Nutraceuticals for joint health and OA biomarkers

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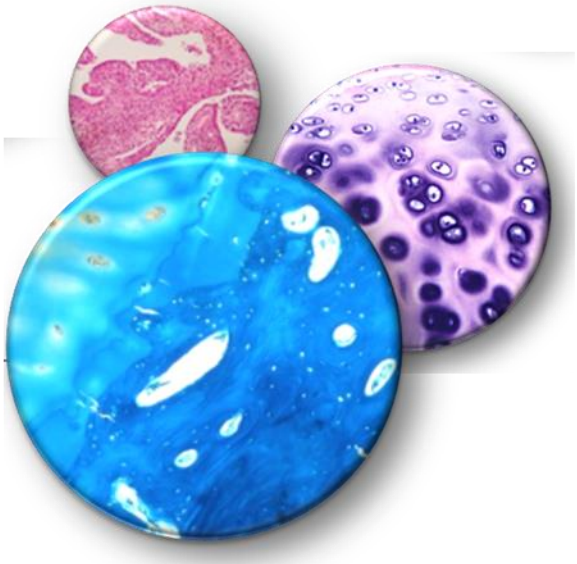

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Osteoarthritis an «old disease»

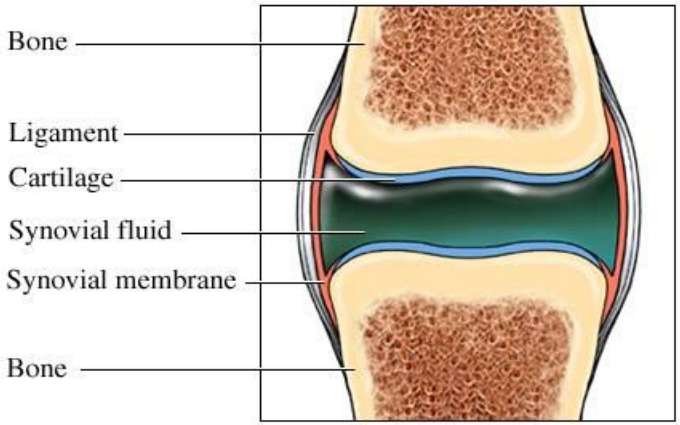
Act I: Local mechanical disease

Overloading
Overuse
Joint instability
Malignancy

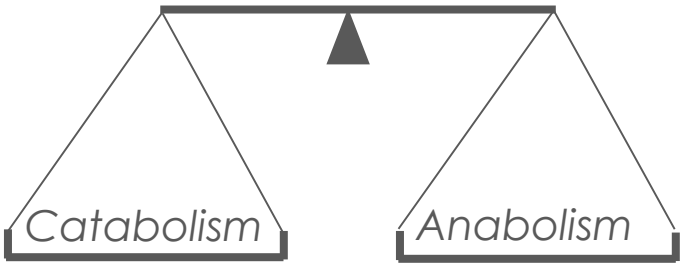
Cartilage degradation

Act II: a dysregulation of chondrocyte metabolism

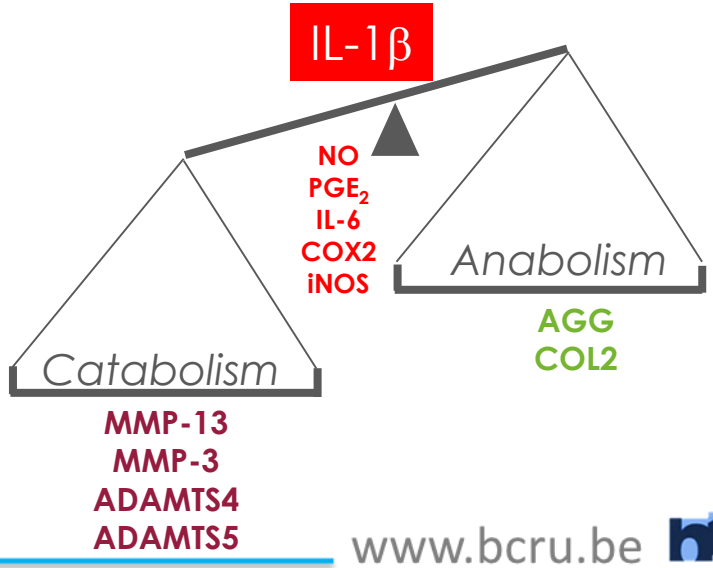
Healthy



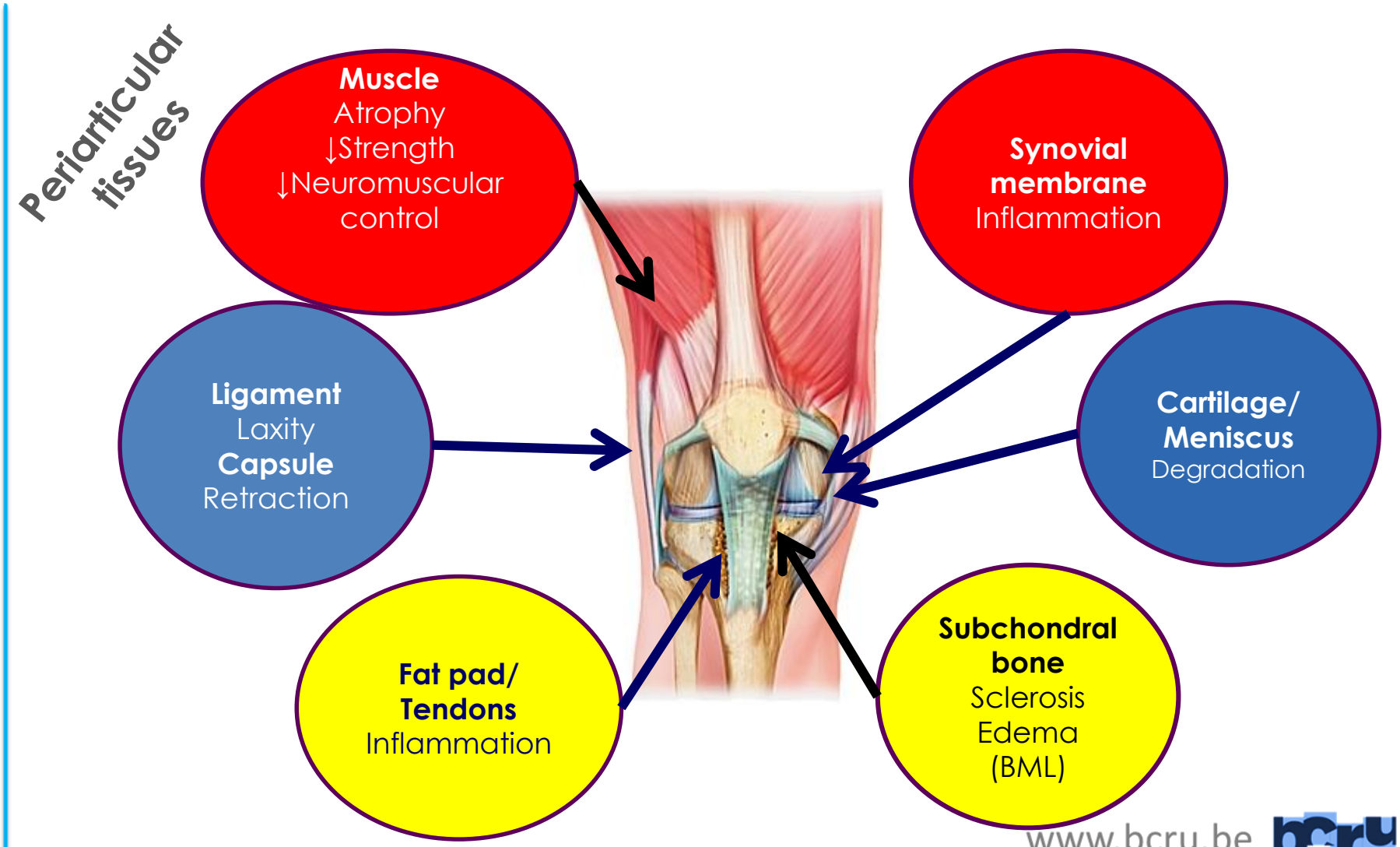
Cross section of a healthy joint

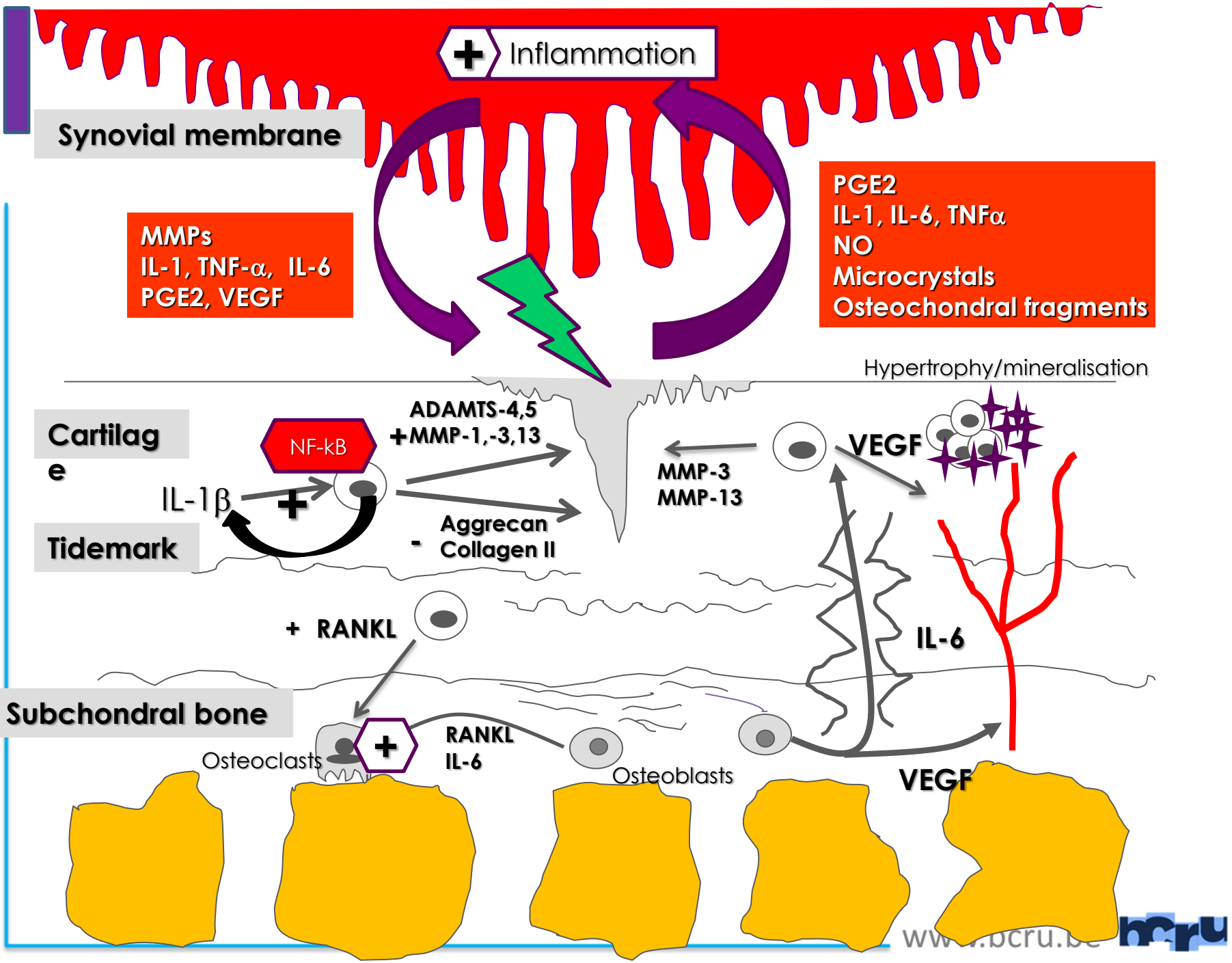


