

# INNOVATION DANS L'ARTHROSE

Y. HENROTIN



# Conflits d'intérêts

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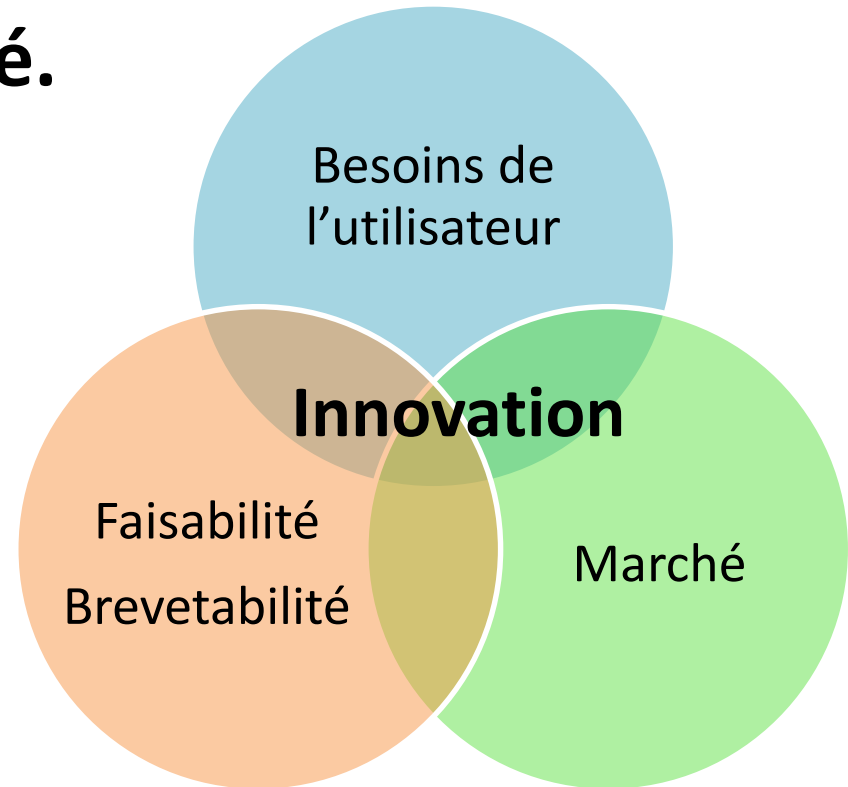
- Artialis SA
- Synolyne Pharma
- Tilman SA
- Biolberica
- Expanscience
- Nestlé
- Flexion Therapeutics
- Royal canin
- LABHRA

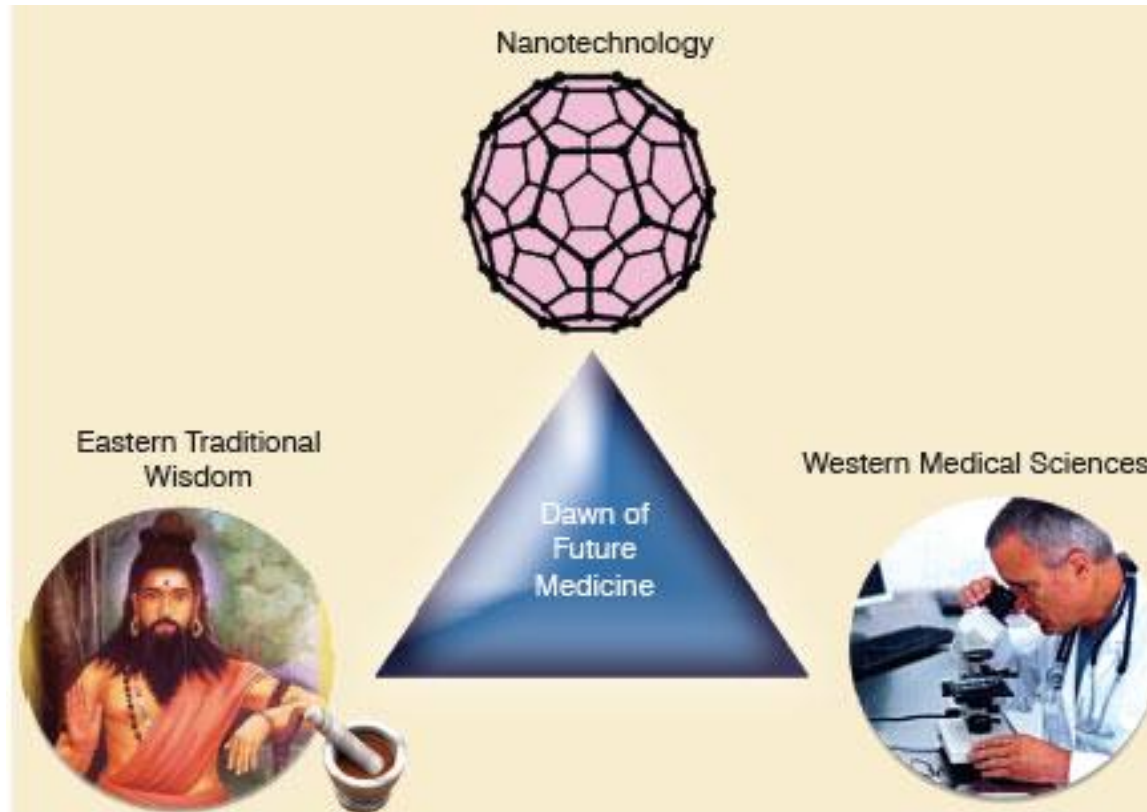
# INNOVATION

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- **Une innovation est une nouveauté, un nouveau produit, un nouveau service qui a pu être implémenté.**

- ❖ Compléments alimentaires
- ❖ Dispositifs médicaux
- ❖ Médicaments biologiques





# COMPLÉMENTS ALIMENTAIRES

# La curcumine: médecine ayurvédique

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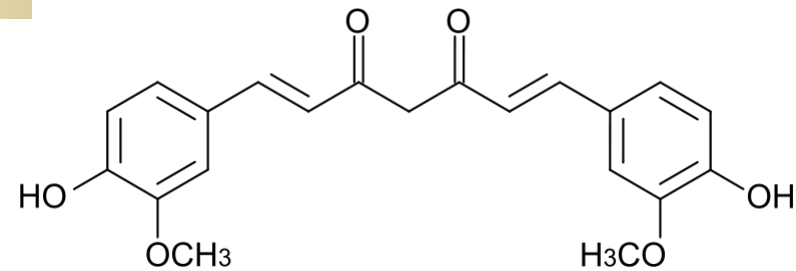
Plante de curcuma Longa  
Zingiberaceae



