Biomarkers of prognosis and efficacy of treatment OA

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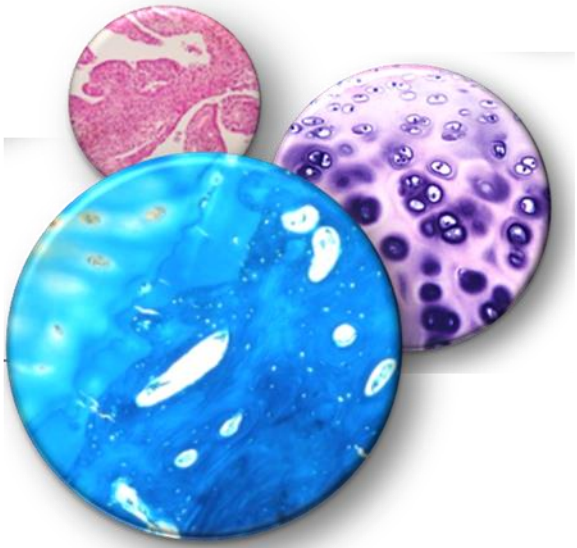
ARTHROPÔLE LIÈGE



Université de Liège

Bone and Cartilage Research Unit

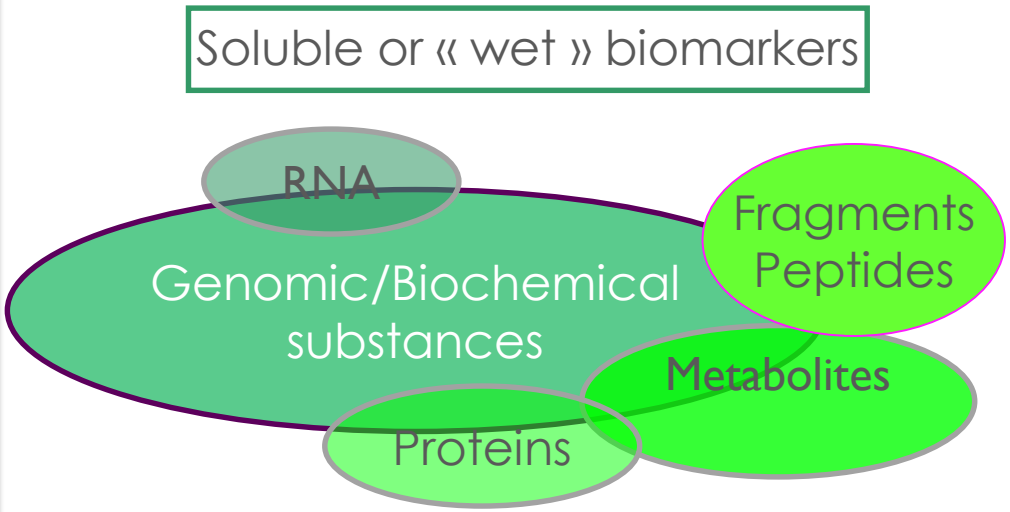
D-BOARD

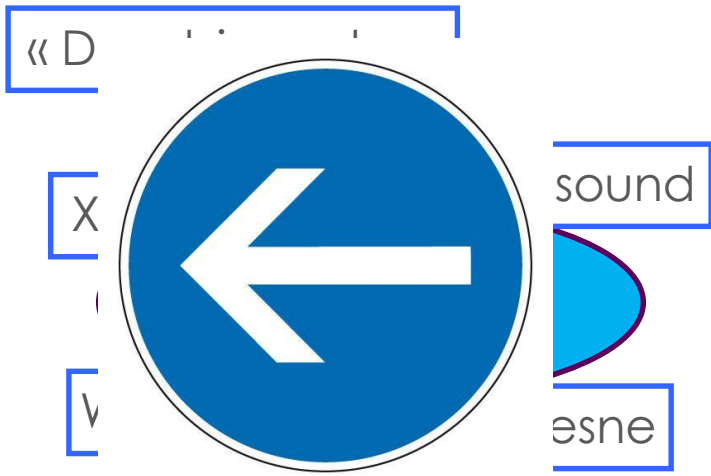
European partnership for biomarker discovery

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**. »

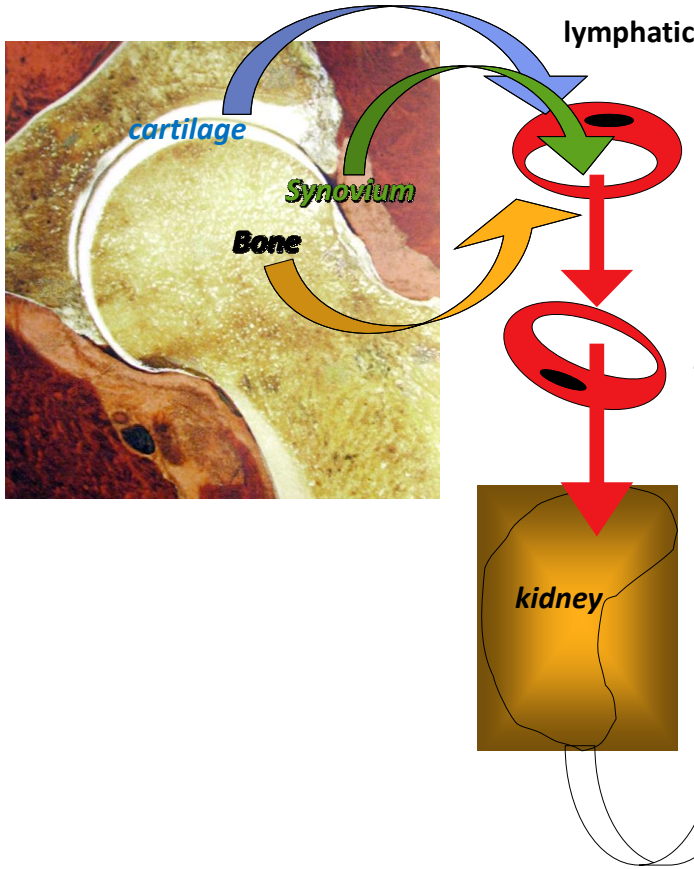
Biomarkers Definitions Working Group I. Biomarkers and surrogate endpoints: preferred definitions and conceptual framework. Clin Pharmacol Ther 2001; 69: 89-95.





