Biochemical markers to monitor the effects of drugs in knee OA patients

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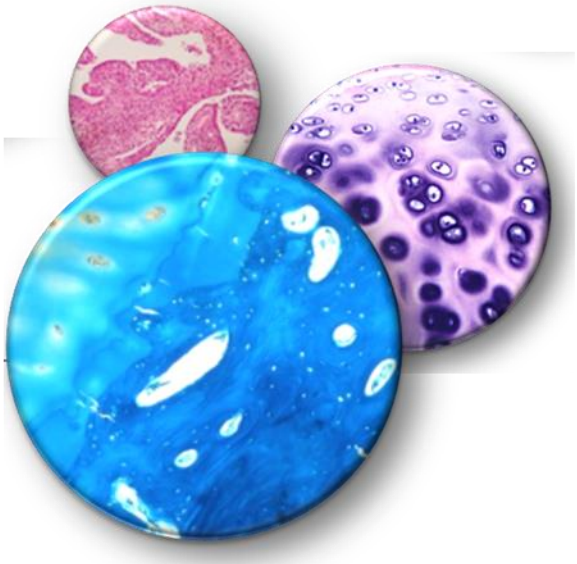

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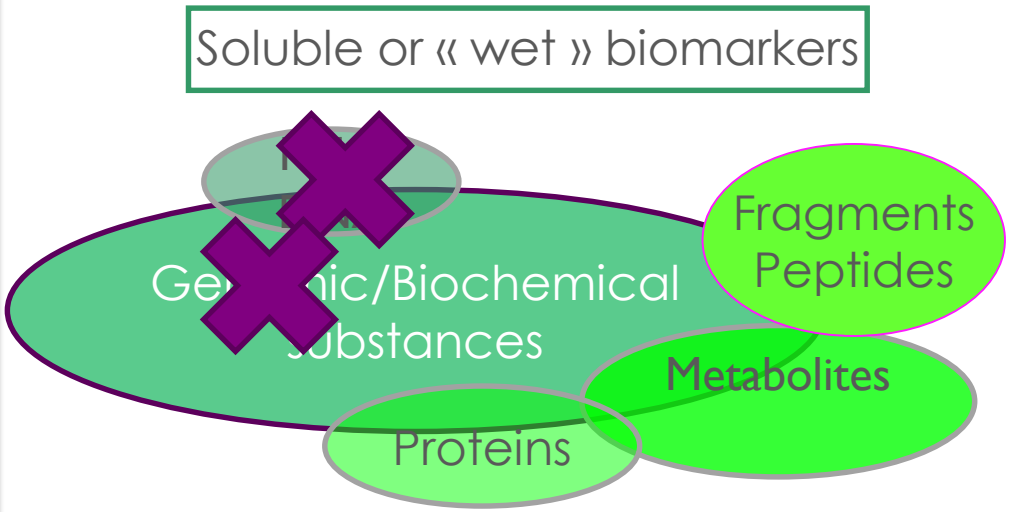
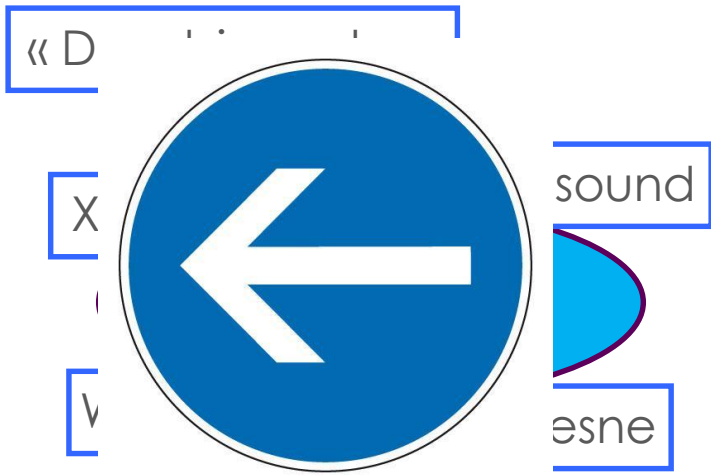
Definition - Classification

