

Intraarticular Lubricin Supplementation is Chondroprotective and Prevents Cartilage Degeneration in Experimental OA

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Cartilage lubrication: historical perspectives



www.nlm.nih.gov
Prof. Sir John Charnley (1911-1982)
FRS, FRCS; 1974 Lasker Award Winner

"... Nature has conveniently covered the rubbing surfaces of the bones with a highly polished layer of cartilage... and has provided a viscous liquid (synovial fluid) to moisten these surfaces."

"It might seem unduly contentious... to suggest that the synovial fluid of a joint is not a lubricant; this is, however, the object of this paper."

from: Charnley J. 1959. *The lubrication of animal joints.*
In: *Symposium on Biomechanics.*
Institution of Mechanical Engineers, London, pp. 12-22.

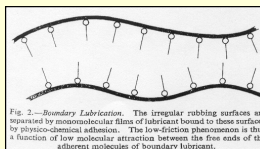


Fig. 2.—Boundary Lubrication. The irregular rubbing surfaces are separated by monomolecular films of lubricant bound to these surfaces by physico-chemical adhesions. The low-friction phenomenon is thus a function of low molecular attraction between the free ends of the adhered molecules of boundary lubricant.

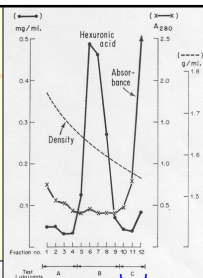
The Discovery of Lubricin

Radin EL, et al. 1970. *Nature* 228:378-379.

Separation of a Hyaluronate-free Lubricating Fraction from Synovial Fluid

Harvard Medical School,
Massachusetts General Hospital,
Boston, Massachusetts 02114.

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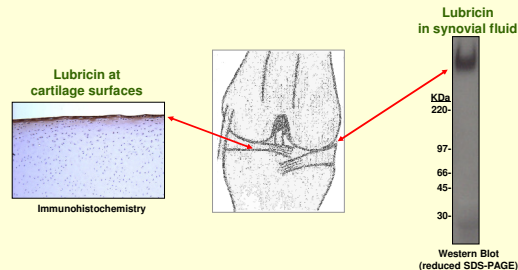
Swann DA, et al. 1981. *J Biol Chem* 256:5921-5925.

The Molecular Structure of Lubricating Glycoprotein-I, the Boundary Lubricant for Articular Cartilage*

David A. Swann, Henry S. Slayter, and Fred H. Silver
From the Departments of Surgery, Pathology, and Physiology, Harvard Medical School, at the Shivers Burns Institute, Massachusetts General Hospital and the Sidney Farber Cancer Institute, Boston, Massachusetts 02114.

expected based on its extended dimensions. The name of "lubricin" is suggested for this lubricating glycoprotein.

Lubricin is a synovial glycoprotein which localizes to and protects cartilage surfaces

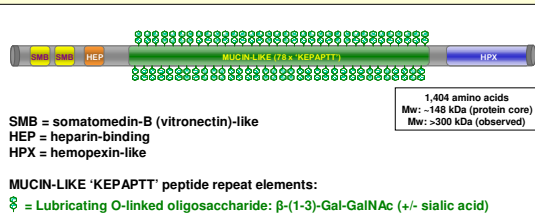


Lubricin functions as a boundary lubricant and anti-adhesive at joint tissue surfaces, to help prevent wear and degeneration.

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Lubricin

- 1970-80s: Isolated from synovial fluid and characterized (Swann, et al.).
- Early 1990s: Gene cloned at Genetics Institute; described as 'MSF'.
- Late 1990s: Identity of MSF with lubricin established.



SMB = somatomedin-B (vitronectin)-like
HEP = heparin-binding
HPX = hemopexin-like

MUCIN-LIKE 'KEPAPTT' peptide repeat elements:

⊗ = Lubricating O-linked oligosaccharide: β -(1-3)-Gal-GalNAc (+/- sialic acid)

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In vivo depletion of lubricin: pathology

Human lubricin gene mutations (CACP syndrome) prevent lubricin synthesis. Patients exhibit synovial hyperplasia and fibrosis, and early onset cartilage degeneration.
(Marcelino et al. *Nature Genet* 1999)

Lubricin KO mice exhibit cartilage degeneration and loss, synovial hyperplasia and tendon abnormalities.
(Rhee et al. *J Clin Invest* 2005; Wyeth unpublished data)

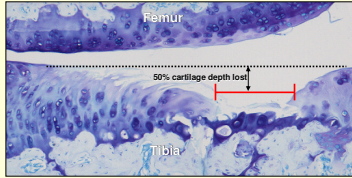
Reduced lubricin expression correlates with disease progression in animal models of osteoarthritis.
(Elsaid et al. *Arthritis Rheum* 2005; Young et al. *Arthritis Res Ther* 2006; Teeple et al. *J Orthop Res* 2008)