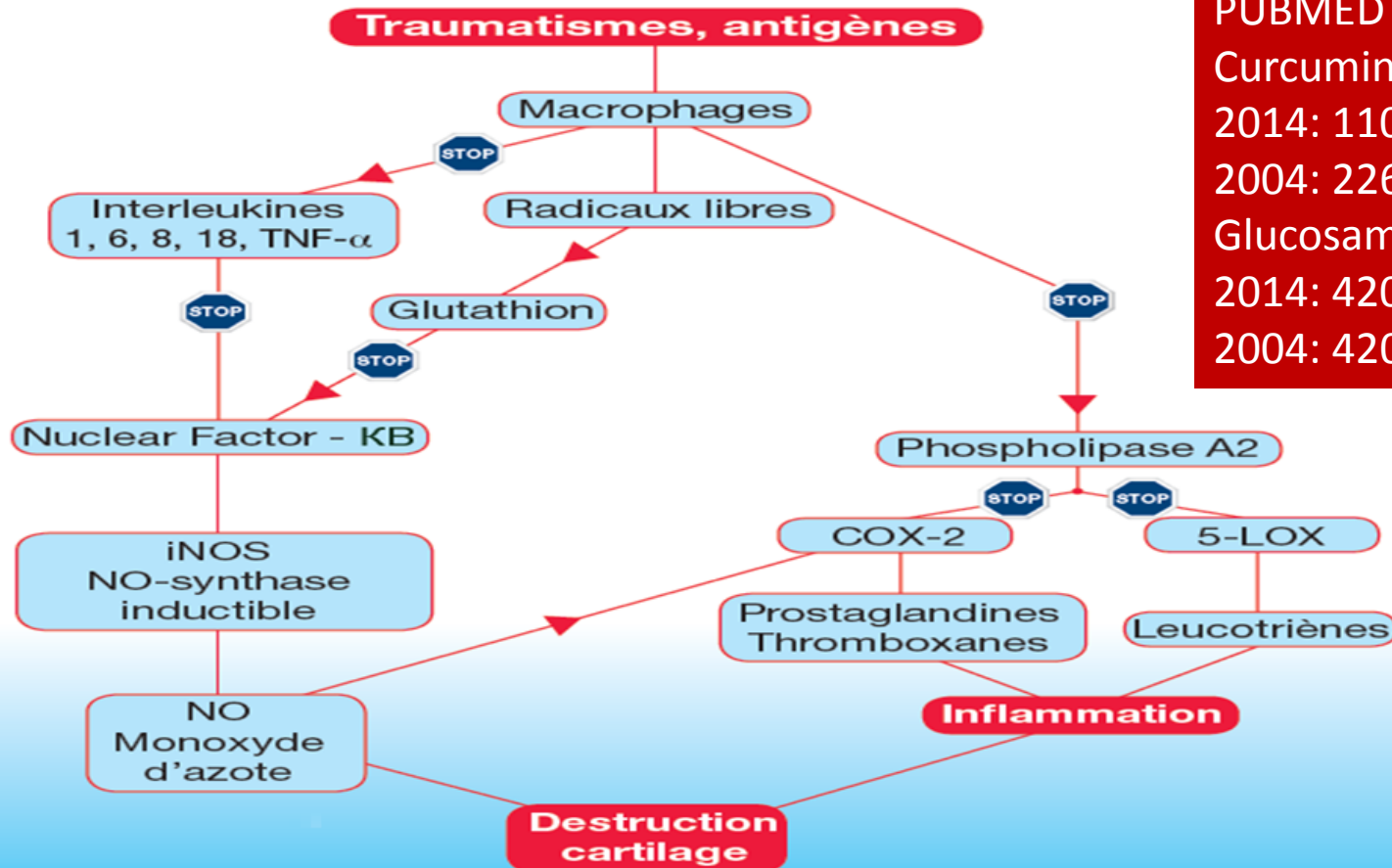
Racine/Rhizome



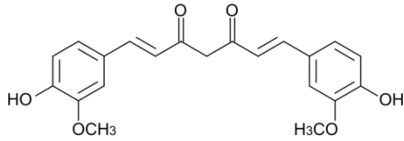
Poudre  
Extrait de Curcuminoids



# Des mécanismes d'action identifiés par la recherche scientifique

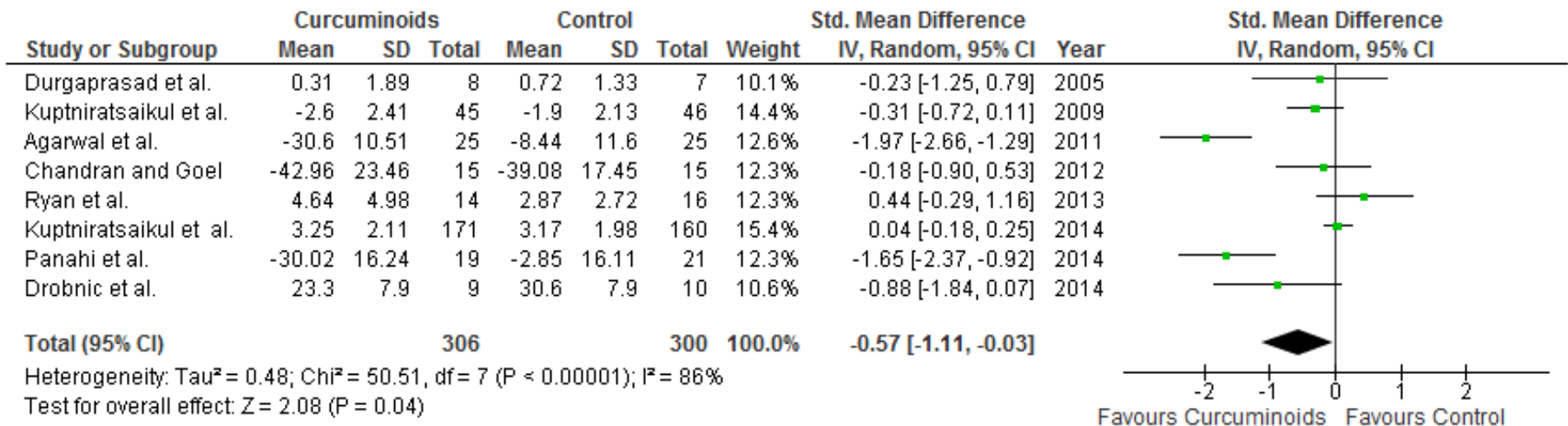
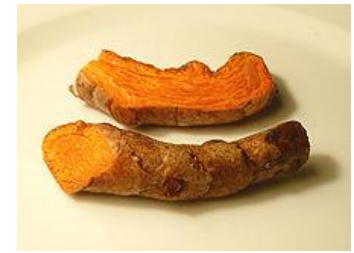


PUBMED  
Curcumin:  
2014: 1100 articles  
2004: 226 articles  
Glucosamine:  
2014: 420 articles  
2004: 420 articles



# Curcuminoids

Sahebkar A, Henrotin Y AJN, 2014 submitted



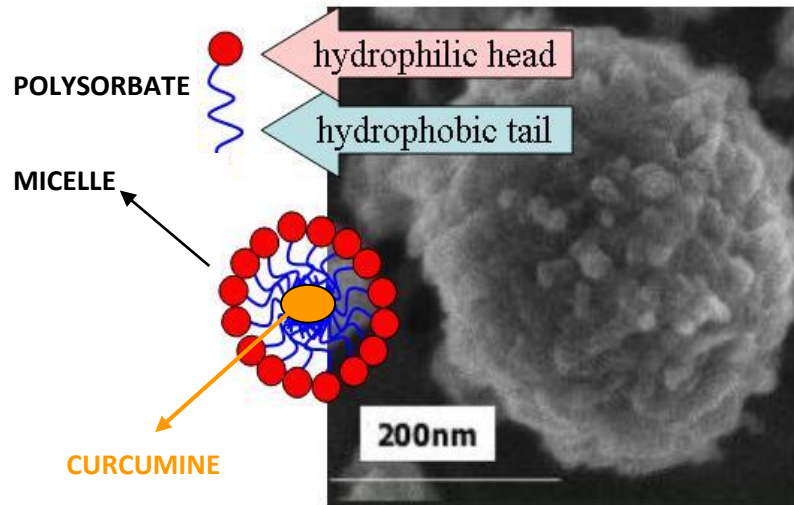
Problème:  
Biodisponibilité faible



- Augmenter la biodisponibilité
- Pipérine
- Liposomes
- Complexe de phospholipies
- Nanoparticules
- Microsphères



# La curcumine bio-optimisée: nanoparticules de polysorbate (Flexofytol)



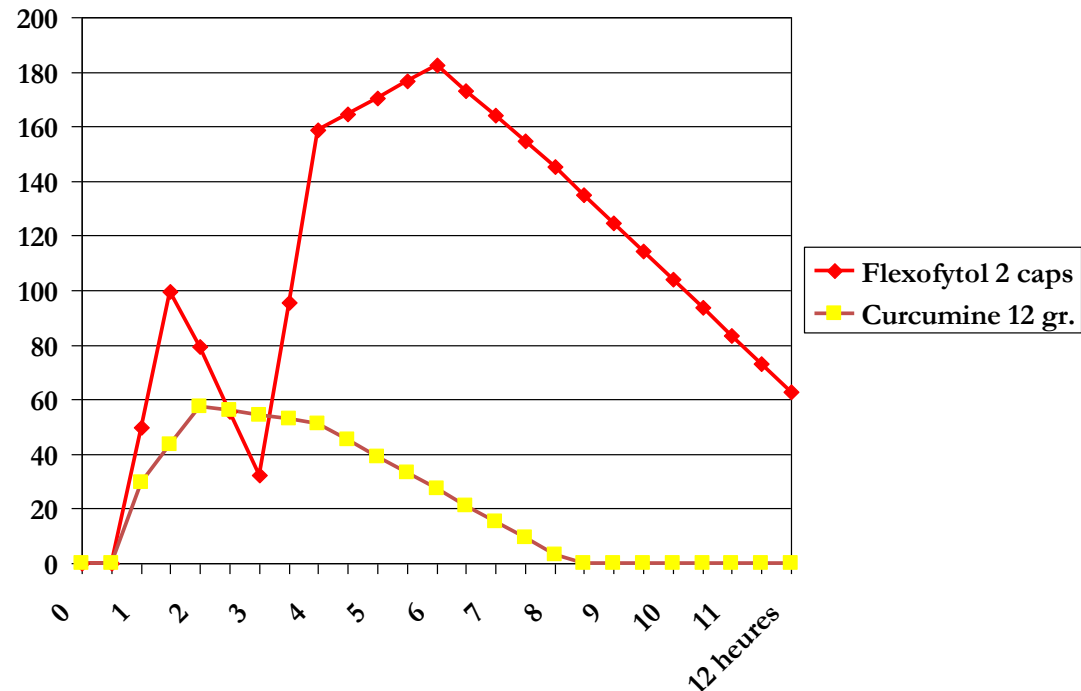
**1 cap = 42 mg de curcumine active**  
Biodisponibilité équivalente à 57 g de curcumine native

Polyoxyéthylène (20) sorbitan monolaurate

ng/ML

**C max**  
2 caps = 0.9  $\mu$ M  
4 caps = 1.6  $\mu$ M  
(extrapolation)

12 volontaires sains par groupe



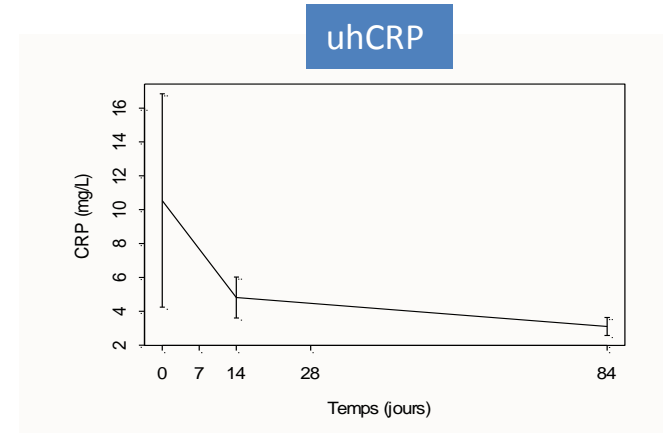
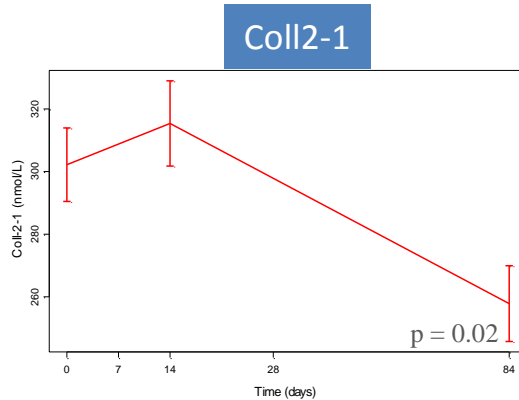
Henrotin et al. Springer plus, 2013



