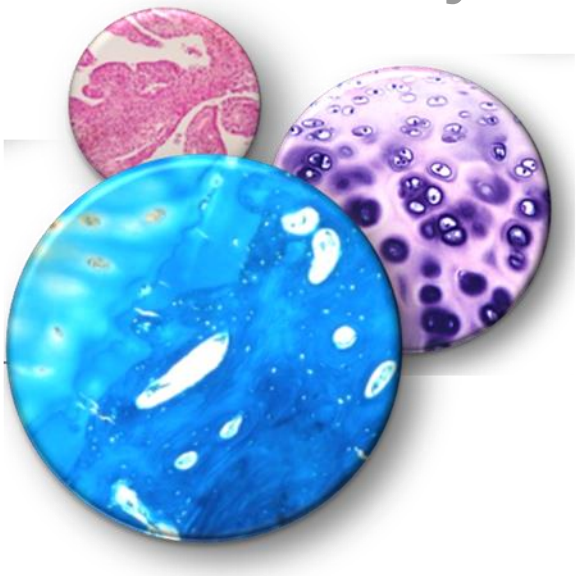
Soluble biomarkers in OA: can they be used as indicator of HA re-injection?

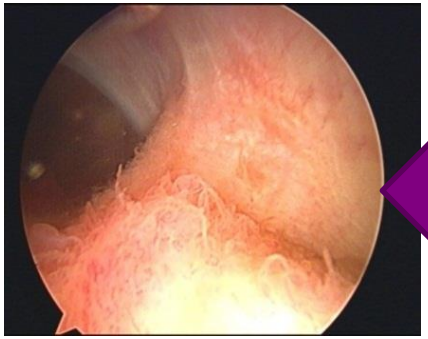
Yves Henrotin, PhD

University of Liège

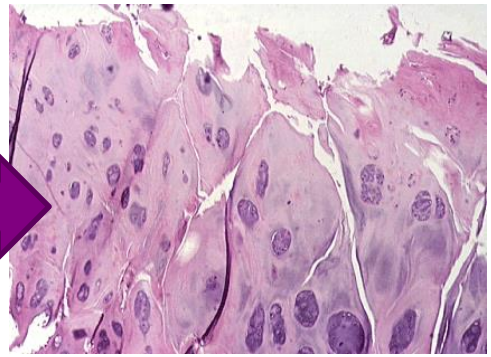


Université de Liège

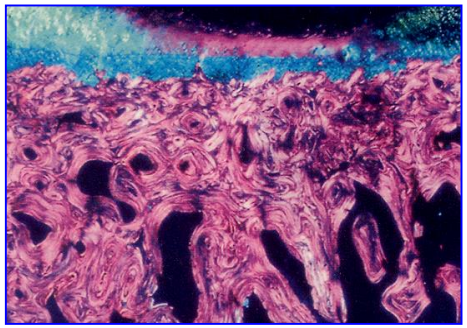
Osteoarthritis: A global disease affecting all joint tissues



Synovial membrane inflammation



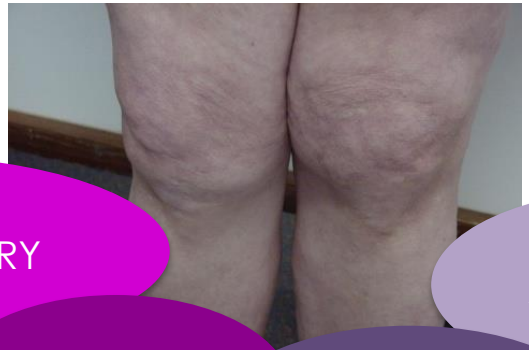
Cartilage degradation
Fibrillation/fissuration
Mineralisation/vascularization



Subchondral bone sclerosis/resorption

…to identify metabolic changes in joint tissues

Joint is an organ



PRO-INFLAMMATORY MEDIATORS

ADIPOKINES

PEPTIDES

GLYCATED PRODUCTS

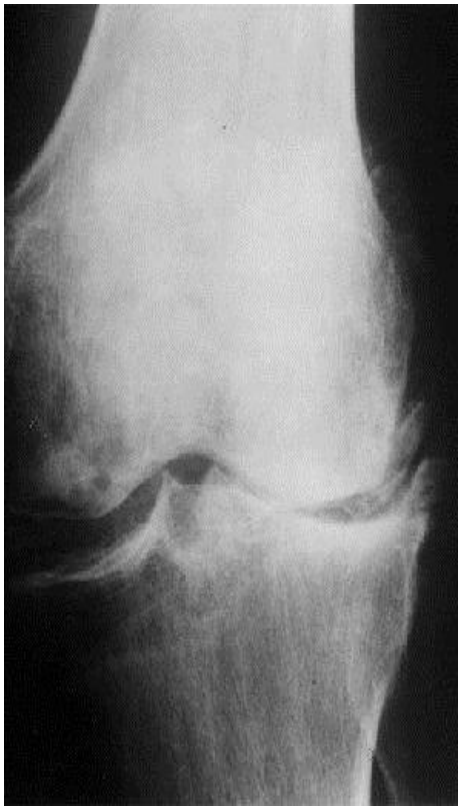
LOCAL INFLAMMATORY REACTION
« Synovitis »

LOW GRADE SYSTEMIC INFLAMMATION
« Inflammaging »

To decrease « degradative peptides » release is a therapeutic target
« Metabolic responders »

