



# QUELS PRODUITS INJECTERONS NOUS DEMAIN DANS NOS ARTICULATIONS?

Y. HENROTIN

# Conflits d'intérêts

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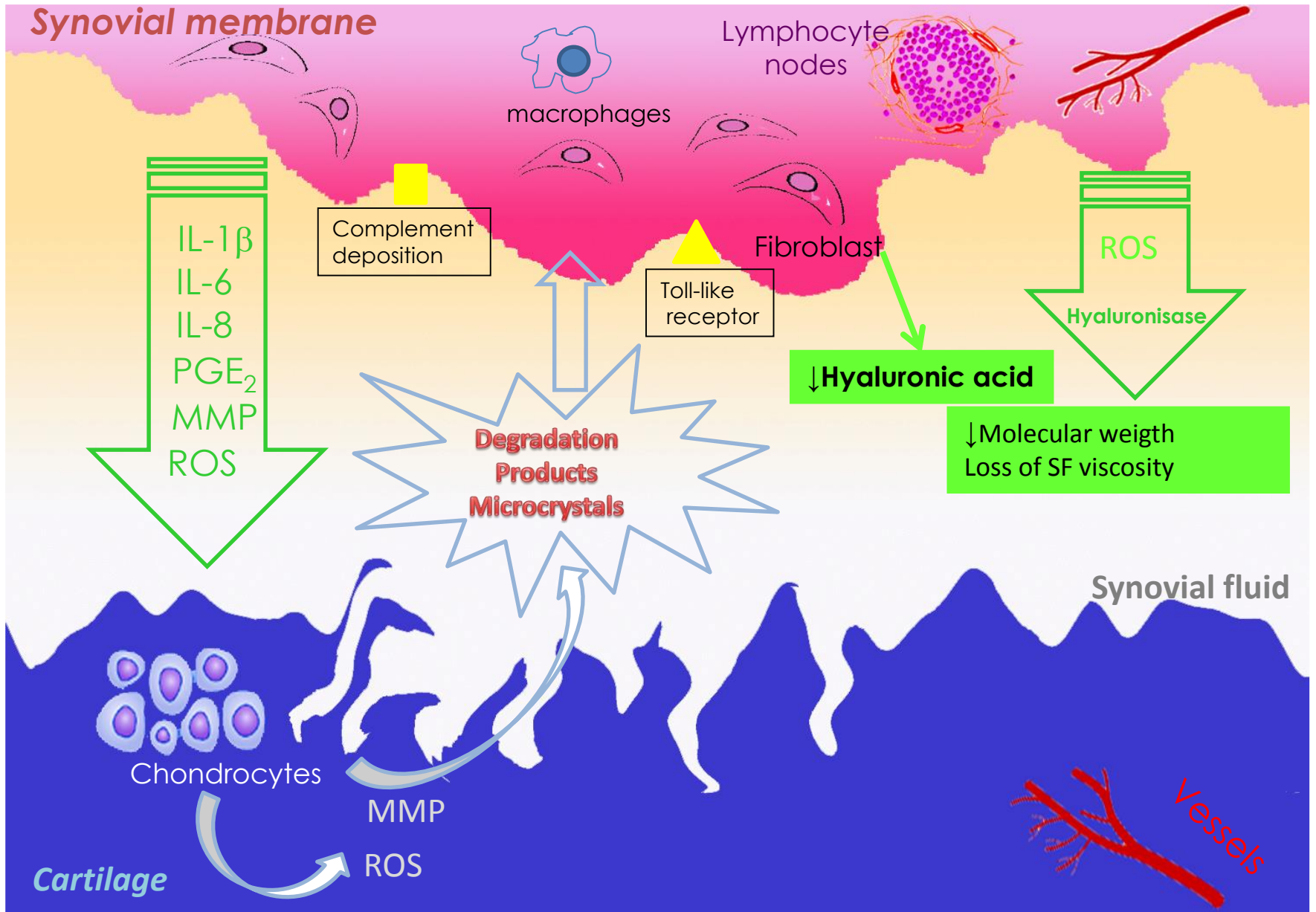
- Artialis SA
- Synolyne Pharma
- Tilman SA
- Biolberica
- Expanscience
- Nestlé
- Flexion Therapeutics
- Royal canin
- LABHRA
- Pierre Fabre

# Corticostéroïdes Viscosupplémentation



	ES Pain	ES Function
Acetaminophen	0.14 (0.05,0.23)	0.09 (-0.03,0.22)
<b>NSAIDs</b>	<b>0.29 (0.22,0.35)</b>	-
Aerobic	0.52 (0.34; 0.70)	0.46 (0.25; 0.67)
Glucosamine Sulfate	0.58 (0.30, 0.87)	0.07 (-0.08,0.021)
<b>IAHA</b>	<b>0.60 (0.37, 0.83)</b>	<b>0.61 (0.35,0.87)</b>
IA Corticosteroids	0.58 (0.34, 0.75)	0.20 (-0.14-0.53)

	10 RCT comparing IAC vs IAHA	ES Pain
2 weeks	In favour of IA Corticosteroids	0.39 (0.12-0.65)
4 weeks	=	0.01 (-0.21,0.23)
8 weeks	In favour of IAHA	0.22 (-0.5 ,0.49)
12 weeks	In favour of IAHA	0.35 (0.03, 0.66)



# Acide hyaluronique: limites et besoins

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- Rémanence intra-articulaire courte
- Efficacité clinique faible à modérée
- Pas recommandée par les sociétés savantes



**Augmenter la rémanence  
Augmenter l'efficacité  
clinique**

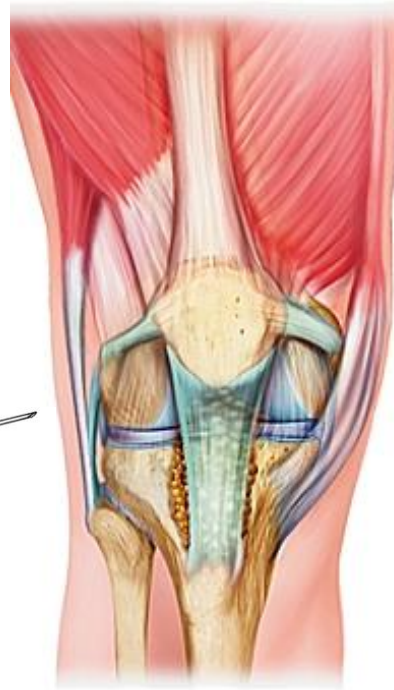
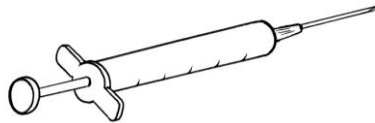


# Viscosupplementation: new directions

## Present

### HYALURONIC ACID

Animal origin  
Bacterial fermentation  
Chemically Cross-linked



## Future

### HA PROTECTION

Manitol  
Sorbitol  
Tocopherol

### DRUGS/ANTIBODY DELIVERY

NSAIDs/Coxibs  
Chlonidine  
Triamcinolone  
Doxycycline  
Chondroitin sulfate



### NEW MOLECULES

Chitosan  
Lubricine

# Protection de l'acide hyaluronique

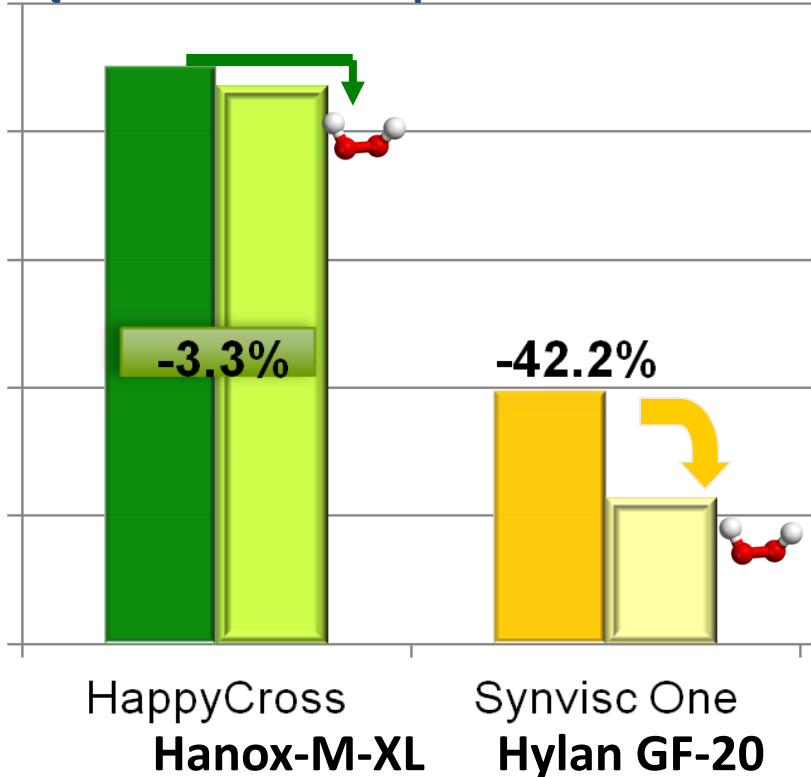
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Nom commercial	Fabriquant	Structure	Nombre d'injections/ volume	Indication	Concentration AH antioxydant	Antioxydant
HappyCross®	LABRHA	Réticulé	1/ 2.2 ml	hanche, cheville épaule	1.6% 3.5%	mannitol
HappyMini®	LABRHA	Réticulé	1/ 1ml	pouce, gros orteil, temporo-M	1.6% 3.5%	mannitol
HappyVisc®	LABRHA	Linéaire	3/ 2ml	genou	1.55% 3.5%	mannitol
Osténil Plus®	TRB Chemedica	Linéaire	1 à 3/ 2ml	genou hanche, cheville épaule	2% 0.5%	mannitol
Synolis-VA® Go-on Matrix®	APTISSEN	Linéaire	1 à 3/ 2 ml	genou	2% 4%	sorbitol

