Lubricin Mimetic Polymer Lubricates Cartilage in Dose-Dependent Manner

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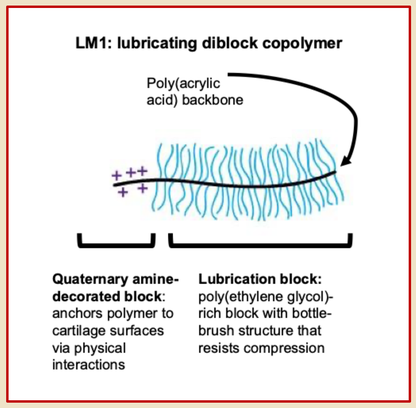
Introduction

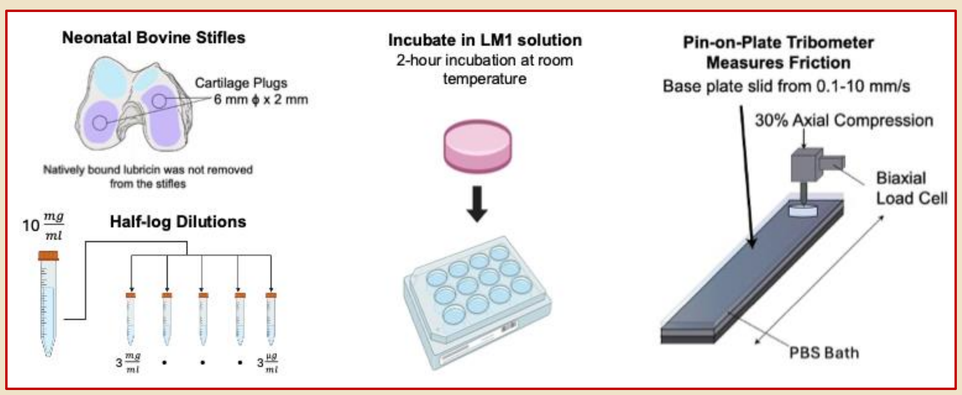
- The low friction nature of articular cartilage is attributed to two molecules in the synovial fluid (SF), lubricin (also known as PRG4) and hyaluronic acid (HA) [1-2].
- HA, a large polysaccharide (~3 MDa) viscous lubricant, has been in use clinically for decades, but the efficacy of HA viscosupplementation is debated.
- Lubricin, a mucinous glycoprotein boundary lubricant, has shown promise for osteoarthritis (OA) treatment in both small and large animal models [3-5]
- However, widescale clinical translation of lubricin as an arthritis therapy has not taken place, largely due to challenges associated with lubricin's stability, purification, yield, and scale of manufacturing.
- The challenges above have led to the need to engineer a synthetic boundary lubricant. [6-9]
- Although, these lubricants[6-9] have been shown to lubricate cartilage, none of these meets or exceed lubricin's lubricating ability.
- Recently, a diblock copolymer that mimics native lubricin's form and function, LM1, has been synthesized. via sequential reversible addition–fragmentation chain transfer (RAFT) polymerization to achieve a diblock structure.
- LM1 is composed of substances that are naturally occurring and components that have been previously used in medical polymers with established safety profiles.
- However, the LM1 has not yet been shown to lubricate healthy or osteoarthritic cartilage.



Objective

Characterize the lubricating behavior of the LM1 diblock copolymer to be used intra-articularly as a treatment for OA.

Methods



Data Analysis & Statistics

- The friction coefficient is calculated as the ratio of the shear load to the normal load, as measured by the biaxial load cell from the pin-on-plate tribometer.
- A linear mixed-effects model was used to fit the friction coefficient data as a function of articulation speed and concentration **(Figure 1)**. Post-hoc pairwise comparisons adjusted for multiple comparisons between the concentrations were conducted.
- A four-parameter variable slope dose-response (**Figure 2)** was fitted to the coefficient of friction-concentration data using the MATLAB curve-fitting toolbox to obtain the EC_{50}, the upper friction plateau *B,* the lower friction plateau *A,* and the steepness of transition *d* , at each articulation speed.
- Kruskal-Wallis tests were performed on the upper plateau coefficient, lower plateau coefficient, and the EC_{50} to test for speed dependency. (**Figure 3)**

References

[1] Jay GD *Mat. Biol* (2014); [2] Bonnevie ED+ *PloS one* (2014); [3] Flannery+ *Arthritis Rheum*, 2009; [4] Jay+ *Arthritis Rheum*, 2011; [5] Waller+ *AOSSM*, 2017; [6] Lakin+ *ACS Biomater*, 2019; [7] Samaroo+ *JOR*, 2017; [8] Sun+ *PNAS*, 2019; [9] Singh+ *Nat Mater*, 2014;

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Results

1. LM1's lubricating ability depends on the incubation concentration

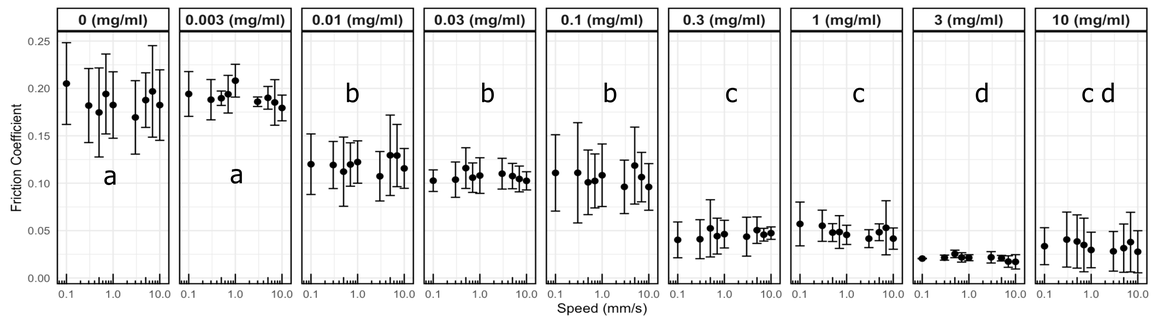

Figure 1. Coefficient of friction across three orders of magnitude of articulation speed at each incubation concentration. Data represents mean±SD of n=3-4 samples per concentration per speed. Post-hoc comparisons of friction at each speed between each concentration of LM1 is represented using letters (a > b > c > d, p<0.01).