osteoarthritis

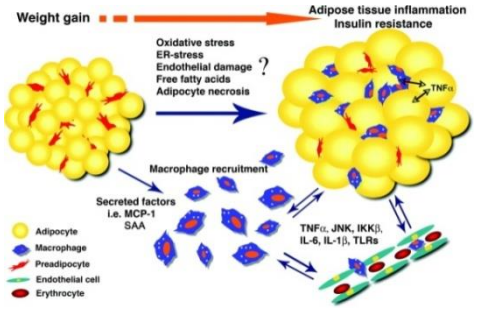


Act III: OA affects the whole joint and surrounding tissue




+ Inflammation
Synovial membrane
MMPs
IL-1, TNF-α, IL-6
PGE2, VEGF
PGE2
IL-1, IL-6, TNFα
NO
Microcrystals
Osteochondral fragments
Hypertrophy/mineralisation
Cartilage
Tidemark
NF-kB
IL-1β
+
ADAMTS-4,5
+MMP-1,-3,13
Aggrecan
Collagen II
-
MMP-3
MMP-13
VEGF
+ RANKL
IL-6
Subchondral bone
Osteoclasts
+
RANKL
IL-6
Osteoblasts
VEGF

ACT IV: a metabolic and systemic disease of an organ « the joint »



Adipokines
Cytokines

Chronic
Mechanical stress

Matrix peptides
Cytokines
Prostanoids
