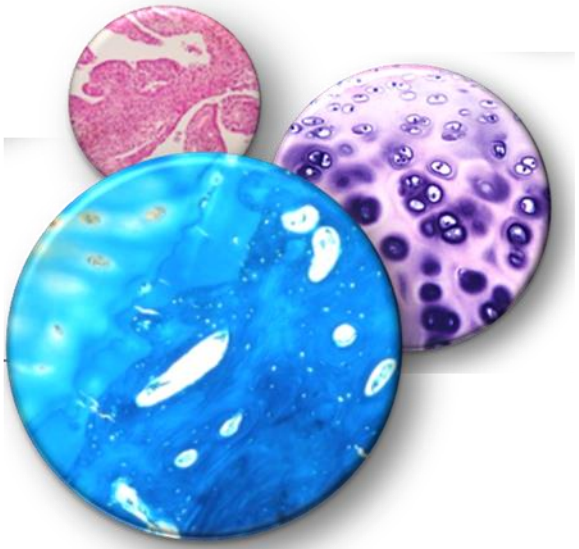
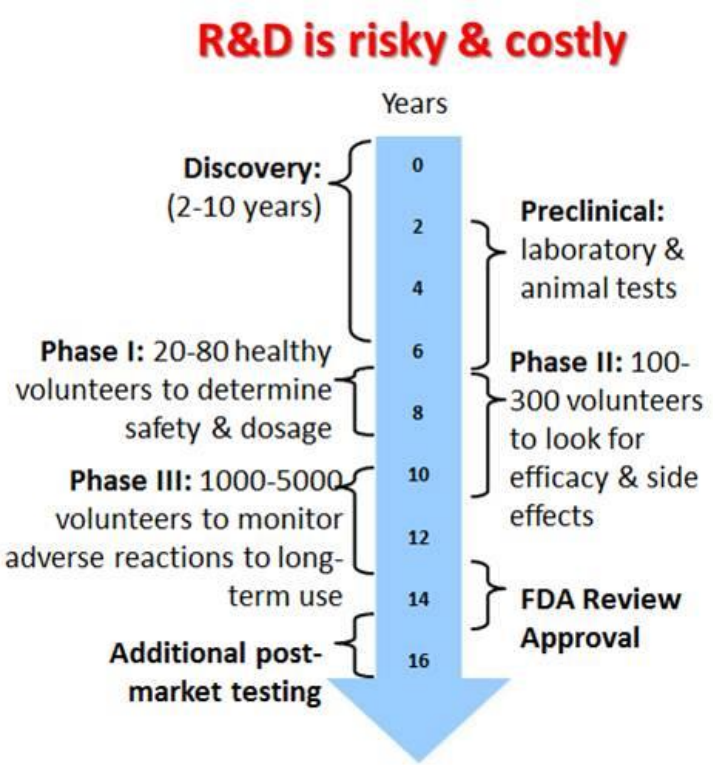
# Biomarkers of prognosis and efficacy of treatment

Yves Henrotin, PhD

University of Liège

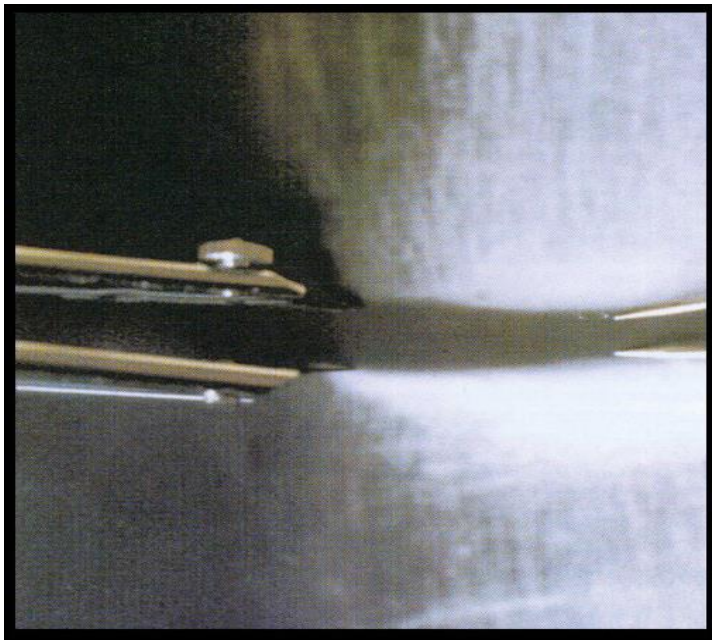


# Drug discovery is protracted, risky and costly




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

# The Gold Standard (Radiography) is inadequate

…We need better methods to predict OA progression and response to therapy

Slide courtesy of Dr A Mobasheri (Nottingham University)