OA diagnosis : symptoms and standard radiography

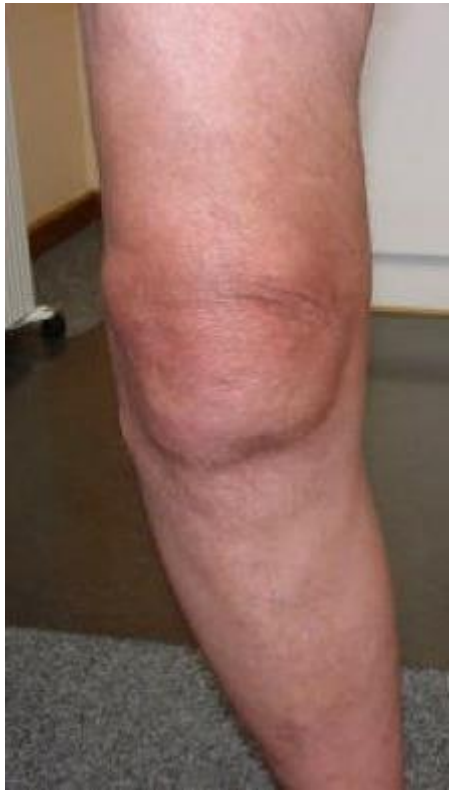
X-ray



Osteophytes
Joint space narrowing
Bone sclerosis
Attrition
Geodes

Symptoms

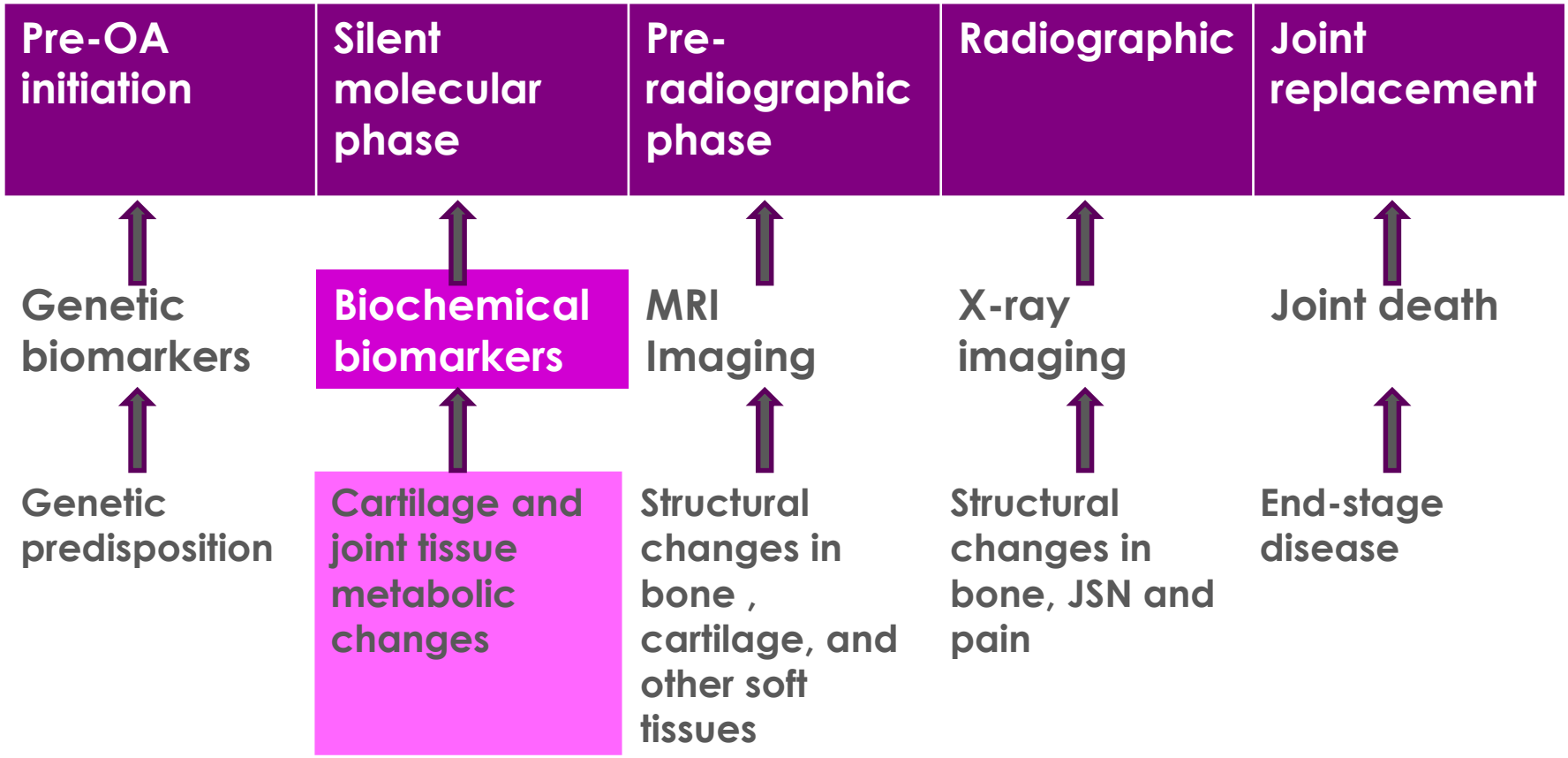
Pain
Stiffness
Swelling
Cracks
Deformity
Malalingment



These signs and symptoms occur in the late stage of the disease

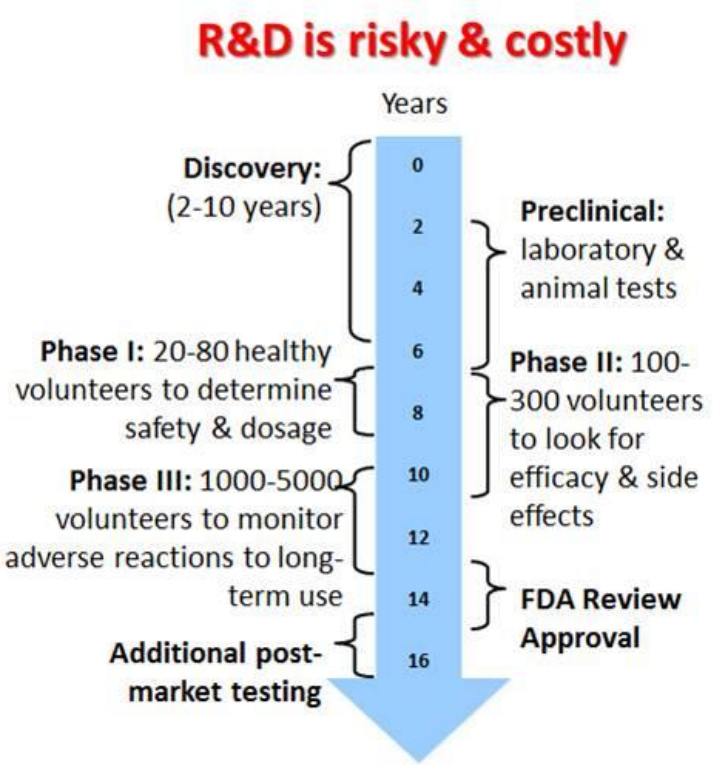
Radiographic and clinical signs are preceeded by a silent molecular phase

(D Patra & L Sandell, J Knee Surg, 2011)



...To diagnose the disease at the silent molecular phase

Drug discovery is protracted, risky and costly



Nothing new to offer at the patients and the OA research community

Clinical trials end-point

- **Symptoms modification** (3 to 6 months)