OA Biomarkers

« Changes in tissues metabolism »



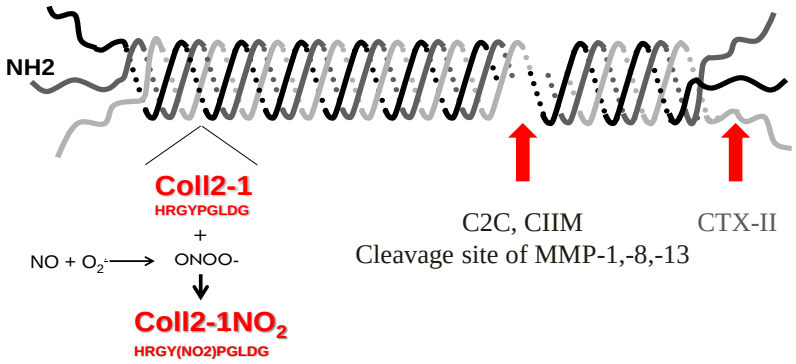
bone
- *sPINP*
- *uCTX-I*

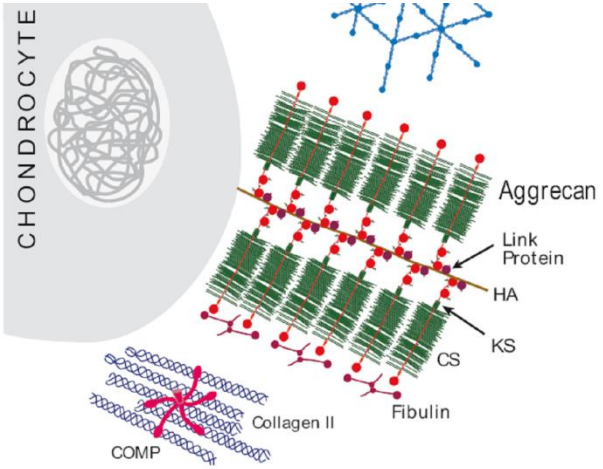
Cartilage
- ***sColl2-1***
- ***sFibulin3***
- ***sCOMP***
- *sYKL40*
- *sC2C*
- ***uCTX-II***
- ***PIIANP***
- ***CPII***
- ***Agrec-1***

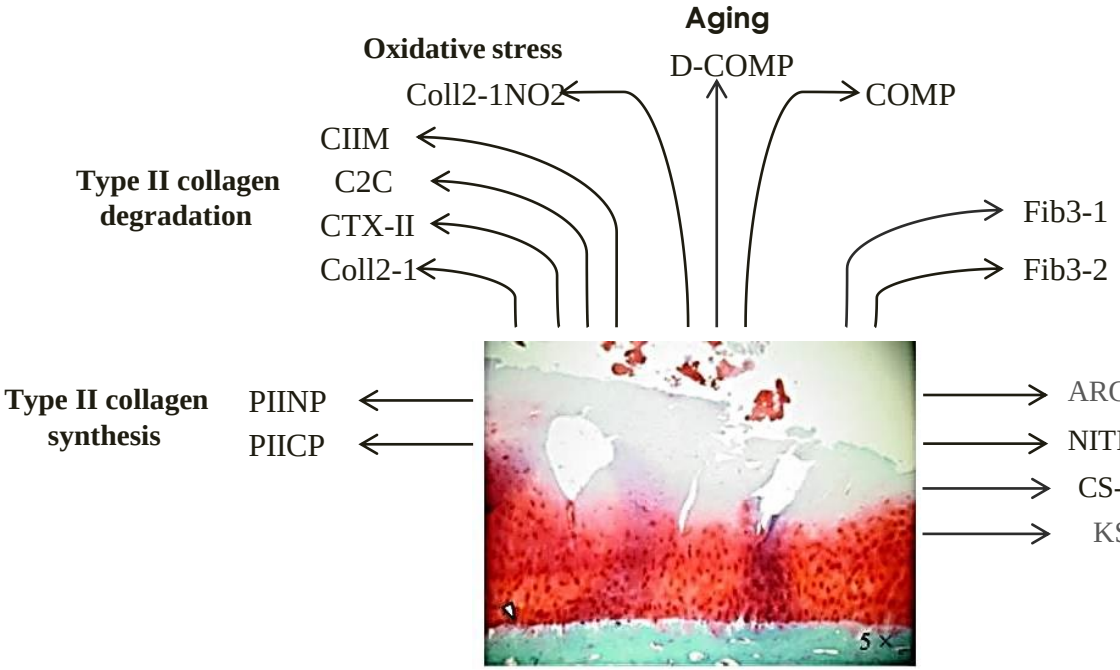
Synovium & inflammation
- **sColl2-1NO2**
- *sPIIINP*
- *sHA*
- ***sCRP ultrasensible***
- ***Cytokines, MPO***

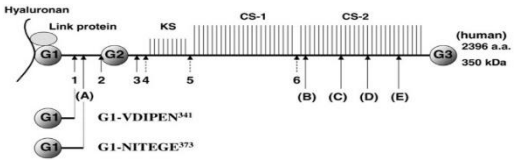
Metalloproteases
- *sMMP1(collagenase)*
- ***sMMP3 (stromelysin***

