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Osteoarthritis unmasked: Identification of nuclear prohibitin as a new specific OA biomarker and therapeutic target

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Le centre hospitalier universitaire mère-enfant

Pour l'amour des enfants

Université de Montréal

6th International Conference on
Biomarkers & Clinical Research
Toronto, Canada Aug 31-Sep 2, 2015

DISCLOSURES

Dr. Moreau's osteoarthritis research program is supported by:

- Canadian Institutes of Health Research



This work led to several patents by Dr. Moreau and own by Sainte-Justine University Hospital:

• Australia	No 2007308715	issued 10/06/2011
• European	No 2 089 546	issued 03/14/2012

- Others patent applications are pending in several countries.

Dr. Moreau is the Chairman, Scientific Officer & co-founder of Inception Therapeutics Inc.

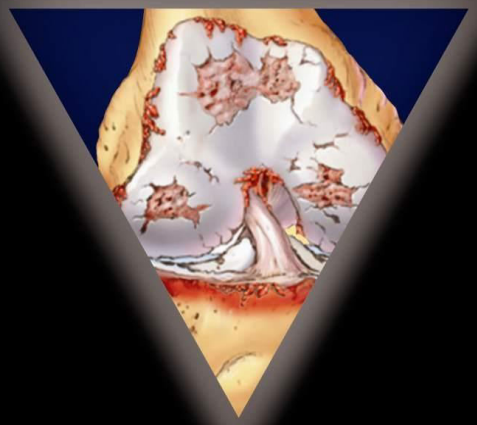
BACKGROUND

What is Osteoarthritis?



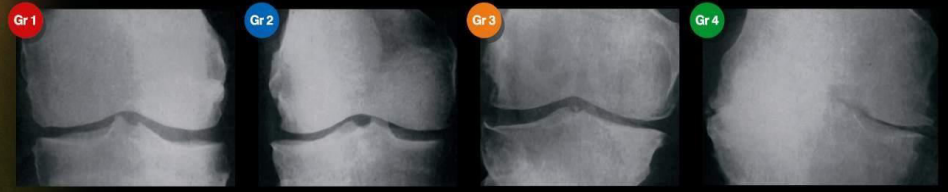
as it is associated with

Pain



⬇ Cartilage regeneration

⬆ Cartilage degeneration



...worsens with further progression



Radiol Clin N Am 2004;42;11-41

OSTEOARTHRITIS

Prevalence & Incidence

- Osteoarthritis (OA) is the most common form of arthritis, and the leading cause of chronic disability in the world.
- OA is only diagnosed when clinical symptoms appear.
- Patients seek medical advice too late in the disease degenerative process.



- The search for disease-modifying drugs is largely hampered by our incapacity to identify rapide OA progressors.



750,000 new OA cases are diagnosed each year in USA

CURRENT MARKET

For Osteoarthritis Diagnostics

The OA market is forecast to grow steadily being fuelled by:

- Increasing ageing population
- Extending life expectancy
- Rising levels of obesity in most of the continents



Up to 81.4 million prevalent cases in adults aged 25 and older suffer from OA in the seven major markets in 2009**.

- Datamonitor -



**USA, Japan, UK, Germany, Italy, France and Spain

UNMET NEEDS

For Osteoarthritis

Why do we need biomarkers for Osteoarthritis?

- Early diagnosis
- Staging of OA disease
- Identification of subpopulations of patients
- Predictive markers of disease progression
- Monitoring response to treatment
- Validation of disease modification