# TIFLEXY

## A proof-of-concept study

Henrotin et al., *BMC Complem Altern Med*, 2014

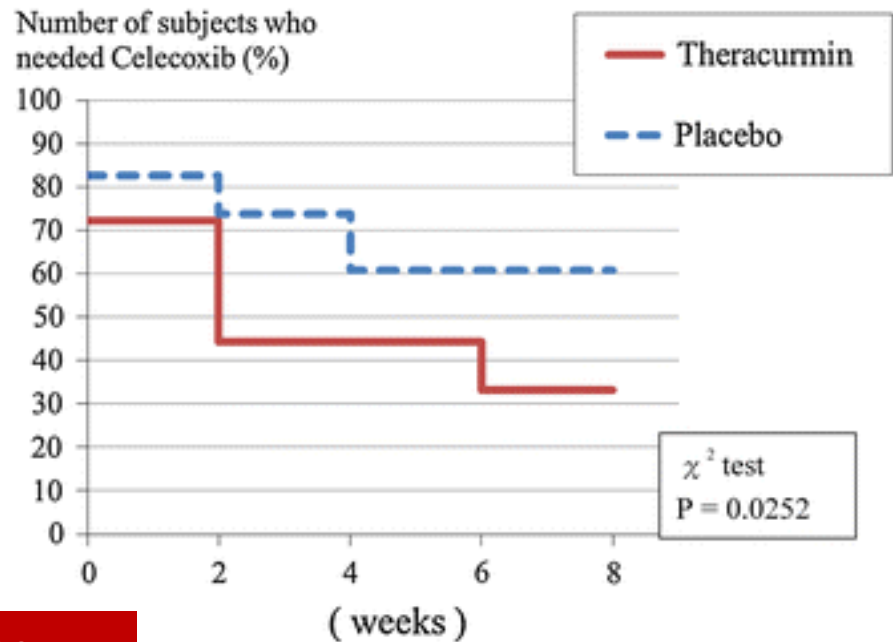
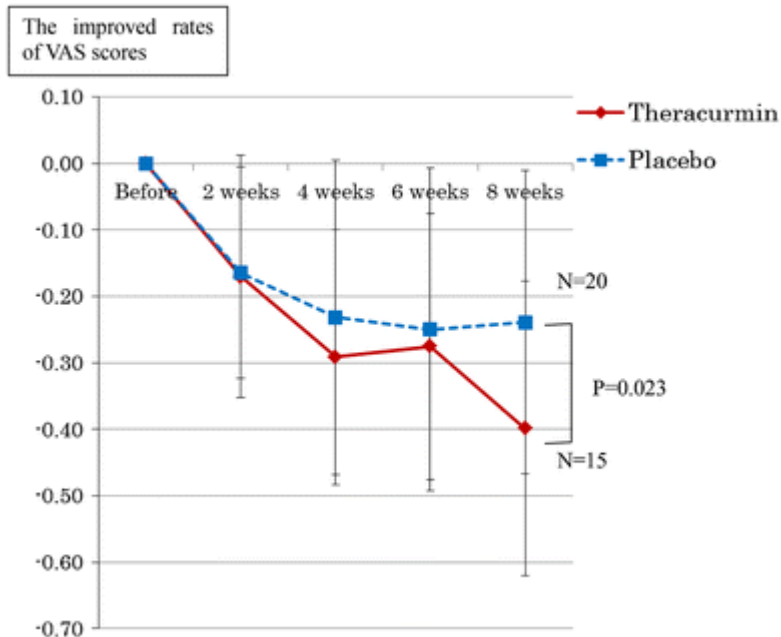


	Baseline	84 days of treatment	p-Value
sColl2-1 (nmol/L)	302.21+/-53	257.84 +/-52.78	0.02*
sColl2-1NO2 (nmol/L)	0.71 +/- 0.78	0.80 +/- 0.24	NS
sCTX-II (ng/L)	11.81 +/-7.98	13.17+/-4.96	NS
sFib3-1 (pmol/L)	707.05 +/- 178.79	765.20 +/- 261.90	NS
sFib3-2 (pmol/L)	580.58 +/- 103.59	636.74 +/- 119.73	NS
sCRP (mg/L)	10.42 +/- 30.27	3.10 +/- 2.40	0.06
sMPO (ng/ml)	27.20 +/- 29.05	21.96 +/- 14.65	NS

# Curcuminoïdes bio-optimisés: nanoparticules glycérine/ghatti gum

(Nakagawa et al. J Orthop Sci 2014)

50 patients (gonarthrose)



Curcumine  
Curcuminoïdes  
Glycérine  
Ghatti gum

Gum Ghatti = complexe de polysaccharides de l'écorce d'Anogeissus latifolia (Dhaora-Combretaceae).

# Phyto-molécules

## Taille de l'effet sur la douleur

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Molécule	Taille de l'effet (Douleur)	Source
Paracétamol	0.14 (0.05, 0.23)	Bannuru, 2010
Ginger	0.30 (0.05, 0.90)	Christensen, 2014
Rosehip	0.37 (0.13, 0.60)	Christensen, 2008
AINS	0.44 (0.33, 0.55)	Lee, 2005
Curcuminoïdes	0.57 (0.03, 1.11)	Shahebkarr, 2014



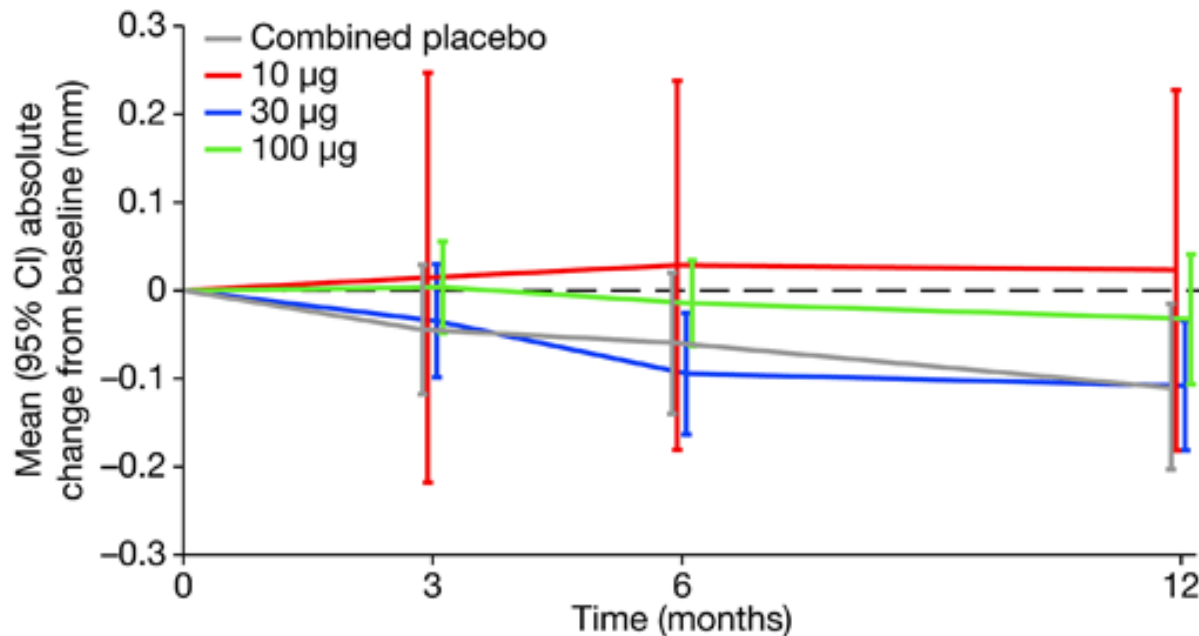
# TRAITEMENTS INTRA-ARTICULAIRES

# 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

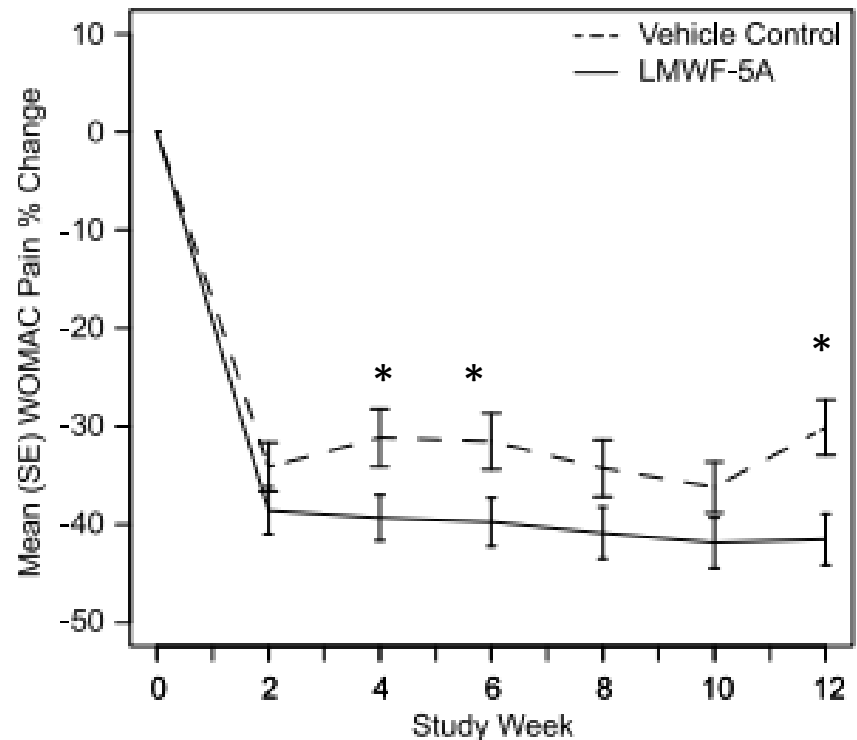
## Epaisseur du cartilage fémoro-tibial latéral (qRMN)