# Le mannitol prévient la dégradation de l'acide hyaluronique par les radicaux libres oxygénés.

Peroxyde d'hydrogène (H<sub>2</sub>O<sub>2</sub>) 

$\ln^*I$  = Viscosité complexe



Rheumatol Ther (2014) 1:45-54  
DOI 10.1007/s40744-014-0001-8

ORIGINAL RESEARCH

**Mannitol Preserves the Viscoelastic Properties of Hyaluronic Acid in an In Vitro Model of Oxidative Stress**

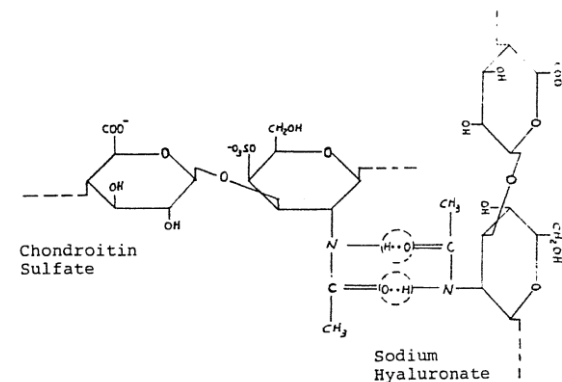
Thierry Conrozier · Pierre Mathieu · Marguerite Rinaudo



# Mélange AH + CS

- Le rôle de la CS est double:
  - 1) Optimiser les caractéristiques rhéologiques de l'AH par des liaisons chimiques .
  - 2) Activités biologiques anti-inflammatoires, anti-cataboliques et pro-anaboliques (synthèse de GAG)

↑ la viscoélasticité du gel

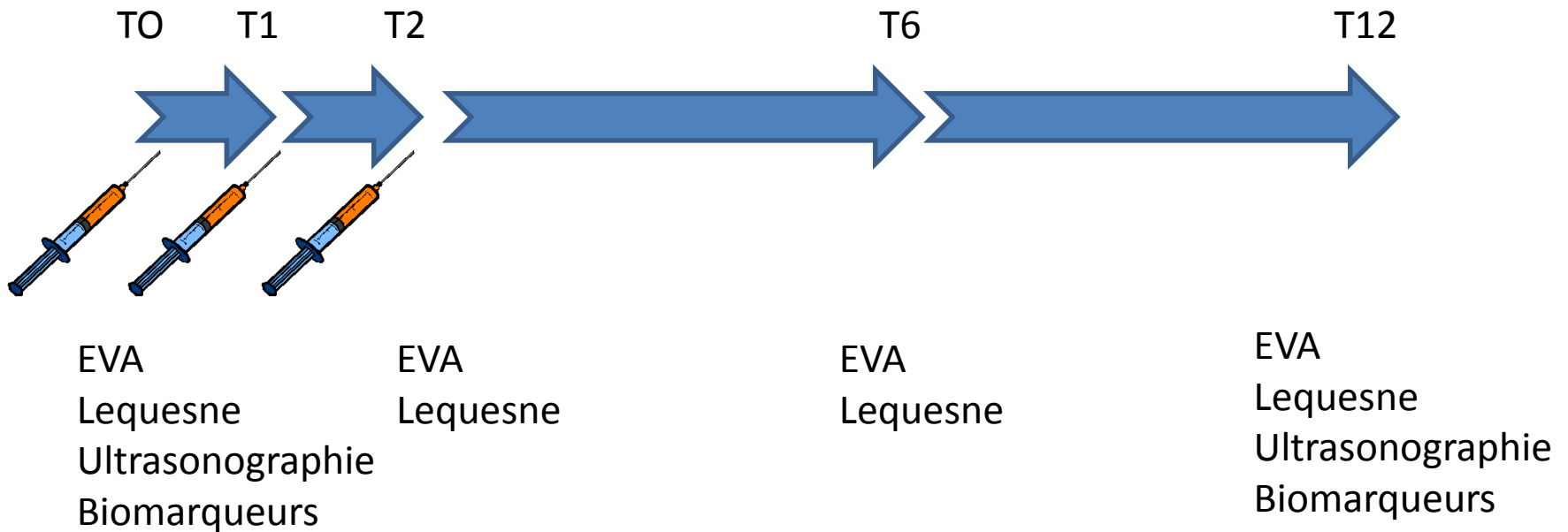


# AH+CS

## Etude pilote non-contrôlée

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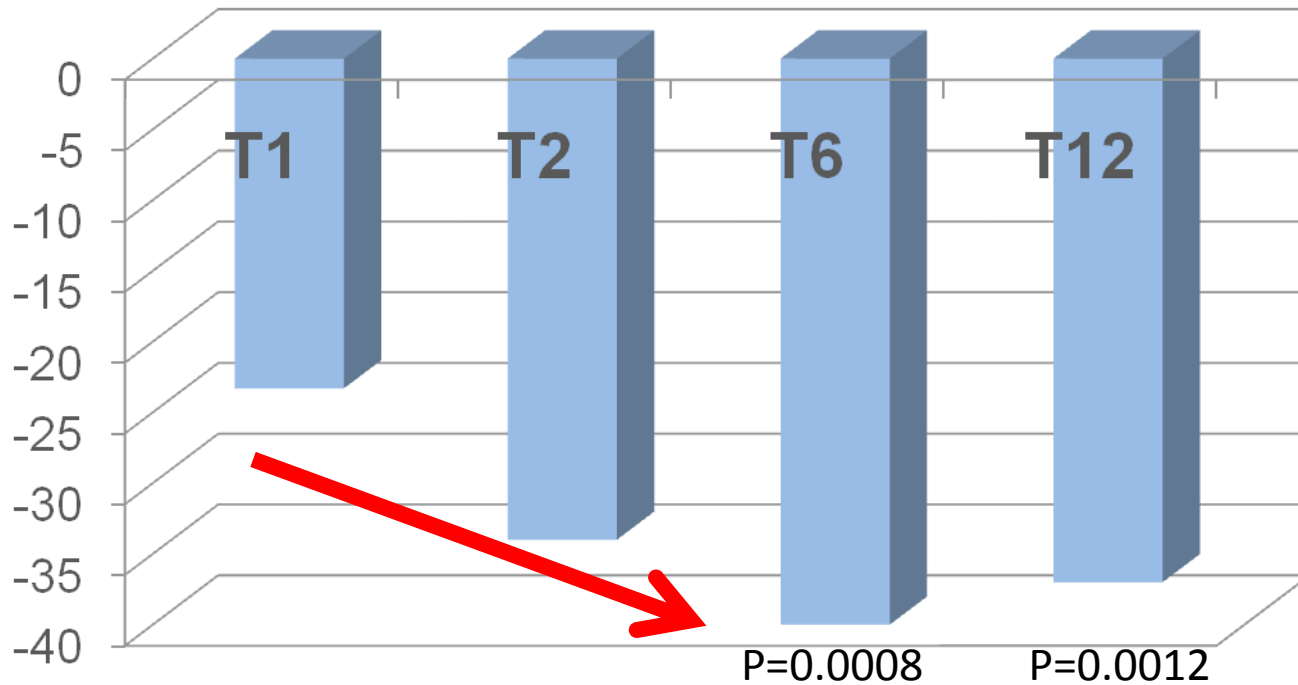
30 patients avec arthrose fémoro-tibiale  
2 ml ( 24 mg AH et 60 mg CS)  
3 injections – 1/sem pdt 3 sem