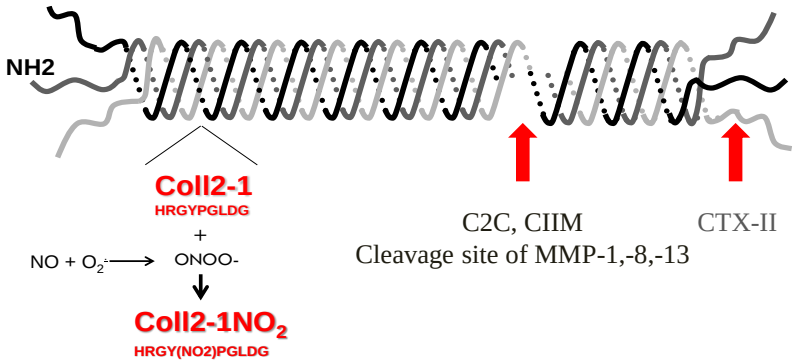
A biomarker is a characteristic that is objectively measured and evaluated as an indicator of normal biologic processes, pathogenic processes, or **pharmacologic responses to a therapeutic intervention**. »

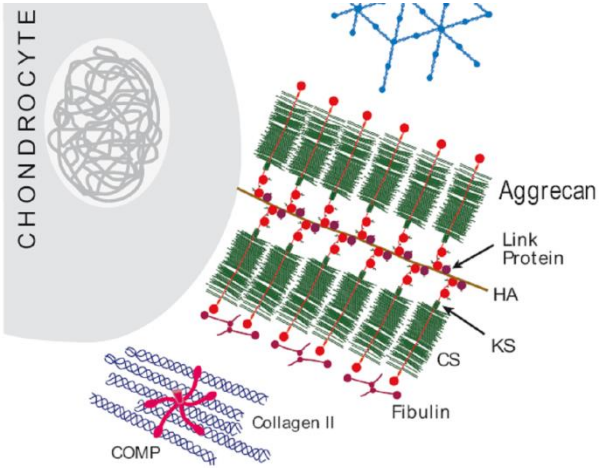
Biomarkers Definitions Working Group I. Biomarkers and surrogate endpoints: preferred definitions and conceptual framework. Clin Pharmacol Ther 2001; 69: 89-95.