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

# 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



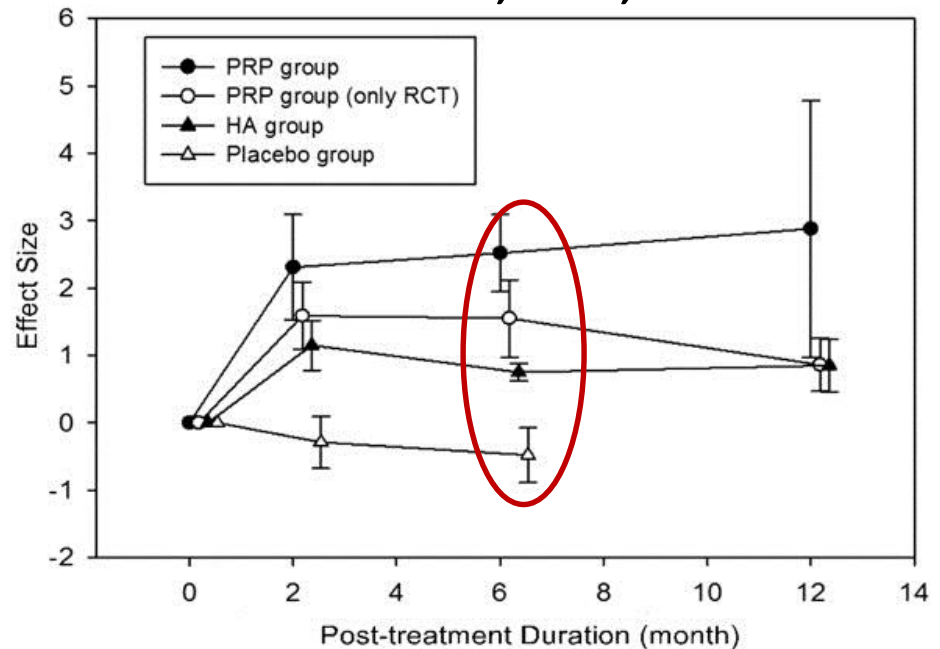
# Platelet-rich Plasma

## 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 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

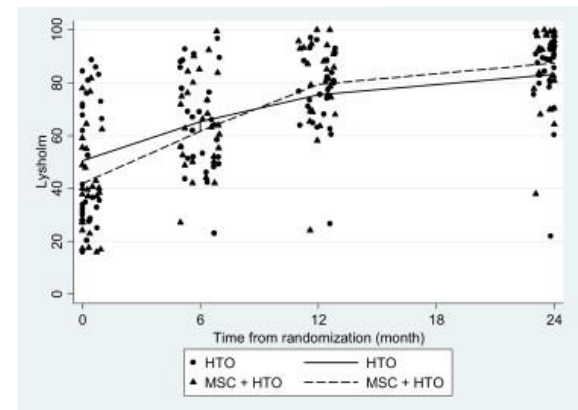
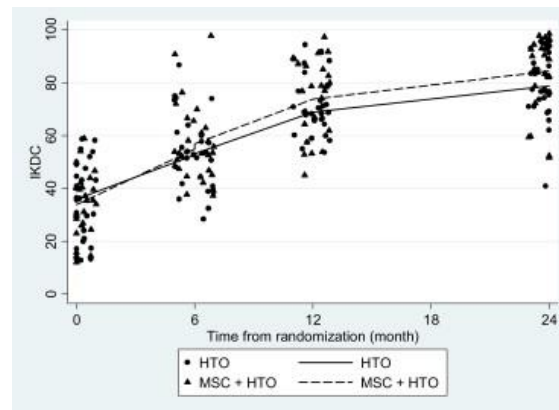
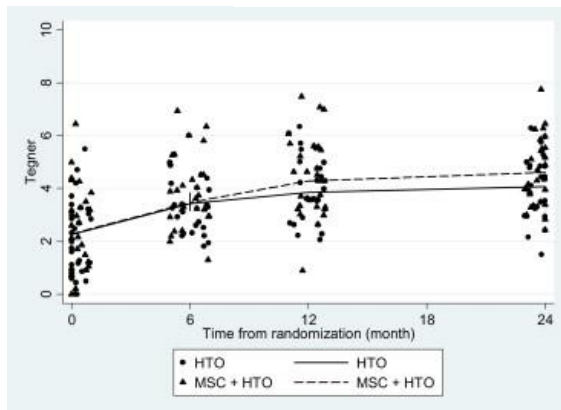
Outcome	Unadjusted			Adjusted*		
	Estimate	95% CI	P Value	Estimate	95% CI	P Value
IKDC score	4.73	-1.31 to 10.77	.124	7.65	3.04 to 12.26	.001
Lysholm score	2.55	-4.93 to 10.02	.504	7.61	1.44 to 13.79	.016
Tegner score	0.45	-0.18 to 1.08	.158	0.64	0.10 to 1.19	.021

Index  
algo-  
fonctionnels



Supériorité  
HA + MSCs

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



# Injection MSC Hématopoïétiques

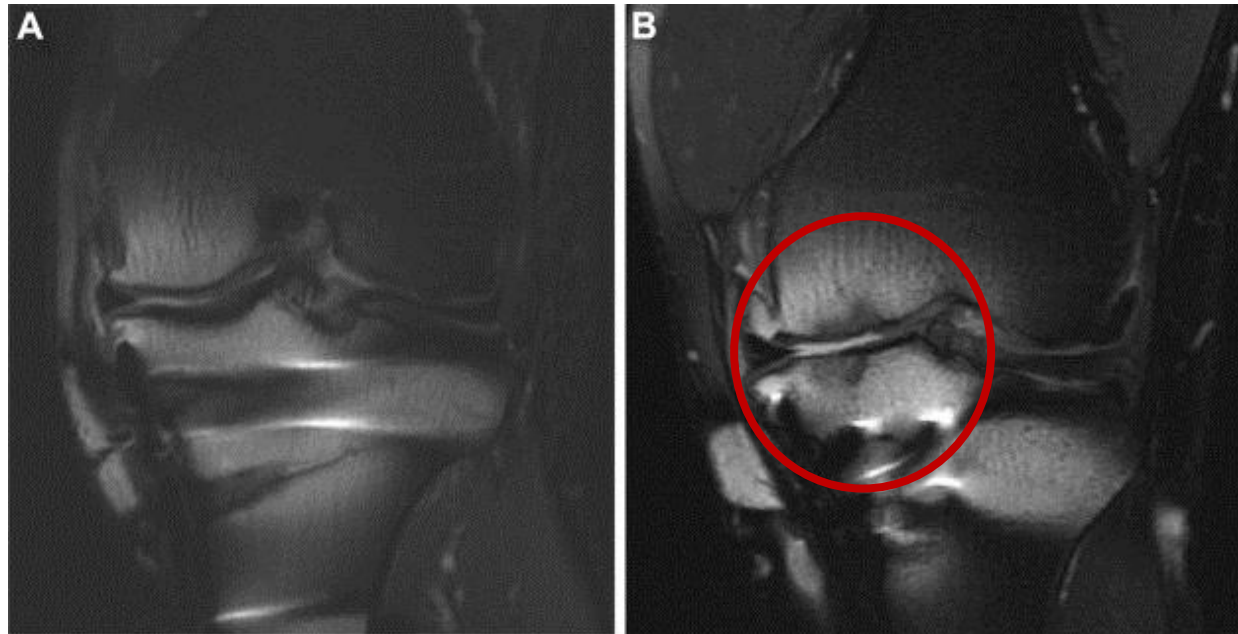
Imagerie RMN

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

HTO + HA + MSCs

HTO + HA

1 an après  
traitement

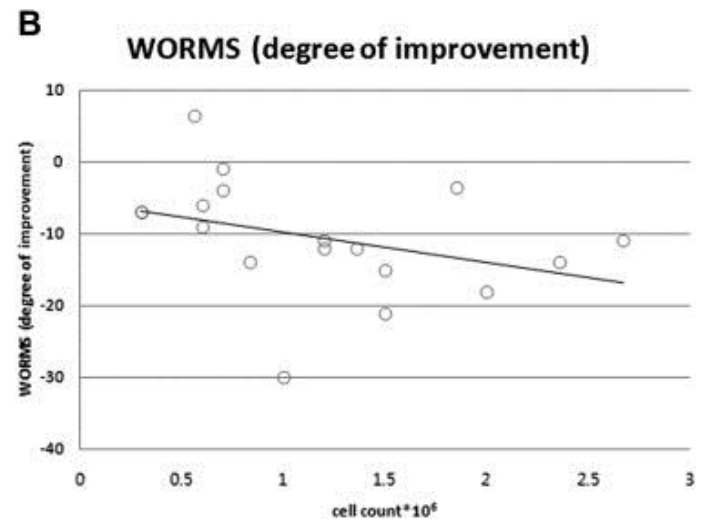
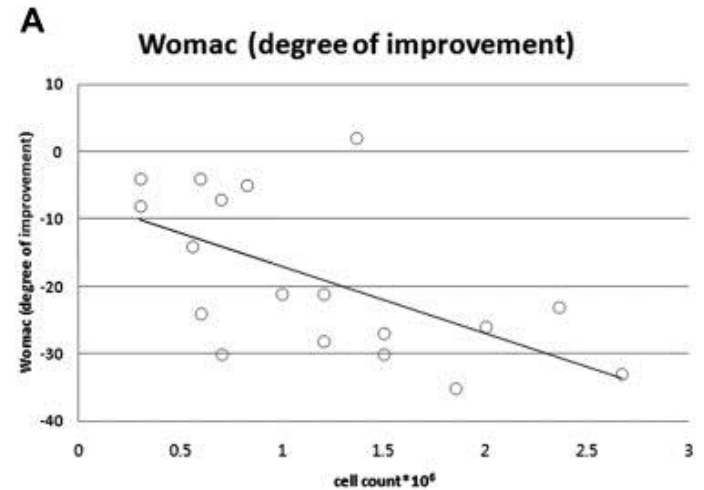
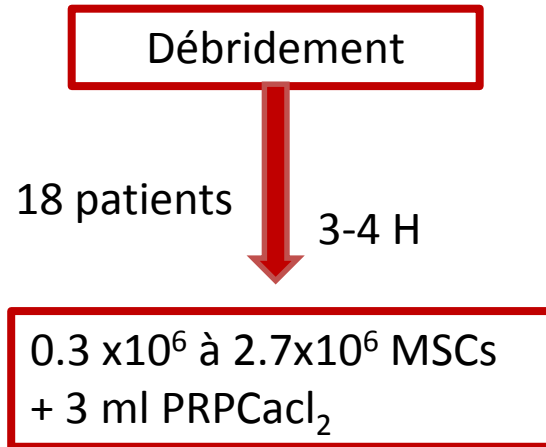


