

Novel Therapies in OA

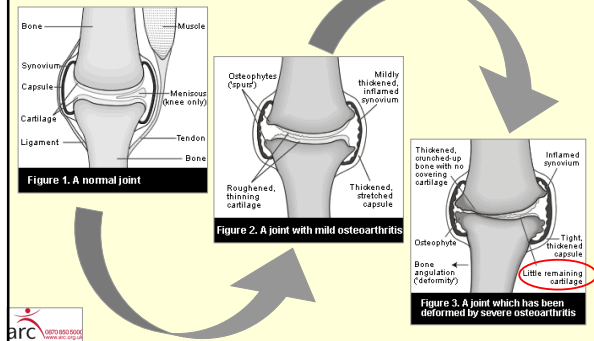


Carl R. Flannery, PhD

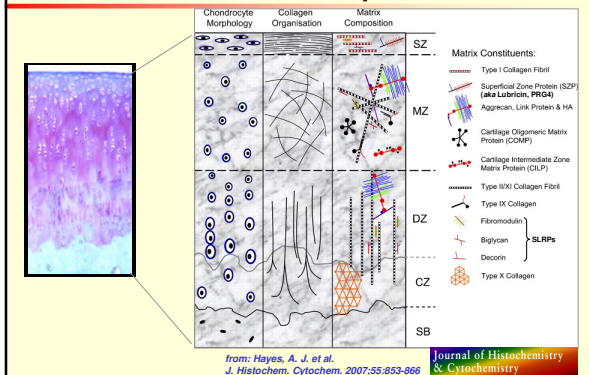
OARSI 2008
Rome, Italy



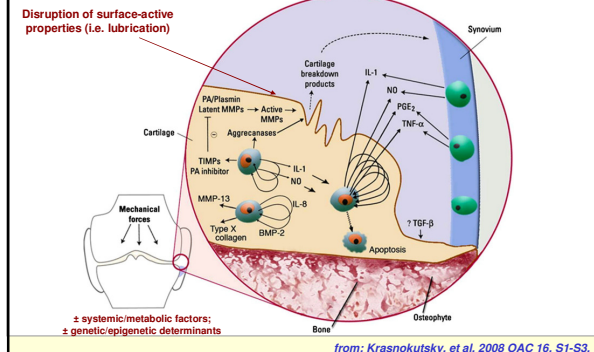
OA progression: therapeutic intervention points?



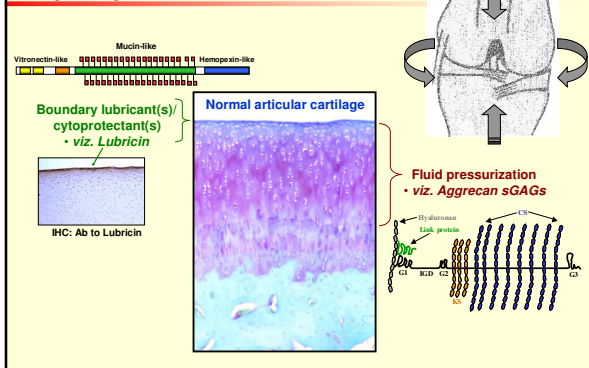
Cartilage structure/function: un tessuto connettivo molto specializzato



