Injectable hydrogel for sustained delivery of lacosamide in treating osteoarthritis

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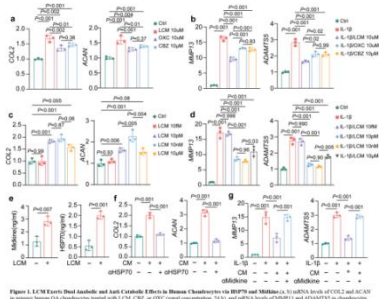
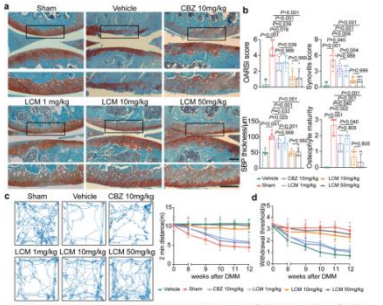
Introduction: We recently reported the voltage-gated sodium channel Nav1.7—traditionally considered specific to peripheral nociceptive neurons—as a previously unrecognized chondrocyte-expressed, osteoarthritis (OA)-associated molecule (Fu et al, *Nature*, 2024). Pharmacological blockade of Nav1.7 with either the selective inhibitor or the clinically approved pan-Nav channel blocker Carbamazepine (CBZ) markedly attenuated structural joint damage and alleviated OA-related pain behaviors (Fu et al, *Nature*, 2024). In the present study, we compared the therapeutic efficacy of several clinically used, non-selective, FDA-approved sodium channel inhibitors, including CBZ, lacosamide (LCM), and Oxcarbazepine (OXC), to identify the most potent candidate for OA treatment. We further evaluated LCM via multiple administration routes in a mouse OA model. To achieve sustained intra-articular delivery, we developed a hydrogel-based LCM formulation enabling prolonged release.

Methods: All animal experiments were performed in accordance with institutional guidelines and approved by the Institutional Animal Care and Use Committee of Yale University. In vitro, primary human chondrocytes and C28/I2 chondrocytes were treated with LCM, CBZ or OXC at various concentrations. The expression of anabolic markers (COL2, ACAN) and catabolic markers (MMP13, ADAMTS5) was quantified by real-time PCR (qPCR). Enzyme-linked immunosorbent assay (ELISA) was used to measure the concentrations of HSP70 and midkine in conditioned media collected from treated chondrocytes. In vivo, destabilization of the medial meniscus (DMM) was surgically induced in 12-week-old wild-type (WT) male mice.

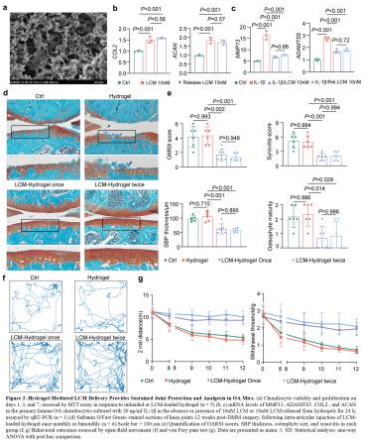
Results: **LCM Exerts Dual Anabolic and Anti-Catabolic Effects in Human Chondrocytes via HSP70 and Midkine.** To assess the translational relevance, we examined Nav1.7 inhibition in primary human chondrocytes from patients with Kellgren–Lawrence grade 3–4 knee OA. IL-1β–induced expression of MMP13 and ADAMTS5 was suppressed by all three Nav1.7 blockers, with lacosamide (LCM) showing the strongest dual effect of promoting COL2 and ACAN while inhibiting catabolic genes (Fig. 1a, b). Under inflammatory conditions, LCM again downregulated MMP13 and ADAMTS5 and upregulated COL2 and ACAN, with a U-shaped dose–response curve peaking at 10 nM (Fig. 1c, d). LCM also increased HSP70 and midkine secretion (Fig. 1e), and blocking experiments showed that HSP70 neutralization abolished its anabolic effects, while midkine blockade eliminated its anti-catabolic effects (Fig. 1f, g).



Systemic LCM Administration Provides Dose-Dependent Structural and Symptomatic Relief in Osteoarthritis. We next evaluated the in vivo therapeutic potential of systemic LCM in DMM mice. Oral gavage of CBZ (10 mg/kg/day) or LCM (1, 10, or 50 mg/kg/day) significantly reduced cartilage loss, synovitis, subchondral bone thickening, and osteophyte formation compared with vehicle (Fig. 2a, b). Both drugs alleviated OA-associated pain, as shown by increased movement distance and higher paw withdrawal thresholds (Fig. 2c, d). LCM at 10 mg/kg provided the most robust protection—reducing cartilage loss, relieving pain, enhancing COL2 expression, and suppressing matrix-degrading enzymes—outperforming CBZ at the same dose. Dose–response analysis revealed that 1 mg/kg LCM reduced cartilage degradation without affecting pain, whereas 10 mg/kg and 50 mg/kg doses produced stronger joint protection and significant analgesia. These results highlight LCM as a potential disease-modifying OA therapy with superior efficacy over CBZ, even at lower doses.



Hydrogel-Mediated LCM Delivery Provides Sustained Joint Protection and Analgesia in OA Mice. SEM imaging revealed an interconnected porous architecture favorable for nutrient diffusion and cell compatibility (Fig. 3a). Hydrogel-released LCM showed comparable effects to free LCM in modulating COL2, ACAN, MMP13, and ADAMTS5 expression in primary chondrocytes (Fig. 3b,c). In DMM mice, intra-articular injection of LCM-loaded hydrogel (monthly or once every two months) starting 4 weeks post-surgery significantly reduced cartilage loss, synovitis, subchondral bone thickening, and osteophyte formation compared with PBS or blank hydrogel (Fig. 3d, e). A single injection provided protection comparable to monthly dosing. LCM-hydrogel treatment also alleviated OA-associated pain, increasing locomotor activity and paw withdrawal thresholds (Fig. 3f, g). These results demonstrate that hydrogel-mediated LCM delivery offers potent structural and analgesic benefits in OA and supports repurposing LCM as a disease-modifying therapy.



Conclusion and significance: This study demonstrates that pharmacological inhibition with the FDA-approved drug LCM exerts dual anabolic and anti-catabolic effects in human chondrocytes via HSP70 and midkine. In a surgically induced OA mouse model, systemic LCM administration provided dose-dependent structural protection and analgesia, outperforming carbamazepine at equivalent doses. Furthermore, hydrogel-mediated intra-articular delivery of LCM enabled sustained release, with even a single injection conferring long-lasting joint protection and pain relief comparable to repeated dosing. Collectively, these findings highlight LCM as a promising disease-modifying OA therapy with strong translational potential, offering a clinically viable strategy to repurpose an FDA-approved drug for both structural preservation and symptom management in OA.

Reference: Fu, et al, *Nature*. 2024;625(7995):557-65.

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