Pain

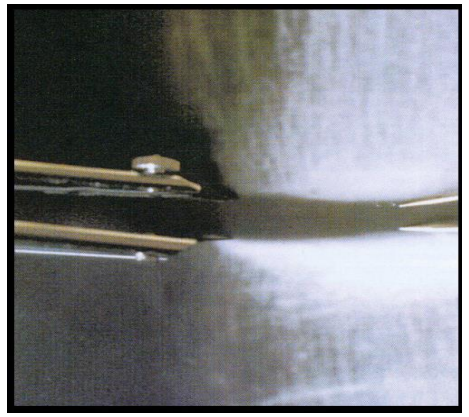
Physical function

Patient global assessment

- **Structure modification** (1 to 3 years)

Imaging outcomes

Joint Space Narrowing



The main limitations of JSN

- Indirect measure of the alteration in articular cartilage.
- Fails to measure a dynamic process
- Confounded by the presence of meniscal lesions and extrusion.
- Changes overtime are small, and occur in only a subset (progressors) of patients.
- Poorly reproducible (full extension).
- Poorly correlated with joint function and pain.

Why do we need biological markers in treatment developement?

- To predict who will respond to a treatment
- To surrogate clinical end-point
- To monitor the effect on tissue metabolism

FDA and EMA recommendations

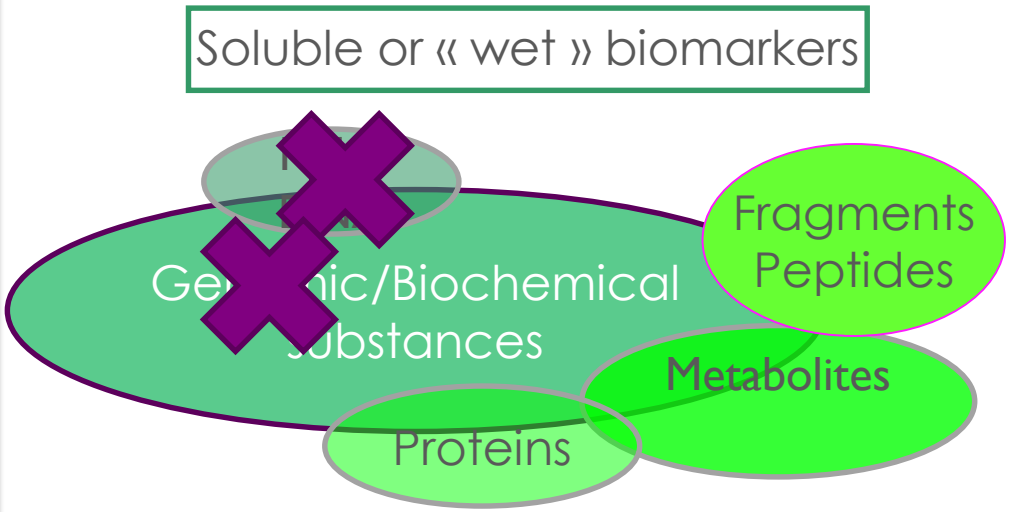
- "a higher level of integration of biomarkers in the development and testing of new drugs to advance decision-making on dosing, time and treatment effect, trial design, and risk/benefit analysis . Biomarkers can be used not only in the process of drug development, but also in assessment of individual patient's response to treatment."

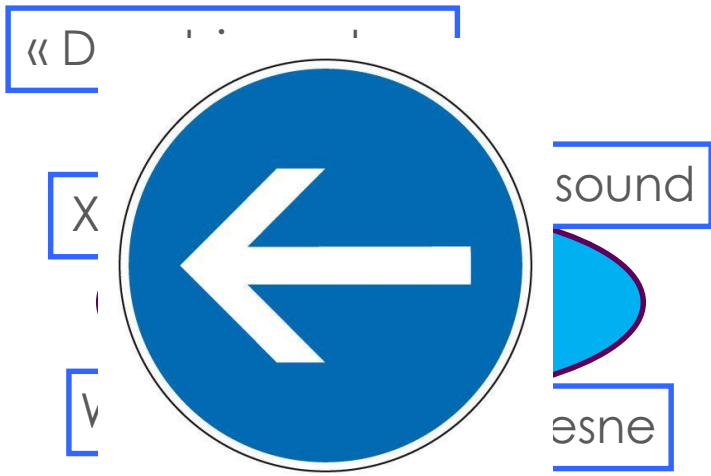
Kraus et al. O&C 2015

Definition - Classification

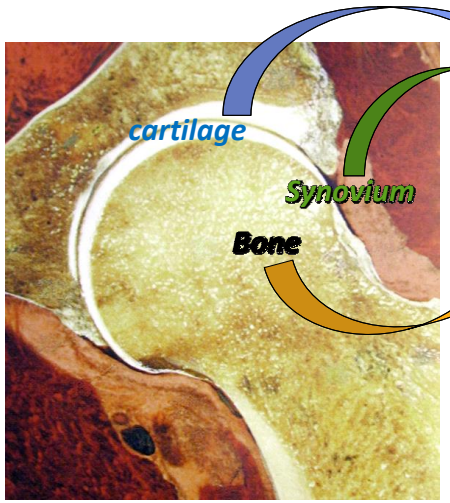
A biomarker is a characteristic that is objectively measured and evaluated as an indicator of normal biologic processes, pathogenic processes, or **pharmacologic responses to a therapeutic intervention**. »

Biomarkers Definitions Working Group I. Biomarkers and surrogate endpoints: preferred definitions and conceptual framework. Clin Pharmacol Ther 2001; 69: 89-95.