Biomarkers of cartilage metabolism



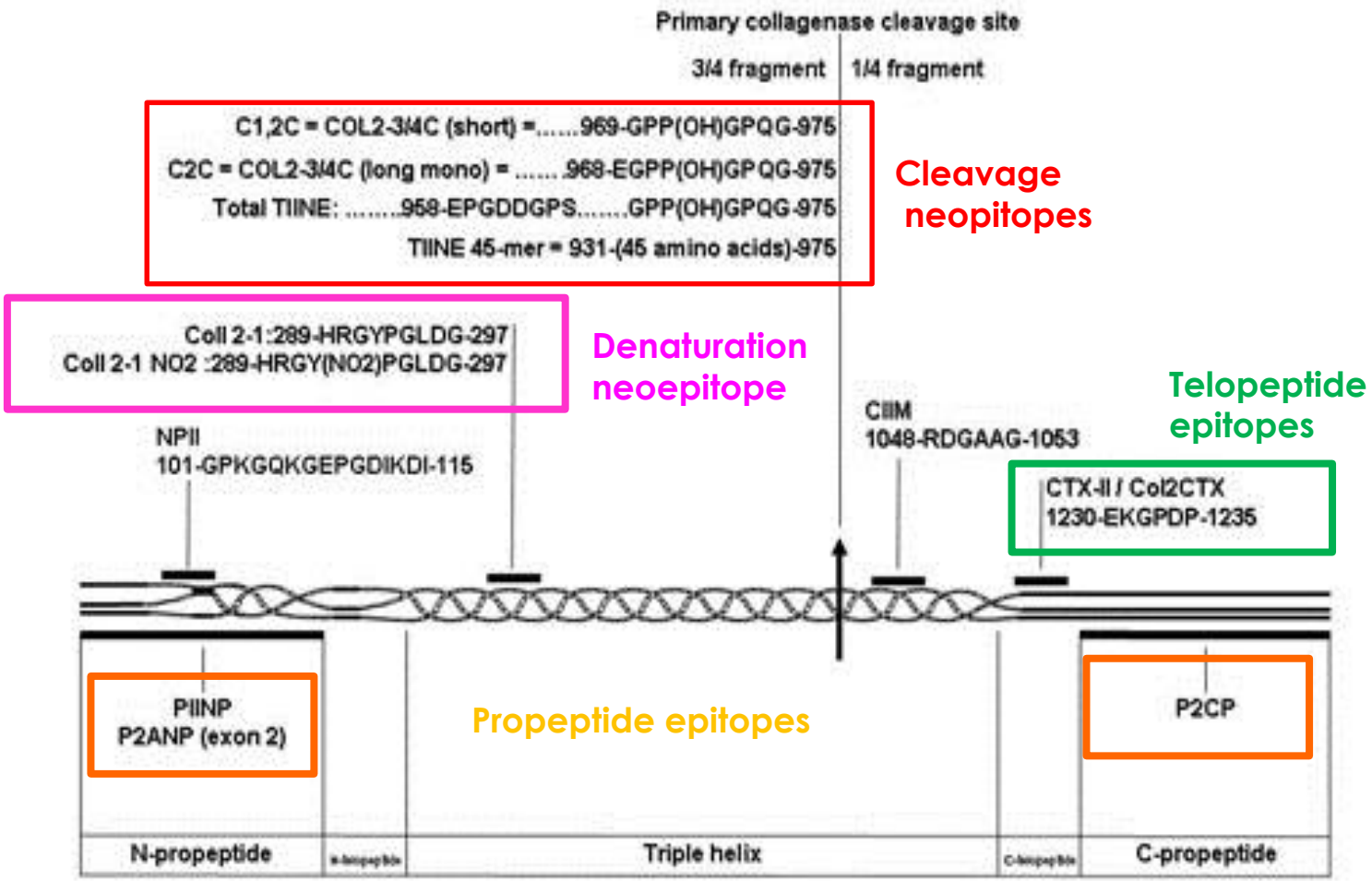






ADAMTS-5

Type II collagen biomarkers



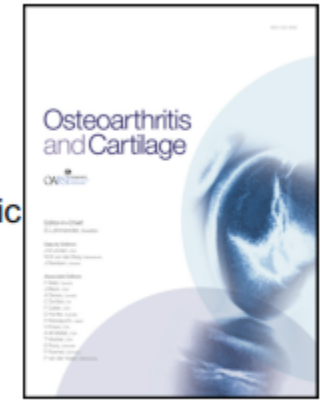
BIPEDS classification

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

Prognostic biomarkers
« Predict incident or progression of the disease or likelihood of response to a treatment intervention. »

Accepted Manuscript



Associations of urinary biomarker COLL2-1NO2 with incident clinical and radiographic knee OA in overweight and obese women

M.L.A. Landsmeer, J. Runhaar, Y.E. Henrotin, M. Middelkoop van, E.H. Oei, D. Vroegindeweij, M. Reijman, G.J.V.M. van Osch, B.W. Koes, P.J.E. Bindels, S.M.A. Bierma-Zeinstra

Université de Liège

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European partnership for biomarker discovery

Erasmus MC
Universitair Medisch Centrum Rotterdam

The PROOF study

(Prevention of knee Osteoarthritis in Overweight Females, ISRCTN 42823086)

High-risk group of:

- 254 Women
- 50 – 60 years
- BMI ≥ 27 kg/m²
- No clinical and radiographic knee OA at baseline
- 30 months follow-up

Proof study
Primary outcome

- The primary outcome: incidence of knee OA in one or both knees at 2.5 years.
- Incidence of knee OA was defined as either:

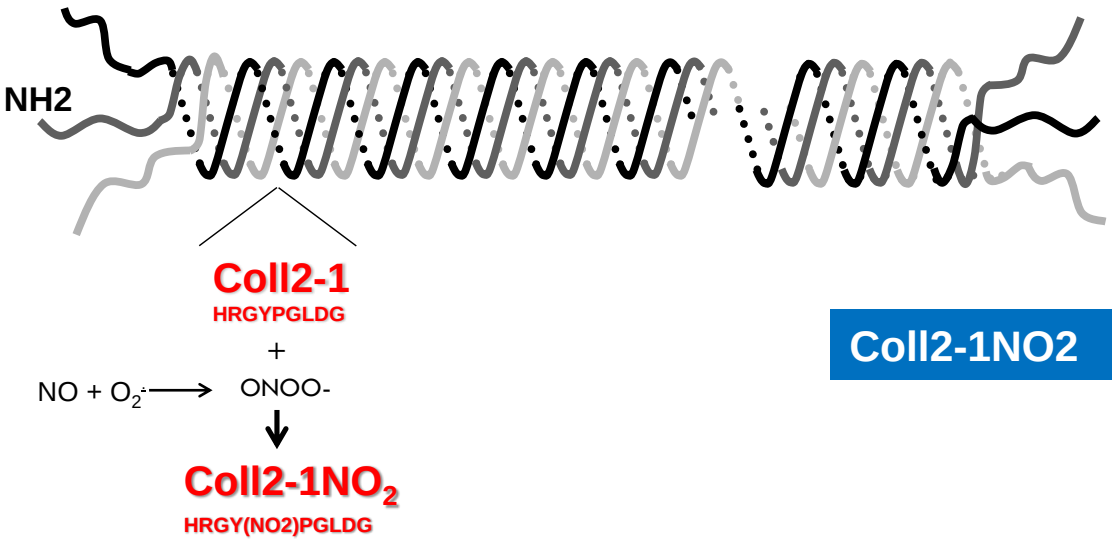
- Kellgren & Lawrence (K&L) grade ≥ 2 or
- joint space narrowing (JSN) of ≥ 1.0mm or
- clinical knee OA according to the combined clinical and radiographic ACR criteria (ACR knee OA).

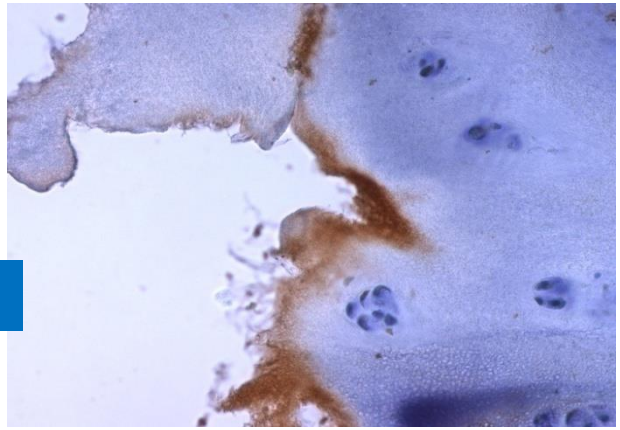
Available data

At baseline and follow-up (2.5 years):

- Semi-flexed PA radiographs
- Questionnaires (i.a. knee complaints, KOOS, physical activity)
- Physical examination

Coll2-1NO2: a cartilage specific biomarkers

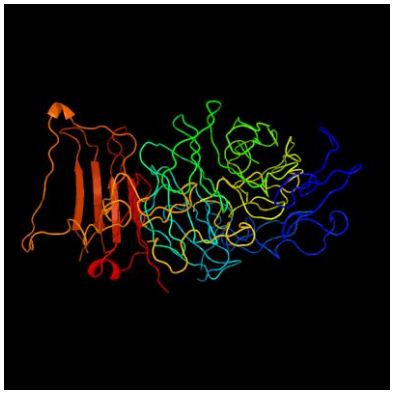




Coll2-1NO2

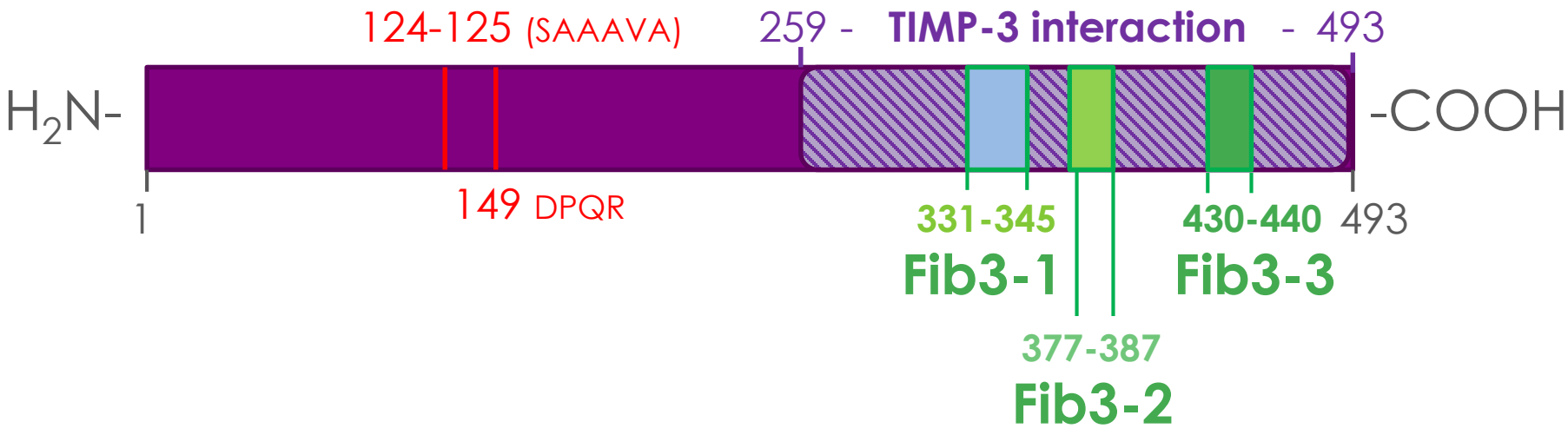
- Specific of degradated cartilage
- Multiple pathological processes (inflammation + degradation)
- Not confounded

Fibuline-3 epitopes



Fibulin-3 (EFEMP1) 54,641 Da

Clivage MMP-1,-2,-3
MMP-7,-9
MMP-12



« Proof »
Patient characteristics at inclusion

N – Subjects	254
Age (yr.)	55.7 ± 3.2
BMI (kg/m²)	32.0 ± 3.9
WOMAC pain (0-100)	6.3 ± 10.7
WOMAC function (0-100)	6.2 ± 10.4
Postmenopausal	69%
K&L 0 K&L 1	45% 55%
Varus alignment	38%
Heberden nodes	26%
History of knee injury	11%

Knee OA incidence

- Incident knee OA according to the primary outcome was found in 72/254 women (28.3%).
- Medial joint space narrowing (JSN)27/254 (10.6%)
- lateral JSN in 26/254 (10.2%)
- ACR knee OA in 20/254 (7,9%)
- K&L grade ≥ 2 in 23/254 (9.1%).