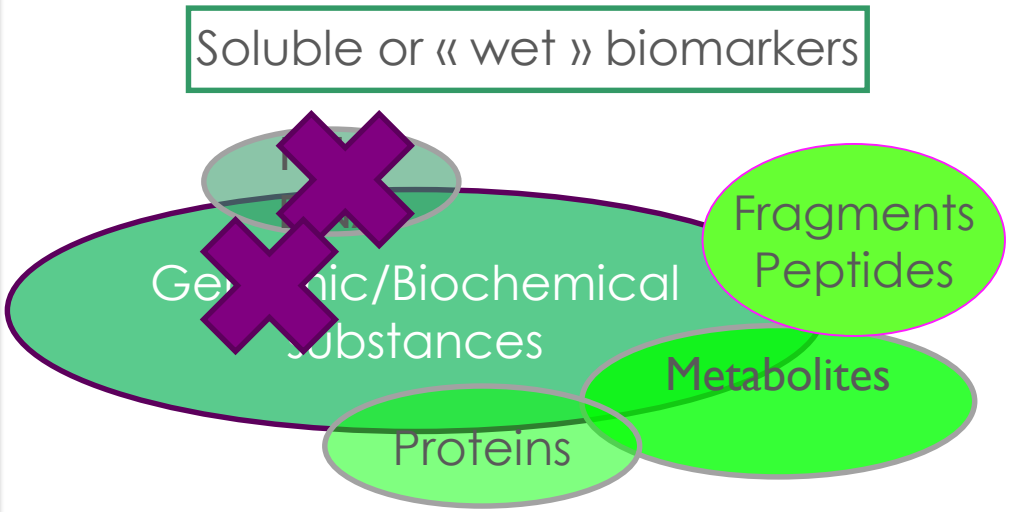
# The main limitations of JSN

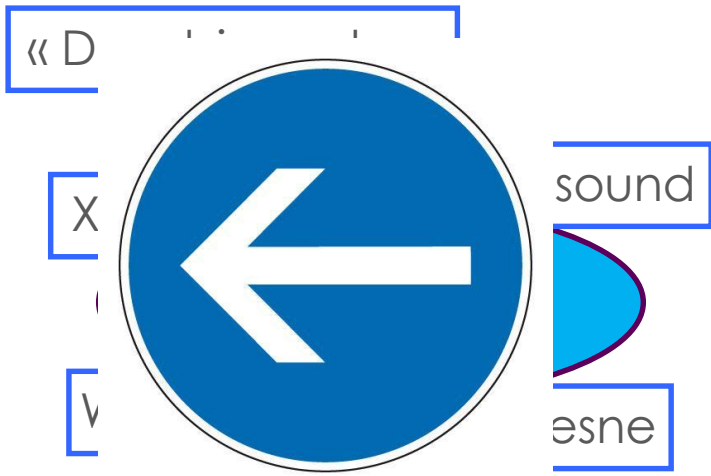
- Indirect measure of the alteration in articular cartilage.
- Fails to measure a dynamic process
- Confounded by the presence of meniscal lesions and extrusion.
- Changes overtime are small, and occur in only a subset (progressors) of patients.
- Poorly reproducible (full extension).
- Poorly correlated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