OA Biomarkers



lymphatics

Blood
~5 liters

kidney

urines

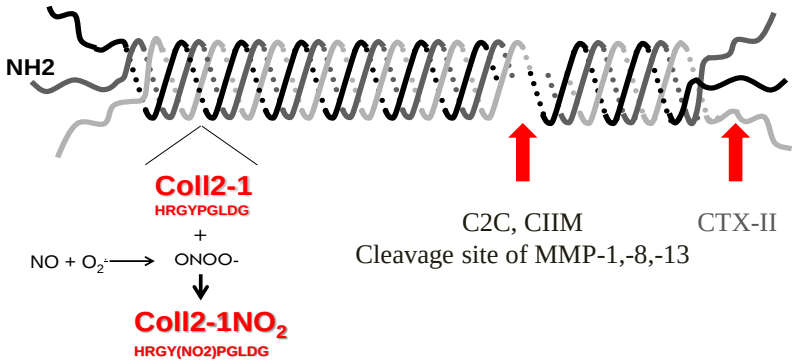
bone
- *sPINP*
- *uCTX-I*

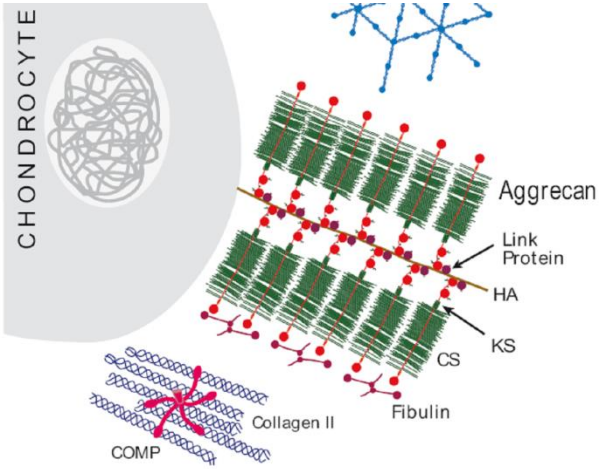
Cartilage
- ***sColl2-1***
- ***sFibulin3***
- ***sCOMP***
- *sYKL40*
- *sC2C*
- ***uCTX-II***
- ***PIIANP***
- ***CPII***
- ***Agrec-1***

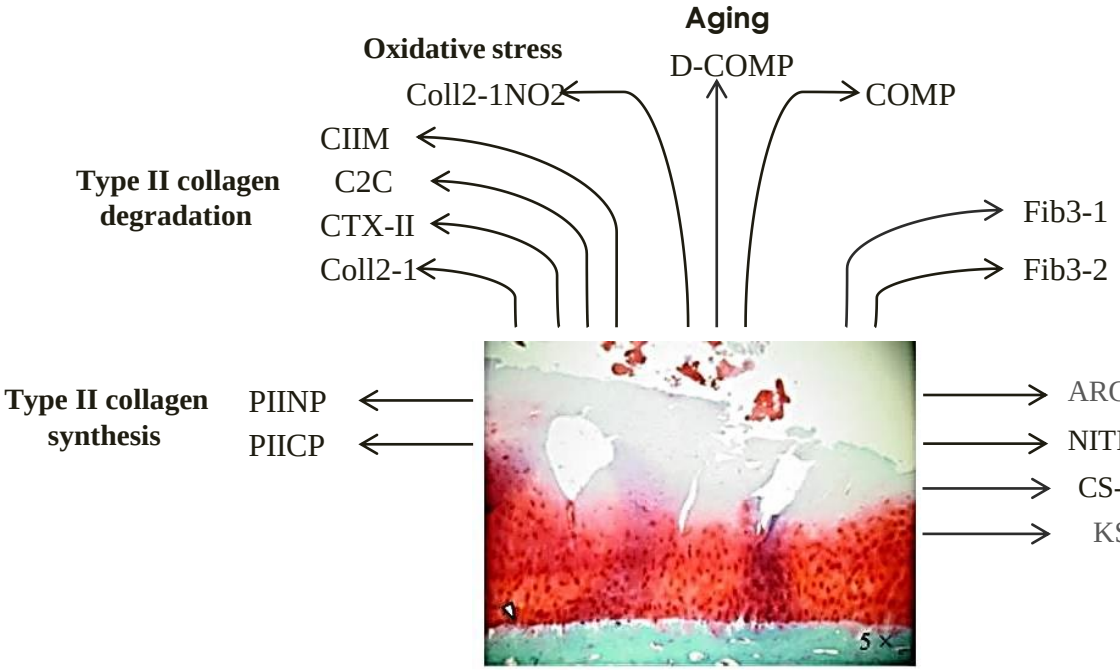
Synovium & inflammation
- **sColl2-1NO2**
- *sPIIINP*
- *sHA*
- ***sCRP ultrasensible***
- ***Cytokines, MPO***

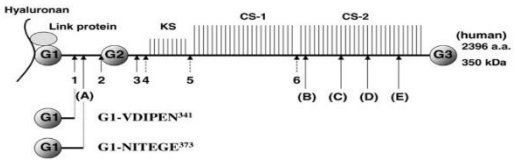
Metalloproteases
- *sMMP1(collagenase)*
- ***sMMP3 (stromelysin***