2. High concentrations of LM1 lubricated better than bovine synovial fluid (BSF)

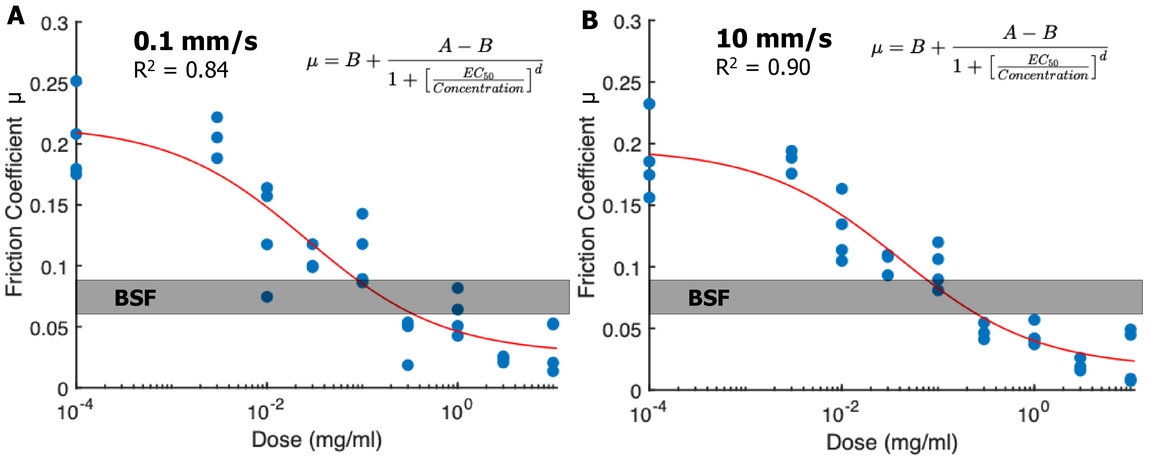

Figure 2. 4-parameter dose response curve fits of friction as a function of LM1 incubation concentration at **A:** articulation speed of 0.1 mm/s and **B:** articulation speed of 10 mm/s. Each dot represents experimentally obtained friction data and the red line represents the fitted curve. The gray shaded region represents the friction coefficients of cartilage slid in healthy BSF.

3. There was no speed dependence across the dose-response fitted parameters

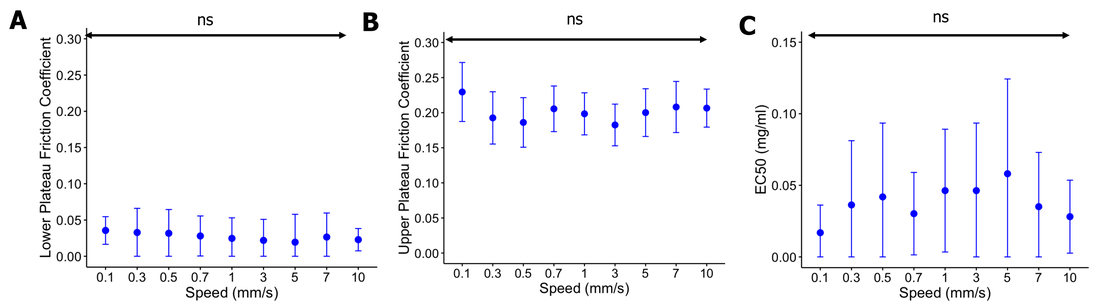

Figure 3. Plots of the mean and 95% confidence interval of the fitted coefficients from the dose-response curve fits at each articulation speed: **A** plots the lower plateau friction coefficient, *A.* **B** plots the upper plateau friction coefficient, *B.* **C** plots the EC_{50}.

Discussion & Conclusions

- LM1 lubricates cartilage in a dose-dependent manner and achieves very low friction coefficients when incubated at high concentrations.
- Previous studies of lubricin-like polymers reported the lowest friction coefficients ranging from 0.03 - 0.14 [6-9], whereas LM1 had measured friction coefficients as low as 0.01, which is also lower than friction coefficients of cartilage slid in a BSF bath.
- There was no speed dependence on the EC_{50}, higher or lower friction coefficient plateaus, indicative of an effective boundary lubricant.
- Low friction coefficients obtained from the methodology of incubation in polymer solution, followed by sliding in the PBS bath, instead of sliding directly in the lubricant bath are noteworthy. This configuration may be more indicative of an effective in-vivo therapeutic, with the lubricant dispersing within the joint and attaching to the cartilage surface.
- Future studies will investigate LM1's lubricating ability on biochemically (IL-1β) degraded cartilage as well as mechanically impacted cartilage, as representatives of osteoarthritic cartilage.
- LM1's prevention of wear and increases of surface roughness will also be studied.

Significance

This study measured remarkably low friction coefficients of cartilage after incubation at high concentrations in the LM1 polymer. This finding shows promising lubricating ability of bottle-brush polymer synthetics that may be used to help treat osteoarthritis.

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