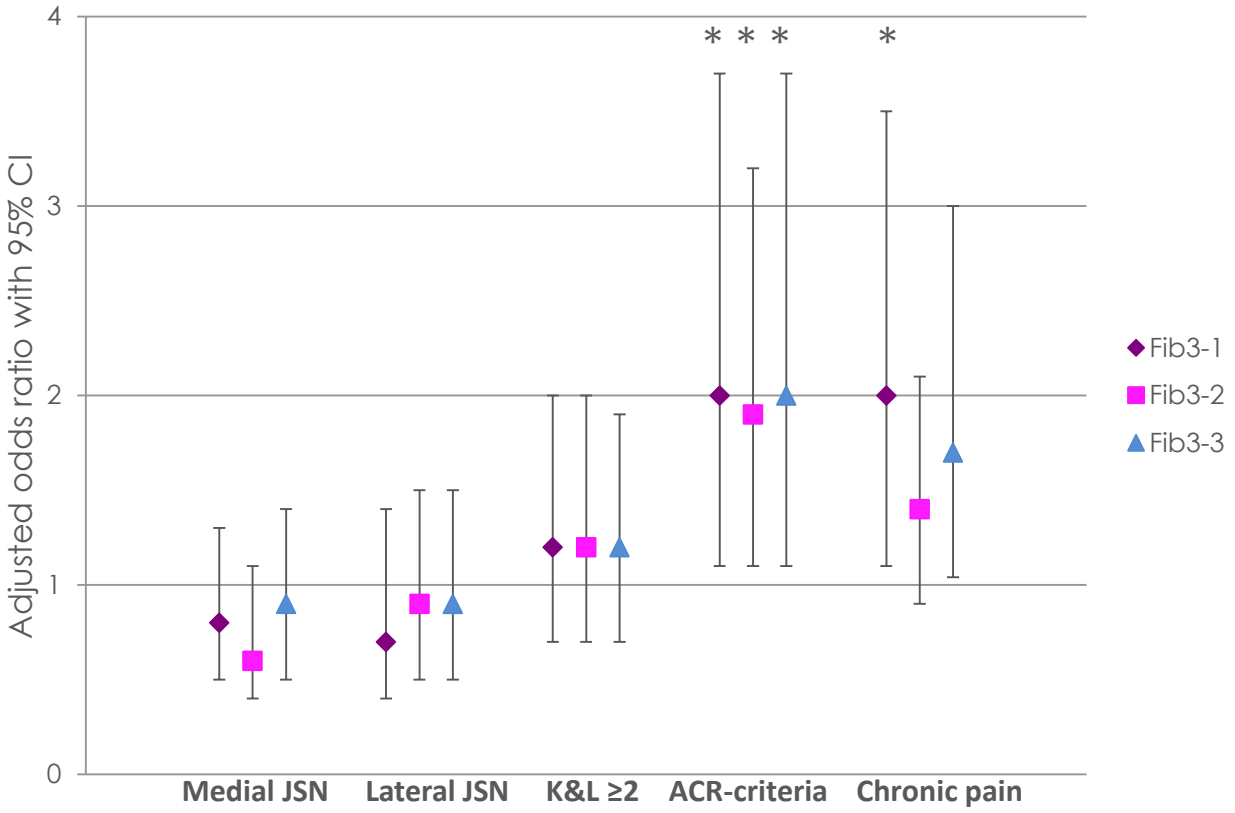
ColI2-1NO2 is predictive of OA

Landsmeer et al. O&C in press

All incidence criteria

Fibuline-3 epitopes: Odd ratio

Runhaar et al. O&C submitted



Conclusions

- Baseline urinary Coll2-1NO2 is negatively correlated with OA incidence while changes overtime is positively correlated.
- Fibuline-3 serum levels is highly predictive of OA incidence

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

Henrotin et al. BMC Complementary and Alternative Medicine 2014, 14:159
http://www.biomedcentral.com/1472-6882/14/159

BMC Complementary & Alternative Medicine

RESEARCH ARTICLE Open Access

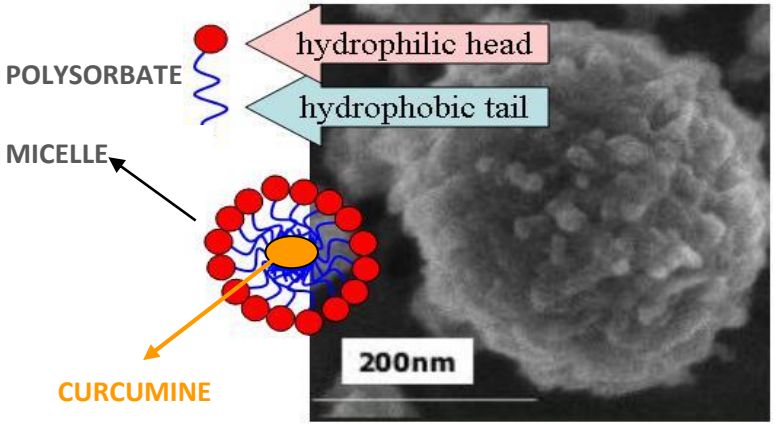
Decrease of a specific biomarker of collagen degradation in osteoarthritis, CollI2-1, by treatment with highly bioavailable curcumin during an exploratory clinical trial

Yves Henrotin[1,2*], Myriam Gharbi[3], Yvan Dierckxsens[4], Fabian Priem[5], Marc Marty[6], Laurence Seidel[7], Adelin Albert[7], Elisabeth Heuse[8], Valérie Bonnet[8] and Caroline Castermans[8]

