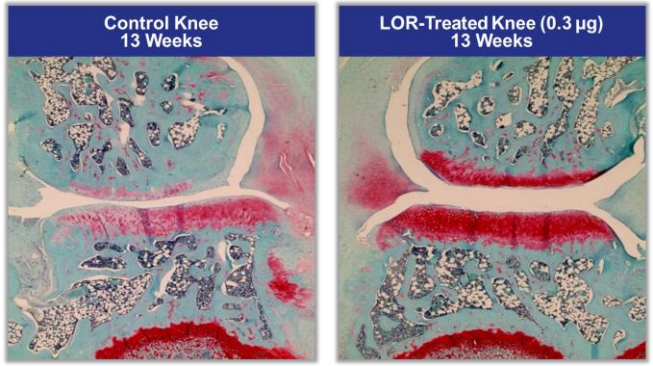


Cytokine assays → **Anti-inflammation**



Animal models → **Sustained PK**





Improved Joint Health
(Animal models)

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Study objective and hypothesis

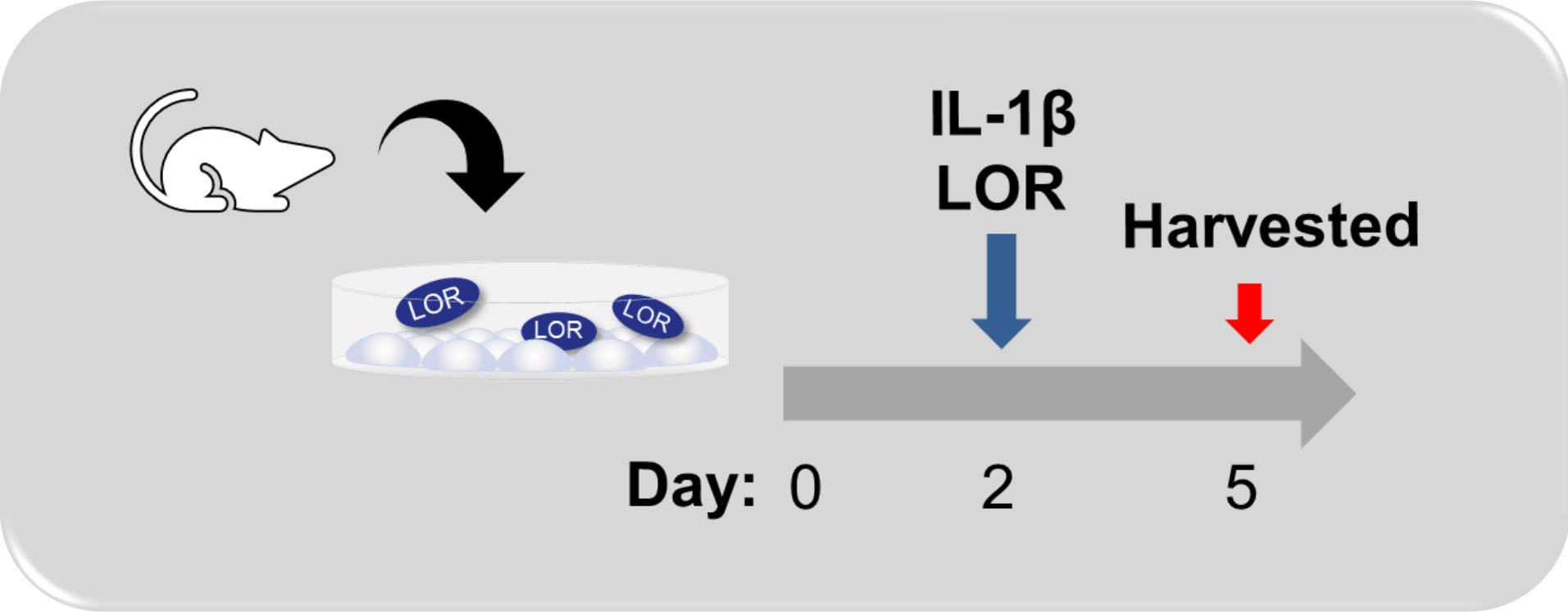
Objective

- LOR was evaluated in preclinical studies to determine its protective and anabolic effects in ex vivo explants and a rat model of inflammatory meniscal degeneration.