# 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.



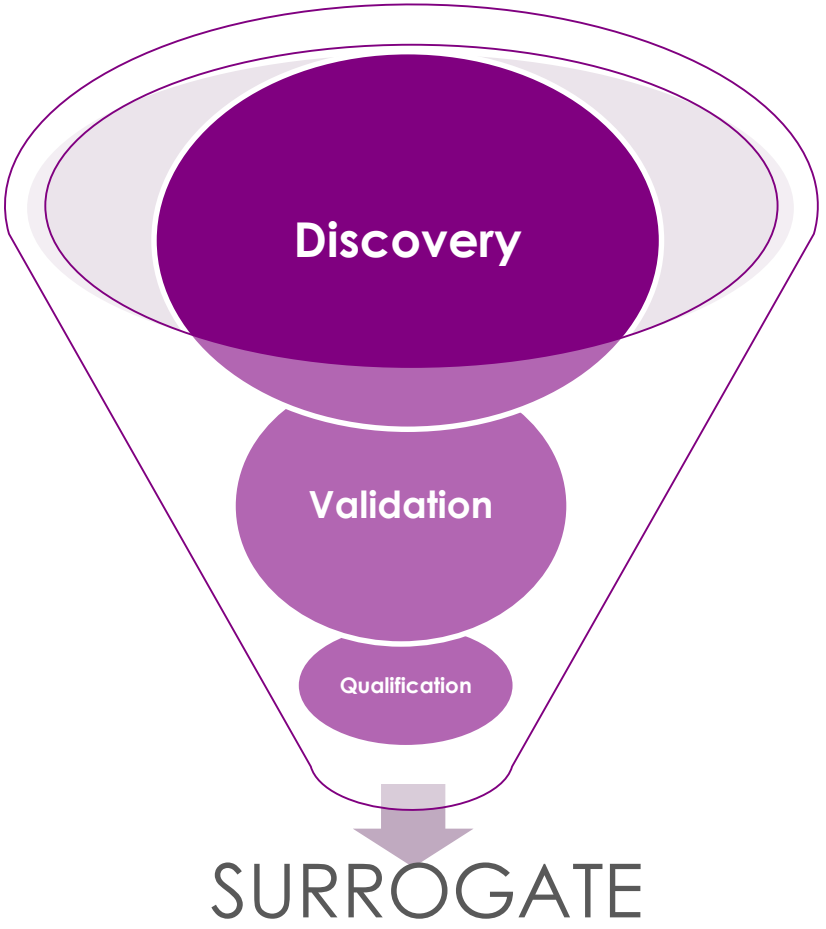
# The long and winding road…

# Process of soluble biomarkers development

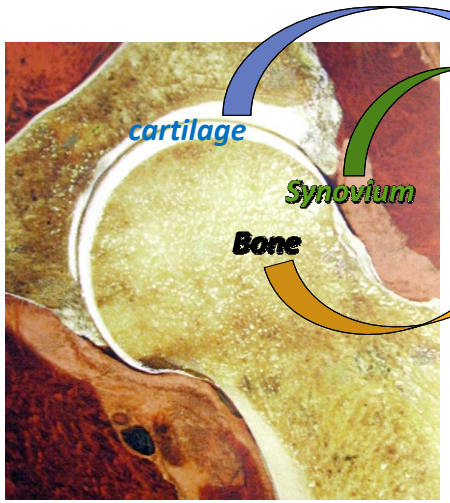
Brain/OMICS technics

Analytical performance of assay

Assessing clinical value



# OA Biomarkers




lymphatics

Blood
~5 liters

kidney

urines

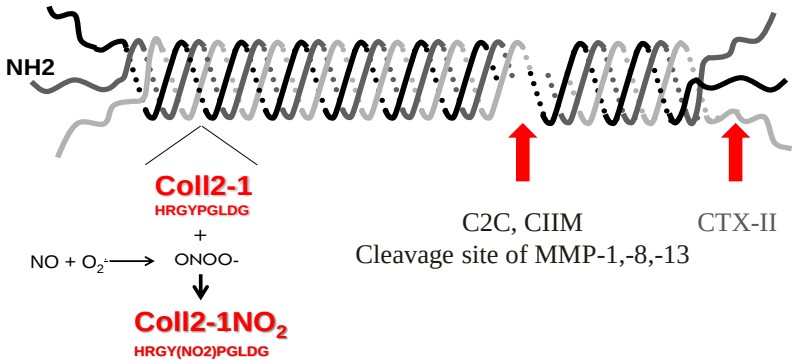