Oxidized lipids

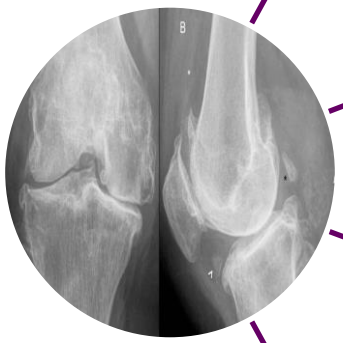
Sedentarity

Aging

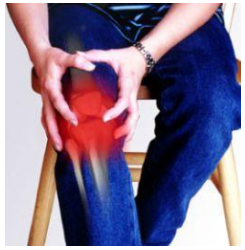
Chronic low-grade inflammation

Metabolic syndrome
-Hypertension
-Type 2 diabetes
-Dyslipidemia

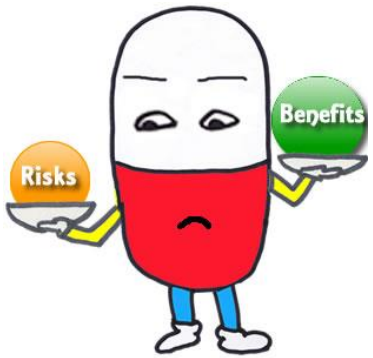
ACT V: a disease with some subphenotypes



- O
  - Obesity-related
  - Metabolic syndrom
- I
  - Inflammatory driven
  - Systemic
  - Local
- T
  - Post-traumatic
- H
  - Hypertrophic
  - Bone driven



OA treatments and limitations

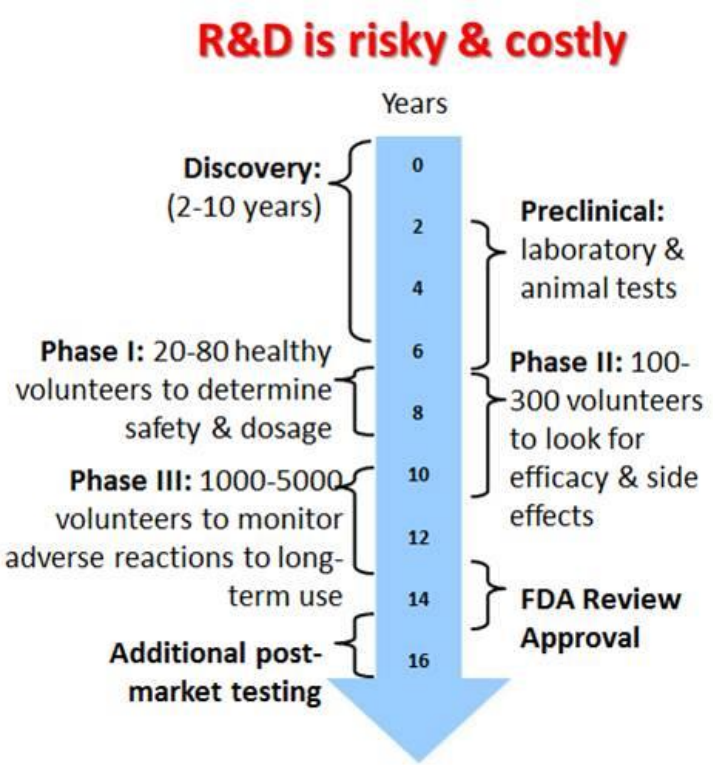


Intraarticular steroids, viscosupplements (GAG), topical NSAIDs, SYSADOA (GAG), Nutraceuticals