Biomarkers of cartilage metabolism



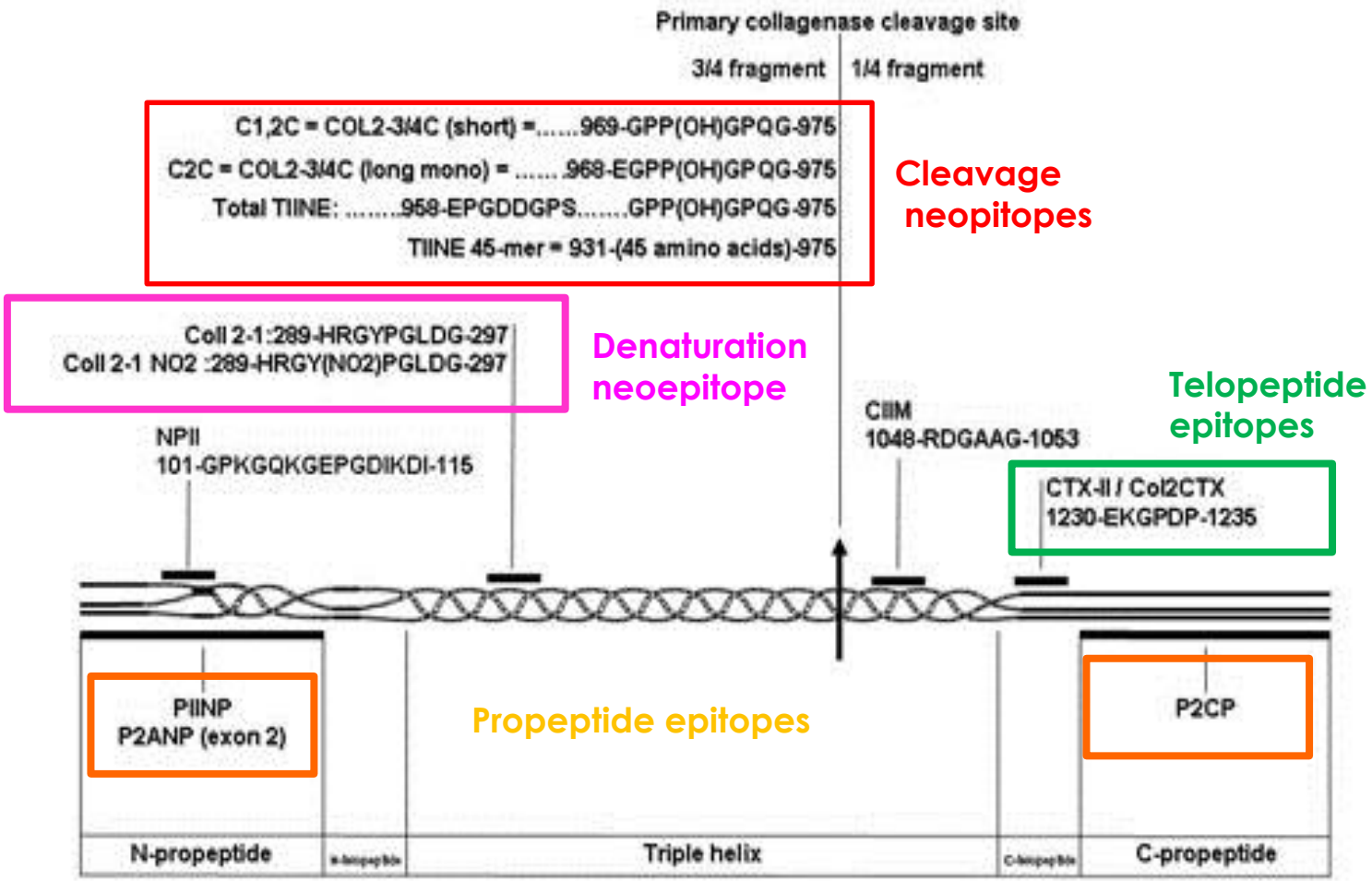






ADAMTS-5

Type II collagen biomarkers



BIPEDS classification

Bauer et al. Osteoarthritis Cart 2006

Burden of disease	• Bio
Investigative	• Bio cat
Prognostic	• Pre like
Efficacy of treatment	• Ind ma
Diagnostic	• Dissociate diseased from non-diseased.
Safety	• Identify adverse effects and provide means of safety.one

Efficacy of intervention
« Indicative or predictive of treatment efficacy and for which the magnitude of the change is considered pertinent to the response. »

Biomarkers of efficacy of treatment (BIPEDS)

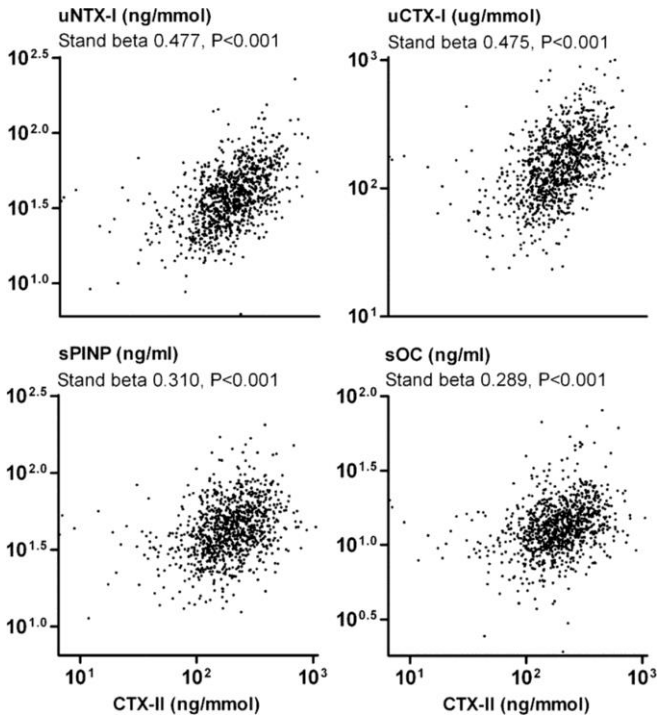
Updated Van Spil et al.2010

« Biochemical marker concentration differed statistically significantly between patient populations with or without treatment, or before and after treatment within patient »

BIPEDS	Biomarkers
Efficacy of intervention	uCTX-II, sColl2-1,sCOll2-1NO2, sC2C, sCOMP, sKS, sYLK40, sPIIANP, uNTX-I, sOC, sHA, sMMP-3, sCRP

Is CTX-II an efficacy of intervention biomarker? Interpretation pitfalls!

Intervention	CTX-II levels
HA	↓
CS	0
Naproxen,Licofelone	0
Tibolone	0
Risedronate	↓
Calcitonine	↓
Strontium ranelate	↓
SERM	↓
Estradiol	↓