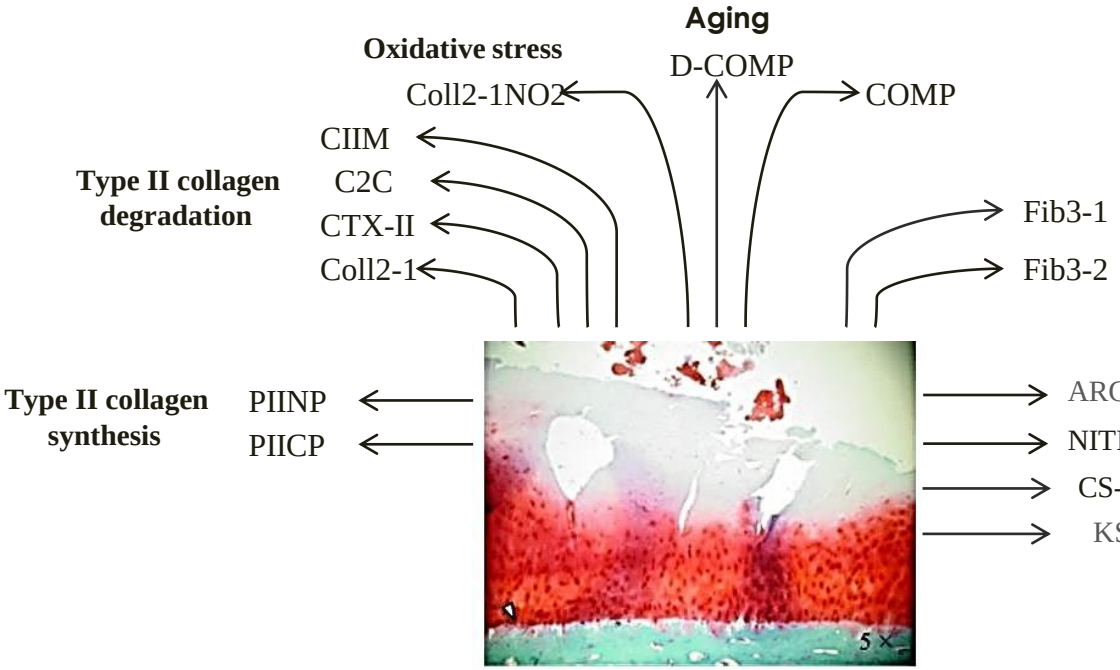


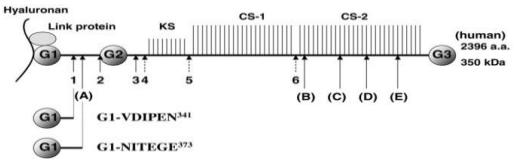


Biomarkers of cartilage metabolism









ADAMTS-5

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)