	Limitations
Surgery	Costly, invasive procedure Primarily indicated for «end stage » OA
Prescription NSAIDs Including COXIB	GI bleeding or other complications CV risks Renalr complications
OTC NSAIDs	GI bleeding or other complications CV risks Renal complications
Acetaminophen	Hepatotoxicity
Patient education, physical and occupational Therapy, weight loss	Poor patient compliance

Modified Clegg et al. Eur J Orthop Surg Traumatol, 2013

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

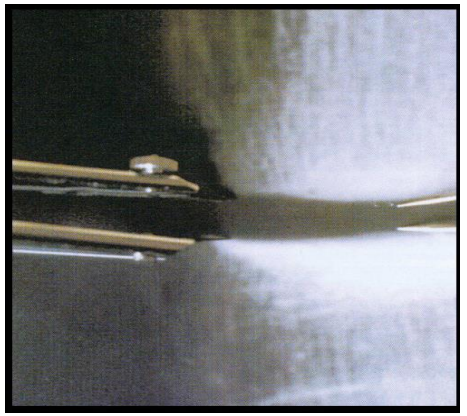
Physical function

Patient global assessment

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

Imaging outcomes

Joint Space Narrowing



The Gold Standard (Radiography) is inadequate

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

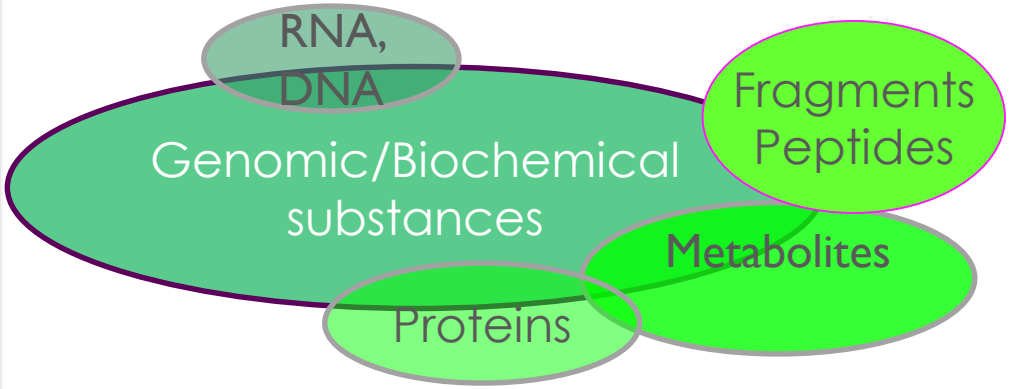
Slide courtesy of Dr A Mobasheri (Nottingham University)

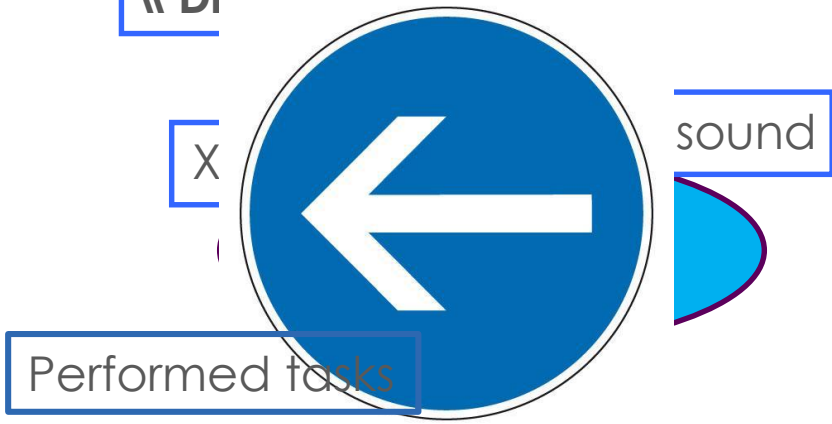
Biomarkers - definition

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.