## MOCART Total score

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

# 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

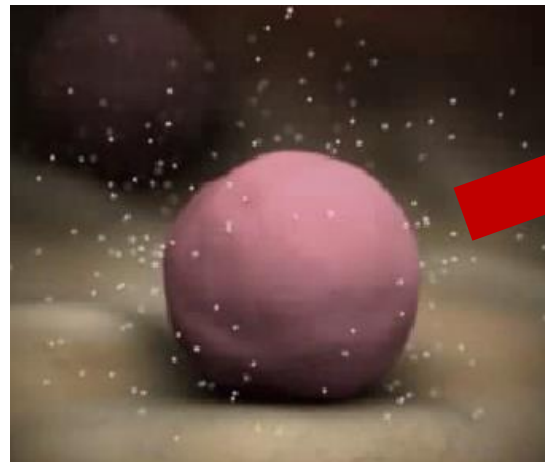
RMN WORMS			
	Pré-op	26 M post-op	P value
WORMS	60,0 ± 33,0	48,3 31,8	<0.001
WORMS cartilage	28,3 ± 11,7	21,7 10,3	<0.001

# DRUG DELIVERY SYSTEM



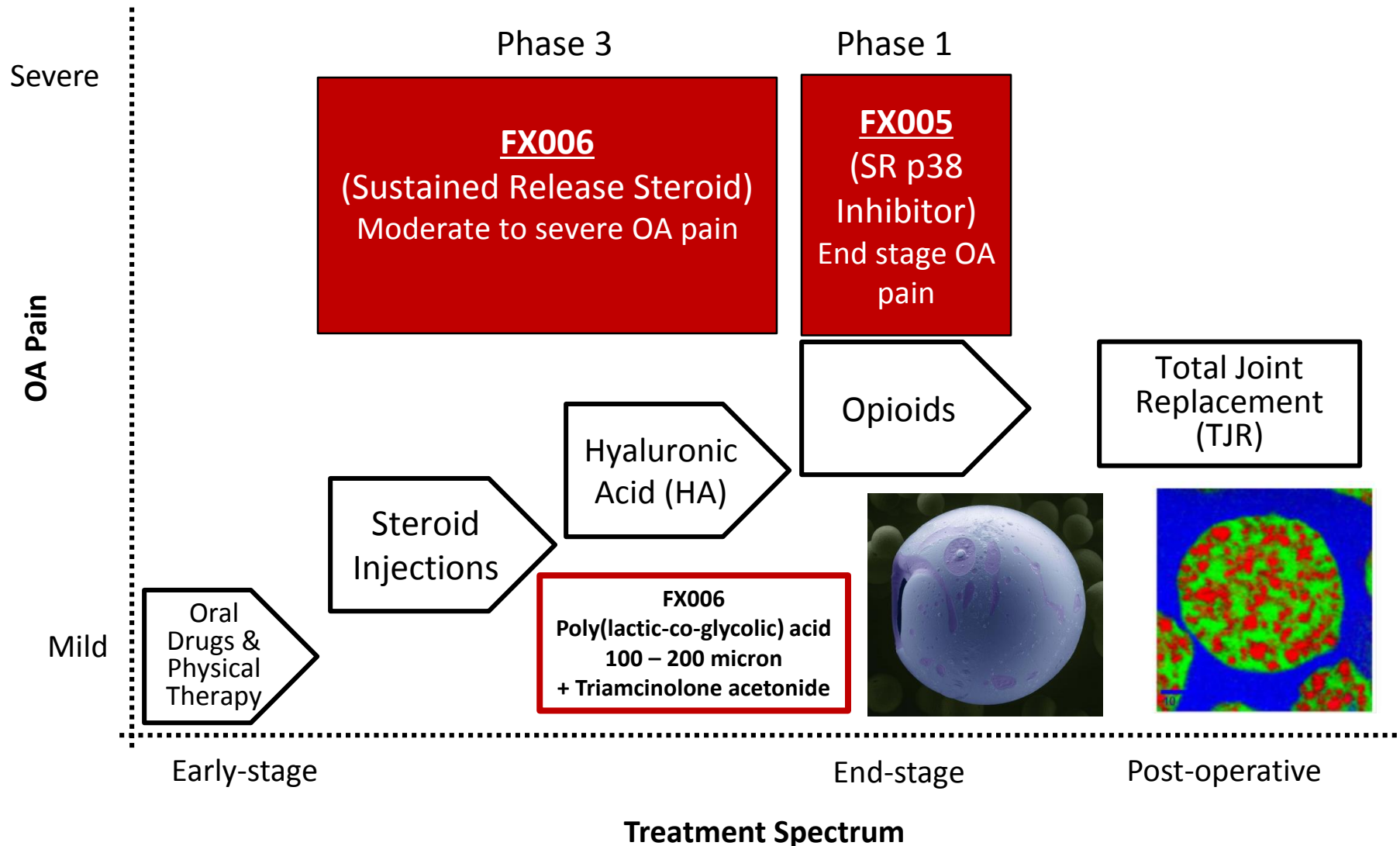
Libération prolongée

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



Corticostéroïdes  
Anticorps monoclonaux  
Curcumine  
AINS

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

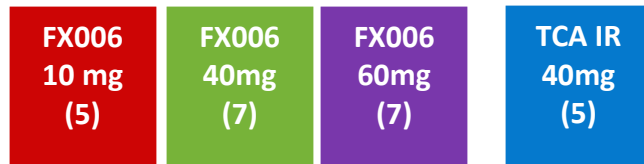


# FX006: pharmaco-cinétique dans le fluide synovial

## Study 1

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

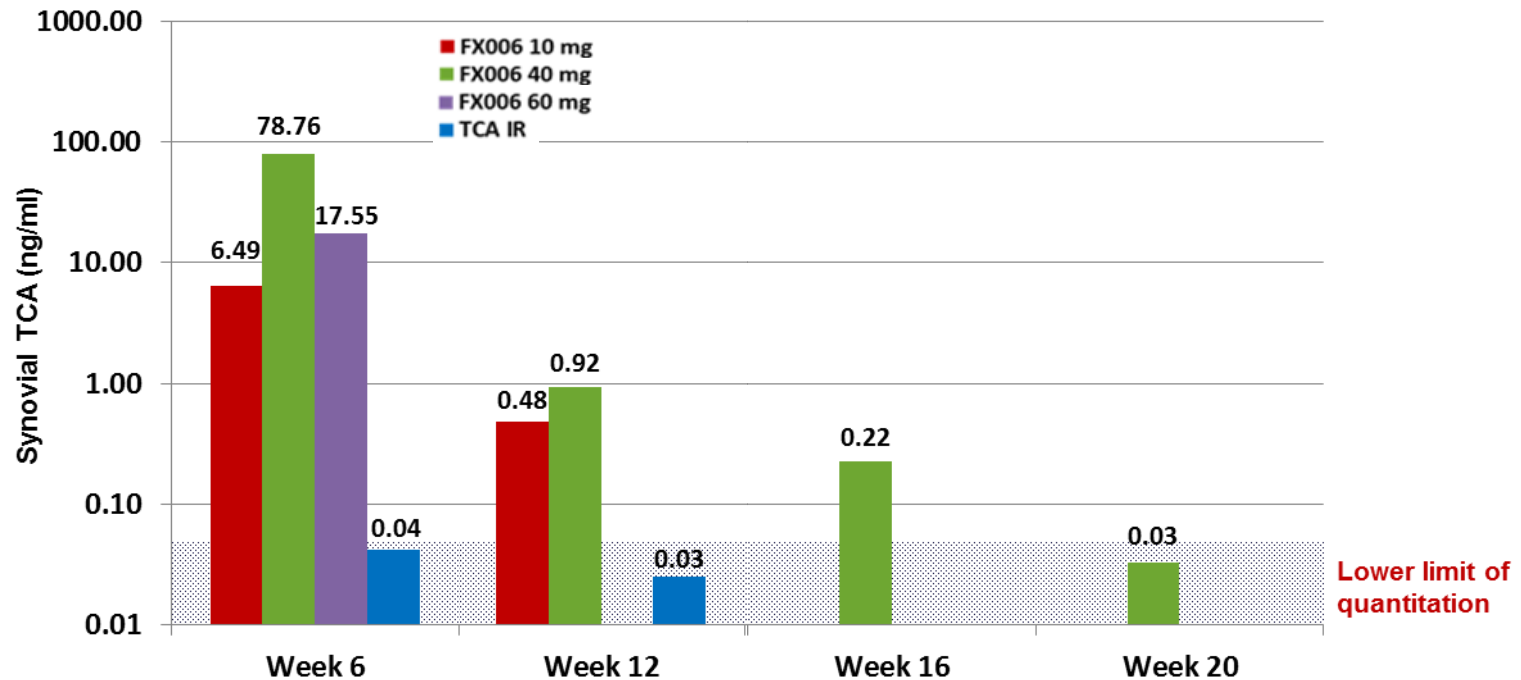
19 OA patients on FX006, 5 on TCA IR



## Study 2

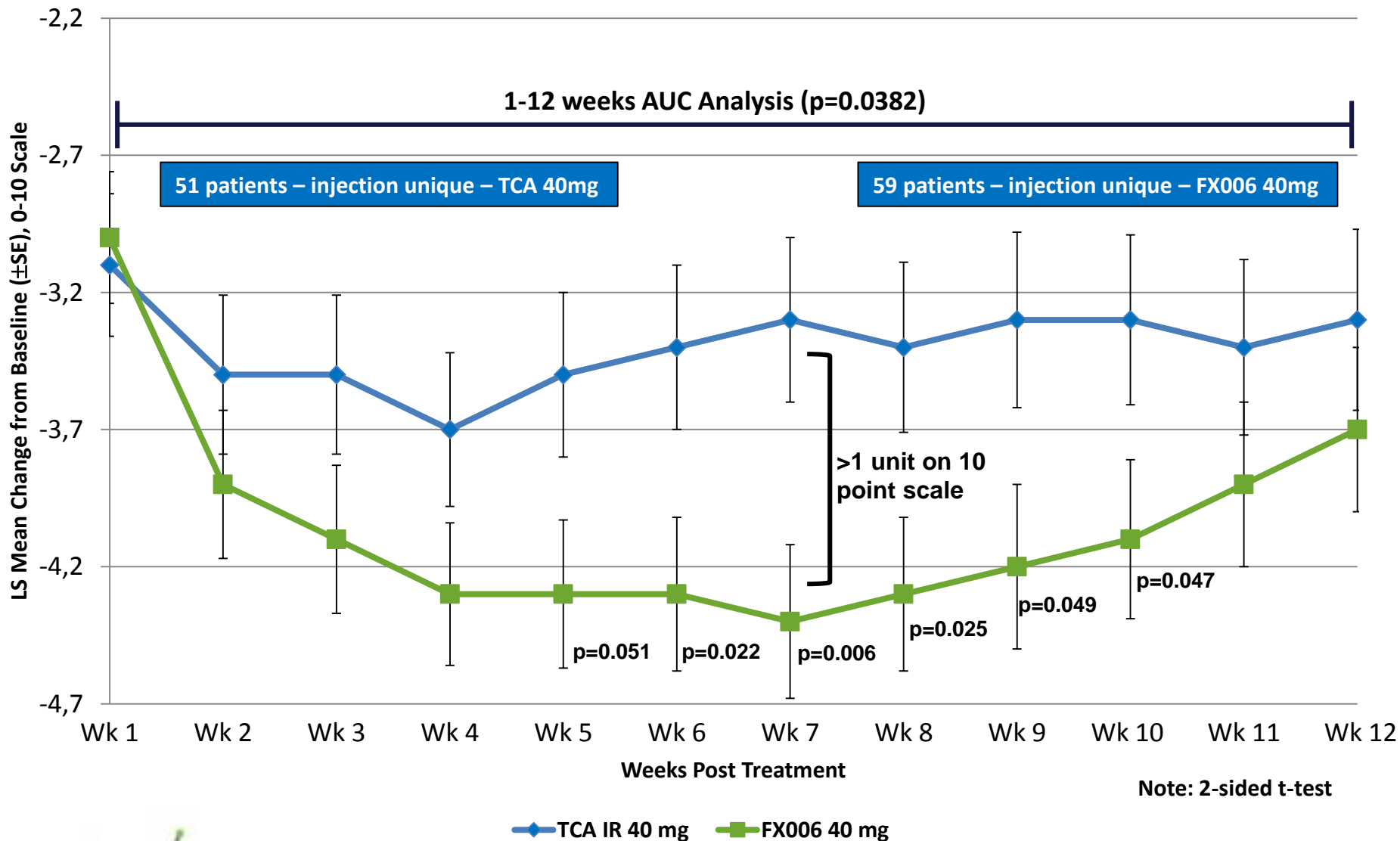
### TCA Concentrations in Synovial Fluid $\geq 12$ Weeks After Single Injection

40 OA patients on FX006, 10 on TCA IR

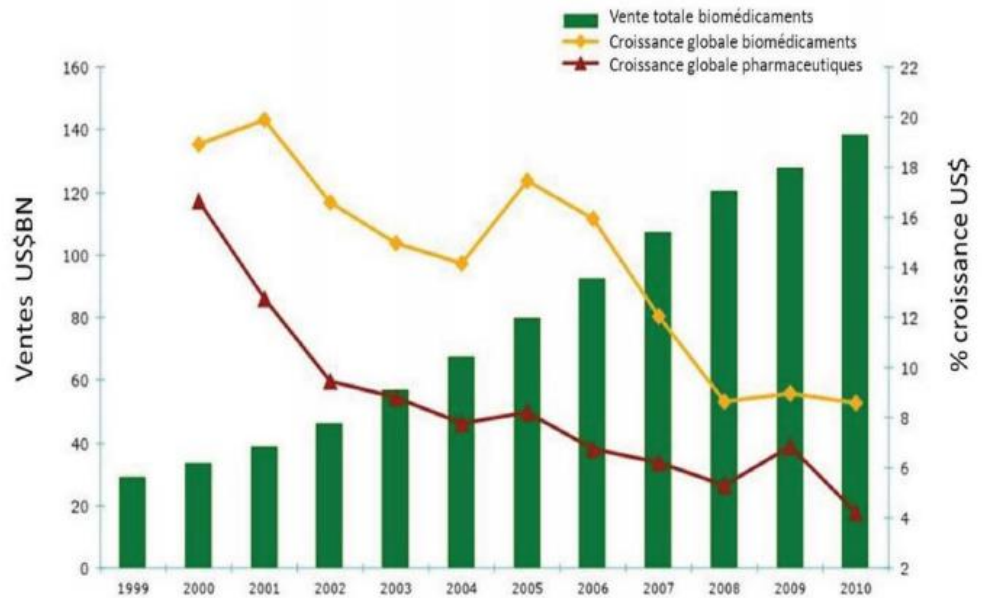