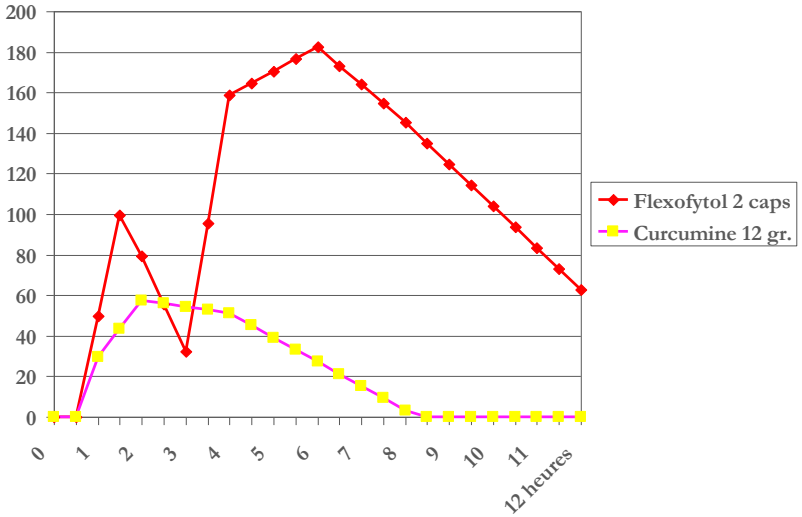
TIFLEXY Study

Bio-optimized curcuminoids (BOC)

Curcuminoids /Low avaibility



Bio-optimized curcuminoids BOC



« Proof-of-concept study »

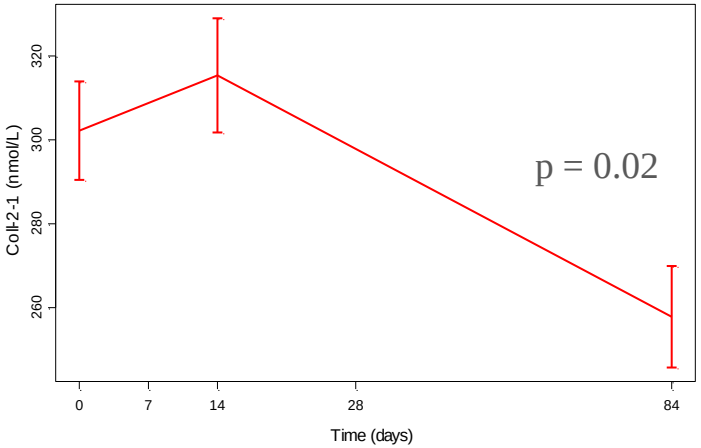
-22 knee OA patients
-2x3 caps (42 mg BOC)/days
-3 months treatment

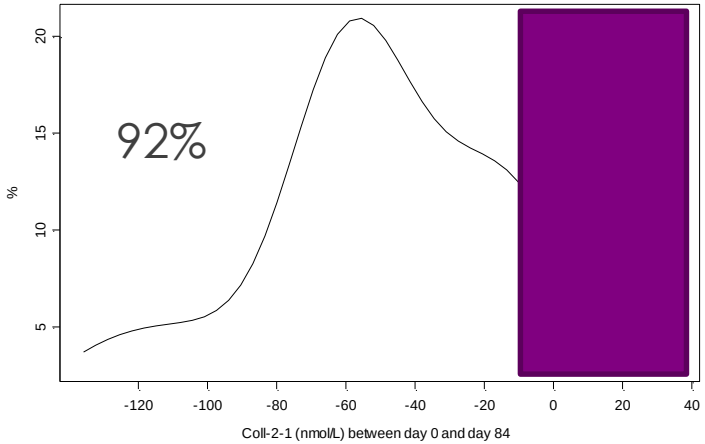
Henrotin Y, Priem F, Mobasheri A, Springerplus, 2013

TIFLEXY Study

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**	**0.002***
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	NS
sMPO (ng/ml)	27.20 +/- 29.05	21.96 +/- 14.65	NS

Early Decrease of Serum Biomarkers of Type II Collagen Degradation (Coll2-1) and Joint Inflammation (Coll2-1 NO_2) by Hyaluronic Acid Intra-Articular Injections in Patients With Knee Osteoarthritis: A Research Study Part of the Biovisco Study