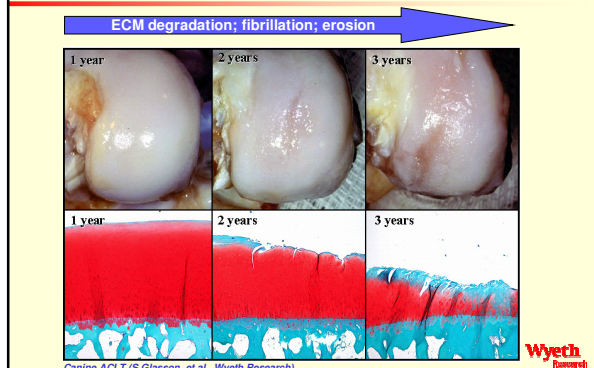
Molecular pathogenesis of OA



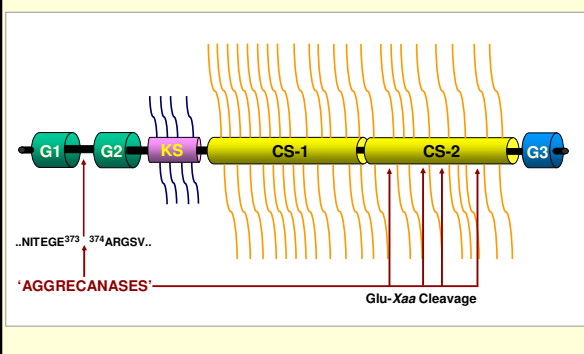
Targeting the 'Tribosome'



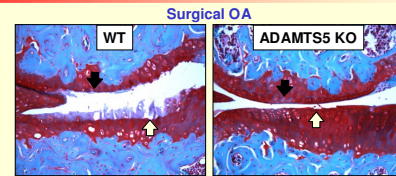
Cartilage degeneration during OA



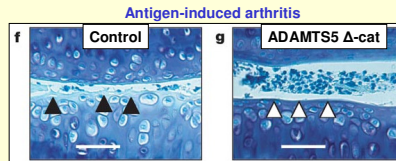
Aggrecan (Cartilage Proteoglycan): Pathologically Catabolized by Aggrecanases in OA



In vivo inactivation of ADAMTS5: chondroprotection



Glasson SS, et al. 2005. Nature 434:644-648.



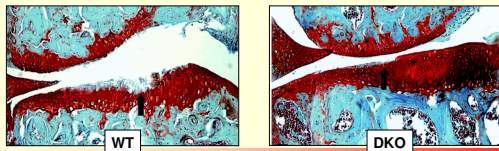
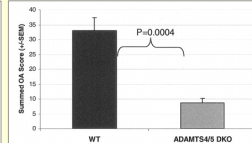
Stanton H, et al. 2005. Nature 434:648-652.

Aggrecanase inactivation: implications for therapeutic safety

Majumdar, et al. A&R 2007

Double-Knockout of ADAMTS-4 and ADAMTS-5 in Mice Results in Physiologically Normal Animals and Prevents the Progression of Osteoarthritis

Mann K, Majumdar, Roger Askew, Scott Schelling, Nancy Siedman, Tracy Bluscher, Bei Hopkins, Elisabeth A. Morris, and Sonja S. Glasson



Wyeth Research

Issues for therapeutic delivery in the joint: turnover rates in synovial fluid

Owen, et al. Br J Clin Pharmacol 1994

Br J Clin Pharmacol 1994; 38: 349-355

Disappearance kinetics of solutes from synovial fluid after intra-articular injection

S. G. OWEN¹, H. W. FRANCIS² & M. S. ROBERTS³
¹School of Pharmacy, ²Department of Medicine, University of Tasmania and ³Department of Medicine, University of Queensland, Queensland, Australia

Five rheumatoid patients with a knee joint effusion participated in the study. An aqueous solution (0.1 to 0.2 ml) containing paracetamol, salicylate, diclofenac and [¹²⁵I]-albumin was injected into a given joint to yield target concentrations of approximately 20 µg ml⁻¹ for diclofenac, salicylate and paracetamol and 10⁷ counts ml⁻¹ for [¹²⁵I]-albumin.

T1/2: ~13h (albumin); 5h (diclofenac); ~2h (salicylate); ~1h (paracetamol).

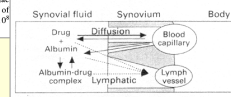


Figure 1 Pharmacokinetic model showing (1) transfer of drug between synovial fluid and the body by diffusion through the synovium into the blood perfusing the joint, (2) transfer of albumin and albumin-drug complex into the body via the lymphatic and circulatory systems and (3) transfer of unbound solute via the lymphatic system. The model is based on the injection of drug into the synovial fluid.