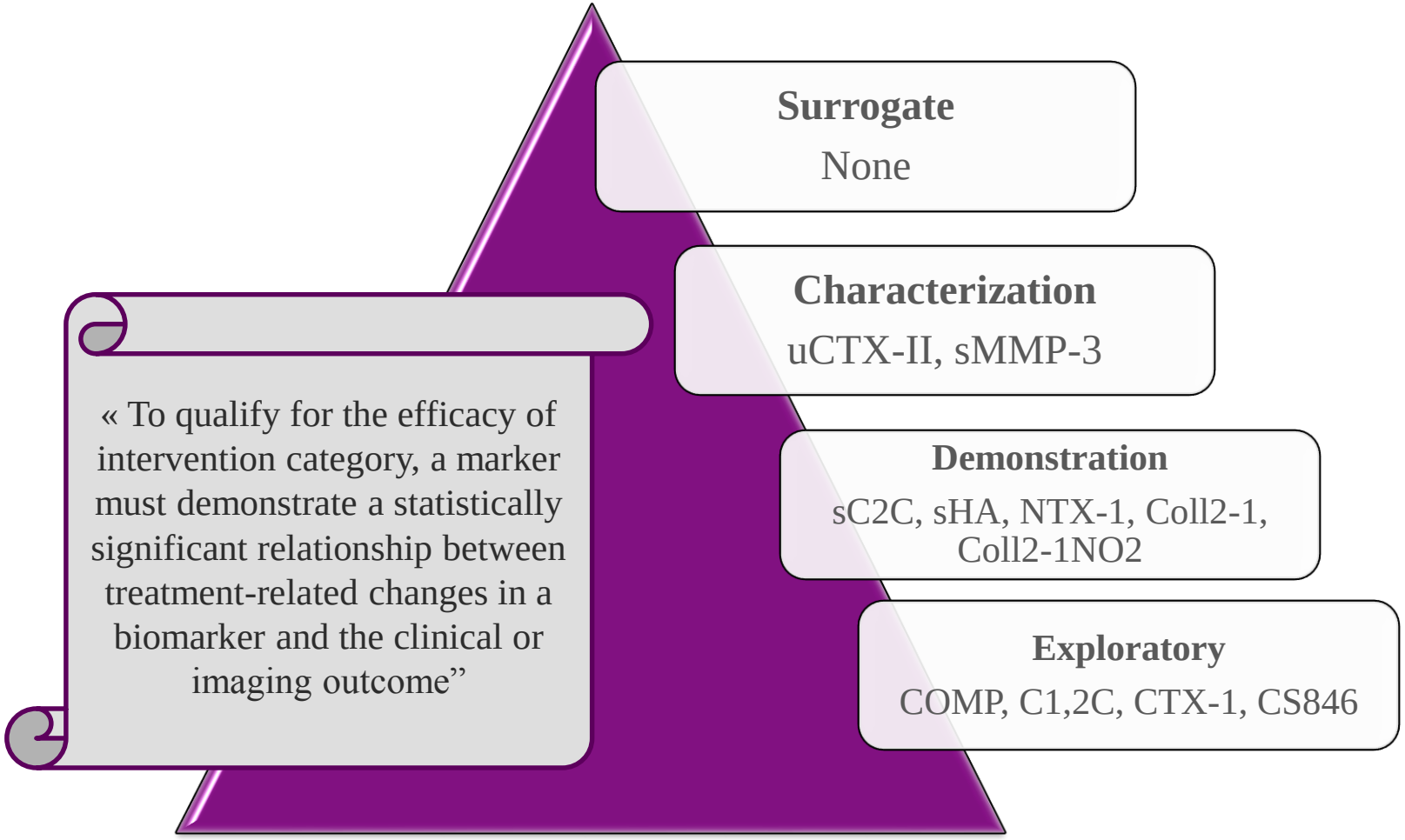
Updated Van Spil et al.2010

« 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

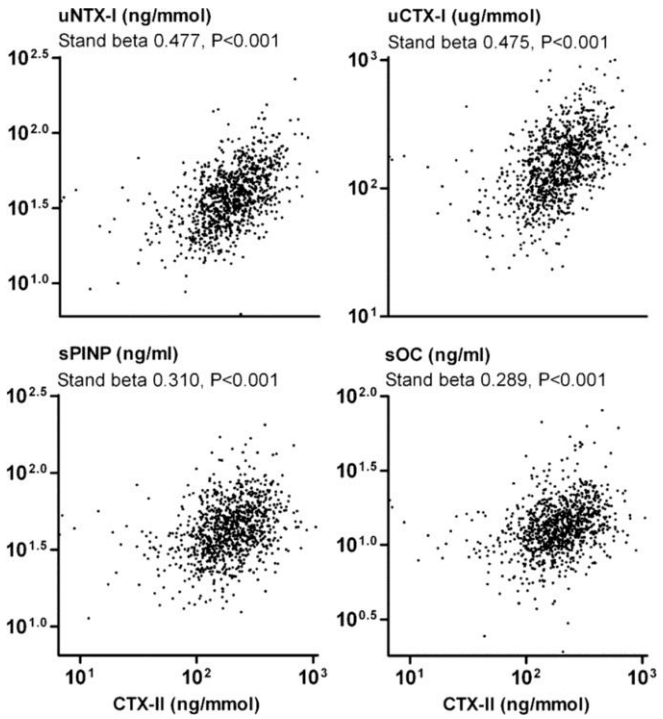
Levels of qualification of biomarkers for drug development use

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

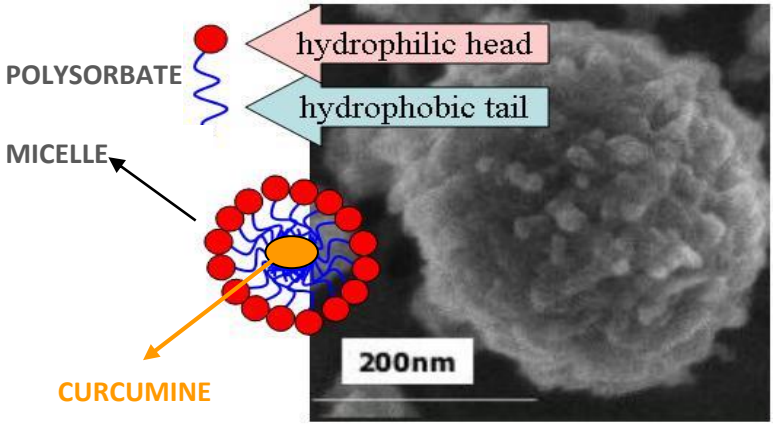
u CTX-II reflects bone rather than cartilage metabolism