# AH+CS

## EVA

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# HA + CS

## Ultrasonography

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	T0	T12
Articular effusion (n,%)		
No Liquid	12 (40%)	17 (57%)
Only at isometric contraction	14 (47 %)	11 (36%)
Synovial thickness in extension (mm)	1,7±2 1	1.6 ±0.9

**No significant effects but**

**HA/CS tends to reduce the number of effusion and synovial thickness**

# HA + CS Biomarkers

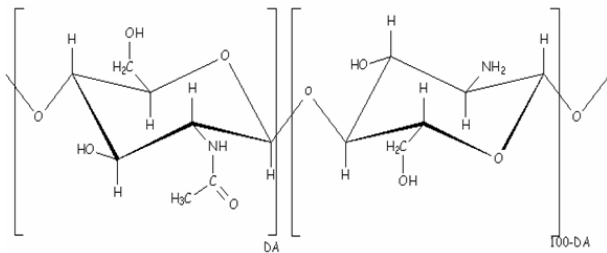
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	$\Delta T0 - T12$	Trends	
Coll2-1 (nM)	$-11 \pm 78$	↓	<b>Degradation</b>
Coll2-1NO2 (nM)	$-0.06 \pm 0.41$	↓	<b>Oxidative stress</b>
CS-846 (ng/ml)	$+1 \pm 17$	↑	<b>Synthesis</b>
CPII ng/ml)	$-41 \pm 867$	↓	<b>Synthesis</b>
IL-6 (pg/ml)	$-5667 \pm 21769$	↓↓↓	<b>Inflammation</b>

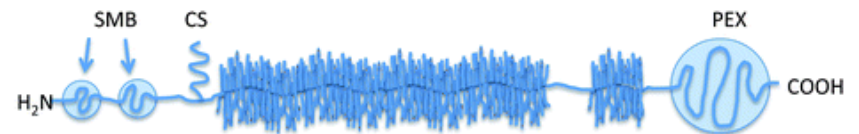
Biomarkers changes suggest that HA/CS tends to promote return to cartilage homeostasis

# Viscosupplémentation: Nouvelles molécules

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Chitosan



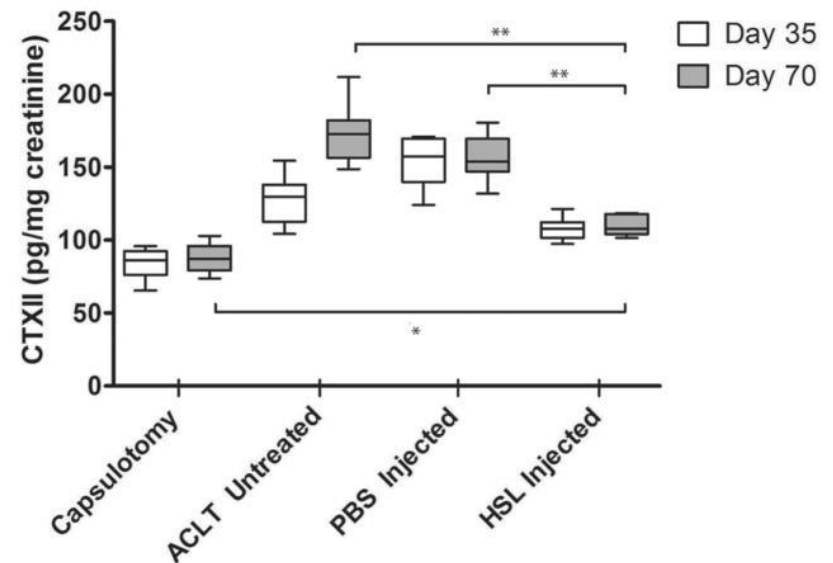
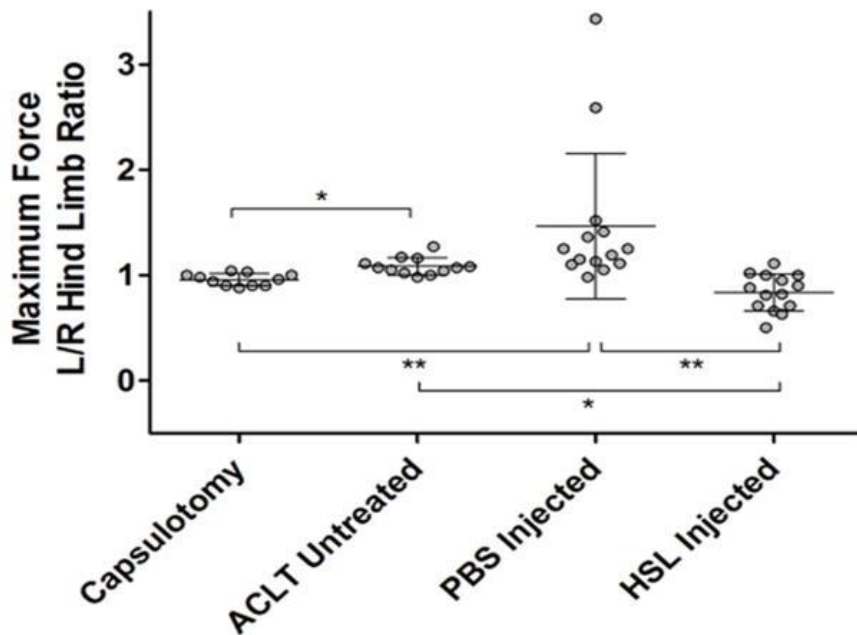
Proteoglycan-4 or Lubricin

Tribo-supplémentation

# Lubricin- Tribosupplementation

Rat ACL transection Model  
Right knee  
70 days follow-up

Four groups  
Capsulotomy alone (sham, no injection)  
ACL untreated  
ACL + IA PBS (placebo treatment)  
ACL + IA HSL (80  $\mu\text{g}/50\mu\text{l}$ )



# Chitosan smartbeads®+ chitosan hydrogel (Arthrovisc)

➤ Diameter: 600-900  $\mu\text{m}$

➤ Mushroom Chitosan :  
0.5% - 42Kda

➤ Alginate (Pronova UP):  
1.4%



Alginate-chitosan (AC) beads

+

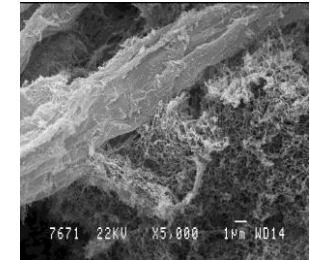
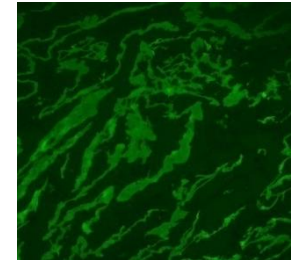
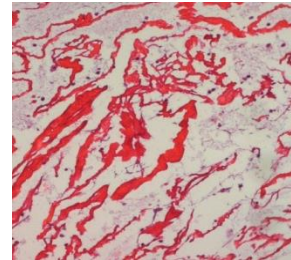
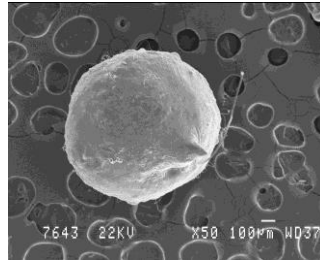
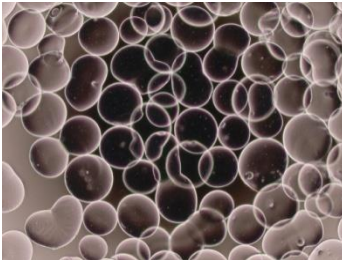
➤ Thermogelling  
➤ 1% trimethylchitosan  
➤ 132 Kda