Dosing considerations for effective therapeutic delivery in OA

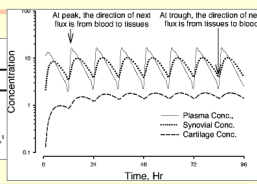
Wang, et al. Pharm Res 2008

Pharmaceutical Research, Vol. 25, No. 7, July 2008 (© 2008)
 DOI: 10.1002/jps.11518

Research Paper

In Vitro-In Vivo Correlation on Delivery of Drug Candidates to Articular Cartilage

Qin Wang,^{1,2} Sonja Glasson,¹ Uma Ramu,¹ Jamie Emerson,¹ Tracy Bluscher,² Gary Wilson,² Richard Siedman,² Nevena Medovic,³ Elisabeth Morley,³ Xun Xu,¹ and Vikram S. Patel^{1,2}



Test Articles	Plasma Protein Binding	Average Cartilage/Medium Ratio	Dose Regimens (mg/kg)	Plasma Conc. (ng/ml)	SF Conc. (ng/ml)	SF/Plasma Ratio	Observed Cartilage Conc. (ng/gram)	Projected Cartilage Conc. (ng/gram)
A	~99.6%	10.1	P.O. 71 mg B.I.D. P.O. 71 mg B.I.D. + 100 mg S.C. 3x/wk 140 mg S.C. 3x/wk	76±43 385±138	24±20 219±97	32% 57%	4.1±0.4 15.1±5.9	4 15
B	~99.8%	33.4	5 mg/kg S.C. 3x/wk 25 mg/kg S.C. 3x/wk	976±334 729±248	313±151 291±11	32% 40%	32 96±44	39 49
C	~98.6%	5.1	10 mg/kg S.C. 3x/wk 50 mg/kg S.C. 3x/wk	2,585±879 7,007±3,991	957±371 2,361±1,277	37% 34%	306±179 821±464	185 500

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Tissue targeting of therapeutics in OA: material carriers and formulations

Rothenthal, et al. Nature Materials 2008

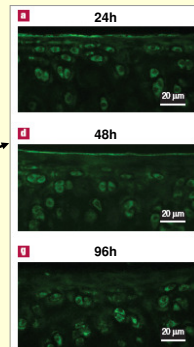
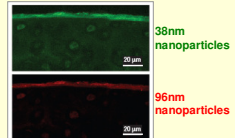
Biofunctional polymer nanoparticles for intra-articular targeting and retention in cartilage

DOMONVIA A. ROTHENTHAL¹, HARRY BERMUDEZ^{2,3}, CONLIN P. O'NEIL¹ AND JEFFREY A. HUBBELL^{1,4}

WYRGL identified as COL2-binding peptide by phage display/biopanning.

Distribution of fluorescein-WYRGL-poly(propylene) sulphide nanoparticles in mouse articular cartilage following intraarticular injection.

particle size matters:



Depot strategies for therapeutic delivery

Shamji, et al. *A&R* 2007

ARTIFICIAL INTELLIGENCE
Vol. 16, No. 11, November 2007, pp. 300-360
DOI: 10.1002/ajit.2007
© 2007, American College of Rheumatology

also see: Shamji, et al.
J Control Release 2008
(ELP-sTNFR1)

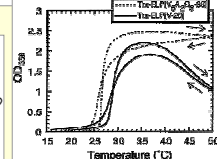
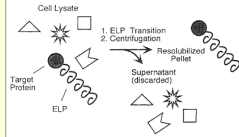
Development and Characterization of a Fusion Protein
Between Thermally Responsive Elastin-like Polypeptide and
Interleukin-1 Receptor Antagonist

Sustained Release of a Local Antiinflammatory Therapeutic

Mohammed F. Shamji,¹ Helene Bétré,¹ Virginia B. Kraas,² Jun Chen,¹ Ashutosh Chilkoti,¹
Rajewari Pichika,² Koschi Masuda,² and Lori A. Setton²

ELP = (V-P-G-X-G)_n
X = guest residue
(not Pro)

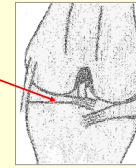
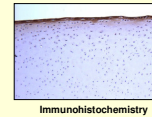
Inverse phase transition of ELPs



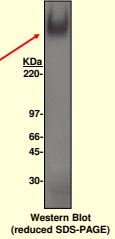
Meyer, et al. *Biotechnol Prog* 2001

Lubricin: therapeutic potential of a tissue-targeted, chondroprotective biotherapeutic