**bone**
- *sPINP*
- *uCTX-I*

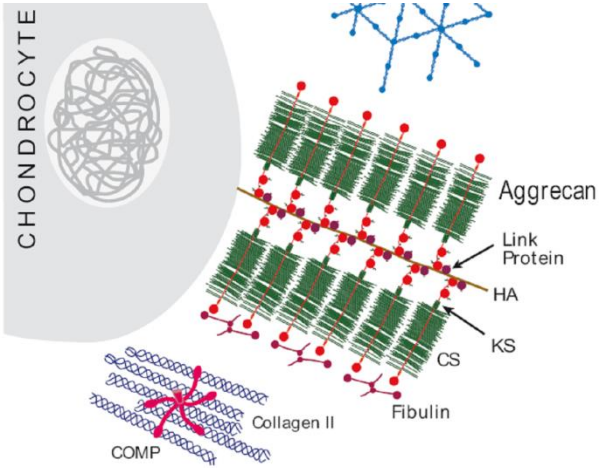
**Cartilage**
- ***sColl2-1***
- ***sFibulin3***
- ***sCOMP***
- *sYKL40*
- *sC2C*
- ***uCTX-II***
- ***PIIANP***
- ***CPII***
- ***Agrec-1***

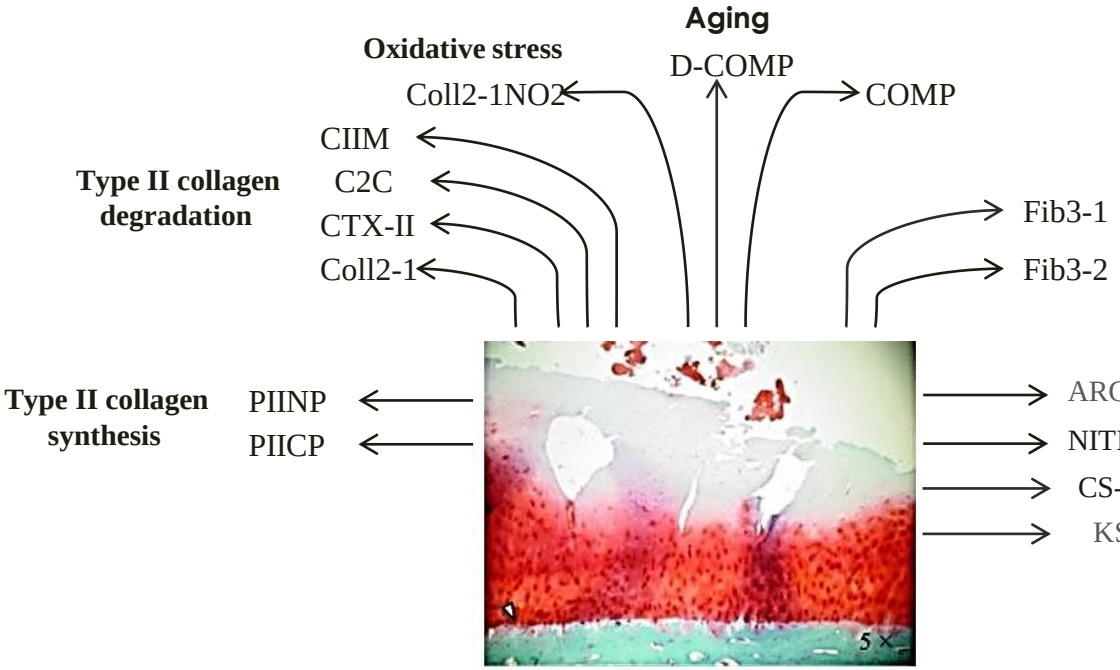
**Synovium & inflammation**
- **sColl2-1NO2**
- *sPIIINP*
- *sHA*
- ***sCRP ultrasensible***
- ***Cytokines, MPO***