Indicates lubricin supplementation would be beneficial in treating joint disease

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Other objective scoring

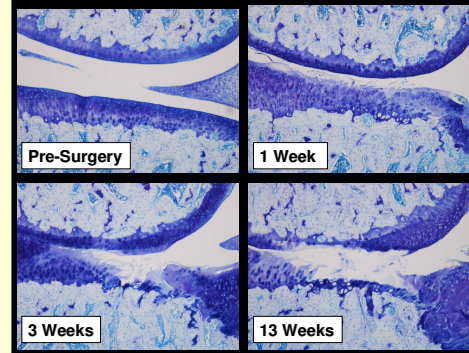
- Matrix loss: micrometer measurements of the width of cartilage damage
 - Total width of cartilage loss: Incorporates collagen loss and fibrillation.
 - >50% loss of cartilage depth = severe lesions.



- Fibroplasia assessed by measuring width of the medial joint capsule.

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Progression of Cartilage Lesions Post-MT



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Study design to assess DMOAD activity

N=20 rats/group.

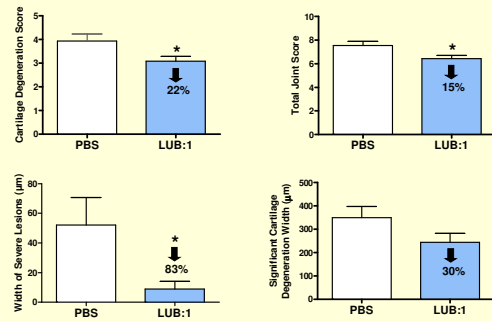
Unilateral hind-limb MT surgery performed; treatment started one week later.

Treatment groups:

- Study 1: **PBS (40µl)** } 3X/week dosing for 4 weeks
LUB:1 (20µg) }
- Study 2: **PBS (40µl)** } 1X/week dosing for 4 weeks
LUB:1 (20µg) }

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LUB:1 significantly attenuates OA progression (3X/week dosing)

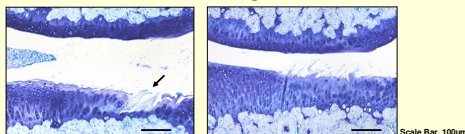


*p < 0.05 vs. PBS

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Representative histological appearance

3X/week dosing

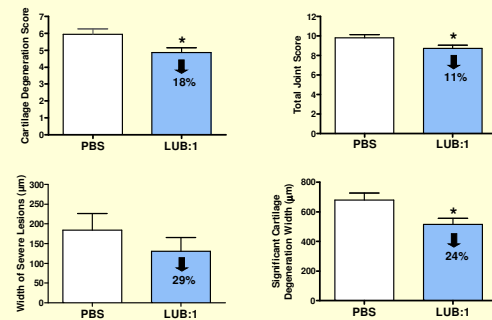


PBS-treated
 Cart. Degen. Score = 4.00
 (Group mean = 3.93 ± 0.29)

LUB:1-treated
 Cart. Degen. Score = 3.00
 (Group mean = 3.08 ± 0.20)

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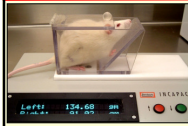
LUB:1 significantly attenuates OA progression (1X/week dosing)



*p < 0.05 vs. PBS

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Assessment of LUB:1 efficacy in a preclinical model of OA pain

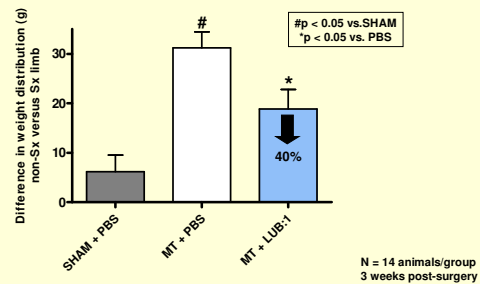


Incapitance meter: time-averaged dual channel weight bearing.

- Perform unilateral hind-limb surgery (sham or meniscal tear).
- Intraarticular treatment with PBS (vehicle) or LUB:1.
- Measure hind-limb weight bearing distribution.

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LUB:1 treatment significantly improves weight bearing in the rat MT model



Acknowledgments: Lilly Mark, Garth Whiteside, Wyeth Neuroscience

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Lubricin supplementation studies: summary

- Supplementation with LUB:1 (3X/week or 1X/week for 4 weeks) prevented cartilage degeneration in the rat MT OA model.
 - ▶ No evidence of fibroplasia (joint capsule thickening) or other adverse effects were observed.
 - ▶ No difference in bone scores between treatment groups (indicates equivalent joint loading).
- Supplementation with LUB:1 improves signs & symptoms in the rat MT OA model:
 - ▶ Enhanced weight-bearing of OA knee following LUB:1 treatment.
- Radiolabeled LUB:1 localizes to appropriate joint tissues following intraarticular administration (M. Rivera-Bermudez, et al. OARSI 2008 poster #74).
 - ▶ Localized LUB:1 remains detectable for at least 28 days post-injection.

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