van Spil W E et al. Ann Rheum Dis 2013

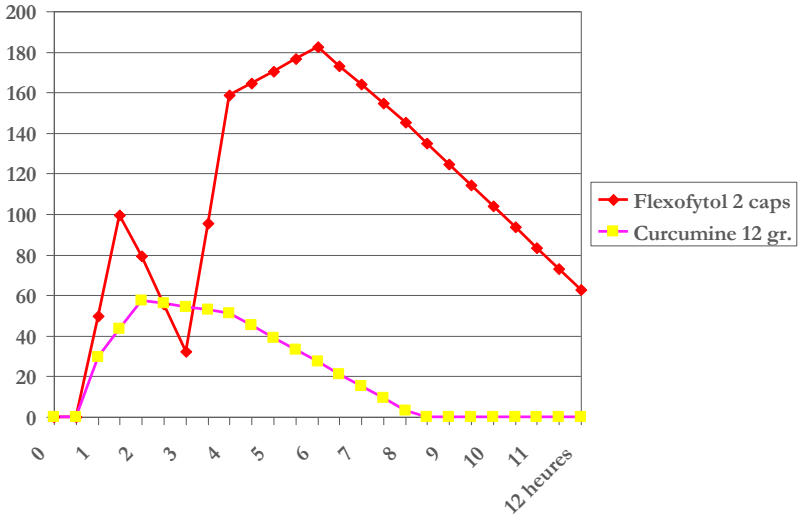
TIFLEXY Study

Bio-optimized curcuminoids (BOC)

Curcuminoids /Low avaibility



Bio-optimized curcuminoids BOC



« Proof-of-concept study »

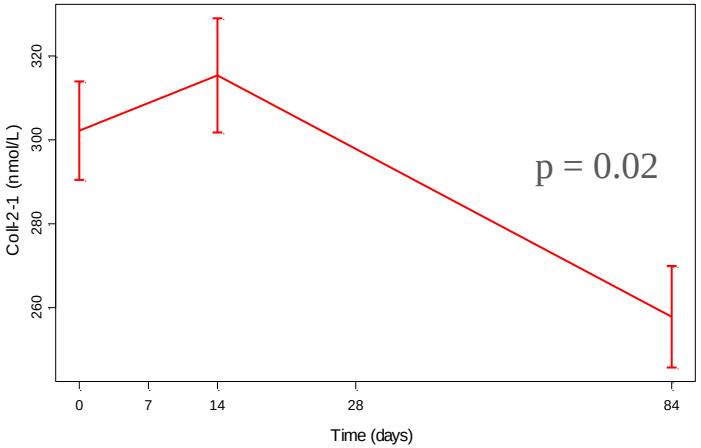
-22 knee OA patients
-2x3 caps (42 mg BOC)/days
-3 months treatment

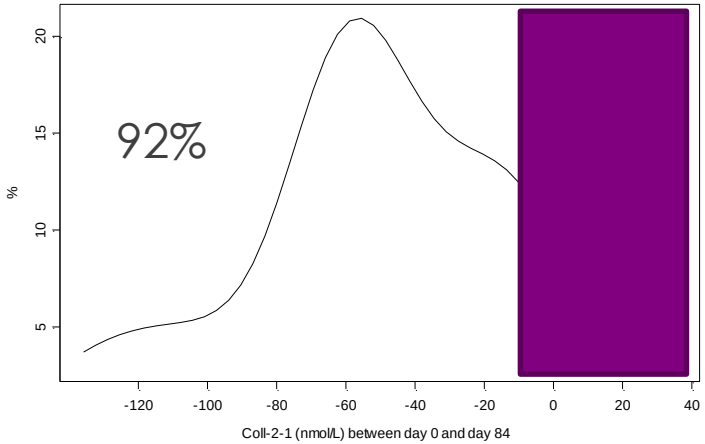
Henrotin Y, Priem F, Mobasheri A, Springerplus, 2013