Data represented with geometric means

# FX006 40 mg: Effets sur la douleur







Source: IMS Health, MIDAS, MAT Dec 2010, Biologic market only

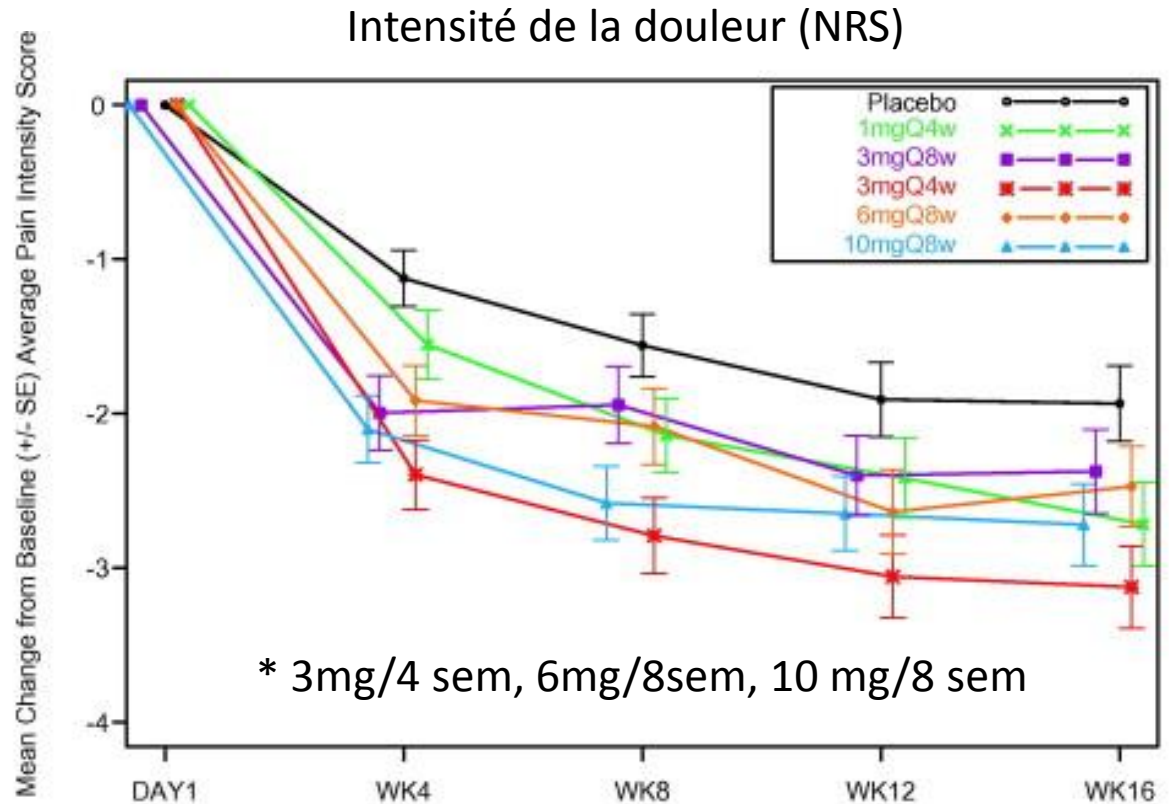
# MÉDICAMENTS BIOLOGIQUES

# Fulranumab

Human monoclonal anti-NGF

Sanga P et al. Pain, 2013

- 468 OA (Cox/Gon)
- Sous-cutané
- RCT 6 bras
- 1 ou 3 mg toutes les 4 sem.
- 3, 6 ou 10 mg toutes les 8 sem.



Autres cibles : Cathepsin K, VEGF, aggrecanases (ADAM-TS5)

# Peu d'innovation: pourquoi?

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Mauvaise  
connaissance de la  
maladie

Essais cliniques  
longs et coûteux

Manque de  
volonté  
politique

Contraintes  
réglementaires  
fortes

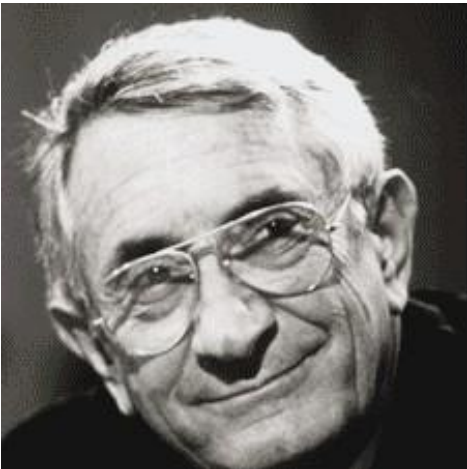
Marché peu  
réceptif

# A méditer !

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**«L'innovation est une alliance entre recherche, marketing, instinct, imagination, produit et courage industriel.»**

Antoine Riboud



Antoine Riboud est un homme d'affaires français, fondateur et président de Danone.