Hypothesis

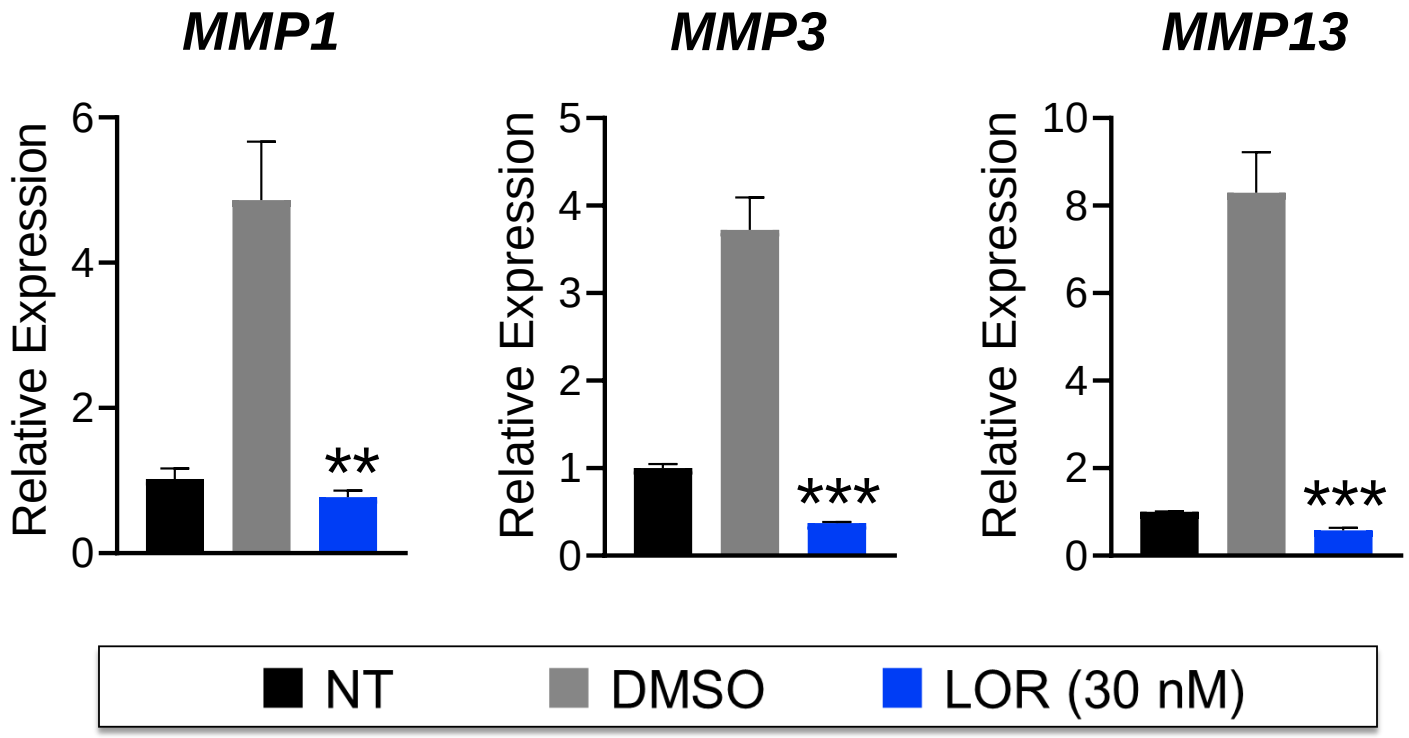
- Treatment with LOR will decrease catabolic enzyme and inflammatory cytokine gene expression and increase collagen gene expression.

Ex vivo explant model



Rat menisci were isolated and cultured in media for 2 days. Cultures were then stimulated with IL-1β (10 ng/ml) and treated with DMSO or LOR (30 nM) for 72 hours.

LOR inhibited catabolic enzyme gene expression ex vivo



Rat menisci were isolated and cultured in media for 2 days. Cultures were then stimulated with IL-1β (10 ng/ml) and treated with DMSO or LOR (30 nM) for 72 hours. Gene expression was measured by qRT-PCR. N=3, Mean ± SEM, $^{**}P<0.01$, $^{***}P<0.001$, one-way ANOVA; NT: Not treated.