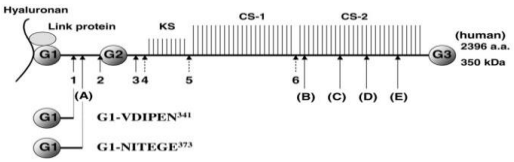
**Metalloproteases**
- *sMMP1(collagenase)*
- ***sMMP3 (stromelysin***

# Biomarkers of cartilage metabolism




ADAMTS-5

# BIPEDS classification

*Bauer et al. Osteoarthritis Cart 2006*

| | |
|---|---|
| **B**urden of disease | • Bio |
| **I**nvestigative | • Bio cat |
| **P**rognostic | • Pre like |
| **E**fficacy of treatment | • Ind ma |
| **D**iagnostic | • Dissociate diseased from non-diseased. |
| **S**afety | • 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)

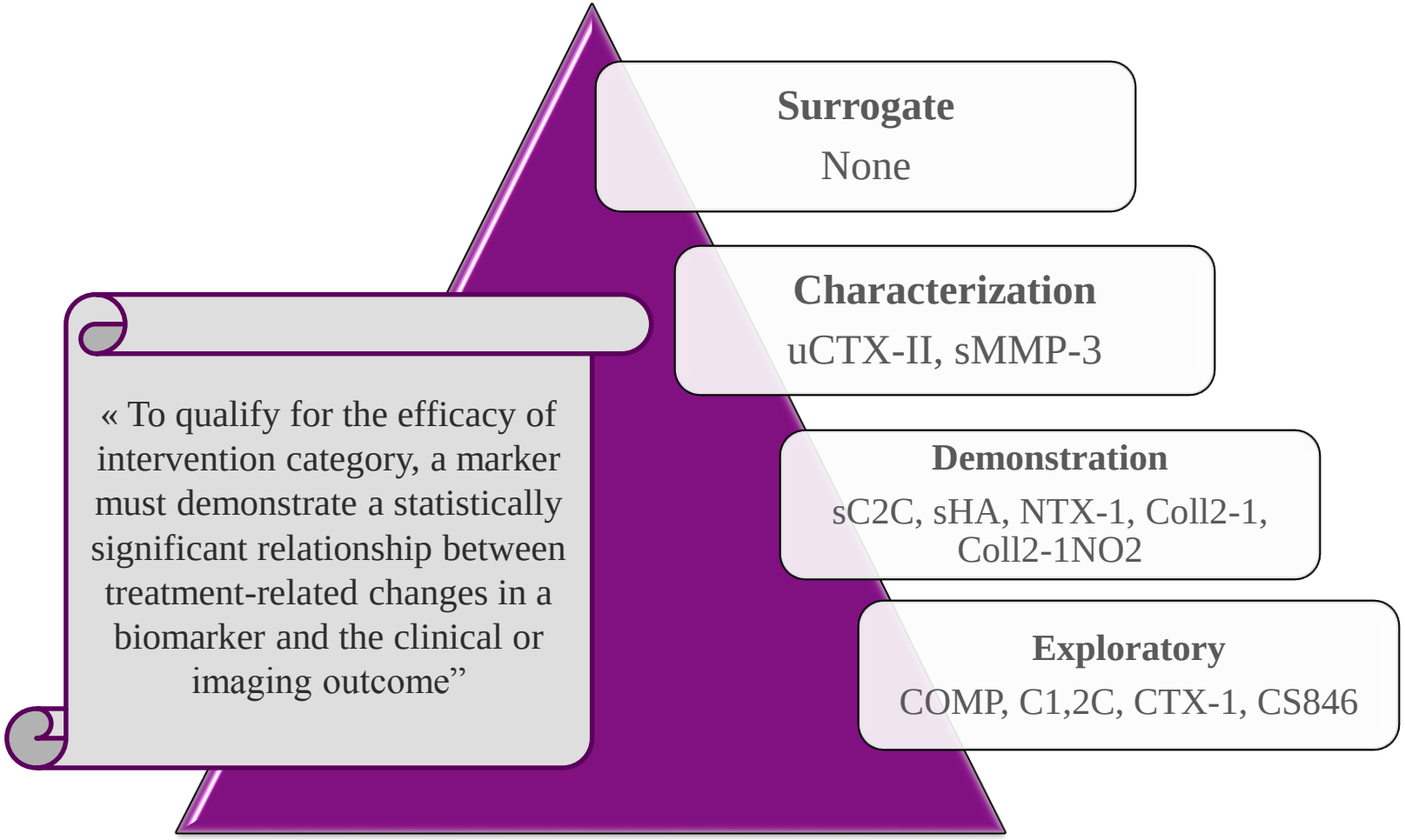
*Updated Van Spil et al.2010*

**« 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 |

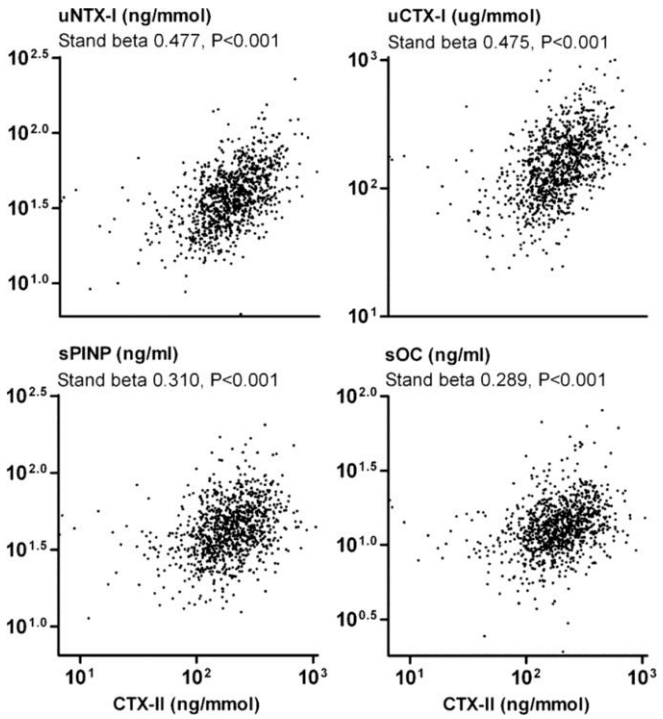
# Levels of qualification of biomarkers for drug development use