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

BIOVISCO study
An open label observational prospective study

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

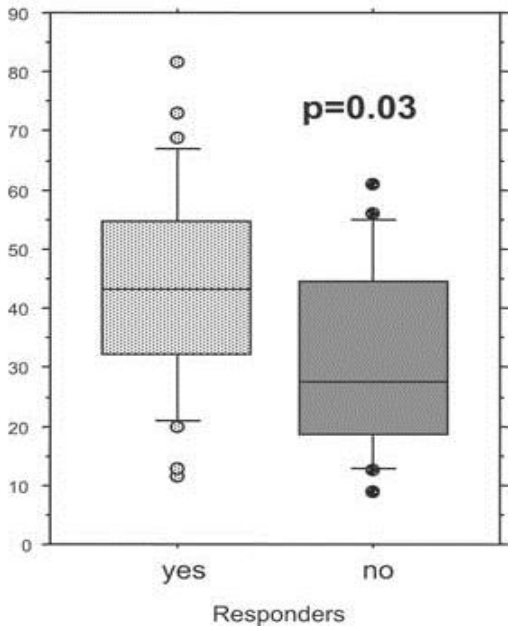
- ✓ 45 patients with unilateral symptomatic tibiofemoral and/or patellofemoral OA
- ✓ 3-weekly intraarticular injection of hyalan G20 (Synvisc®)
- ✓ Follow-up D1, D30 and D90 after the last injection

	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

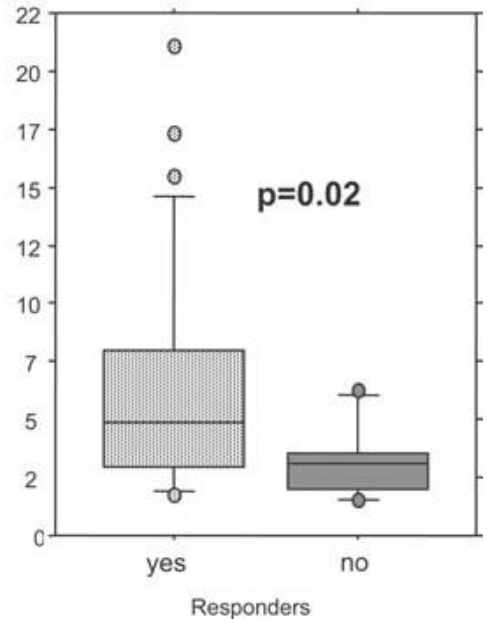
BIOVISCO study
Other observations

✓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)

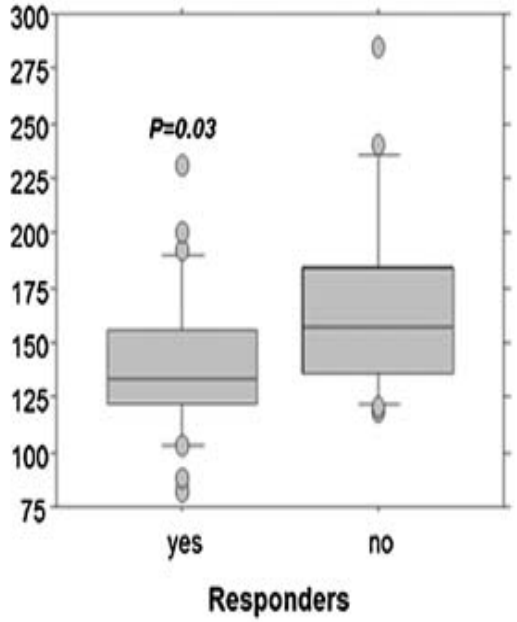
uCTX-II



sHA



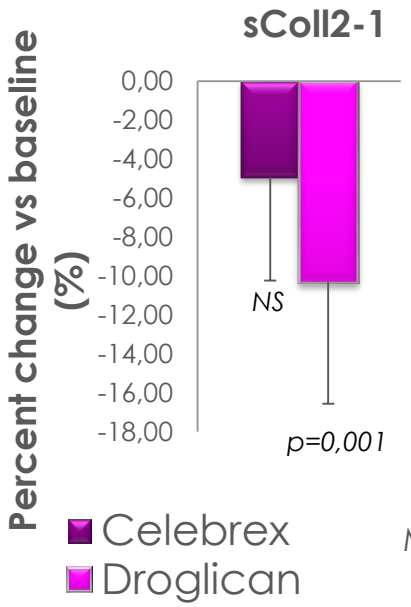
sColl2-1



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)