- OA Biomarker: Global Initiative Workshop 2010 -

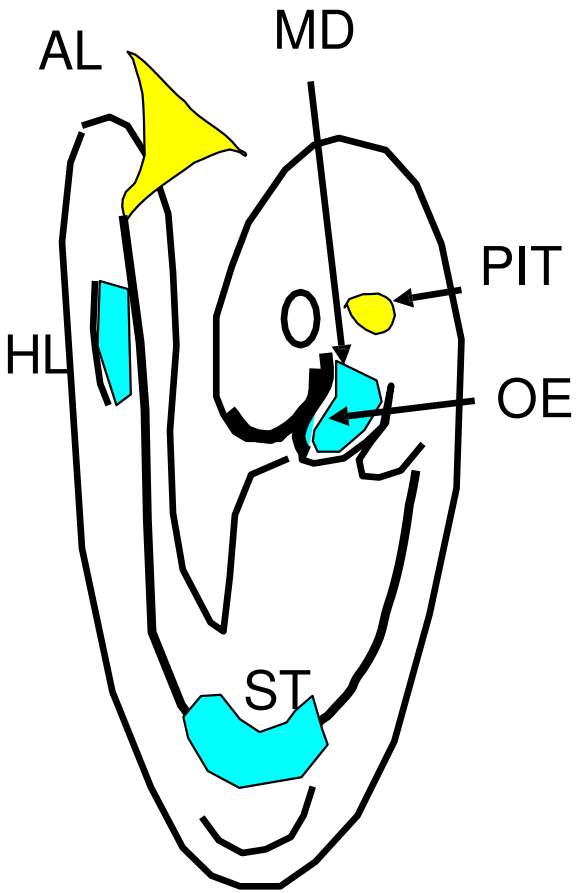




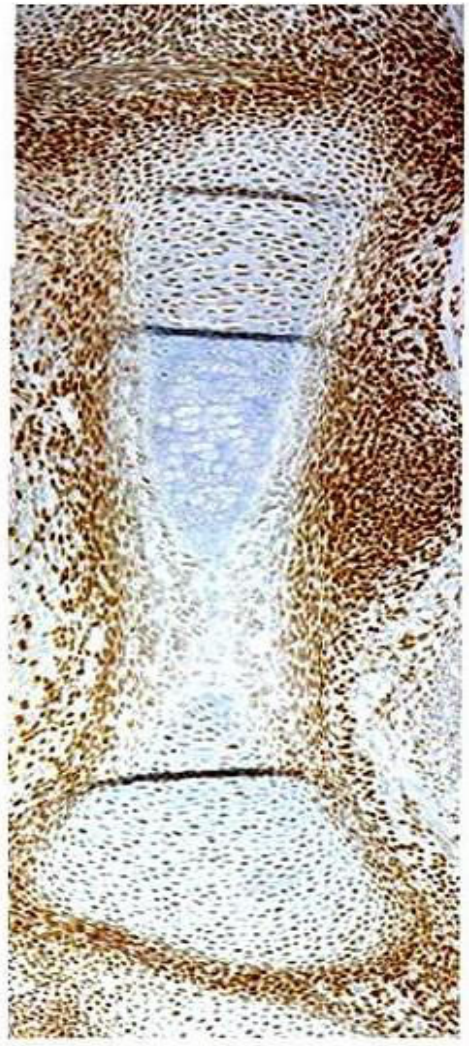
DISCOVERY

PITX1 is essential forbone and cartilage development

Lanctôt, Moreau et al., Development, 126: 1805-1810, 1999