Chitosan-derived hydrogel

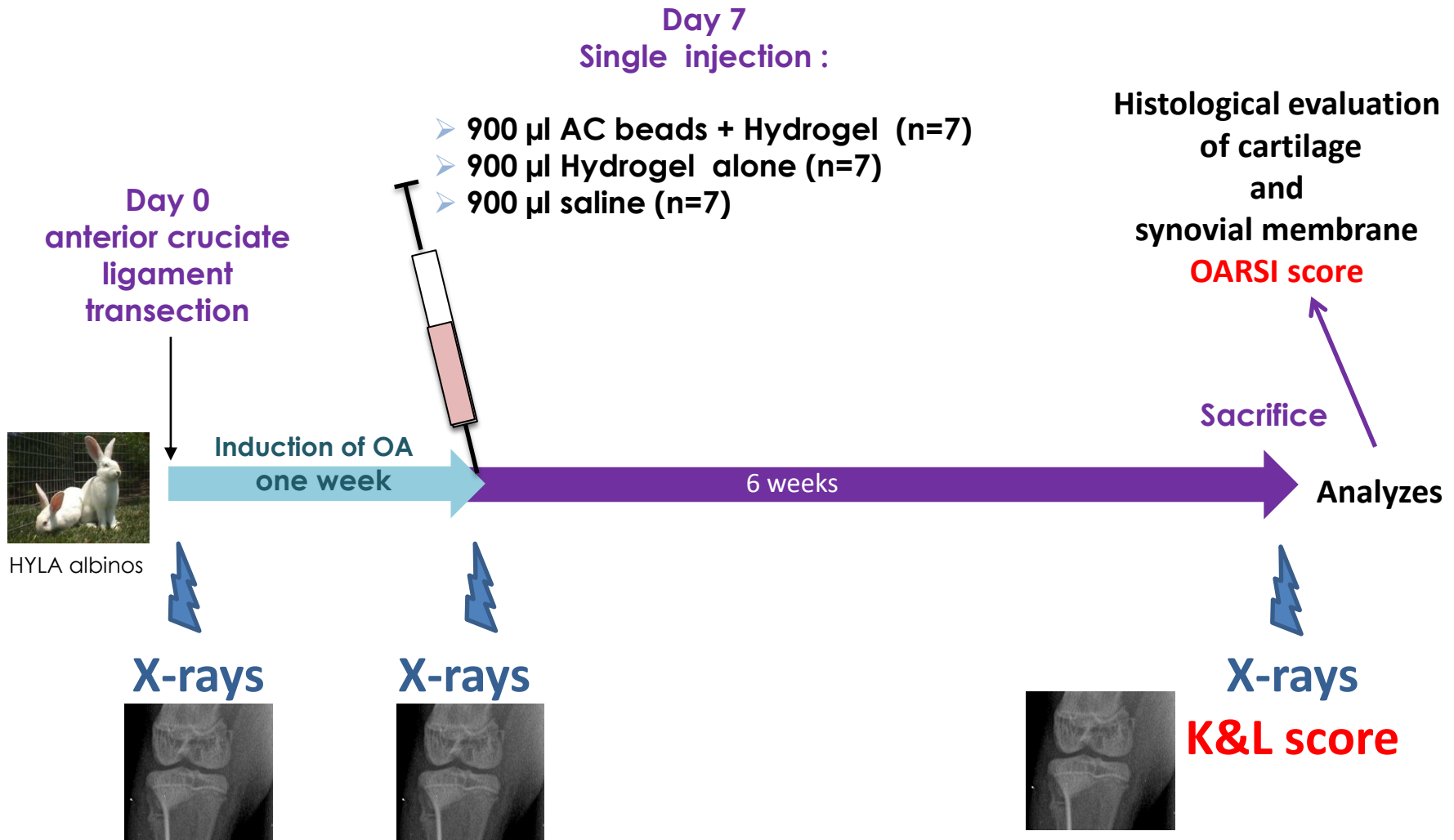
**Biphasic biomaterial**

**Ratio 1/1 w/w**

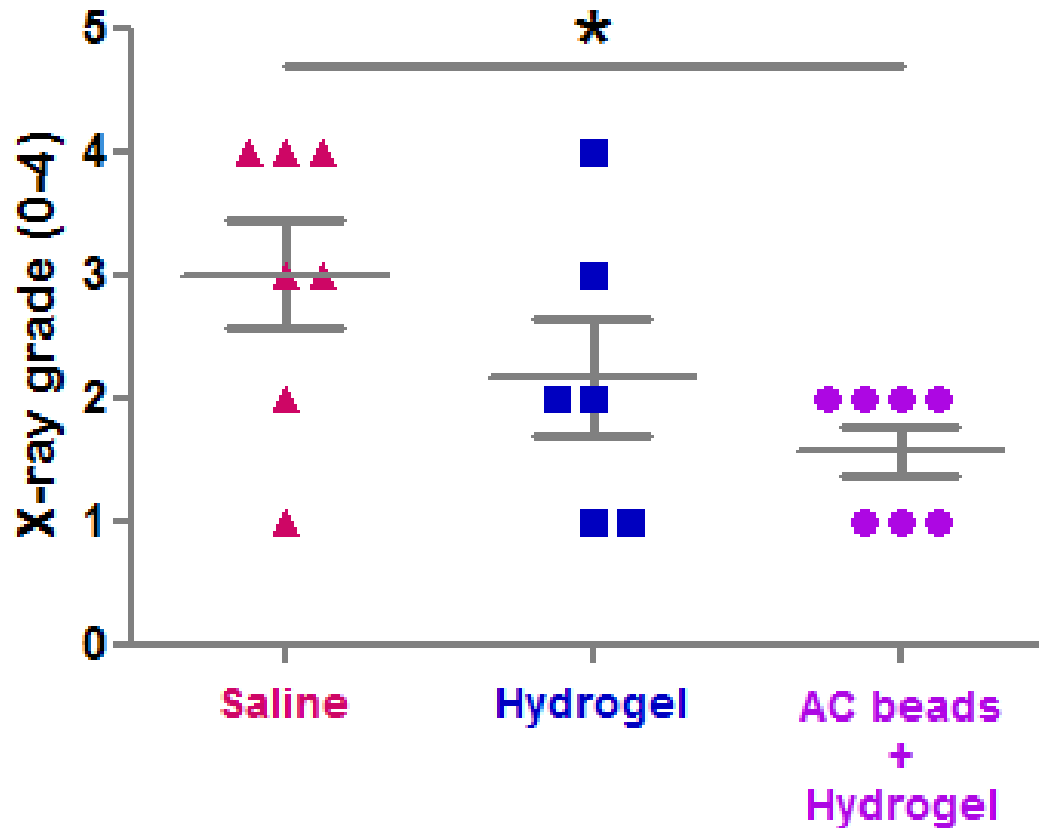




# Study design



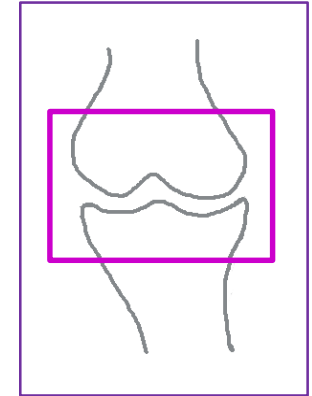
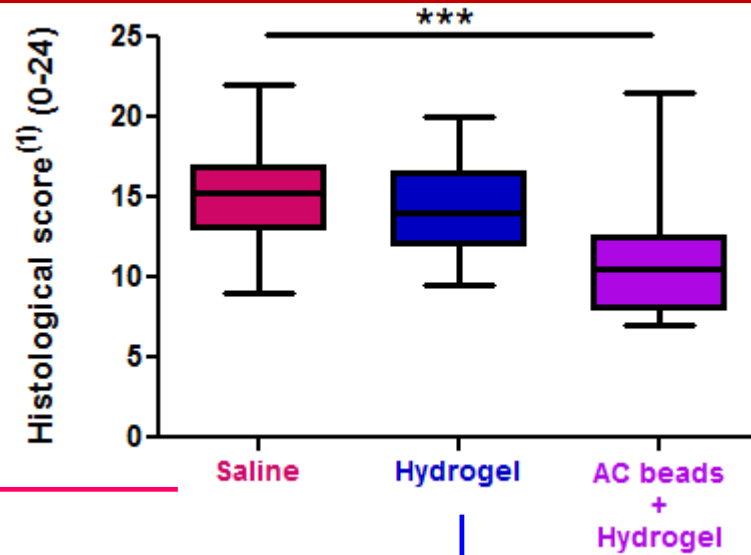
# X-rays



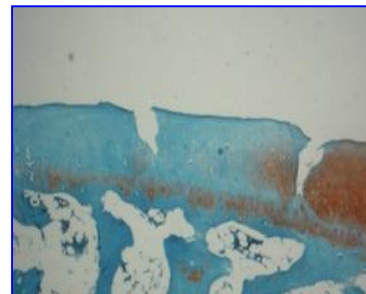
**AC beads + Hydrogel prevented radiological OA development**

\*  $p < 0.05$  versus saline (Control)