All antiresorptive therapies decrease CTX-II

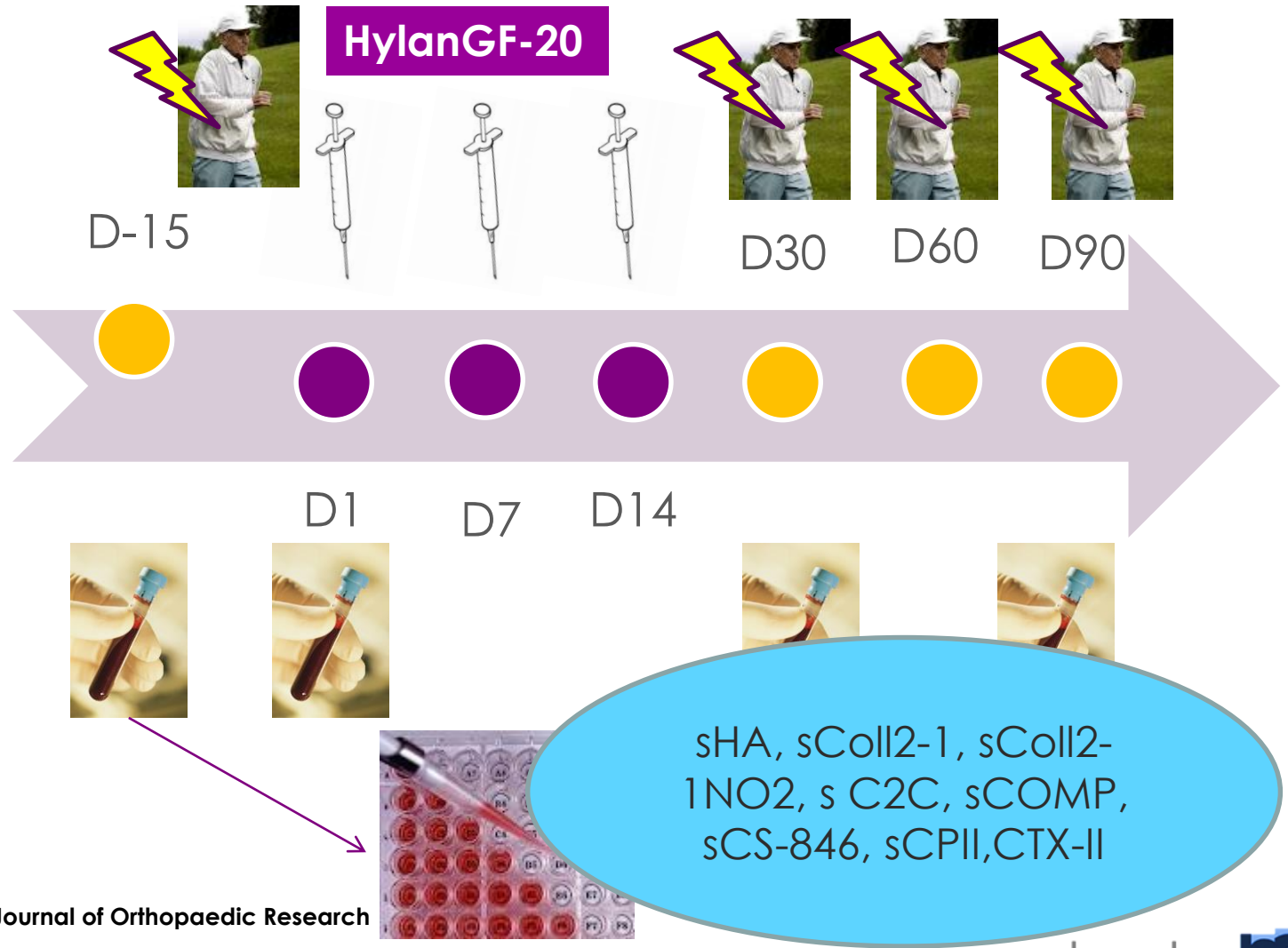
Richette, Roux Osteoporosis Int 2012

u CTX-II reflects bone rather than cartilage metabolism

van Spil W E et al. Ann Rheum Dis 2013

BIOVISCO study: Study design

Open-label, observational prospective study



Henrotin Y et al. Journal of Orthopaedic Research
19 FEB 2013

BIOVISCO study

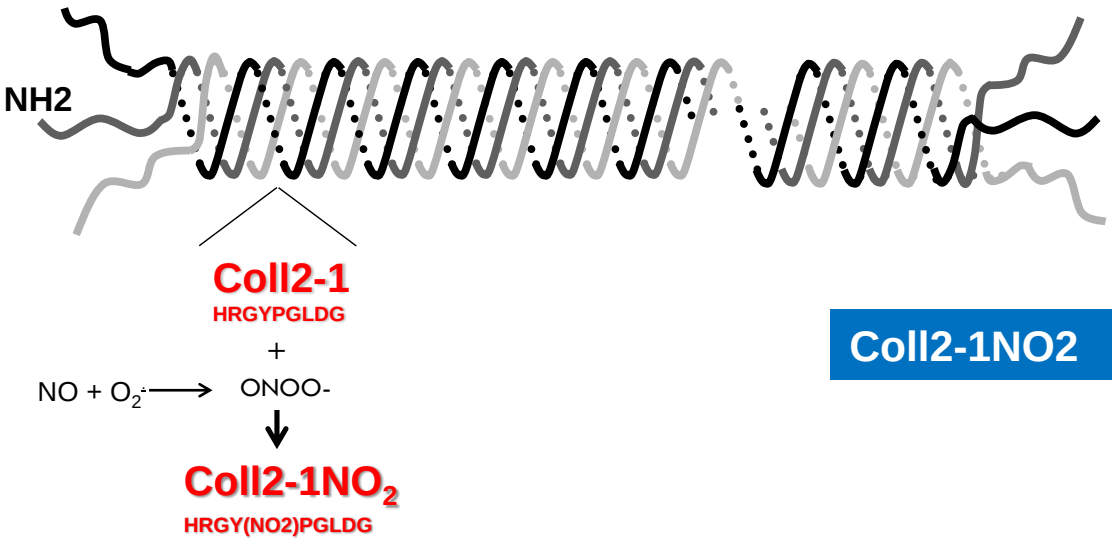
An open label observational prospective study

Conrozier et al, J Orthp Res, 2012; Henrotin et al, J Orthp Res,2013.

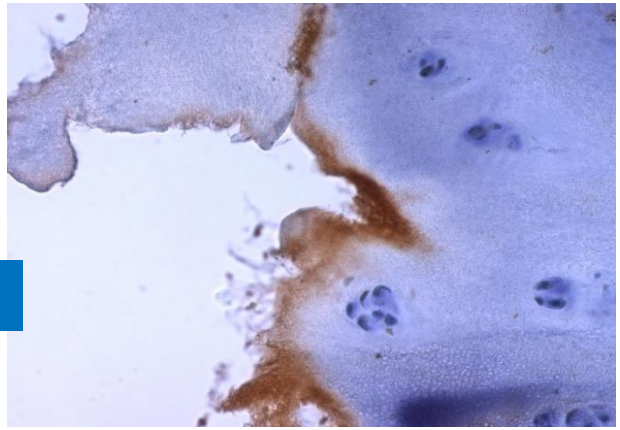
- ✓ 45 patients with unilateral symptomatic tibiofemoral and/or patellofemoral OA
- ✓ 3-weekly intraarticular injection of hyalan G20 (Synvisc®)
- ✓ Follow-up D1, D30 and D90 after the last injection

	D1 (after the last injection)	90 days (after the last injection)	p-Value D1 vs D90
sColl2-1 (nM)	**140.34(882.44-285.32)**	**128.41 (85.6-241.34)**	**0.05***
sColl2-1NO2 (nM)	**0.400 (0.050-1.010)**	**0.370 (0.14-0.870)**	**0.025***
uCTX-II (ng/nmolcreat)	**392.7 (90.0-816.4)**	**306.0 (90-1123.9)**	**0.02***
sPIICP (ng/ml)	817.9 (131.4-1848.6)	874.8.3 (326.4-1435.0)	0.41
sC2C (ng/ml)	223.6 (99.4-329)	209.5 (135.9-291.7)	0.11
sCOMP (U/L)	10.9 (6.0-20.2)	10.5 (6.0-20.0)	0.82
sCS846 (ng/ml)	99.8 (45.9-172.3)	102.2 (53.0-190)	0.38
sHA (ng/ml)	34.1 (15.4-211)	33.3 (9.5-230.1)	0.38