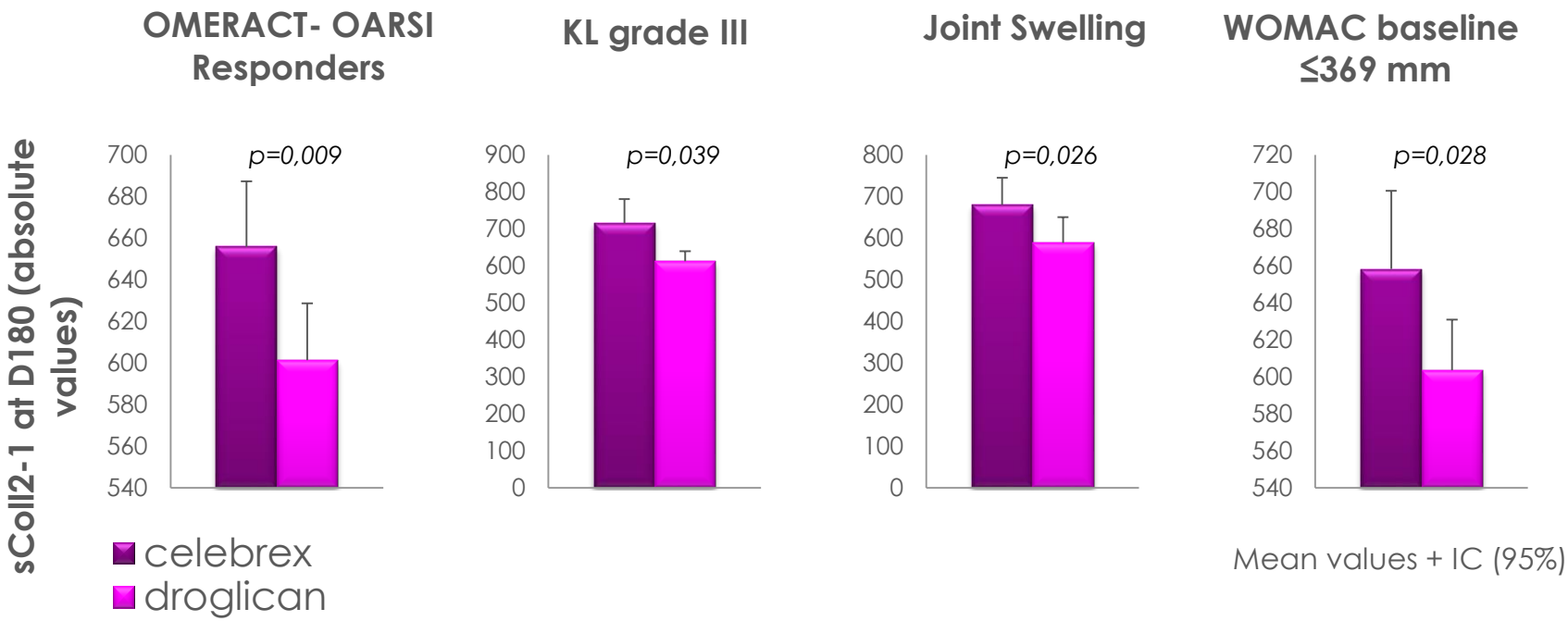


Mean values – IC (95%)

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

→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)
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P Richette (Lariboisiere, France)
J Runhaar (Erasmus MC, Rotterdam)