*Kraus et al. Osteoarthritis Cart, 2011*



# 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**

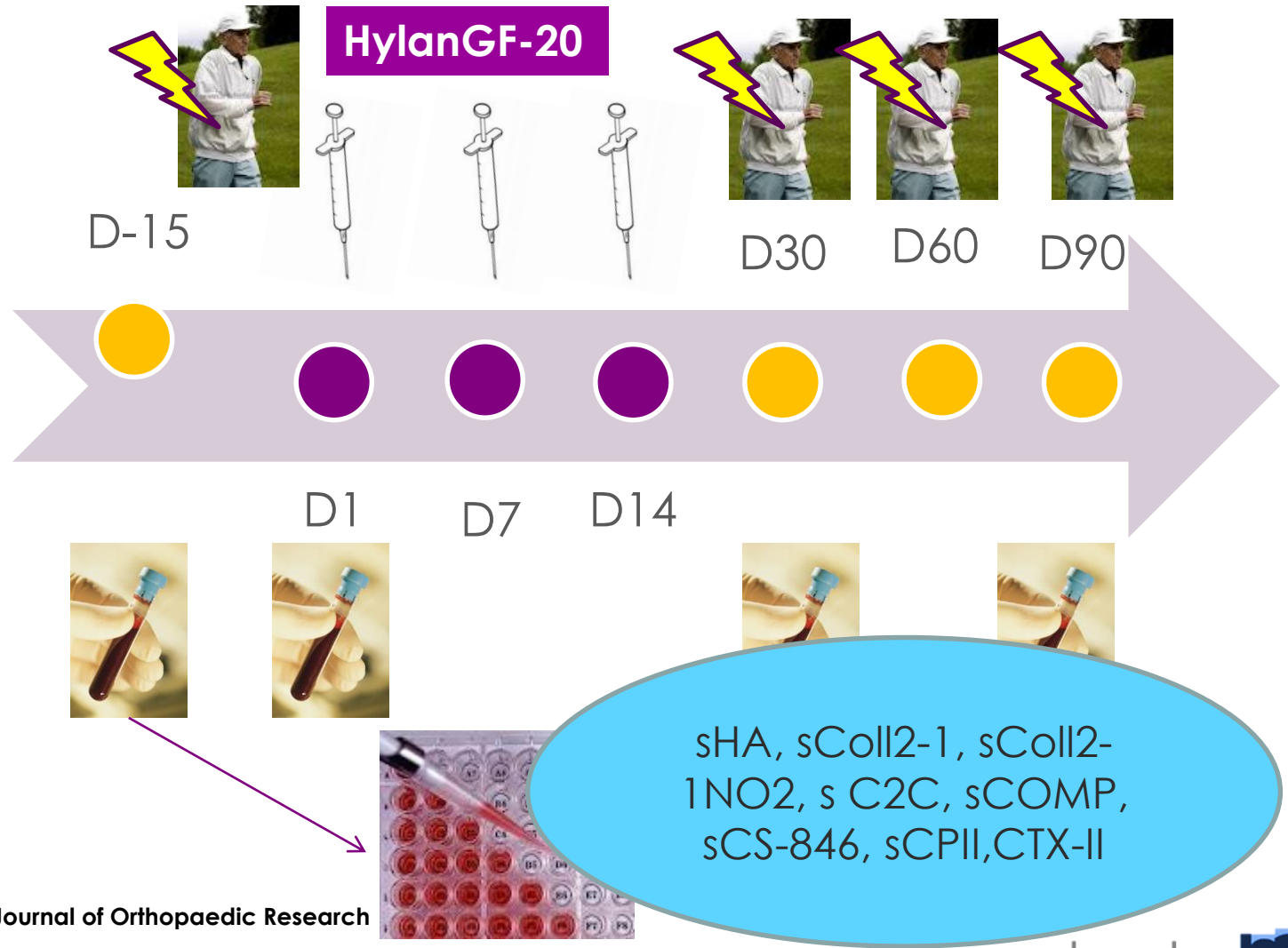
*Richette, Roux Osteoporosis Int 2012*

**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

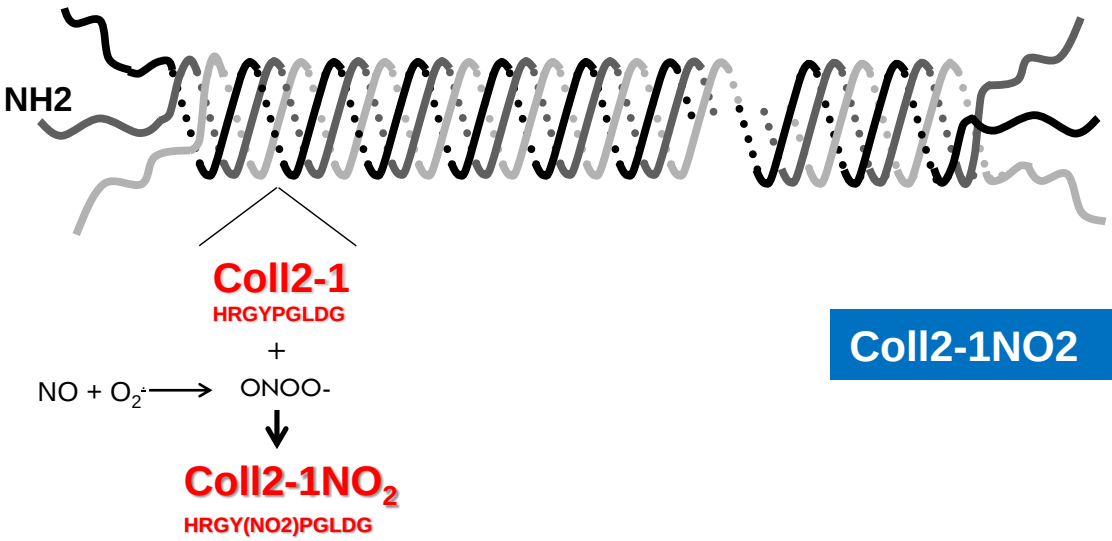
## An open label observational prospective study

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

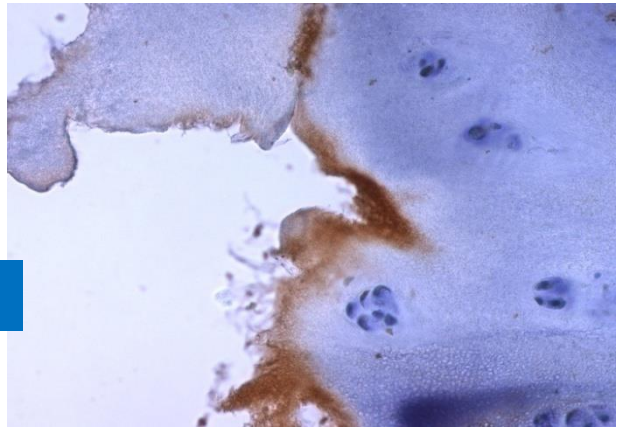
- ✓ 45 patients with unilateral symptomatic tibiofemoral and/or patellofemoral OA
- ✓ 3-weekly intraarticular injection of hyalan G20 (Synvisc®)
- ✓ Follow-up D1, D30 and D90 after the last injection