Soluble or « wet » biomarkers





THE CURRENT SITUATION

28 identified biochemical makers[1]

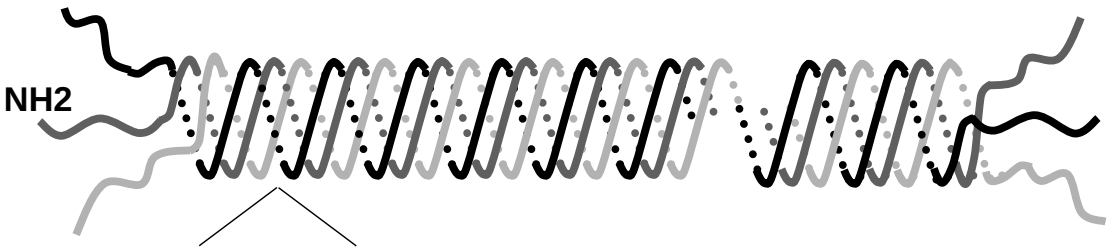
1 WE van Spil et al. Osteoarthritis cart, 2010; 18: 605-12

Cartilage metabolism
CTX-II, Coll2-1,C2C, C1,2C, ARGS epitope, KS, COMP, D-COMP

Bone metabolism
PYD, DPD, NTX-I, CTX-I, osteocalcine, BSP

Synovium metabolim
Glu-Gal-PYD, HA, PIIINP, COMP

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



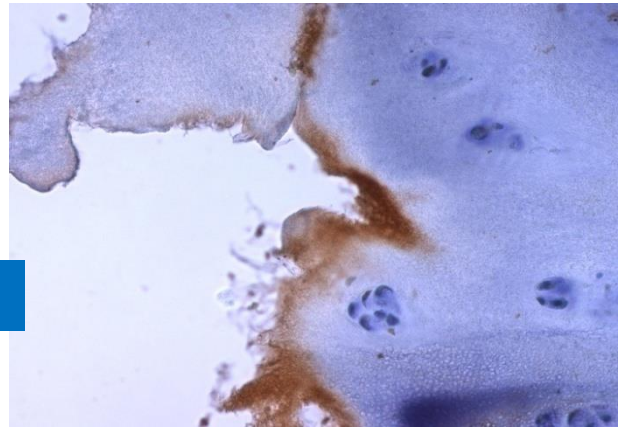
Coll2-1
HRGYPGLDG

\+

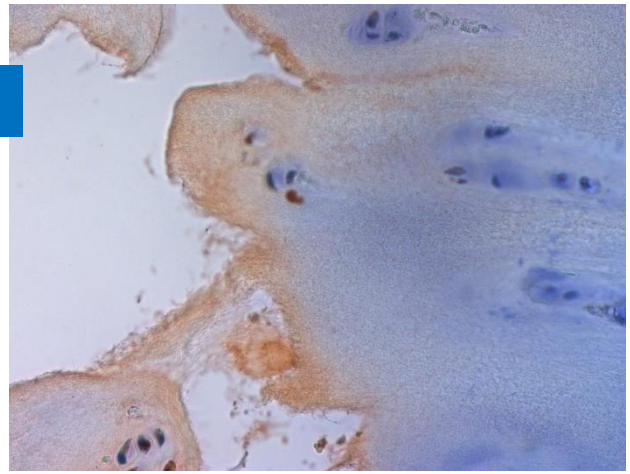
$NO + O_2^{\cdot} \longrightarrow ONOO^-$