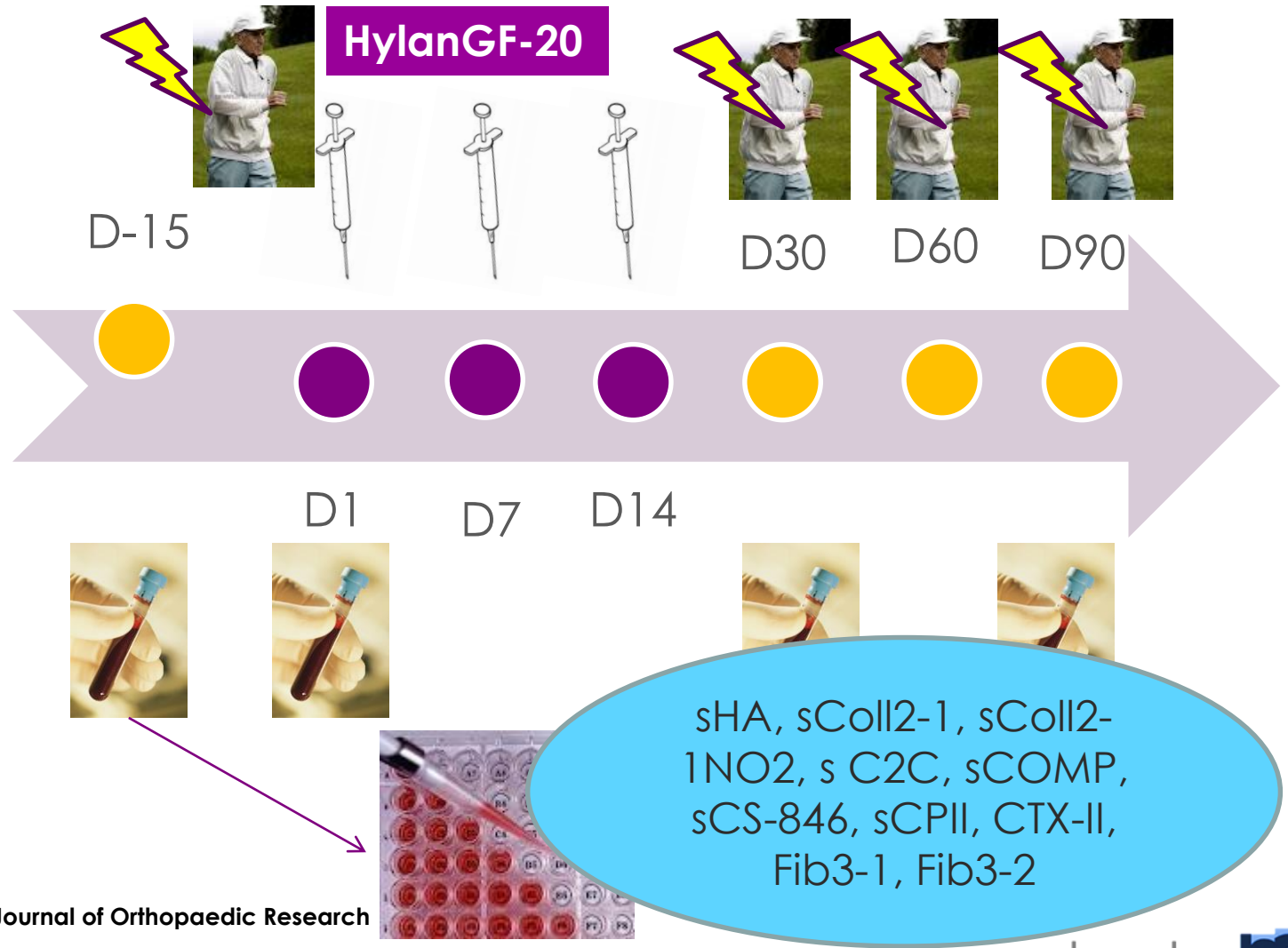
Y. Henrotin,[1] X. Chevalier,[2] M. Deberg,[3] J.C. Balblanc,[4] P. Richette,[5] D. Mulleman,[6] B. Maillet,[7] F. Rannou,[8] C. Piroth,[9] P. Mathieu,[10] T. Conrozier[11] and On behalf of the Osteoarthritis Group of the French Society of Rheumatology

[1]Bone and Cartilage Research Unit, University of Liège, Institute of Pathology, Level 5, Chu Sart-Tilman, 4000 Liège, Belgium, [2]Department of Rheumatology, Hopital Henri Mondor, Créteil, France, [3]Artialis S.A., Liège, Belgium, [4]Department of Rheumatology, Centre Hospitalier de Belfort-Montbéliard, Belfort, France, [5]Department of Rheumatology, Hopital Lariboisiere, Paris, France, [6]Hopital Trousseau, Tours, France, [7]Department of Rheumatology, Clinique Ste Odilon, Moulins, France, [8]Department of Rheumatology and Rehabilitation, Hopital Cochin, Paris, France, [9]Department of Rheumatology, Centre Hospitalier de Dijon, Dijon, France, [10]Department of Rheumatology, Centre Hospitalier Lyon Sud, Pierre-Bénite, France, [11]Hospices Civils de Lyon, Direction à la Recherche Clinique, Lyon, France

Journal of Orthopaedic Research, 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.

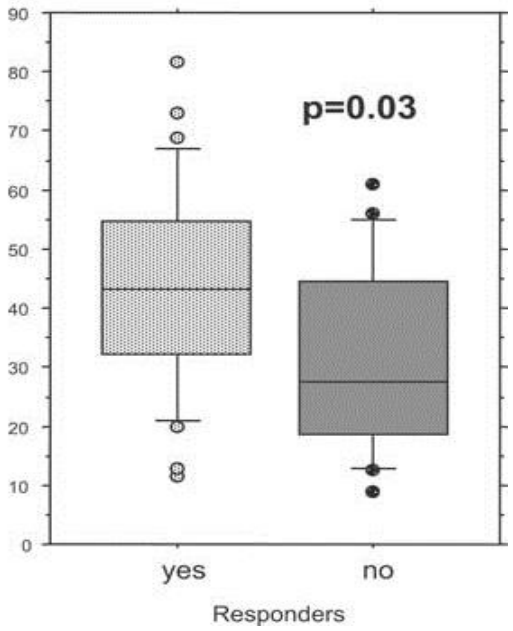
- ✓ 45 patients with unilateral symptomatic tibiofemoral and/or patellofemoral OA
- ✓ 3-weekly intraarticular injection of hyalan G20 (Synvisc®)
- ✓ Follow-up D1, D30 and D90 after the last injection

	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

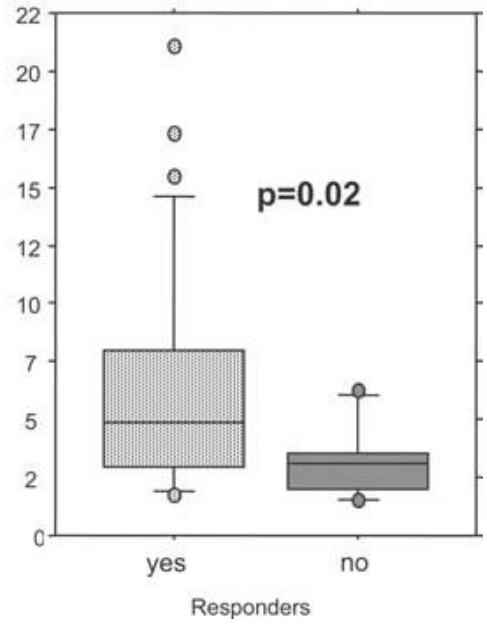
BIOVISCO study
Other observations

✓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)