Posterior lateral plate





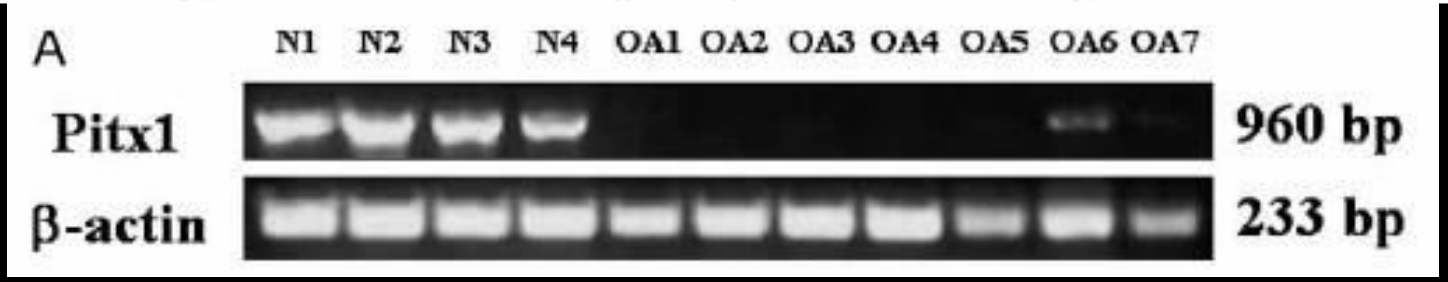
DISCOVERY

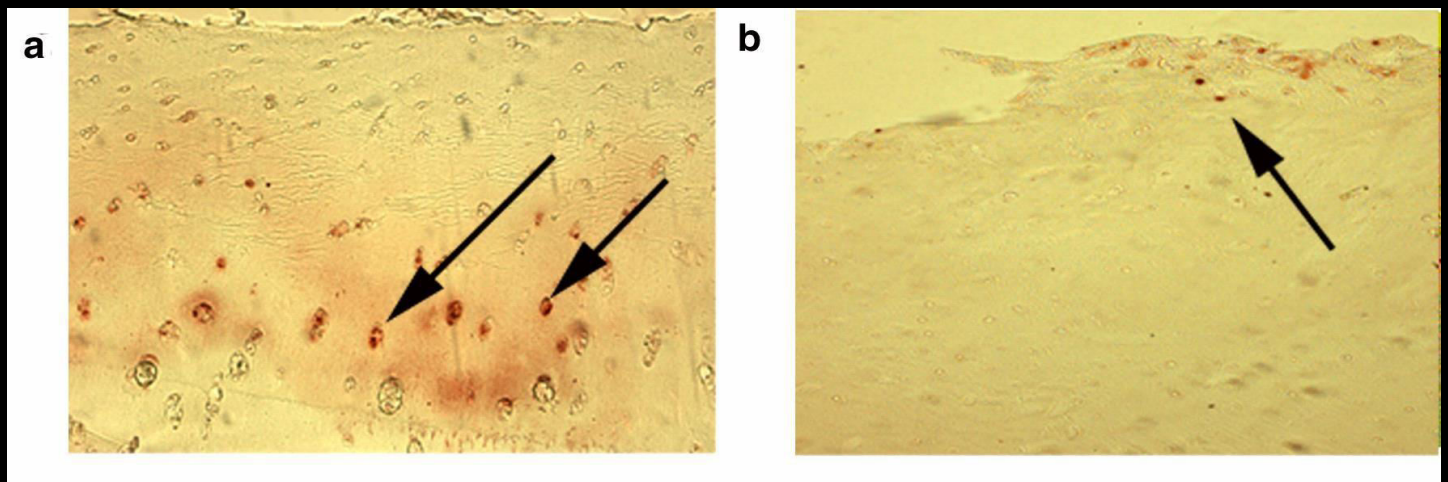
PITX1 is repressed in OA

CLINICAL ORTHOPAEDICS AND RELATED RESEARCH
Number 462, pp. 59–66
© 2007 Lippincott Williams & Wilkins