# Histology-Global



AC + H ≠ Saline (\*\*\*)  $p \leq 0.001$   
AC + H ≠ hydrogel (##)  $p \leq 0.01$



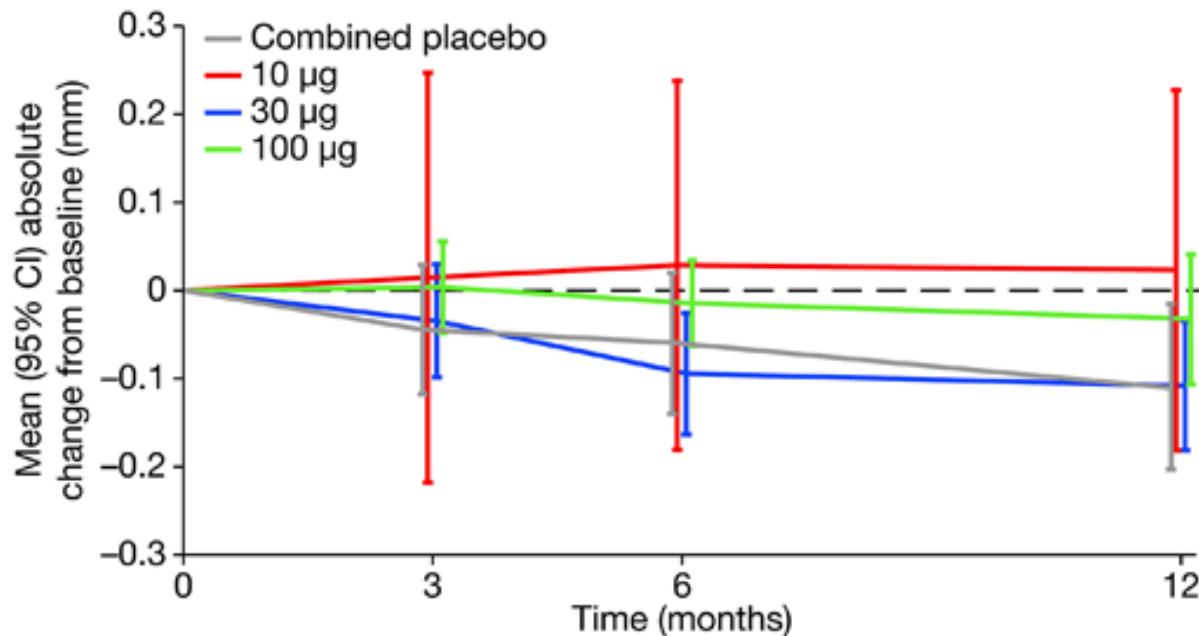
**AC beads + Hydrogel significantly reduced the histological score of cartilage lesion severity**

# Intraarticular Sprifermin

(Recombinant Human Fibroblast Growth Factor 18)

Lohmander et al. Arthritis Rheum 2014

## Epaisseur du cartilage fémoro-tibial medial



RCT 192 gonarthroses  
2 cycles de 3 injections  
1 injection/sem  
T 0 et T3 mois

Pas d'effets sur la douleur  
et la fonction  
Pas d'effets secondaires locaux  
ou systémiques

## Epaisseur du cartilage fémoro-tibial latéral (qRMN)

Placebo	10 µg	30 µg	100 µg	
- 0.04 mm	- 0.02 mm	+ 0.02 mm	+0.04 mm	P = 0.031

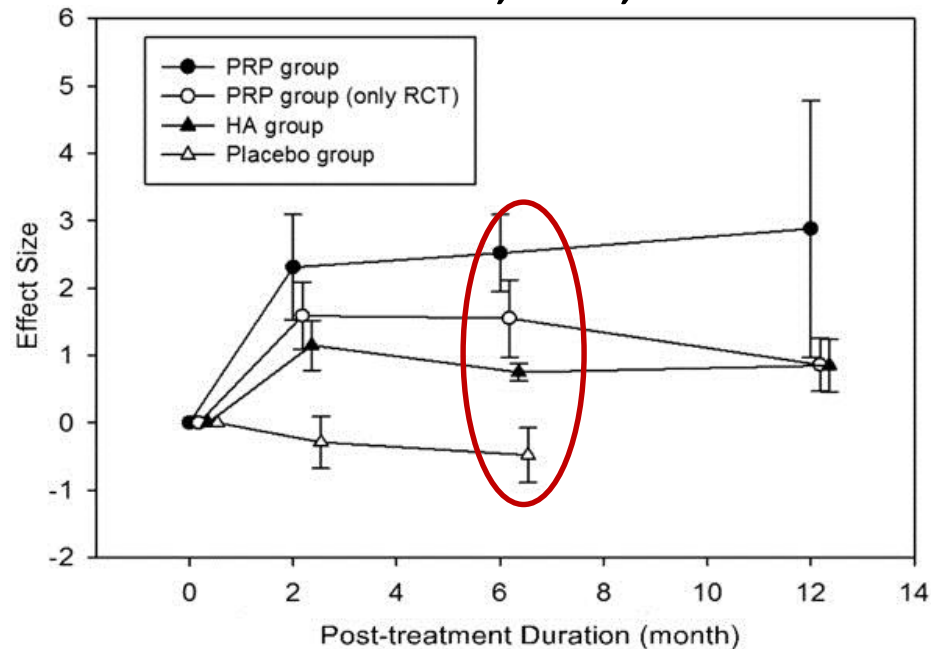
# Platelet-rich Plasma

## Méta-analyse

Chang et al., Arch Phys Med Rehab, 2014

- 16 études inclues
- 26 groupes expérimentaux
  - 18 groupes PRP
  - 7 groupes HA
  - 1 groupe solution saline
- 1543 patients avec gonarthrose (majoritairement KL III)

### Taille de l'effet fonction WOMAC, IKDC, KOOS

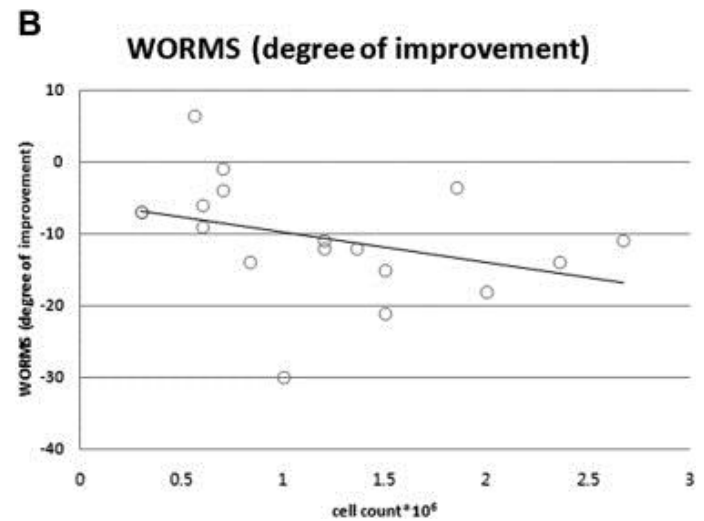
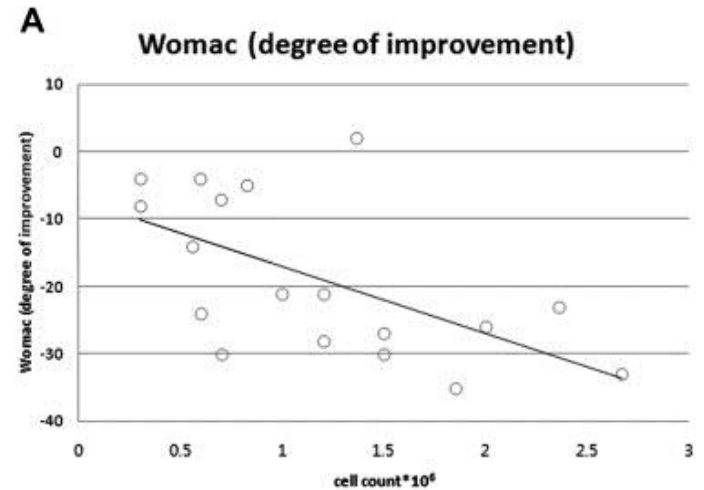
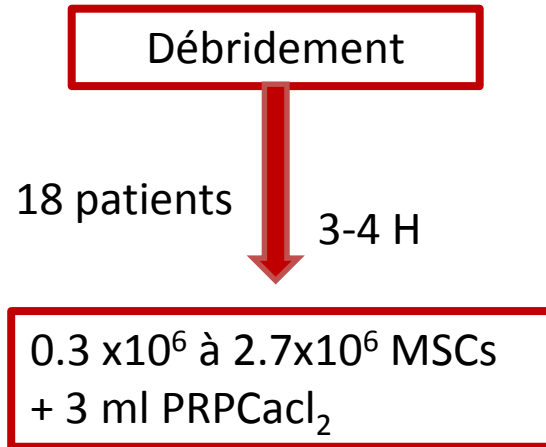