Coll2-1NO$_2$
HRGY(NO2)PGLDG

Coll2-1NO2



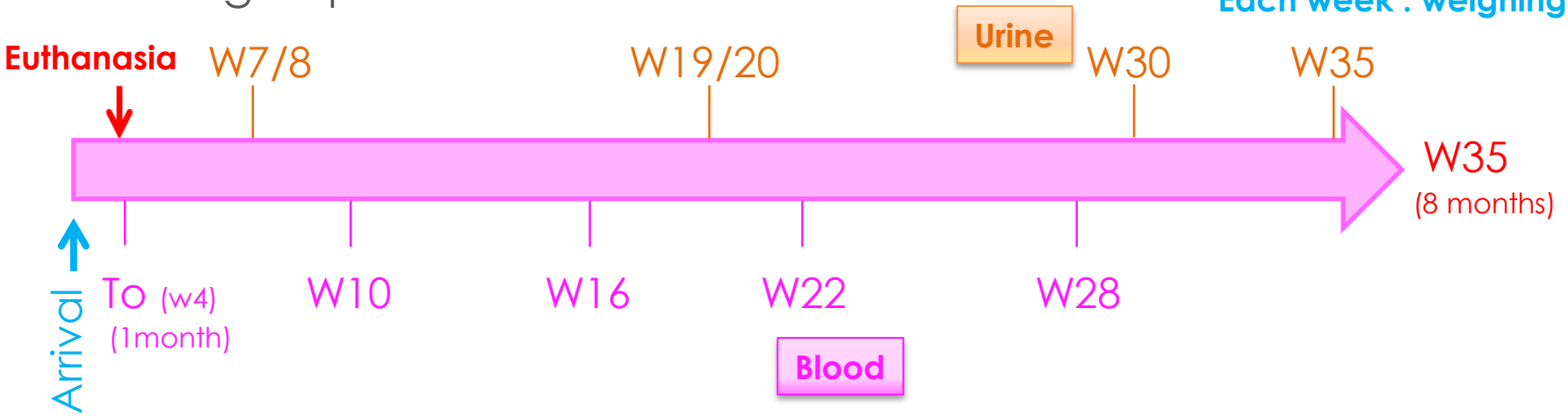
Coll2-1



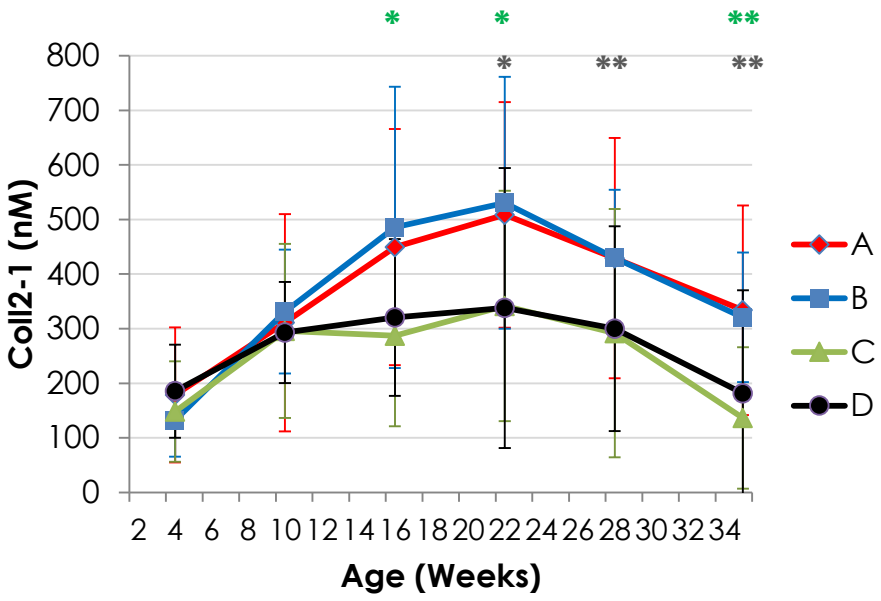
- Specific of degradated cartilage
- Multiple pathological processes (inflammation + degradation)
- Not confounded

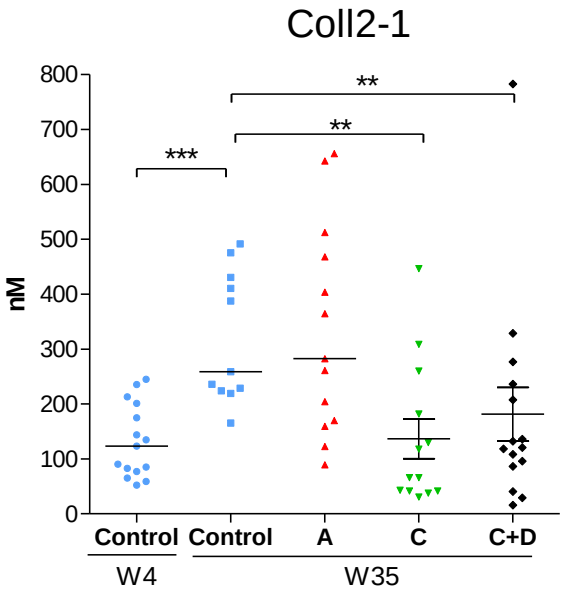
Hartley Guinea Pig

- 65 male HA guinea pigs
- 2/3 w old + 1w acclimatation
  - 5 « Baseline », sacrified at T0 (group **E**)
  - 15 group **A Oleuropein**
  - 15 group **B** (control)
  - 15 group **C** Rutin
  - 15 group **D** Rutin + Curcumin