New Emerging Role of Pitx1 Transcription Factor in Osteoarthritis Pathogenesis

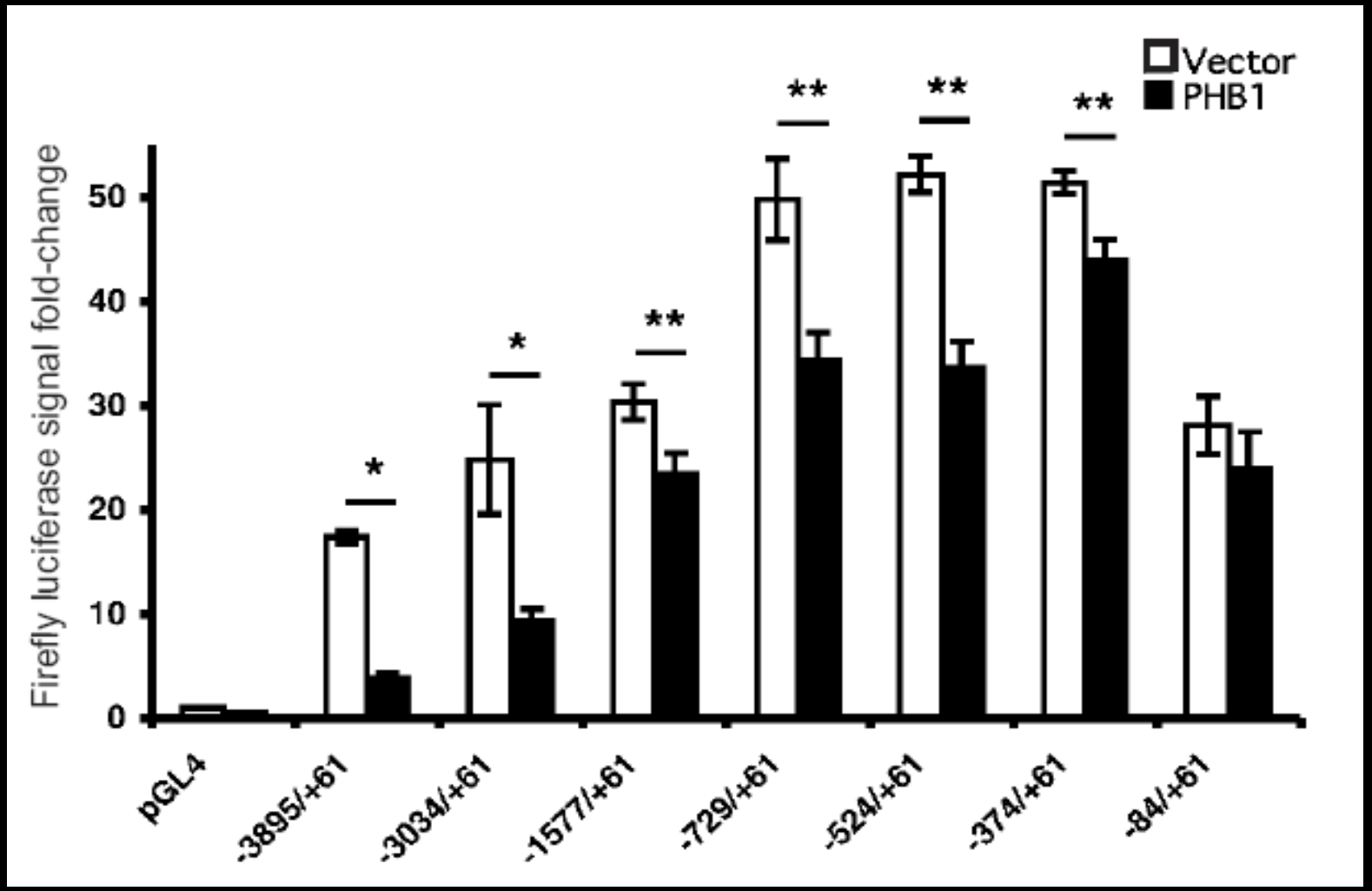
Cynthia Picard, BSc[*]; Bouziane Azeddine, MSc[*]; Florina Moldovan, MD, PhD[,†]; Johanne Martel-Pelletier, PhD[‡]; and Alain Moreau, PhD[*,†,||]*