| | 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 |

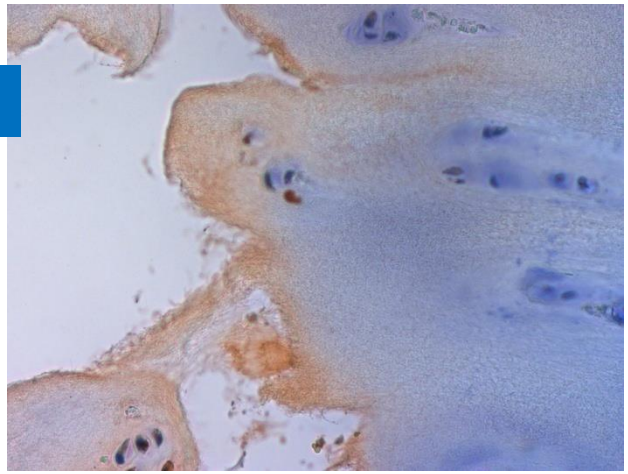
# Coll2-1 and Coll2-1NO2: two cartilage specific biomarkers




Coll2-1NO2



Coll2-1

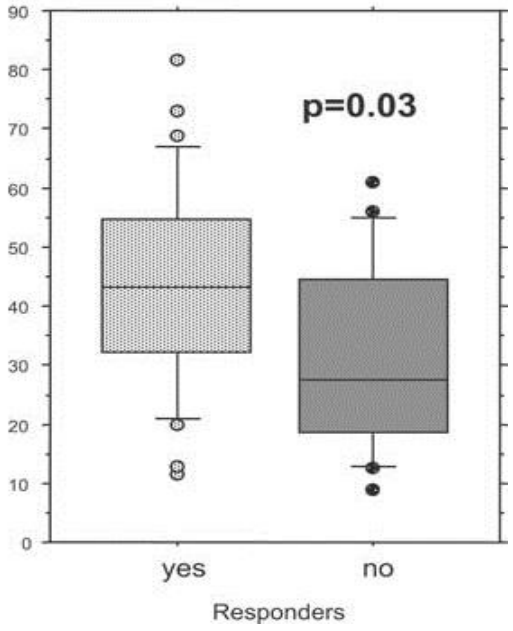


- Specific of degradated cartilage
- Multiple pathological processes (inflammation + degradation)
- Not confounded

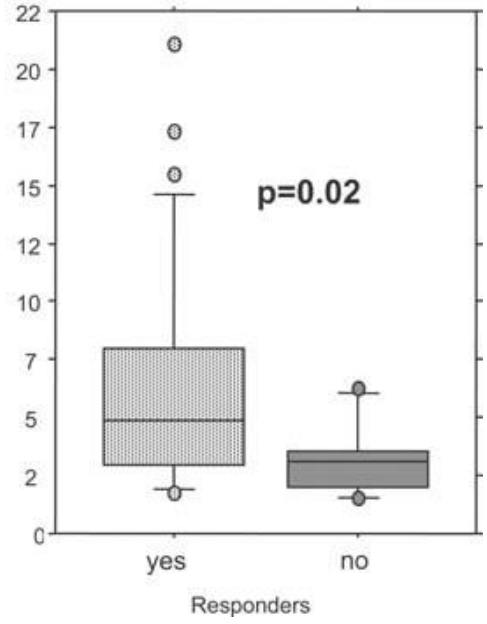
# BIOVISCO study
## Other observations

✓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)**

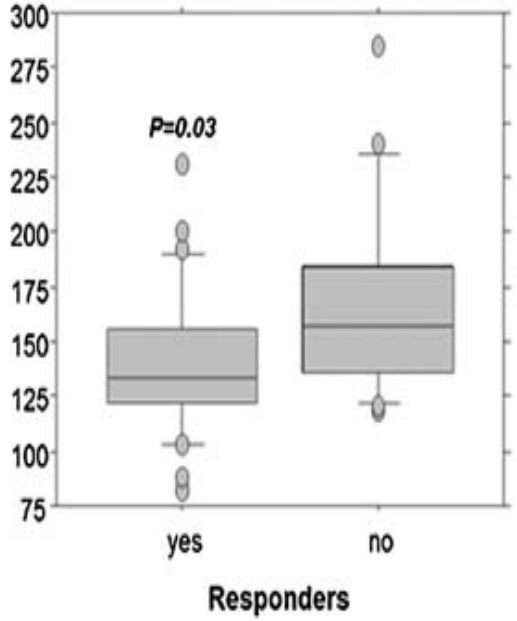
**uCTX-II**




**sHA**




**sColl2-1**

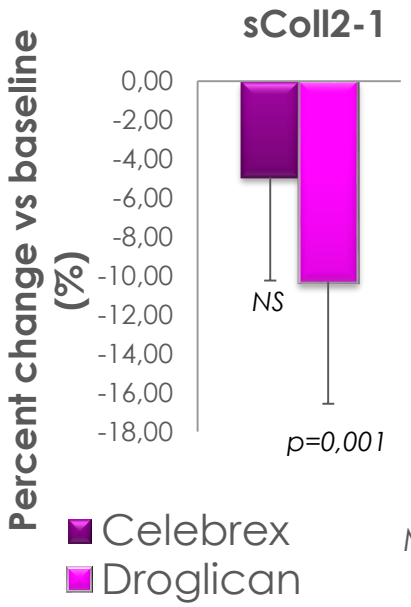


# MOVES study

## CS + GuHCL (Droglican)vsCelecoxib Preliminary data

- 416 knee OA (PP)
- 1200 mg CS/1500 GuHCL
- 200 mg celecoxib
- 6 months treatment