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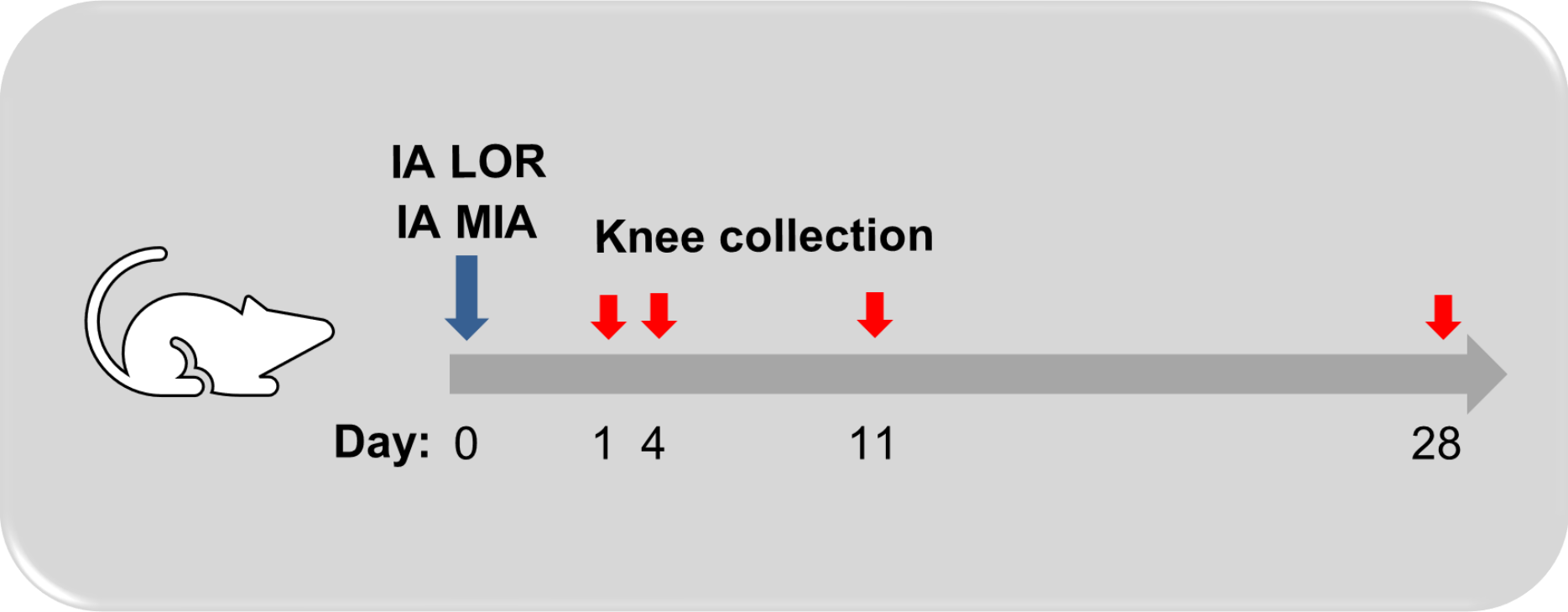
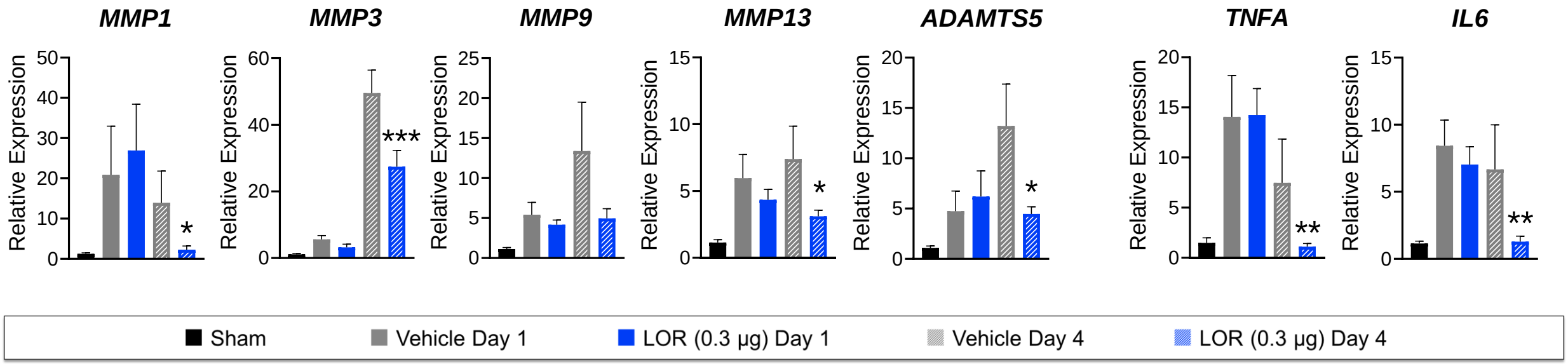
In vivo rat model