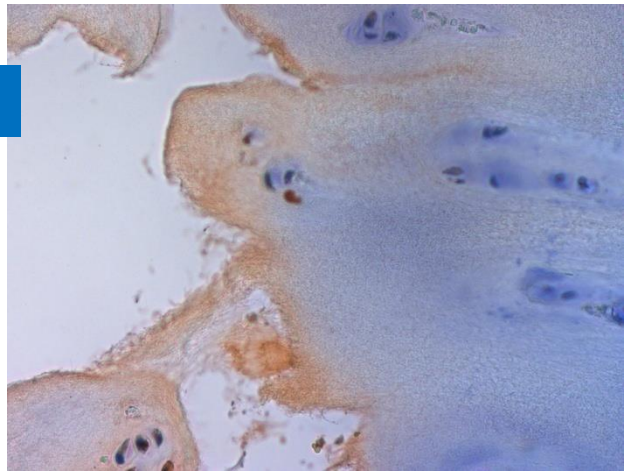
Coll2-1 and Coll2-1NO2: two cartilage specific biomarkers



Coll2-1NO2



Coll2-1

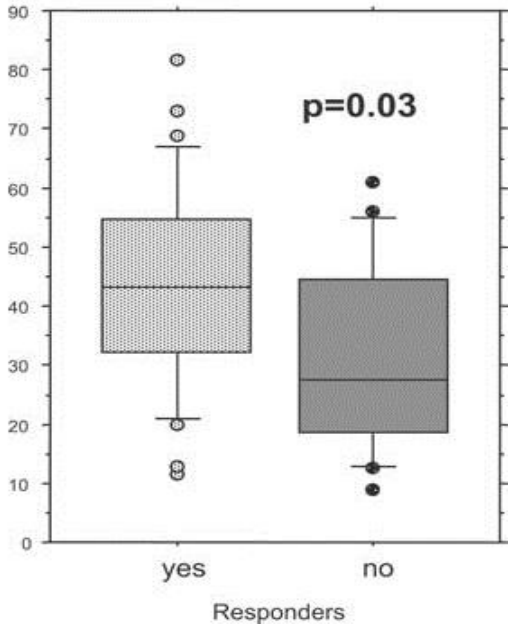


- Specific of degradated cartilage
- Multiple pathological processes (inflammation + degradation)
- Not confounded

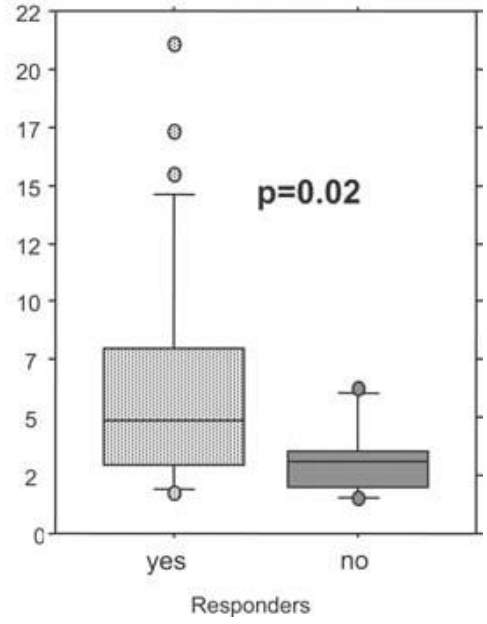
BIOVISCO study
Other observations

✓Only sColl2-1 was significantly decreased 30 days after final injection
✓Only uCTX-II variation correlated with clinical response (walking pain decrease)
✓uCTX, sColl2-1 and sHA were independently predictive of clinical response
(WP decrease > 30 mm over 90 days)