DISCOVERY

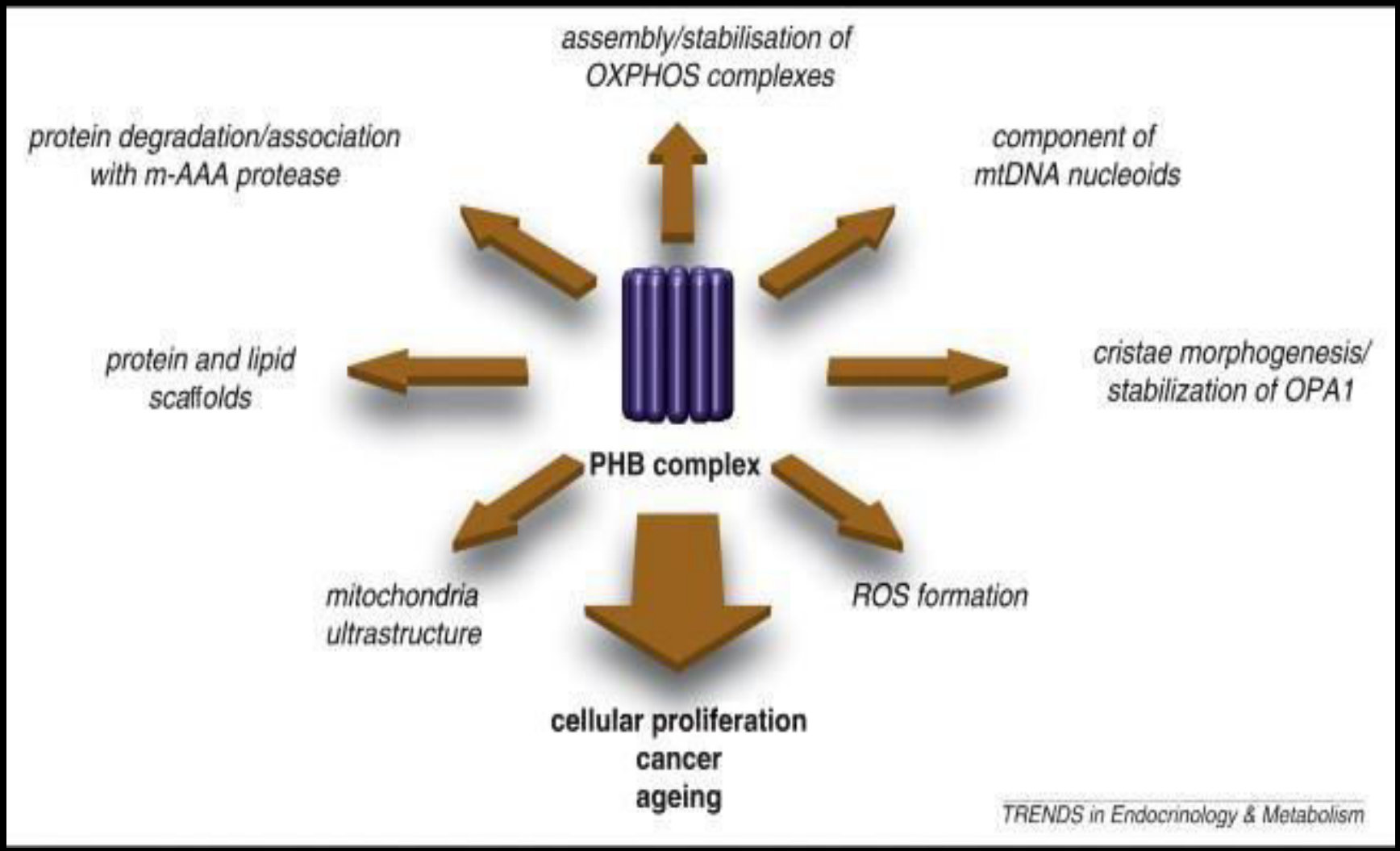
Nuclear PHB1 inhibits Pltx1 expression



Picard, Pellicelli *et al*. 2013, Arthritis Rheum. 65(4): 993-1003

PROHIBITIN

A molecule for all seasons?