Biomarkers in serum : Coll2-1



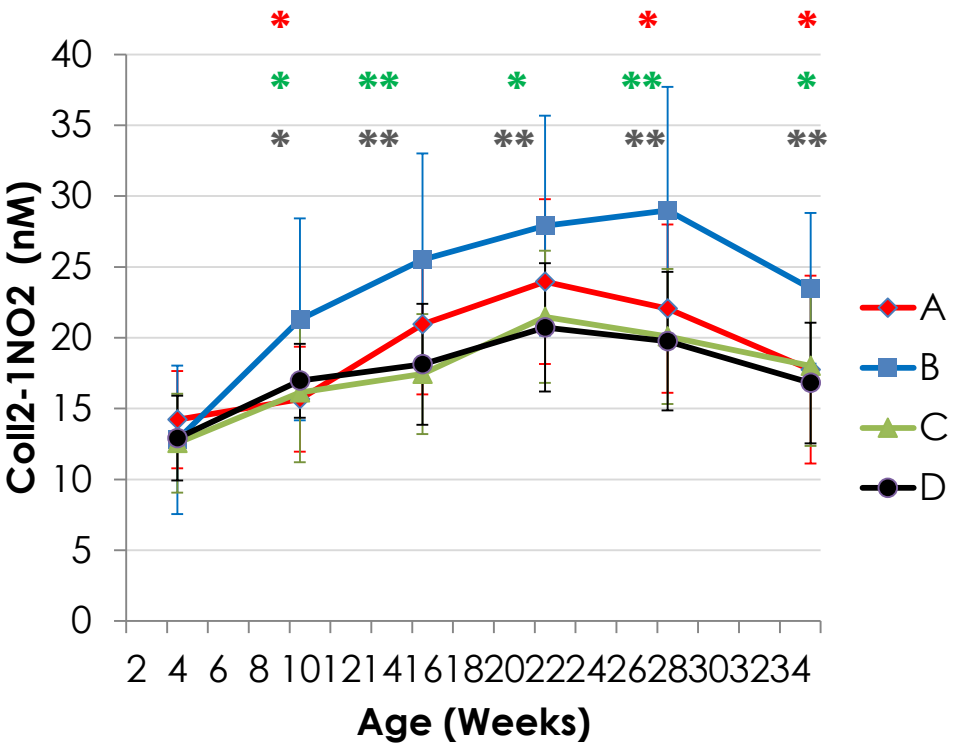


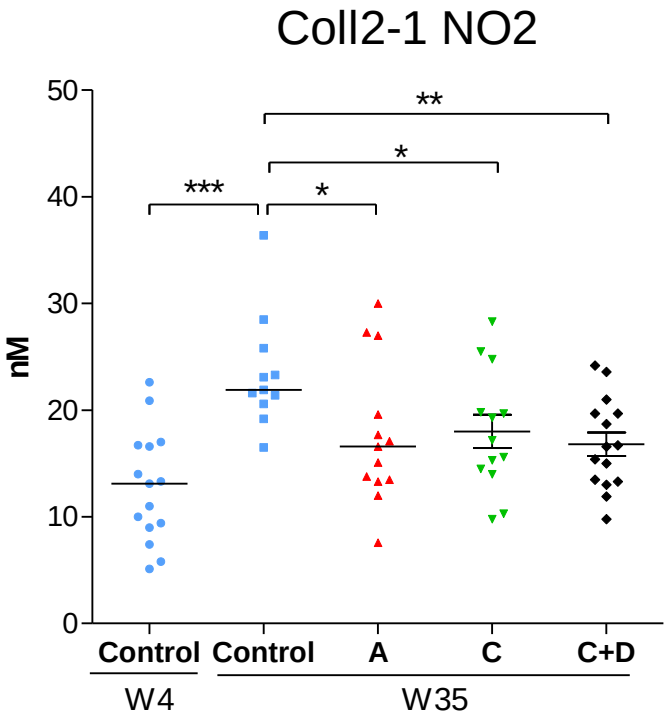
A= Oleuropein
B = Control
C= Rutin
D = Rutin + Curcumin