Bone and Cartilage Research Unit



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)



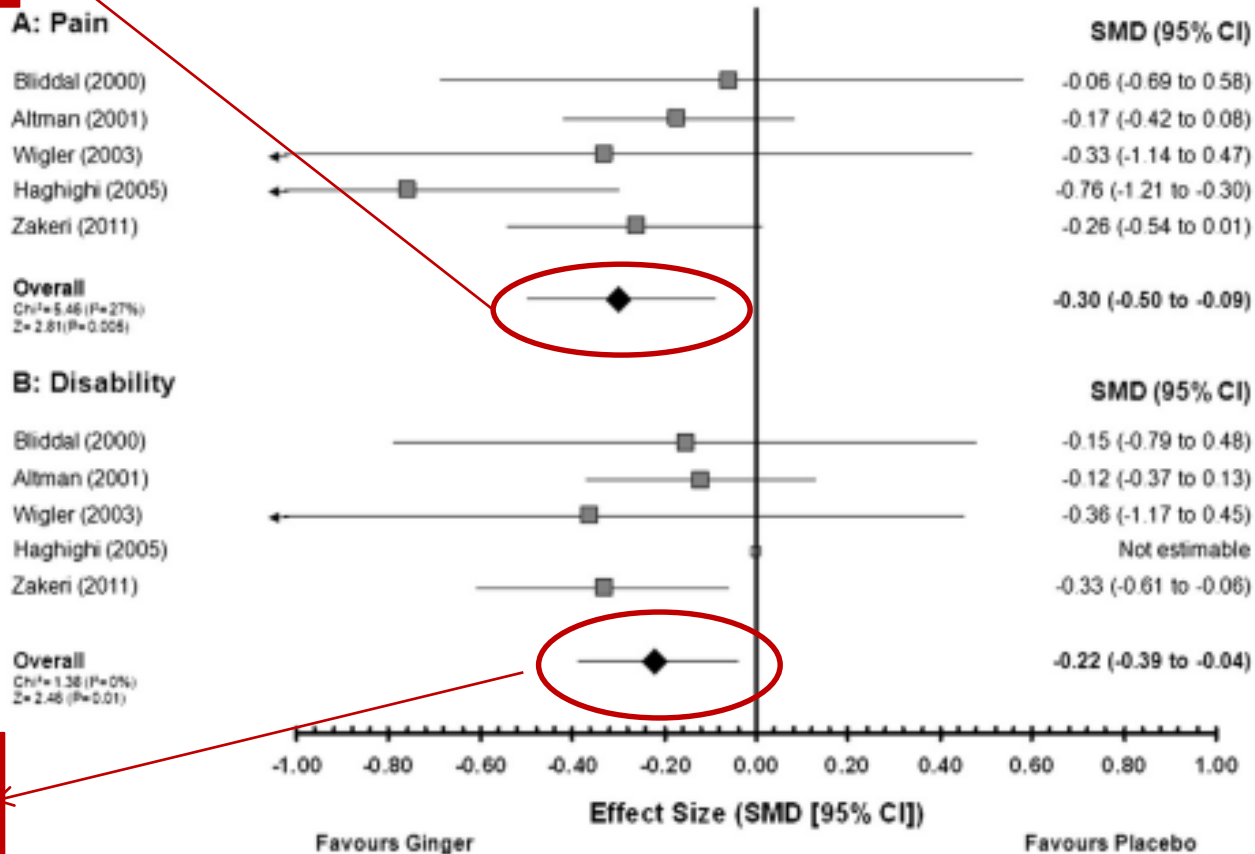


# Ginger

Bartels et al. Osteoarthritis Cart, 2014

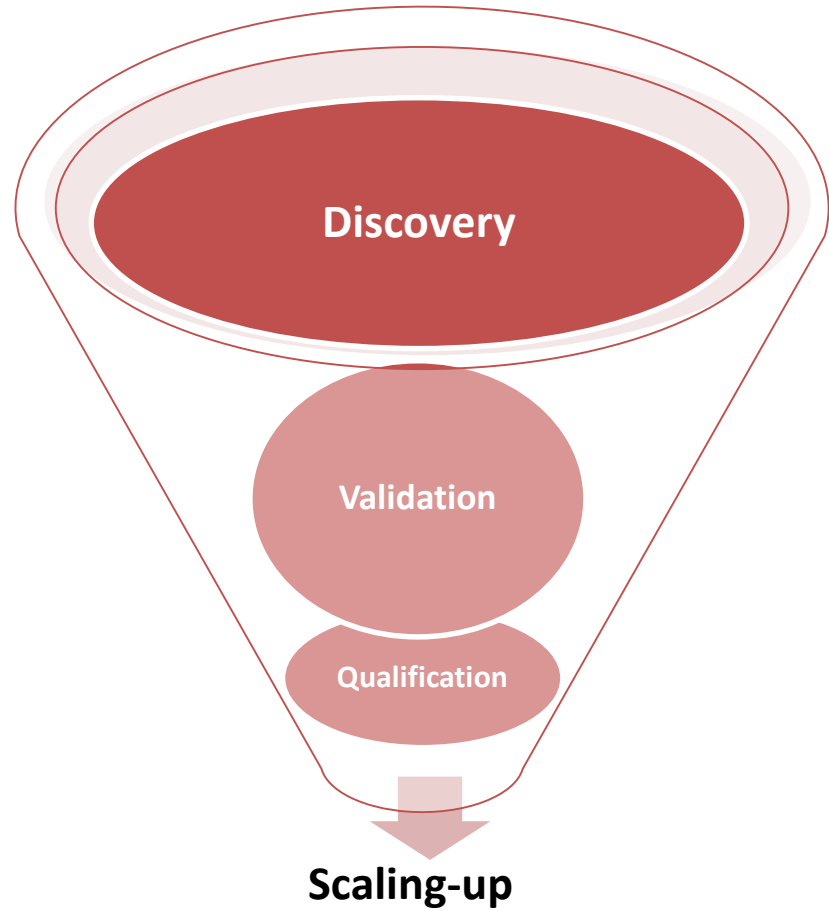


**SMD = -0.30**  
**L<sup>2</sup> = 27%**



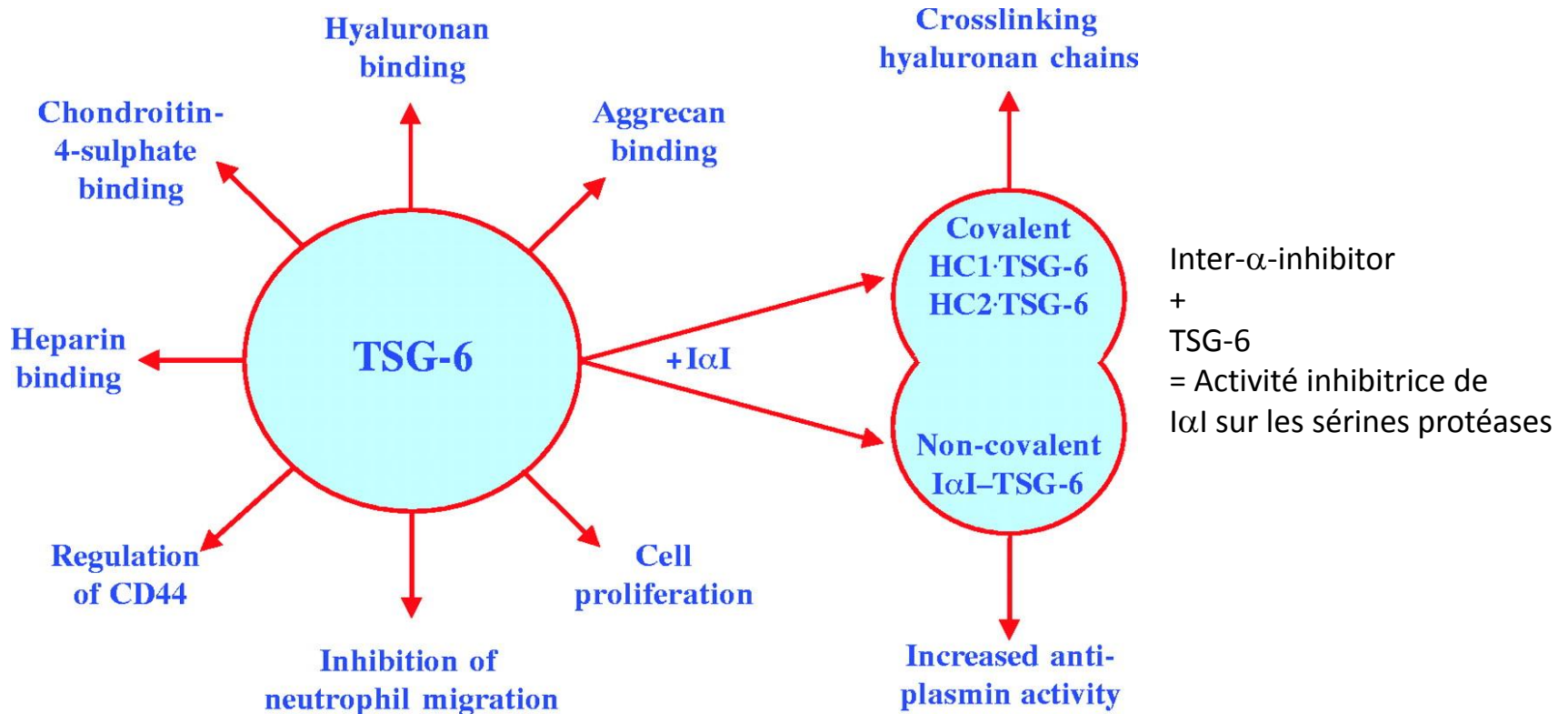
**SMD = -0.22**  
**L<sup>2</sup> = 27%**