A 6 mois RCT : 1,55 PRP vs 0,75 HA

Pas plus d'effets secondaires que HA

# Injection MSCs adipeuses

Koh Y et al. J Arthr Rel Surg 2013



Critères cliniques			
	Pré-op	26 M post-op	P value
WOMAC	49,9 ± 12,6	30,3 ± 9,2	<0.001
Lysholm	40,1 ± 12,1	73,4 ± 13,5	<0.001
EVA	4,8 ± 1,6	2,0 ± 1,1	<0.001

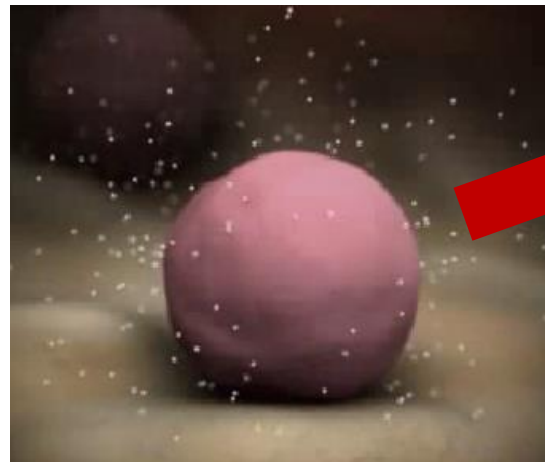
RMN WORMS			
	Pré-op	26 M post-op	P value
WORMS	60,0 ± 33,0	48,3 31,8	<0.001
WORMS cartilage	28,3 ± 11,7	21,7 10,3	<0.001

# DRUG DELIVERY SYSTEM



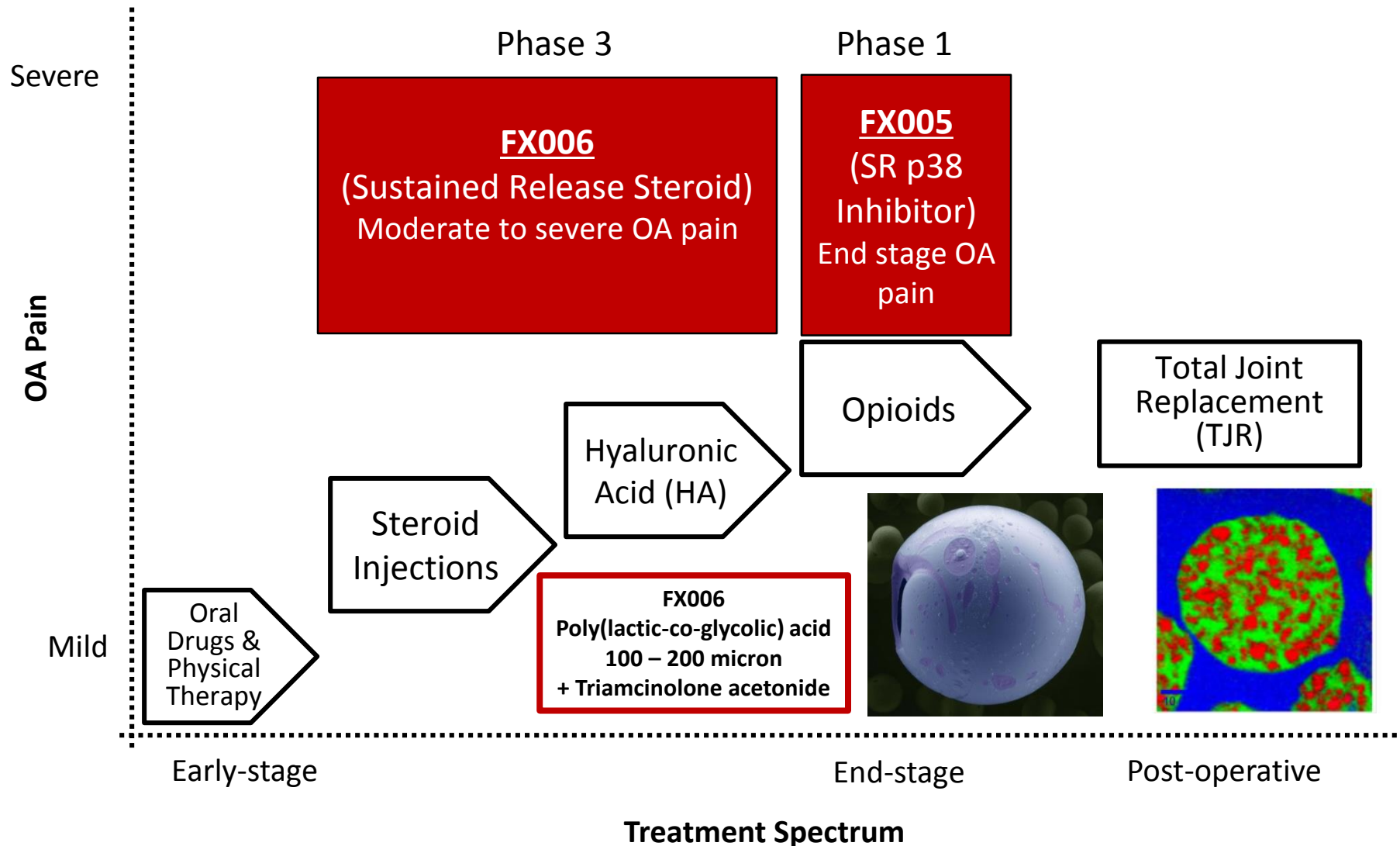
Libération prolongée

Acide polylactique (Billes)  
Chitosan (Billes ou gel)  
Acide hyaluronique (Gel)