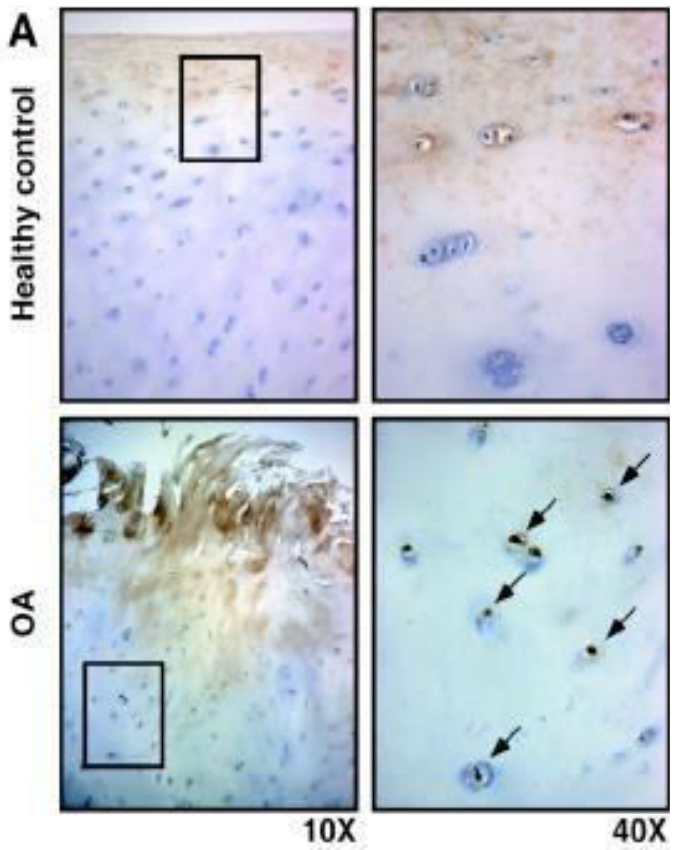
DISCOVERY

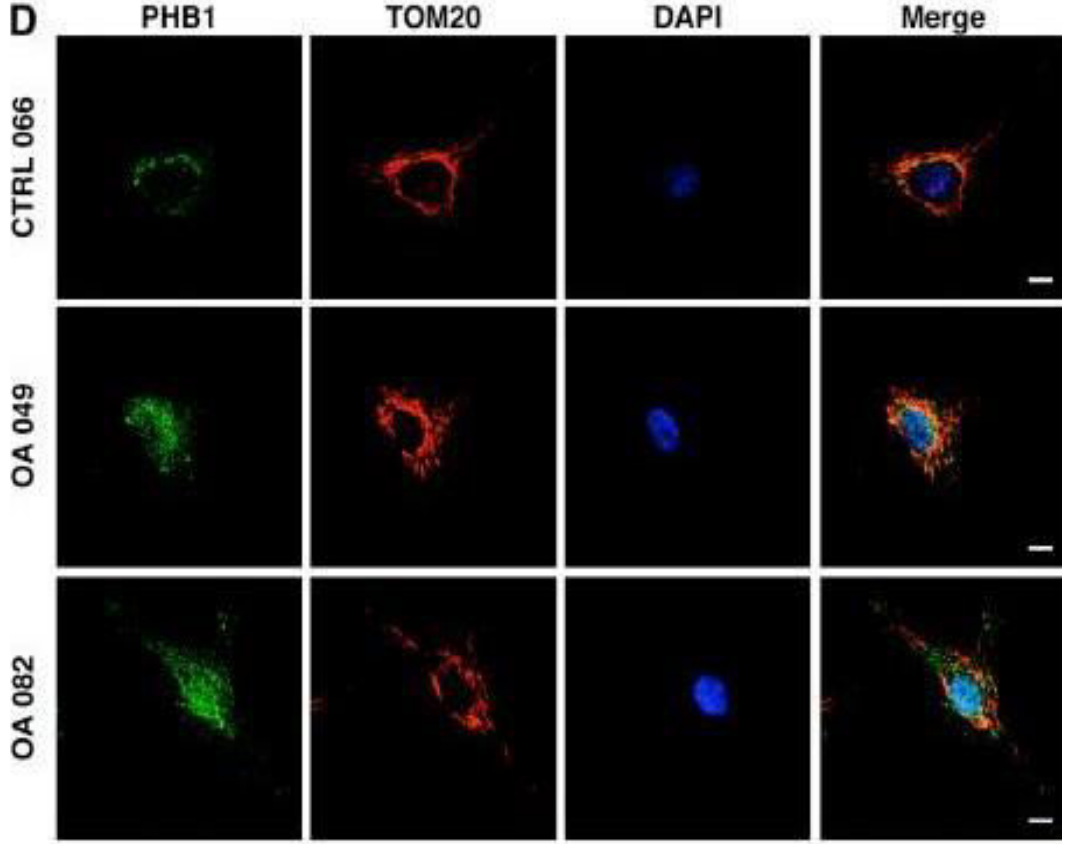
Nuclear PHB1 is increased in OA

Picard, Pellicelli *et al*. 2013, Arthritis Rheum. 65(4): 993-1003

Nuclear Accumulation of Prohibitin 1 in Osteoarthritic Chondrocytes Down-Regulates *PITX1* Expression

Cynthia Picard,[1] Martin Pellicelli,[1] Maryam Taheri,[2] Jean-Francois Lavoie,[1] Roxanne Doucet,[1] DaShen Wang,[2] Lauriane Bernard,[1] Saadallah Bouhanik,[2] Patrick Lavigne,[3] and Alain Moreau[1]