N=53

W35

Biomarkers in serum : Coll2-1NO2



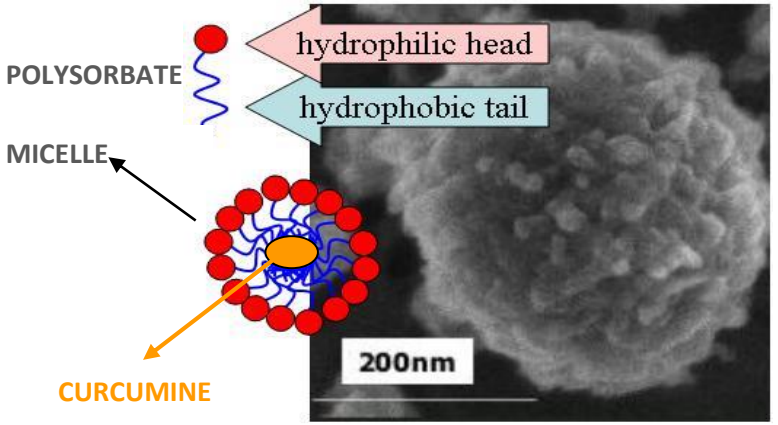


A= Oleuropein
B = Control
C= Rutin
D = Rutin + Curcumin

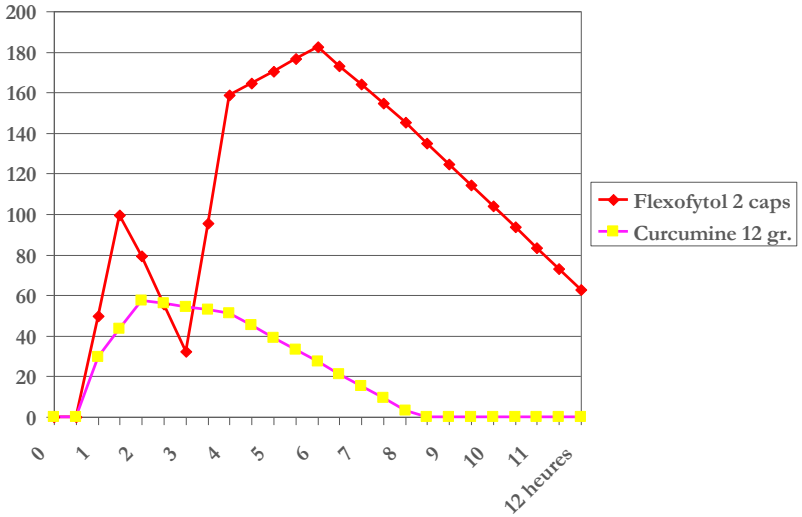
TIFLEXY Study

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

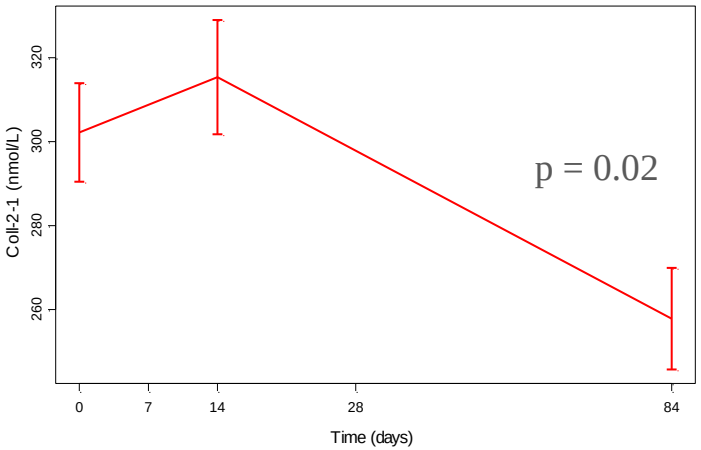
Criteria of efficacy

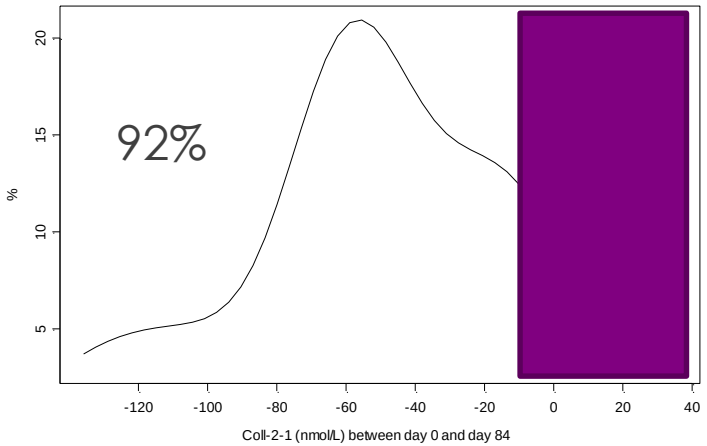
- Primary end-point : Biomarkers variation
  - Coll-2-1 (nmol/L)
  - Coll-2-1NO2 (nmpm/L)
  - Fib3-1 (pmol/L)
  - Fib3-2 (pmol/L)
  - CRP (mg/L)
  - CTX-II (ng/L)
- Secondary end-point:
  - Variation of pain on movement during the last 24H
  - Variation of Global Patient Assessment on disease activity

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

FDA/OARSI Recommendation to advance the science of biomarkers

- The co-development (Drug + biomarker) pathway should be determined early in development.
- Used biomarkers in combination rather than individually
- Used in combination with imaging (MRI)
- Biomarkers may serves as titration tools; falicitating dose setting in early clinical study
- Appropriate analytical validation of immunoassay

bcru Team

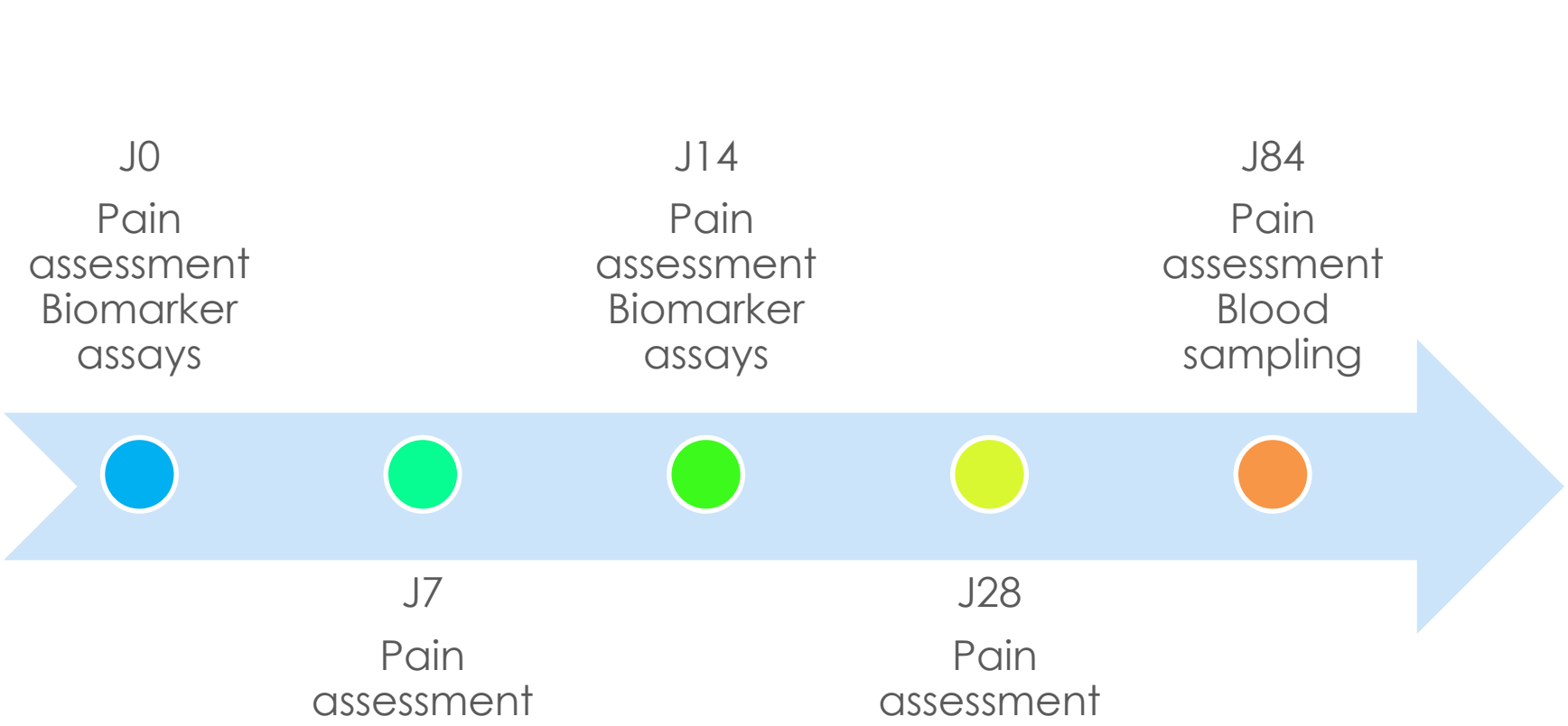
Bone and Cartilage Research Unit

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)

Design



Flexofytol 2 X 3 caps/days during 3 months