Corticostéroïdes  
Anticorps monoclonaux  
Curcumine  
AINS

# Flexion's Product Portfolio: Spanning the OA Pain Spectrum



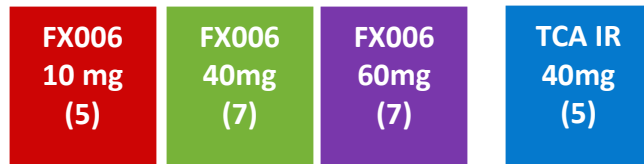


# FX006: pharmaco-cinétique dans le fluide synovial

## Study 1

### TCA Concentrations in Synovial Fluid 6 Weeks After Single Injection

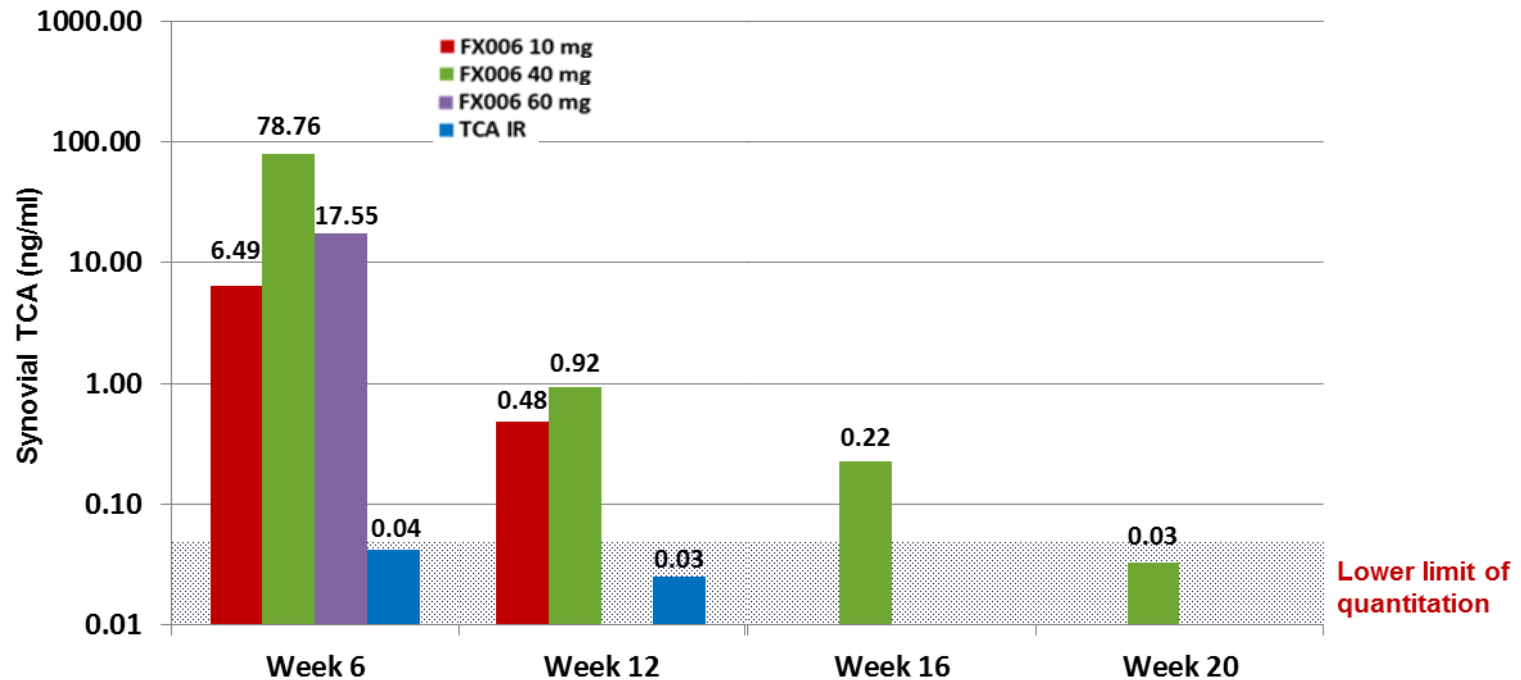
19 OA patients on FX006, 5 on TCA IR



## Study 2

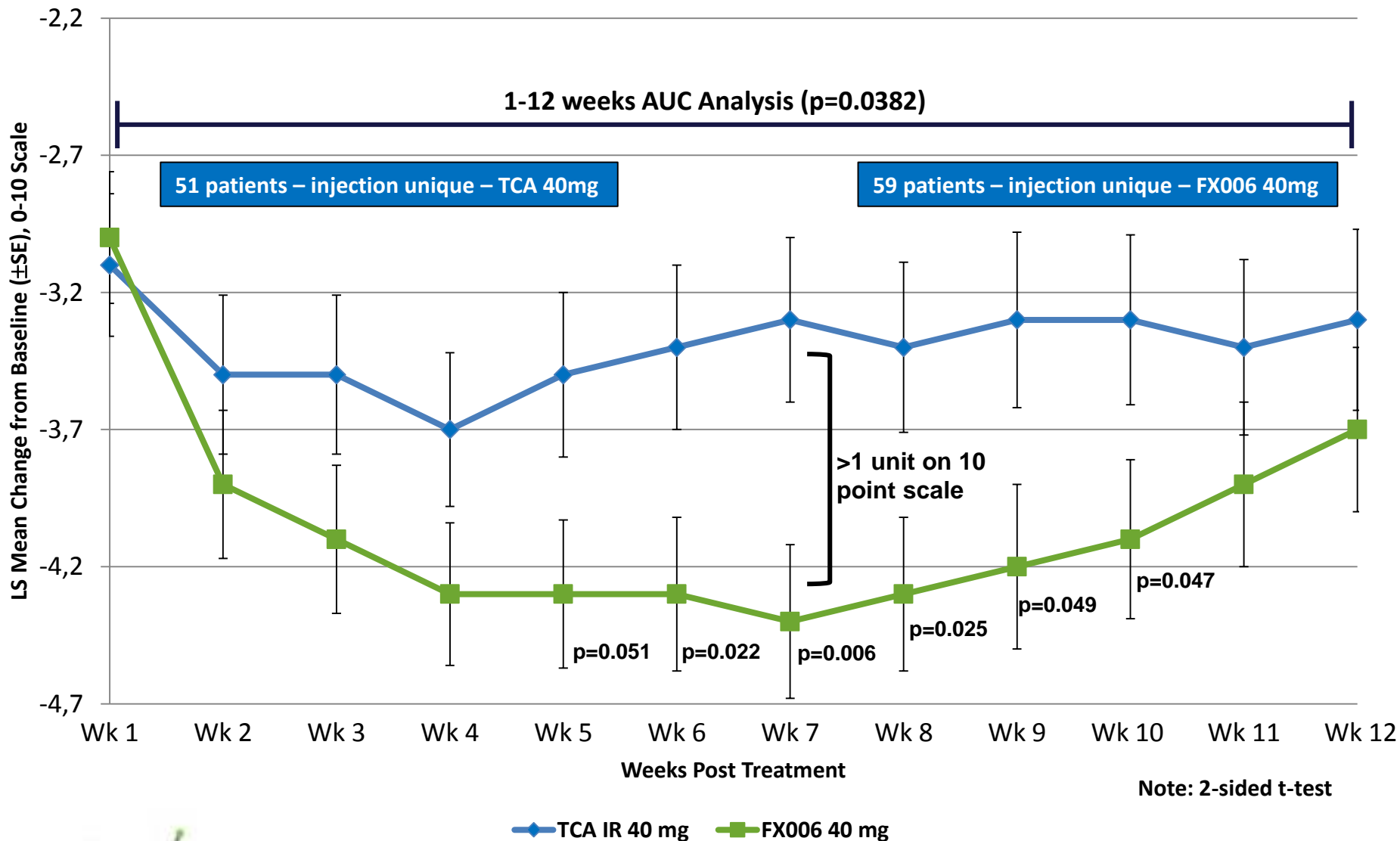
### TCA Concentrations in Synovial Fluid $\geq 12$ Weeks After Single Injection

40 OA patients on FX006, 10 on TCA IR



Data represented with geometric means

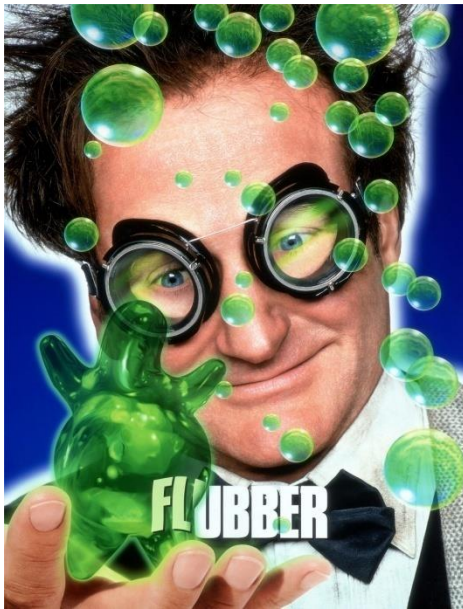
# FX006 40 mg: Effets sur la douleur



# Perspectives

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So...What's about the future?



Viscosupplementation  
Tribosupplementation  
Drug delivery system  
Biologic therapy



« Breakthrough » product  
Indication



Perhaps not only a dream!



MERCI!

**International collaborations:**

- F Blanco (La coruna, Spain)
- T Conrozier (CHU Lyon, France)
- V Kraus (Duke University, USA)
- L Punzi (University of Padova, Italy)
- A Mobasher (University of Nottingham, UK)
- J Monfort (Hospital del mare (Spain)
- P Richette (Lariboisiere, France)
- J Runhaar (Erasmus MC, Rotterdam)