# MARQUEURS BIOLOGIQUES





# TNF-stimulated gene 6 (TSG-6)

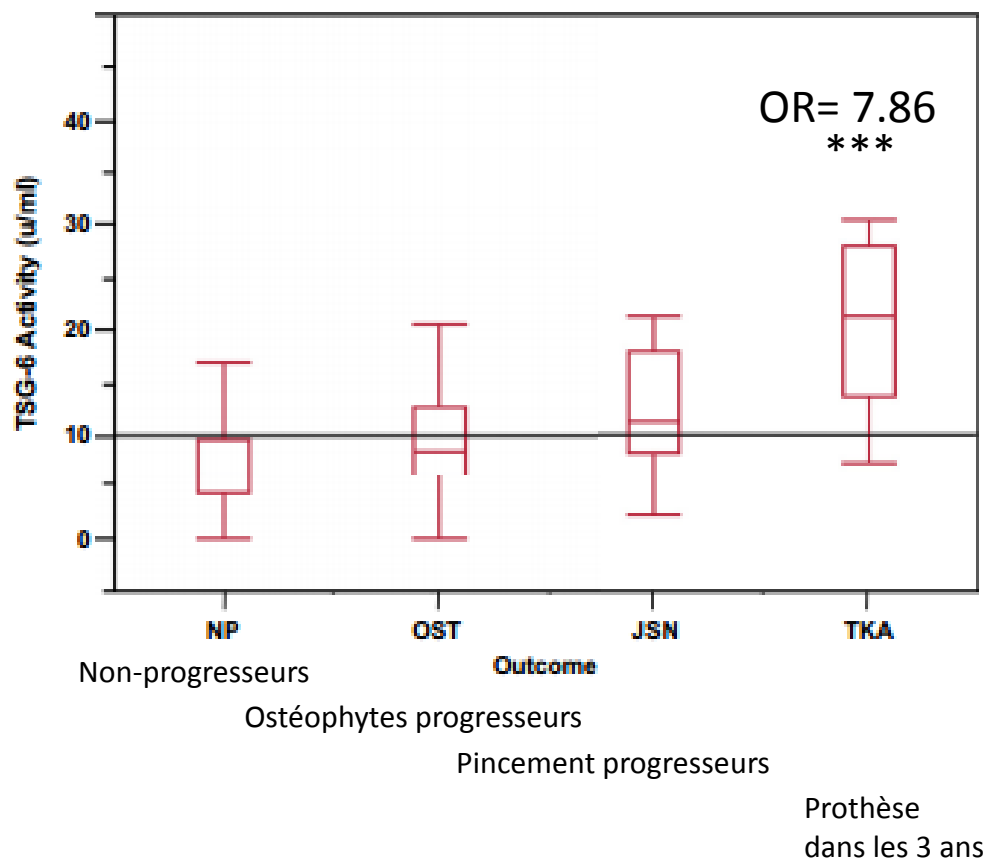


- ❖ Anti-inflammatoire
- ❖ Inhibiteur de l'activité des ostéoclastes
- ❖ Inhibiteur de la différenciation des ostéoblastes
- ❖ Stabilisateur de la matrice extracellulaire

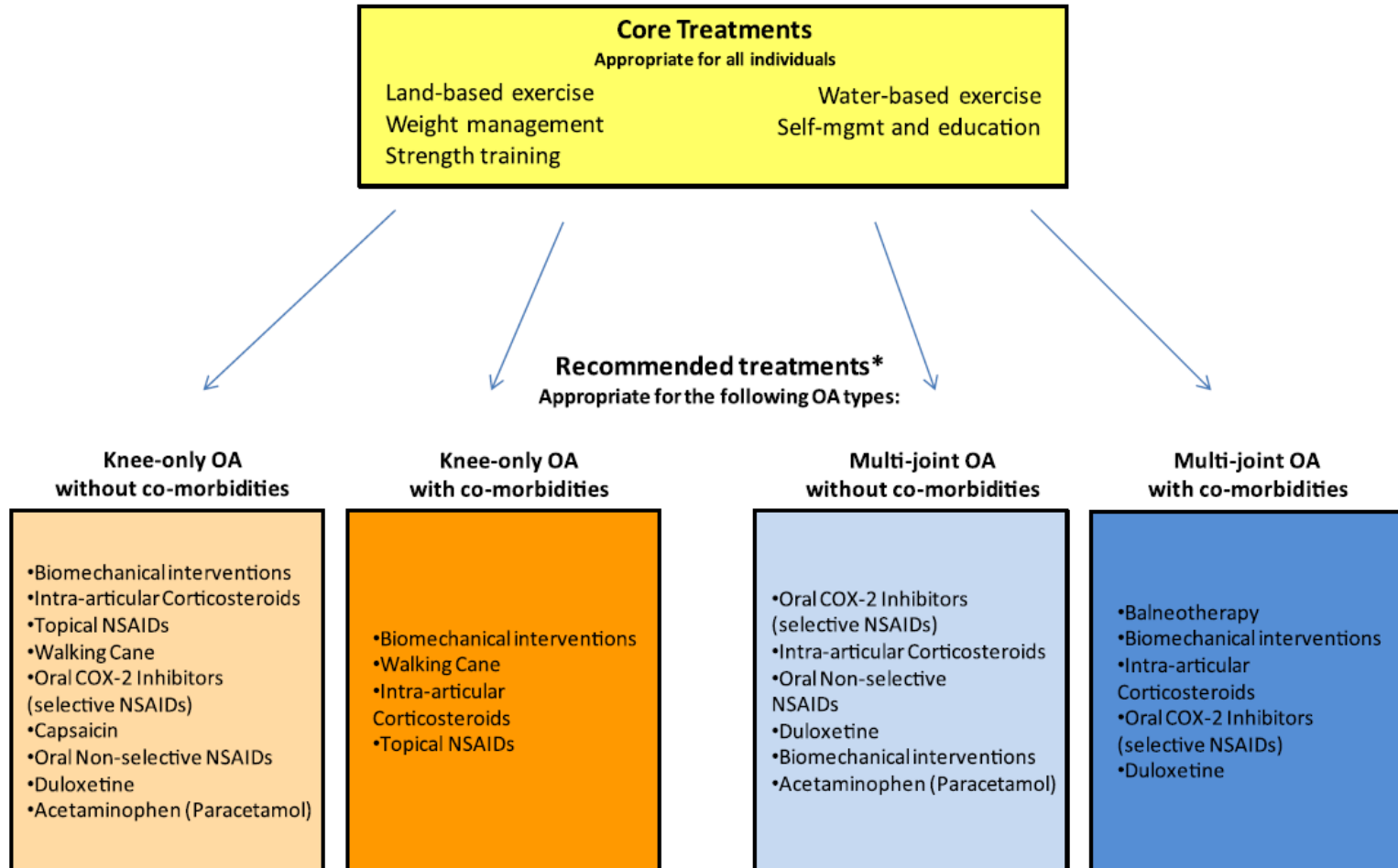
# TNF-stimulated (TGS)-6 protein activity

Wisniewski et al. Osteoarthritis Cartilage 2014

- 132 fluides synoviaux
- Arthrose KL  $\geq 1$
- RX à T0 et T3 ans
- OARSI score



## OARSI Guidelines for the Non-surgical Management of Knee OA



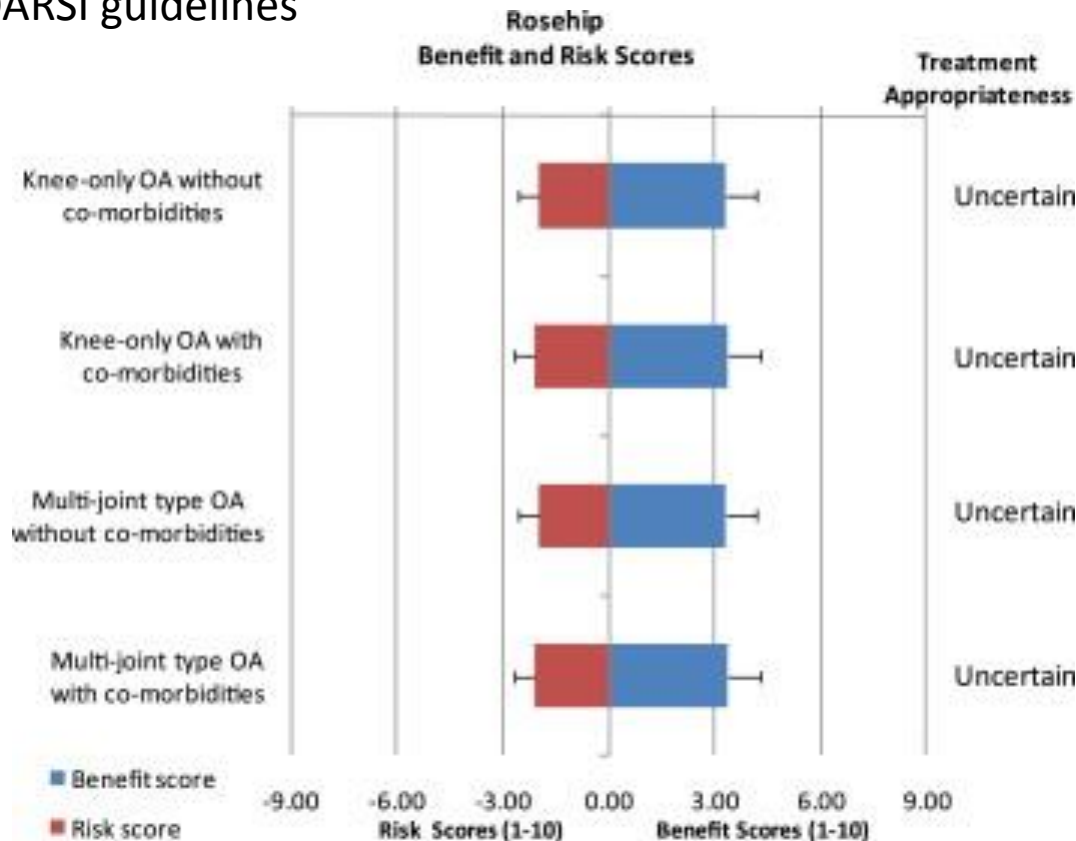
\*OARSI also recommends referral for consideration of open orthopedic surgery if more conservative treatment modalities are found ineffective.

# Rosehip

Mc Alindon et al. Osteoarthritis Cart, 2014



OARSI guidelines



## Rosa canina

- ❖ Vitamine C
- ❖ Caroténoïdes
- Beta-carotène
- Lutéine
- Lycopène
- Zeaxanthine

Taille de l'effet douleur = 0.37 (0.13-0.6)

« Uncertain »