

# Cartilage Protection with a Tissue-Penetrating Hydrogel Depends on Meniscus Rehealing in a Rat MMT Model

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**INTRODUCTION:** Traumatic joint injuries place a biomechanical and inflammatory burden on the articular cartilage. This typically initiates breakdown of the pericellular matrix (PCM) around chondrocytes [1] and commences a deteriorative cycle [2], motivating preventative therapies to curb arthritis progression. Previously, we developed a tissue-penetrating hyaluronic acid hydrogel (tpHA) that integrates within cartilage and protects it from subsequent deterioration in *in vitro* explant culture models [3,4]. The objective of this study was to evaluate tpHA in a rat medial meniscus transection (MMT) model [5] to determine its *in vivo* protective capacity in a post-traumatic osteoarthritis (PTOA) model.

**METHODS:** Lewis rats (male, 10-12 weeks old) were subject to a transection of the medial collateral ligament and medial meniscus (n=16 total rats; Fig 1A). To half of animals, we applied 10µL of 4% w/v methacrylated HA (20kDa, +0.05% LAP photocrosslinker) to joints, allowed five minutes for diffusion into tissues, and photocrosslinked with blue light (10mW/cm<sup>2</sup>) for 3 minutes. Joints were rinsed with sterile PBS to remove non crosslinked tpHA. In *ex vivo* joints, we applied tpHA supplemented with methacrylated rhodamine, after which tissues were imaged with confocal microscopy. We also verified integration of tpHA into bovine joint tissues (synovium/fat pad, cartilage). At 8-weeks, animals were euthanized for retrieval of joint tissues. Meniscus remnants and other soft tissue growing in place of the meniscus was extracted and classified as 1) Meniscus Rehealed, 2) Two Halves, 3) Fibrous Scar, 4) One Half. Tibial plateaus were subject to biomechanical mapping for quantification of instantaneous modulus (medial third of tibial plateau; Fig. 2A). Tibial plateau samples were then processed for Safranin O-Fast Green staining.

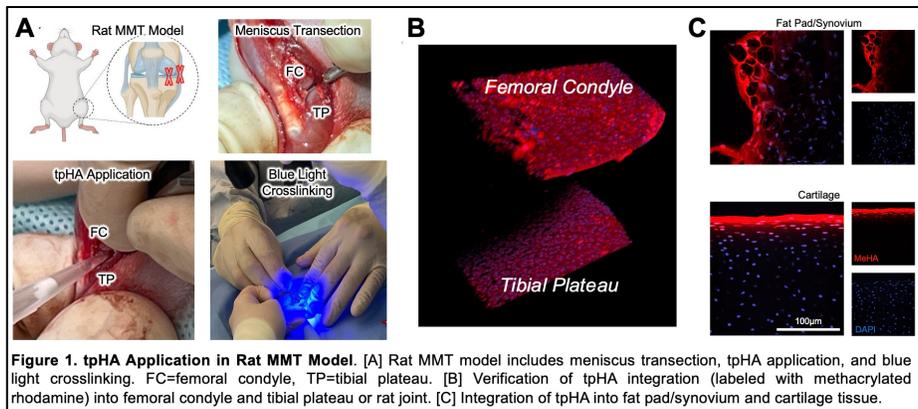
**RESULTS:** Successful integration of tpHA into rat knee cartilage (Fig. 1B) and bovine synovium, fat pad, and cartilage (Fig. 1C) was confirmed with confocal microscopy. In our study, initial quantification of tibial plateau mechanics (Fig. 2B) showed no protective effect of tpHA, though considerable variability was noted. A wide variety of meniscal healing outcomes were noted (Fig. 2C), with modulus values decreasing from classifications 1-4 (Fig. 2D). Interestingly, in cases with more meniscal function (rehealed, two halves), the tpHA treated animals outperformed the nontreated animals with regards to cartilage mechanics. Fibrous scar formation was only observed on nontreated animals. Histological analysis demonstrated in the meniscus rehealed samples that joints treated with tpHA demonstrated greater cartilage thickness (Fig. 3) and slightly improved red proteoglycan staining.