# Injection MSCs hématopoïétiques

## Variables cliniques

Wong K et al., J Arthr Rel Surg, 2013

28 patients → Ostéotomie + microfractures/3 semaines/HA

28 patients → Ostéotomie + microfractures/3 semaines/HA + MSCs

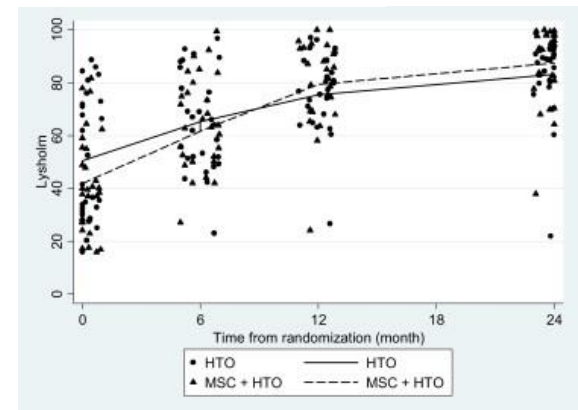
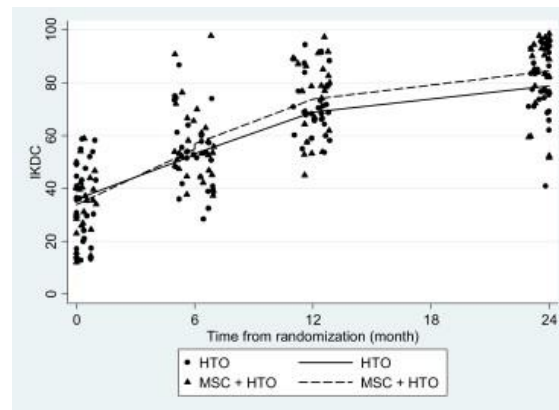
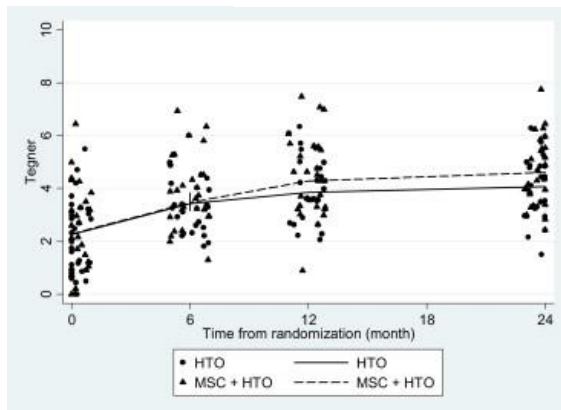
Outcome	Unadjusted			Adjusted*		
	Estimate	95% CI	P Value	Estimate	95% CI	P Value
IKDC score	4.73	-1.31 to 10.77	.124	7.65	3.04 to 12.26	.001
Lysholm score	2.55	-4.93 to 10.02	.504	7.61	1.44 to 13.79	.016
Tegner score	0.45	-0.18 to 1.08	.158	0.64	0.10 to 1.19	.021

Index  
algo-  
fonctionnels



Supériorité  
HA + MSCs

\* Model adjusted for age, baseline score, and time of evaluation.



# Injection MSC Hématopoïétiques

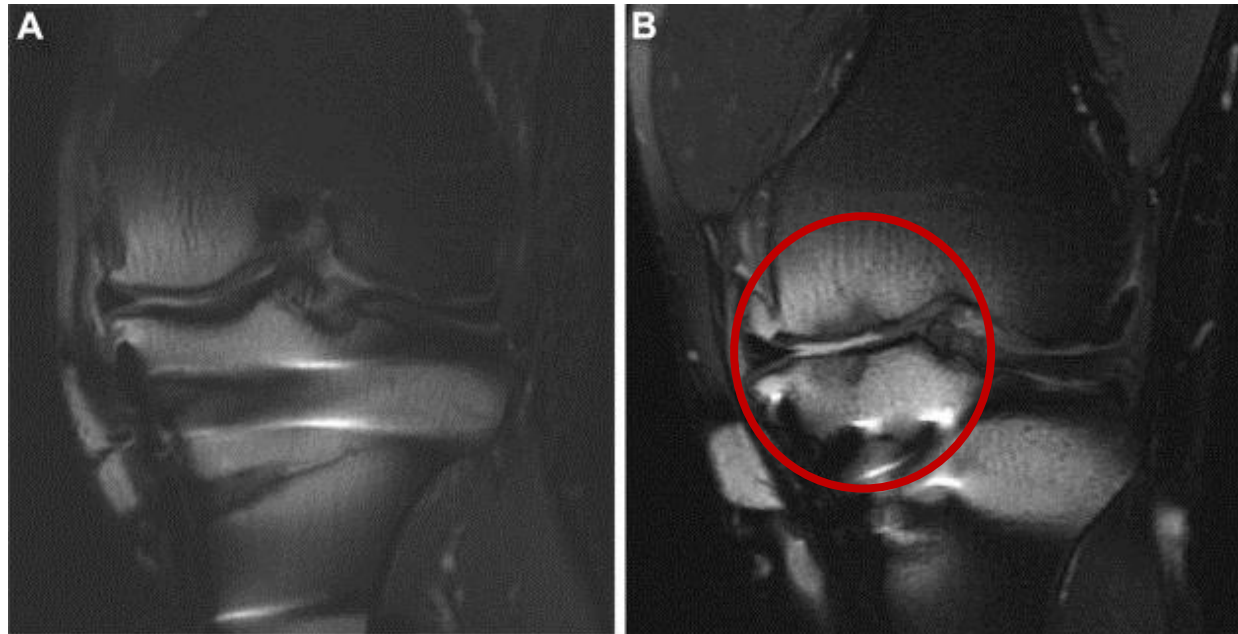
Imagerie RMN

Wong K et al., J Arthr Rel Surg, 2013

HTO + HA + MSCs

HTO + HA

1 an après  
traitement

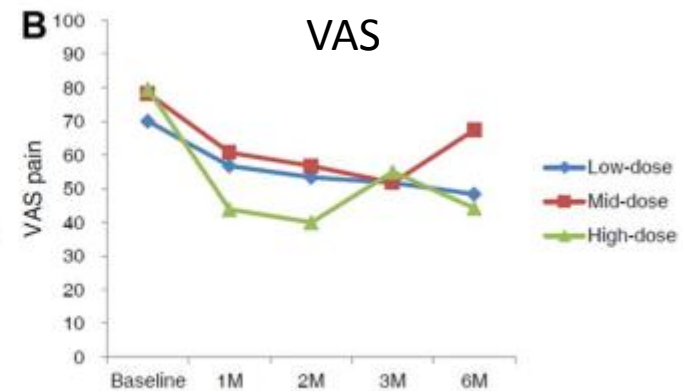
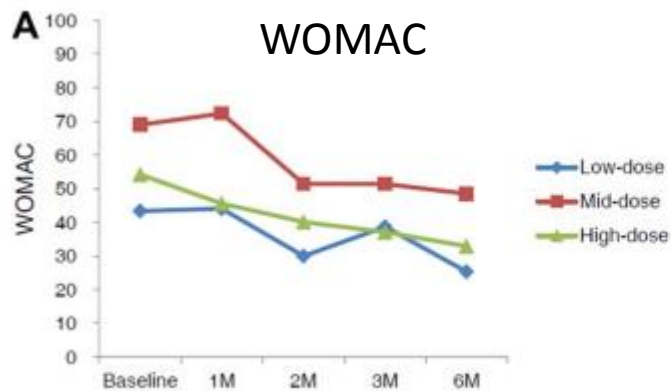


## MOCART Total score

	HTO + MSCs +HA	HTO + HA	
Moyenne (DS)	62.32 (17.56)	43.21 (13.55°)	0.001

# MSC tissu adipeux

Hyunchi C et al. Stem cells 2014



Phase I/II

18 patients with knee OA (KL >3)

Phase I: 3 dose-escalation cohort

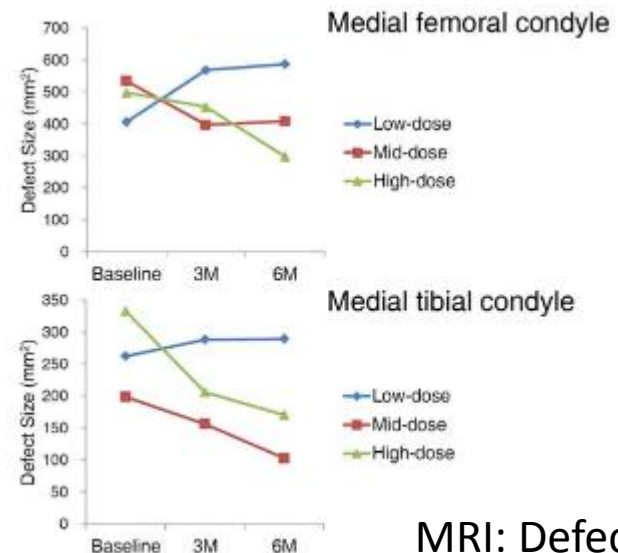
Low dose (n = 3;  $1.0 \times 10^7$  cells)

Mild dose (n = 3;  $5.0 \times 10^7$  cells)

High dose (n = 3;  $1.0 \times 10^8$  cells)

Phase II: (n=9;  $1.0 \times 10^8$  cells)

6 months follow-up



MRI: Defect size

# Intra-articular LMWF-5A

Bar-Or D et al., PLOS one, 2014

- Fraction (<5000 Da) de l'albumine sérique humaine
- Riche en aspartate-alanine diketopiperazine (DA-DKP)  
→ Anti-inflammatoire et immuno-modulateur
- RCT 329 patients avec gonarthrose symptomatique
- 4 bras :  
→ 4 ou 10 ml solution saline  
→ 4 ou 10 ml 5% LMWF-5A