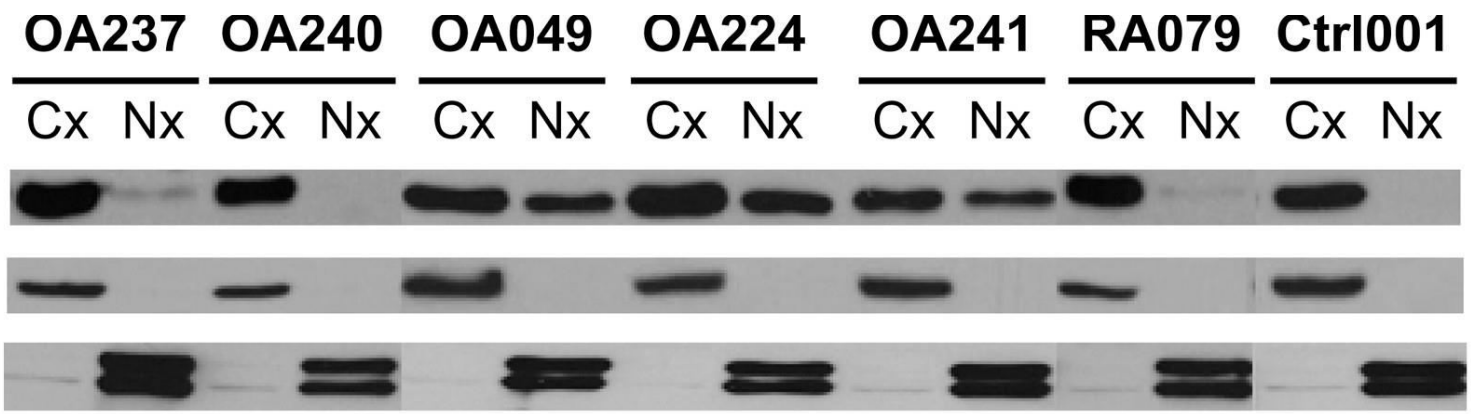




DISCOVERY

Nuclear PHB1 is increased in OA

A

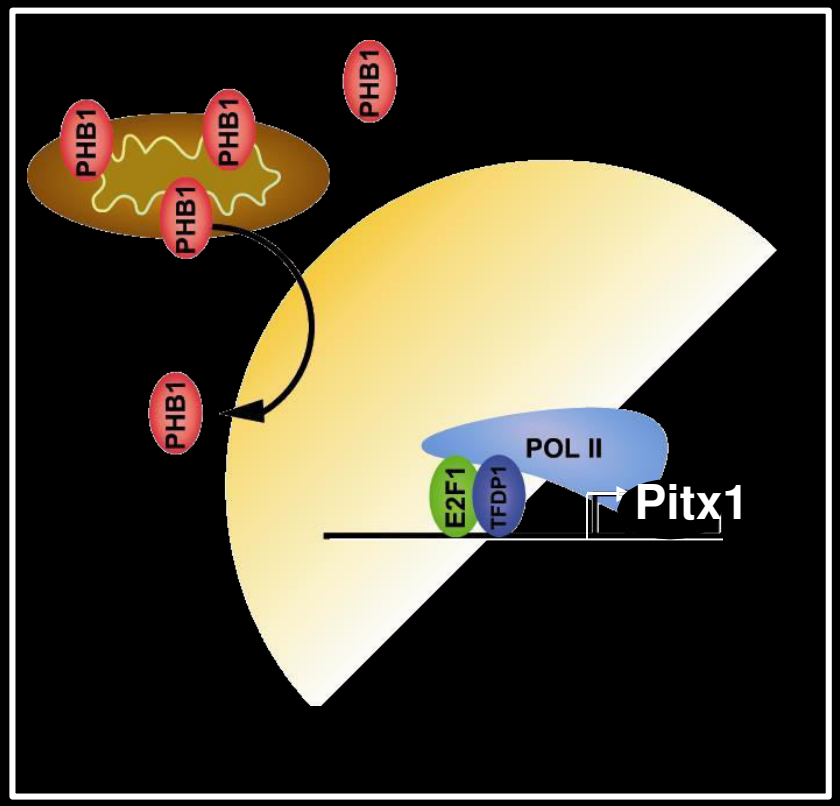


Age	79	61	74	86	76	79	16
Gender	F	F	M	F	M	M	F
K/L score	3	2	3	4	4	N/A	N/A

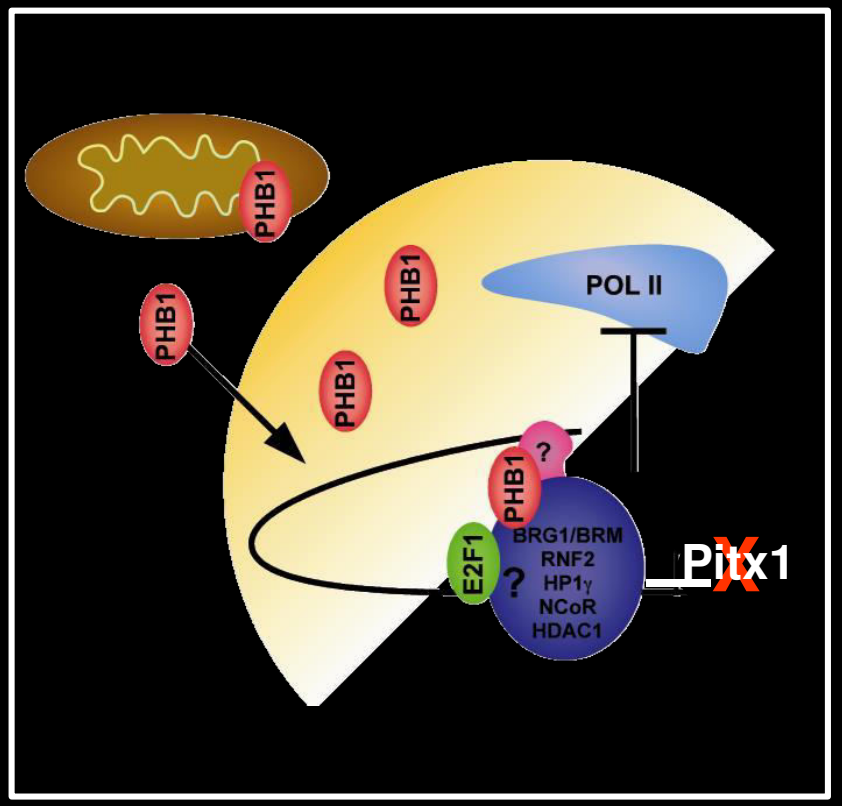
Nuclear accumulation of PHB1 in articular chondrocytes is associated with OA severity but not with RA.