**DISCUSSION:** A tissue-penetrating hyaluronic acid system may protect post-traumatic joints from cartilage deterioration, depending on meniscus rehealing. This motivates the use of tpHA with concomitant reparative procedures (ACL reconstruction, meniscus repair) to restore biomechanical function. Analysis of a cohort of female rats are underway.

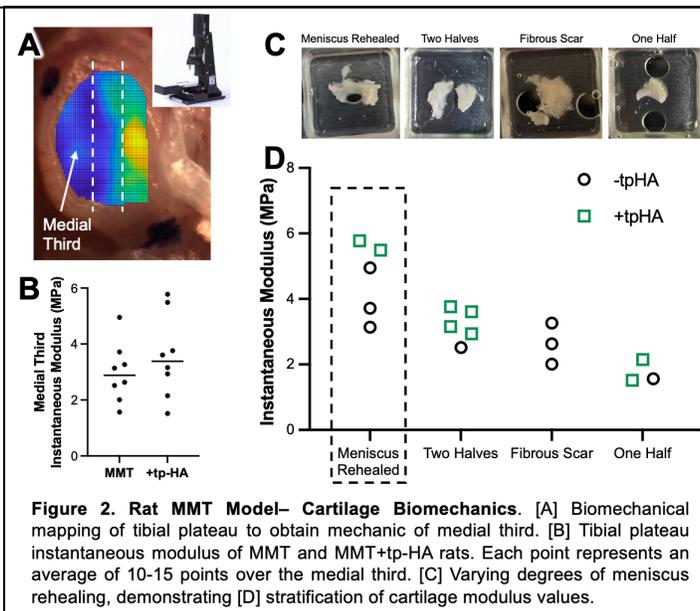
**SIGNIFICANCE/CLINICAL RELEVANCE:** The development of techniques to protect the post-traumatic joint from deterioration would be incredibly useful in preventing PTOA progression, especially in conjugation with surgical reconstruction for restored biomechanics.

**REFERENCES:** [1] Chery+ 2020. [2] Reigger+ 2020. [3] Kowalski+ 2022. [4] Brackin+ 2023. [5] Kaiser+ 2024.

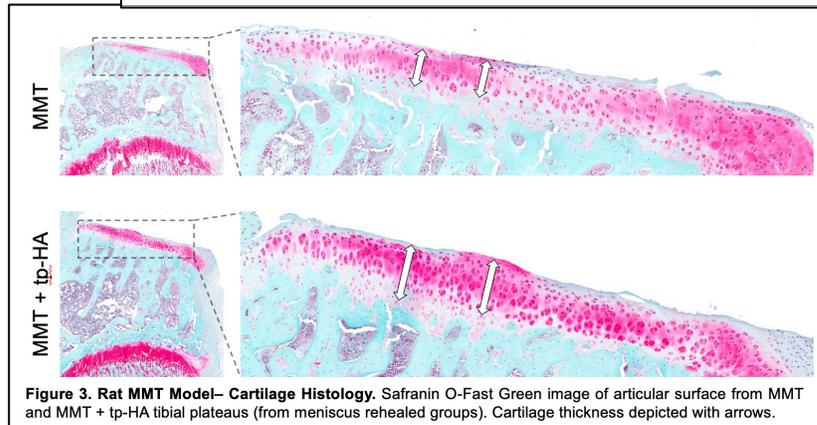
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**Figure 1. tpHA Application in Rat MMT Model.** [A] Rat MMT model includes meniscus transection, tpHA application, and blue light crosslinking. FC=femoral condyle, TP=tibial plateau. [B] Verification of tpHA integration (labeled with methacrylated rhodamine) into femoral condyle and tibial plateau or rat joint. [C] Integration of tpHA into fat pad/synovium and cartilage tissue.



**Figure 2. Rat MMT Model- Cartilage Biomechanics.** [A] Biomechanical mapping of tibial plateau to obtain mechanic of medial third. [B] Tibial plateau instantaneous modulus of MMT and MMT+tp-HA rats. Each point represents an average of 10-15 points over the medial third. [C] Varying degrees of meniscus rehealing, demonstrating [D] stratification of cartilage modulus values.



**Figure 3. Rat MMT Model- Cartilage Histology.** Safranin O-Fast Green image of articular surface from MMT and MMT + tp-HA tibial plateaus (from meniscus rehealed groups). Cartilage thickness depicted with arrows.