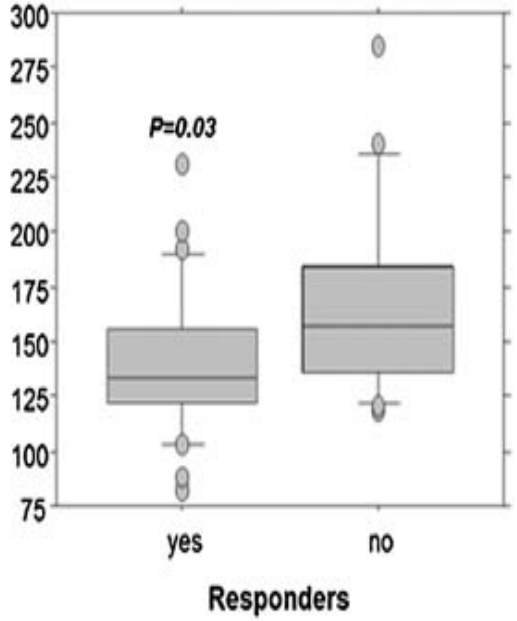
uCTX-II



sHA

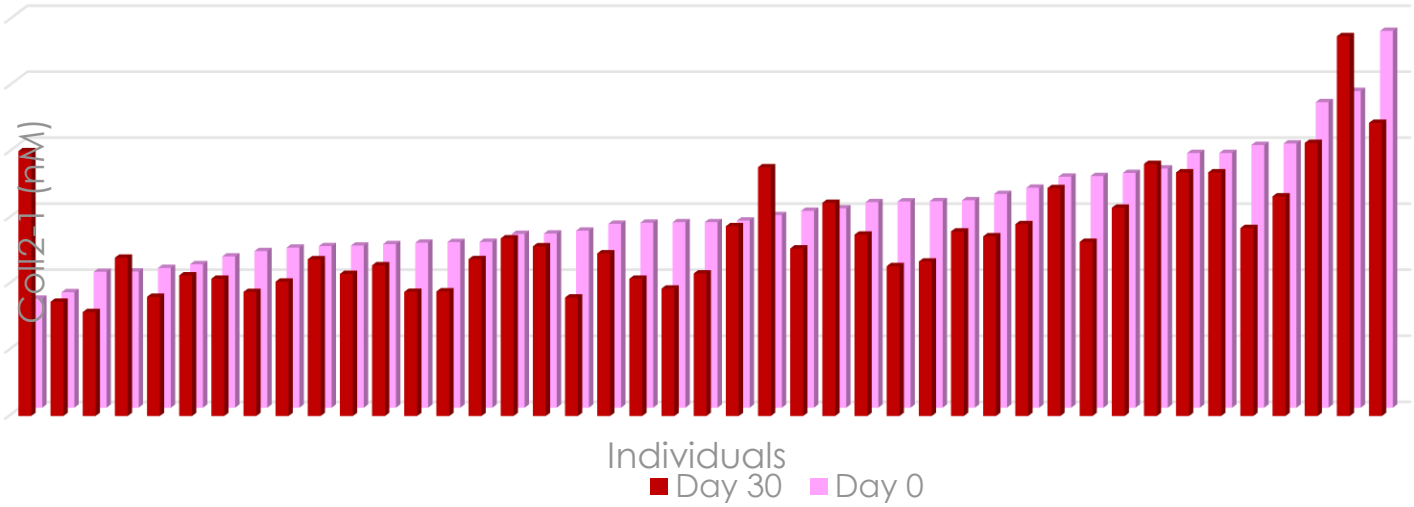


sColl2-1



The concept of « metabolic » responders

- According to clinical trial results, some patients did respond to the treatment in term of catabolism reduction but others did not.



The EPIKART study

Extended report: Reduction of the Serum Levels of a Specific Biomarker of Cartilage Degradation (Coll2-1) by Hyaluronic Acid (KARTILAGE® CROSS) Compared to Placebo in Painful Knee Osteoarthritis Patients: the EPIKART Study

Yves Henrotin [1], Francis Berenbaum [2], Xavier Chevalier [3], Marc Marty [3], Pascal Richette [4], François Rannou [5]

1. Bone and Cartilage Research Unit, Arthropole Liège, CHU Sart-Tilman, Liège, Belgium ;
2. Service de Rhumatologie, Hôpital Saint Antoine, and University Pierre & Marie Curie Paris 6 – INSERM UMRS-938, Paris, France ;
3. Service de Rhumatologie, Hôpital Henri Mondor, Créteil, France;
4. Service de Rhumatologie - Centre Viggo Petersen, Hôpital Lariboisière, Paris, France.
5. Service de Rééducation, Hôpital Cochin, Paris, France,

ARD 2016, under submission

The EPIKART study

- A 6-month prospective, randomized, double blind, controlled study
- A single injection of KARTILAGE® Cross or saline solution
- Primary outcome

  the variation of Coll2-1 in serum between inclusion visit (D-10) and D90 (3 months after injection)

Inclusion criteria

- Men or women aged between 45 and 80 years old
- With symptomatic femoro-tibial OA
- VAS > 40 mm
- K&L II or III

Population

Demographic data of the FAS population (N=81)

	Treatment N=40	Placebo N=41	P value
Age (years)	66.9 ± 10.4	63.0 ± 8.9	0.0752
Sexe - Women - Men	 62.5 % 37.5 %	 75.6 % 24.4 %	 0.2016
BMI (kg/m^2)	29.0 ± 7.4	30.8 ± 7.2	0.2465

IAHA decreased of Coll2-1in the FAS population

	IAHA N=40 at D-10 N=37 at D90	Saline solution N=41 at D-10 N=35 at D90	P value
Serum Coll2-1 at D-10	840.3 ± 375.8 (N=40)	766.1 ± 359.2 (N=41)	0.3663
Serum Coll2-1 at D90	745.4 ± 343.5 (N=37)	782.3 ± 233.7 (N=35)	0.5975
Adjustment on basal value	**-80.2 ± 44.1**	**-14.6 ± 45.3**	**0.0030**
Reduction of at least 10 nmol/l	**56.8 %**	**28.6 %**	**0.0158**

Conclusions

- A single injection of KARTILAGE®Cross induced a reduction of Coll2-1 30 days after treatment

  →sensibility of the biomarker to a single joint metabolic change

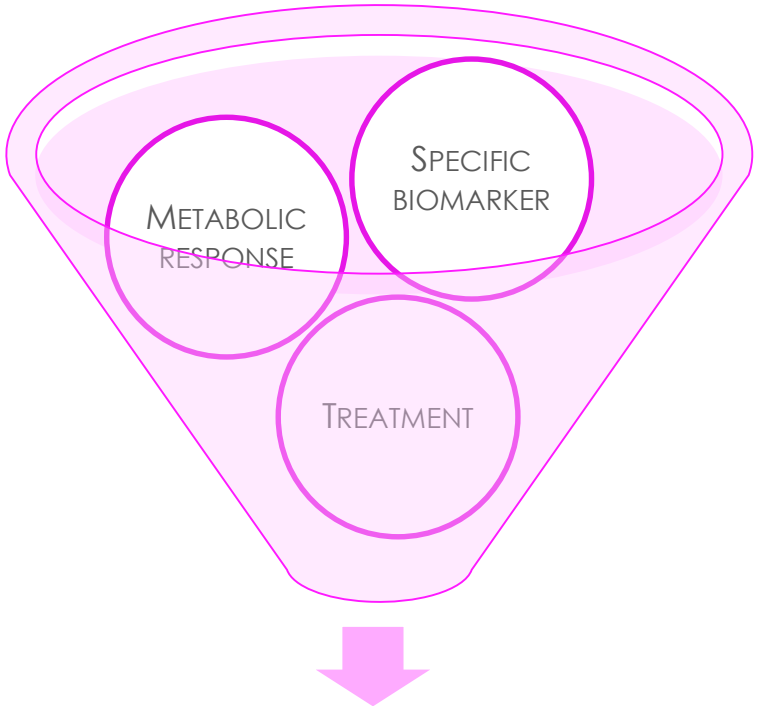
  →IAHA modulate cartilage catabolism « chondromodulator »

  →Confirmatory study

Conclusions

- No clinical effect
  - Concept of « metabolic responders » ≠ « symptomatic responders »
- No effect on other biomarkers (specificity)

To use a specific biomarker of cartilage degradation to identify the metabolic responders



PERSONALIZED HEALTHCARE

L’avenir!

New concepts

- Notion of « metabolic responders »
- Therapeutic algorithm to identify the IAHA responders
- Coll2-1 alone or in « aggregate score » as indicator of reinjection
- Personalized approach of the viscosupplementation

Statements

- The effect of viscosupplementation on cartilage metabolism is a valuable outcome in the follow-up of OA patients.
- Soluble biomarkers are good tools/useful for monitoring the effects of viscosupplementation on cartilage metabolism.
- Soluble biomarkers are predictive of the response to viscosupplementation.
- Soluble biomarkers variation can be used as indicator of HA re-injection

bcru Team

Bone and Cartilage Research Unit

Thank you for your attention !

International collaborations:

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