Lubricin at cartilage surfaces



Lubricin in synovial fluid



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

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Research

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)

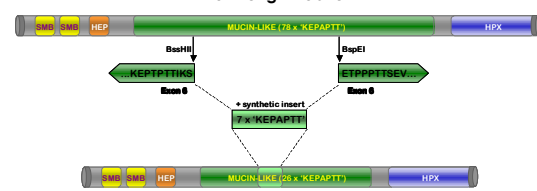
Reduced lubricin expression correlates with disease progression in animal models of osteoarthritis.

(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

Lubricin construct optimization: 'LUB' design (PCT WO 2005/016130 A2)

Full-Length Lubricin



"LUB:1" protein construct
(33% of wild-type repeat elements)

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Lubricin supplementation studies (summary)

- Intraarticular supplementation with LUB:1 prevents cartilage degeneration in the rat meniscal tear (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 of joints 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, and remains detectable for at least 28 days post-injection (M. Rivera-Bermudez, et al. OARSI 2008 Abstract #74).

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Strategies to identify novel pathways/targets: Proteomics

Human Cartilage ('normal' or OA; n=7/group)

4M Guanidine-HCl

Protein Extraction

CsCl gradient centrifugation

D3 Low density

D2

D1 High density

Fractionation

SDS-PAGE

In-gel digestion

Nano-LC-MS

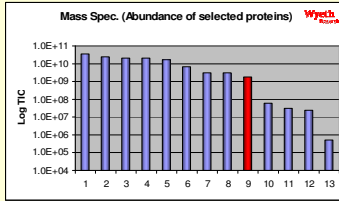
Data processing, Protein ID

Protein Name	# Unique Peptides	log (Normal Mean)	log (OA Mean)	Fold Change	FDR
PRSS11 (HtrA1)	29	8.224	9.133	8.1	0.030
EFEMP1 (Fibulin-3)	20	4.832	7.566	542.5	0.047
MMP-2	14	5.456	7.554	125.3	0.062
TIMP-2	12	6.020	7.531	32.4	0.087
TGFβ	3	5.210	4.000	-16.2	0.073

Zhiyong Yang, Jiang Wu, et al., Wyeth (Wu, et al. *Arthritis Rheum* 2007;56:3675-3684)

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Example: HtrA1 is an abundant protein in OA cartilage



- 1- PRELP
- 2- Decorin
- 3- Fibronectin
- 4- Link protein 1
- 5- COMP
- 6- CLP
- 7- Vimentin
- 8- Chondroadherin
- 9- **HtrA1**
- 10- MMP-3
- 11- MMP-2
- 12- Cathepsin D
- 13- MMP-1

Most abundant matrix proteins All detected proteases

See also studies on HtrA1 presented by P. Mitchell at OARSI 2008, Abstract #A23.

Strategies to identify novel pathways/targets: Transcriptomics

Geyer, et al. OAC in press 2008

Osteoarthritis and Cartilage

ICRS

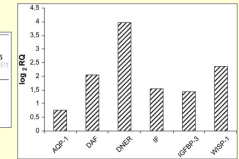
International Cartilage Repair Society

OARSI

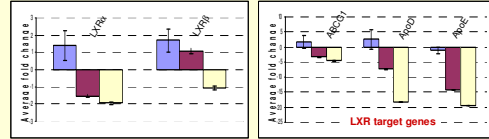
OSTEOARTHRITIS RESEARCH SOCIETY

Differential transcriptome analysis of intraarticular lesional vs intact cartilage reveals new candidate genes in osteoarthritis pathophysiology

M. Geyer M.D.^{1,2}, S. Ourselin Ph.D.¹, R. H. Straub M.D.¹, G. Schett M.D.¹, R. Dierker M.D.¹, J. Grifka M.D.¹, S. Gay M.D.³, E. Neumann Ph.D.¹ and U. Müller-Ladner M.D.¹



Z. Yang, et al. OARSI 2008, Abstract #143



Unaffected cartilage Mild OA Severe OA

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Acknowledgments & Contact Information

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