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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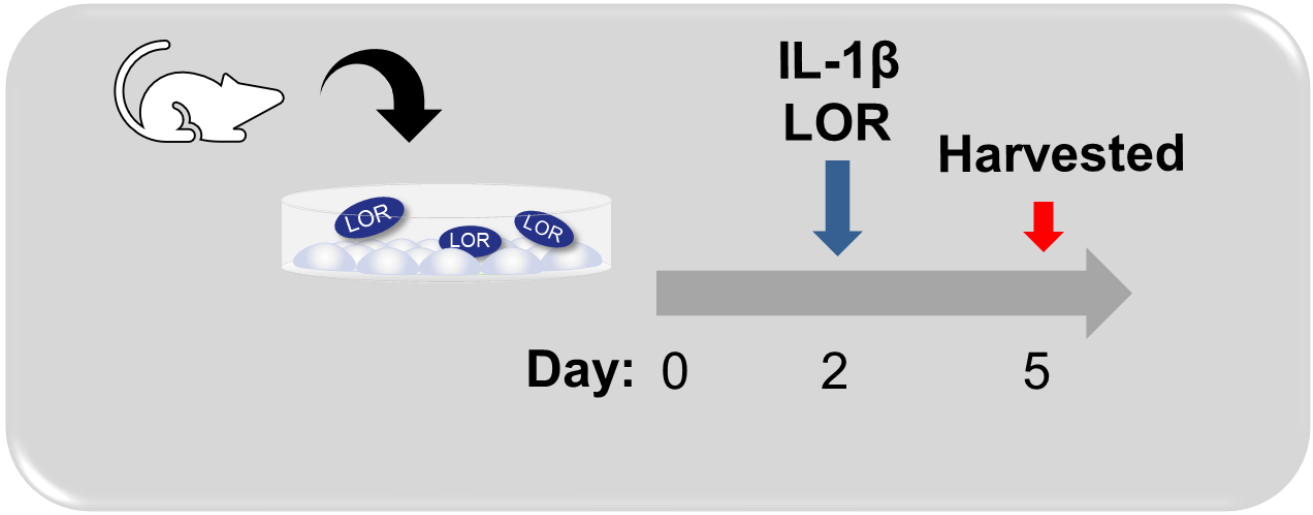
Background

- Meniscal injuries, associated with pain, stiffness, and localized swelling, are the most common pathology of the knee
- Meniscal damage is a frequent finding on MRI of knee osteoarthritis (OA)[1]
- Efforts to repair meniscal damage have been largely unsuccessful and do not prevent the progression of degeneration that leads to knee OA[2]
- The Wnt signaling pathway is regulated during meniscal development,[3] and manipulation of this pathway may influence meniscal regeneration
- Lorecivivint (LOR; SM04690), an intra-articular (IA), small-molecule CLK/DYRK1A inhibitor that modulates the Wnt pathway,[4] was evaluated in preclinical studies to determine its protective and anabolic effects in *ex vivo* explants and a rat model of inflammatory meniscus degeneration

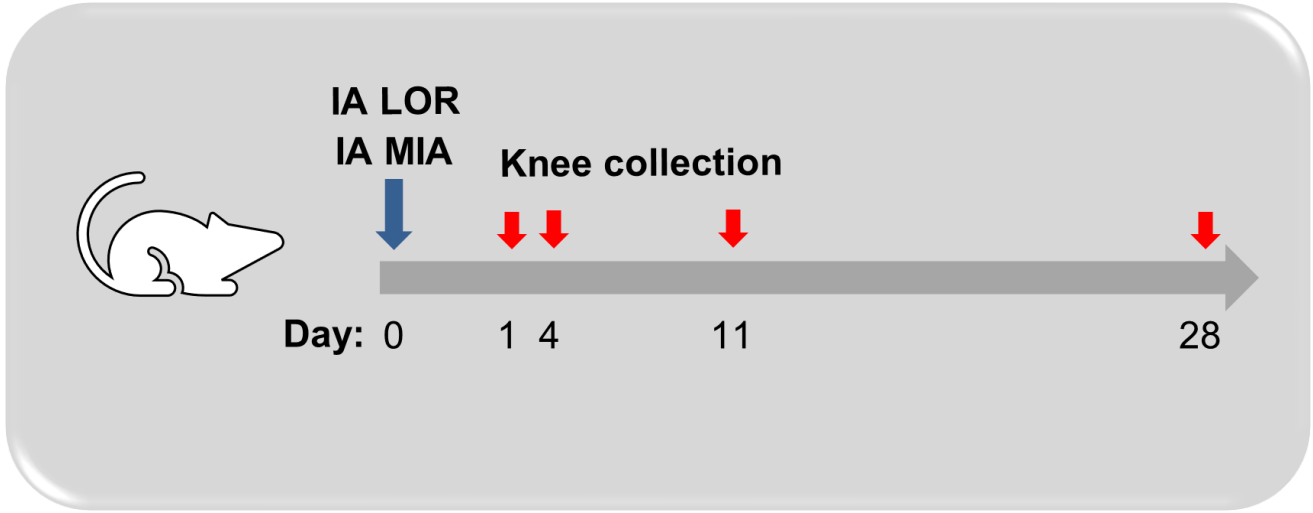
1. Englund M, et al. *Rheum Dis Clin North Am*. 2009.
2. Collins JE, et al. *Arthritis Care Res (Hoboken)*. 2019.
3. Pazin DE, et al. *Dev Dyn*. 2012