A single IA injection of monosodium iodoacetate (MIA; 3 mg) was immediately followed by a single IA injection of LOR (0.3 µg) or vehicle at 10 weeks of age. Knees were harvested on Days 1, 4, 11, and 28 after injection and menisci were isolated.

LOR reduced catabolic enzyme and inflammatory cytokine gene expression in vivo



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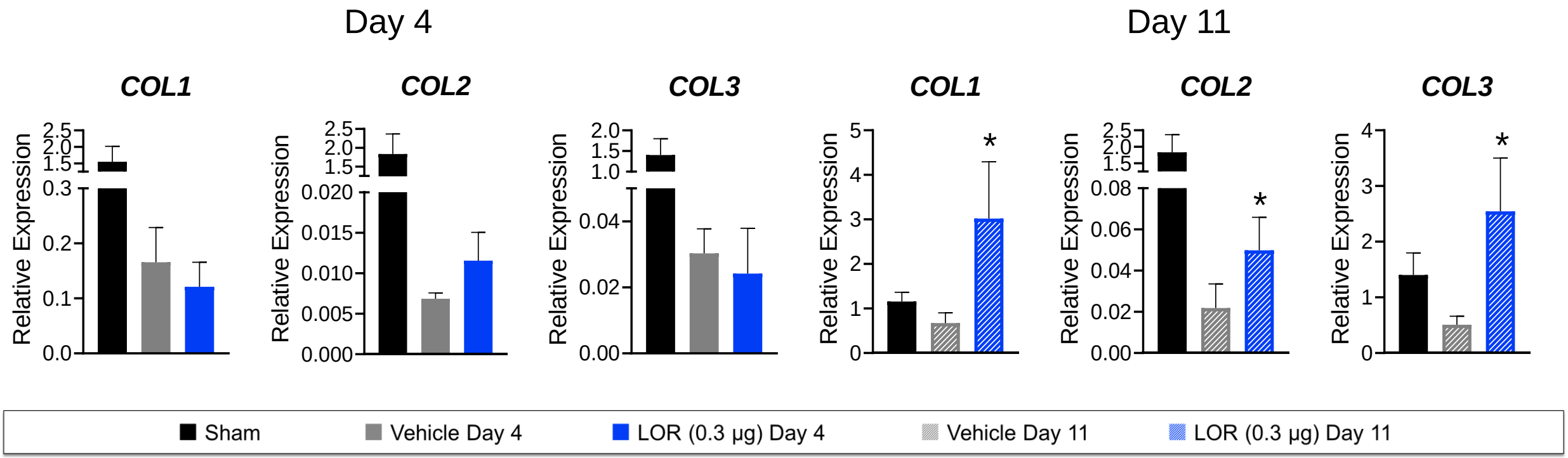
LOR increased collagen gene expression in vivo



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Conclusions and significance

- LOR exhibited protective and anabolic effects in the meniscus, compared with controls, as shown by
  - Inhibition of catabolic enzyme gene expression ex vivo and in vivo.
  - Reduced inflammatory cytokine gene expression in vivo.
  - Increased collagen gene expression in vivo.
- These data support further investigation of LOR as a potential structure-modifying treatment for meniscal damage.
- Intra-articular injection of LOR may slow meniscal degeneration by reducing catabolic enzymes and inflammatory cytokines and/or increasing collagen-building activity.
- LOR may have potential as a structure-modifying treatment for meniscal injuries, which is an area of high unmet clinical need.

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Thank you