| | n | AGE | SEX | Weight (Kg) | Height (cm) | BMI (kg/m2) |
|---|---|---|---|---|---|---|
| celebrex | 202 | 64 (9) | 165/37 (82%) | 78 (14) | 162 (18) | 30 (6) |
| droglican | 214 | 62 (9) | 187/27 (87%) | 81 (16) | 161 (18) | 31 (7) |
| PP | 416 | 63 (9) | 352/64 (85%) | 80 (15) | 162 (18) | 30 (6) |

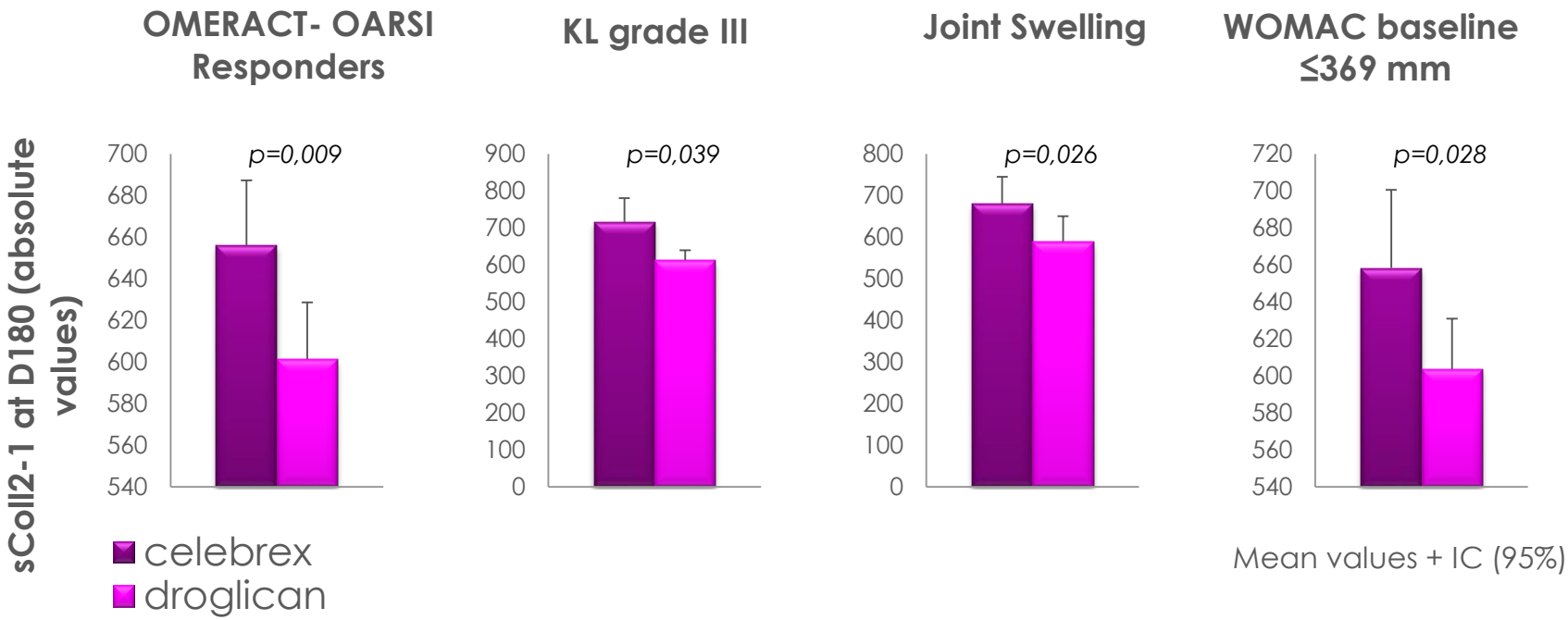



Mean values – IC (95%)

Both drugs decreased sColl2-1
Only Droglican decreased significantly Coll2-1
No significant difference between groups

# MOVES study

## CS + GuHCL (Droglican) vs Celecoxib




P value = droglican vs celebrex

# Conclusions

- Soluble biomarkers should be included early in the development of a drug : **« Drug developement tool »**

→ Preclinical development and phase 1-4 trials

Why?

→ to assist with selection of lead compound

→ to assess safety, mechanism of action, dose finding and selection, dose reponse profile, enrichment of a target population, enrichment for progressors, post-marketing safety surveillance

→Companion biomarker (personalized medicine)

# 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)