Preclinical models used to evaluate LOR

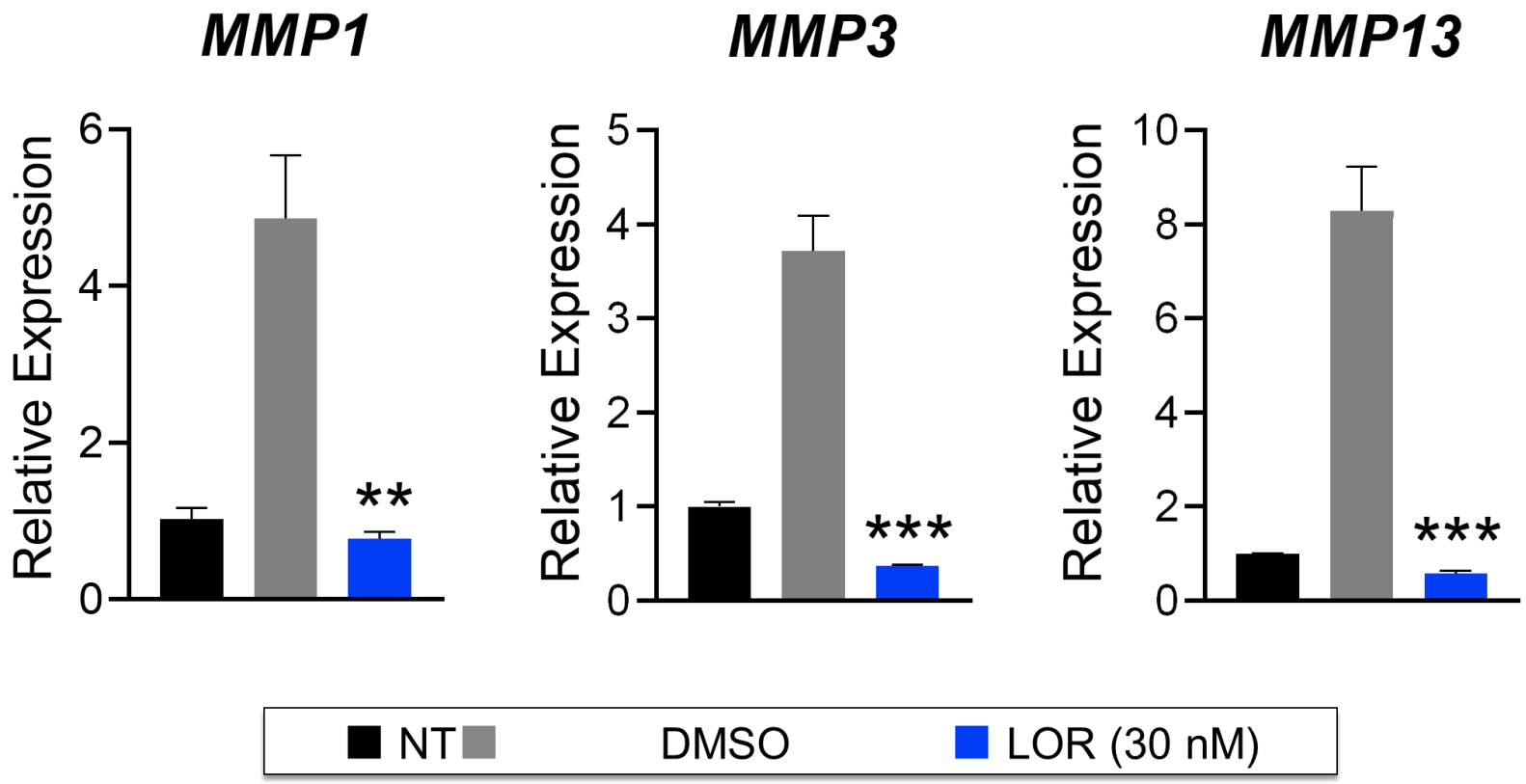
Ex vivo explant model



Rat model of inflammatory meniscus degeneration

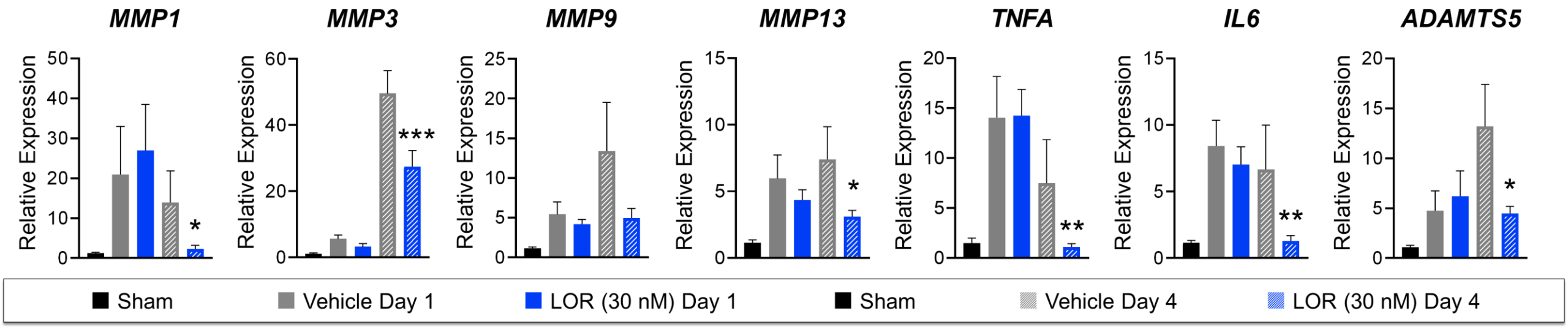


LOR inhibited catabolic enzyme gene expression *ex vivo*



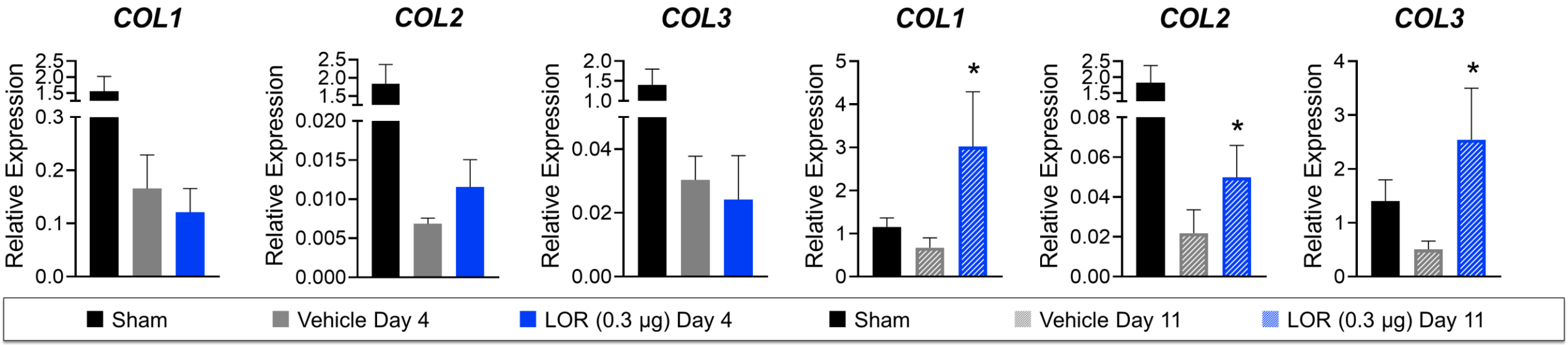
Rat menisci were isolated and cultured in media for 2 days. Cultures were then stimulated with IL-1β (10 ng/ml) and treated with DMSO or LOR (30 nM) for 72 hours. Gene expression was measured by qRT-PCR. N=3, Mean ± SEM, ***P*<0.01, ****P*<0.001, one-way ANOVA

LOR reduced catabolic enzyme and inflammatory cytokine gene expression *in vivo*



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, and 11 after injection and menisci were isolated. Gene expression was measured by qRT-PCR. N=3, Mean ± SEM, **P*<0.05 , ***P*<0.01, ****P*<0.001, one-way ANOVA

LOR increased collagen gene expression *in vivo*



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Conclusions

- 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 disease-modifying therapy for meniscal damage

Thank you