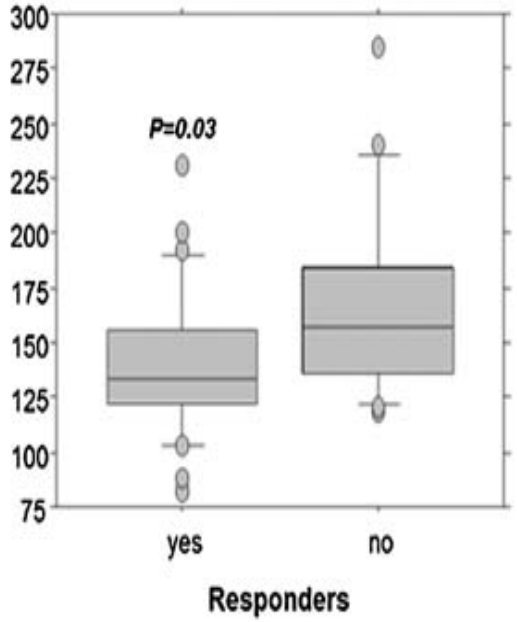
uCTX-II



sHA



sColl2-1



ARD Online First, published on January 14, 2015 as 10.1136/annrheumdis-2014-206792

OPEN ACCESS

EXTENDED REPORT

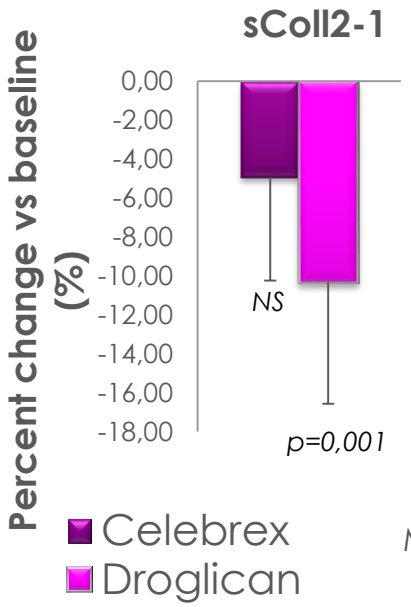
Combined chondroitin sulfate and glucosamine for painful knee osteoarthritis: a multicentre, randomised, double-blind, non-inferiority trial versus celecoxib

Marc C Hochberg,[1] Johanne Martel-Pelletier,[2] Jordi Monfort,[3,4] Ingrid Möller,[5] Juan Ramón Castillo,[6] Nigel Arden,[7,8,9] Francis Berenbaum,[10] Francisco J Blanco,[11] Philip G Conaghan,[12] Gema Doménech,[13] Yves Henrotin,[14,15] Thomas Pap,[16] Pascal Richette,[17,18] Allen Sawitzke,[19] Patrick du Souich,[20] Jean-Pierre Pelletier,[2] on behalf of the MOVES Investigation Group

MOVES study
CS + GuHCL (Droglican) vs Celecoxib
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)

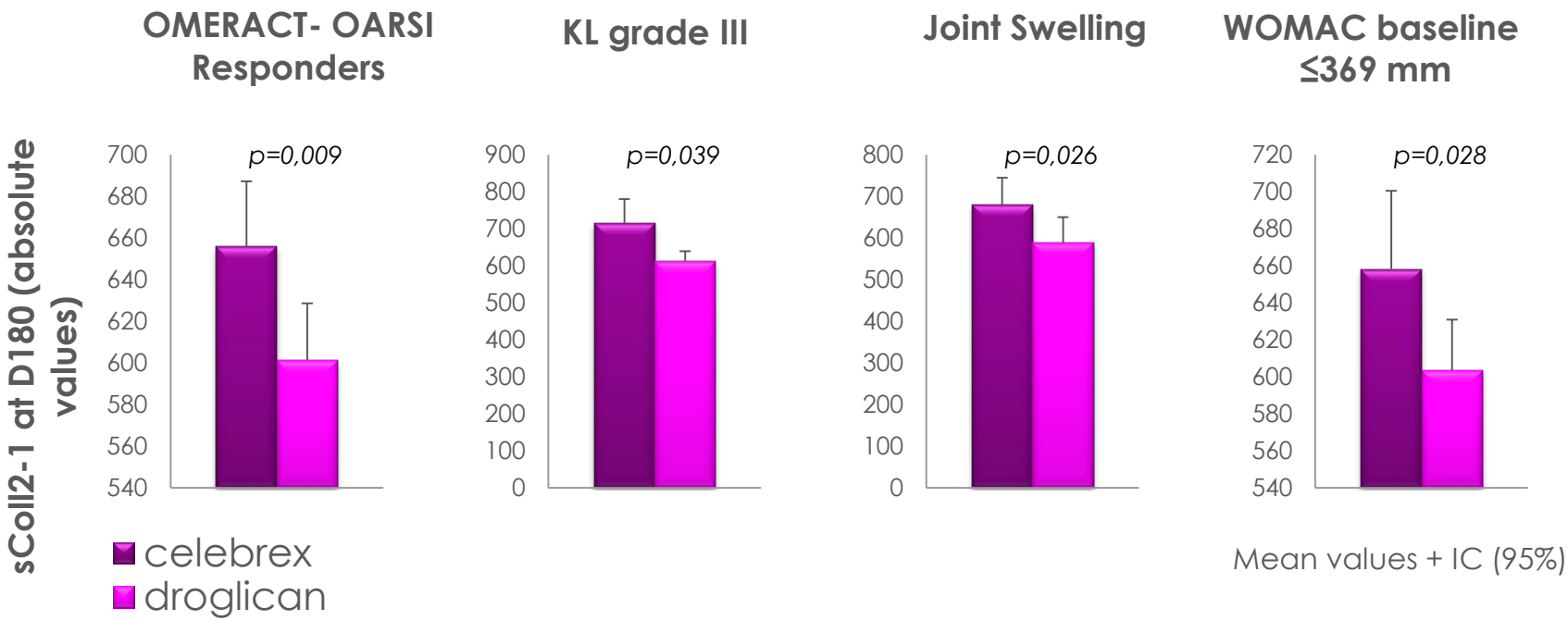


Mean values – IC (95%)

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

→ To predict treatment response (Companion biomarker - personalized medicine)

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)