PROHIBITIN

A New OA Biomarker & Target



NORMAL CHONDROCYTES



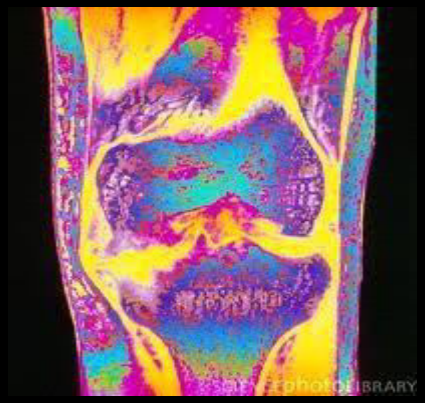
OA CHONDROCYTES

Picard et al., 2007, Clinical Orthopaedic & Related Research, 462: 59-62

COMPETITIVE

ADVANTAGES (1)







X-Ray

MRI
Ultrasounds
Bone Scintigraphy

BIOMARKERS

MOLECULAR

PRERADIOGRAPHIC

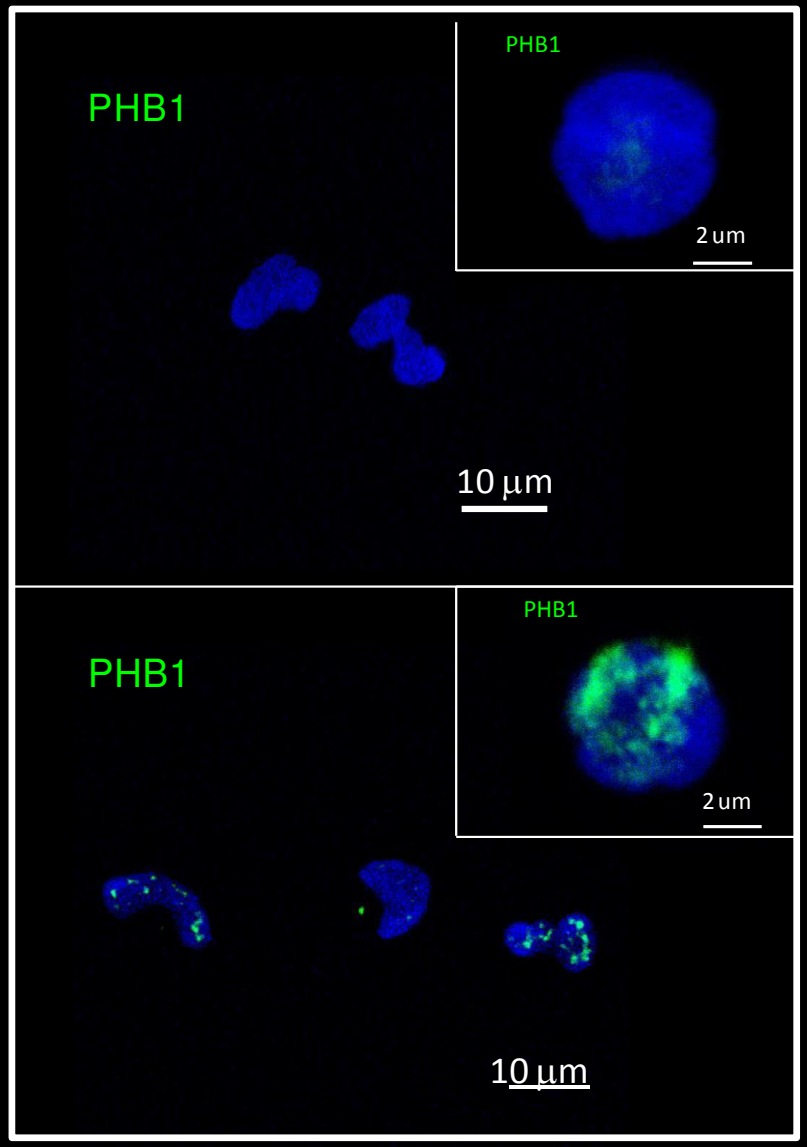
RADIOGRAPHIC

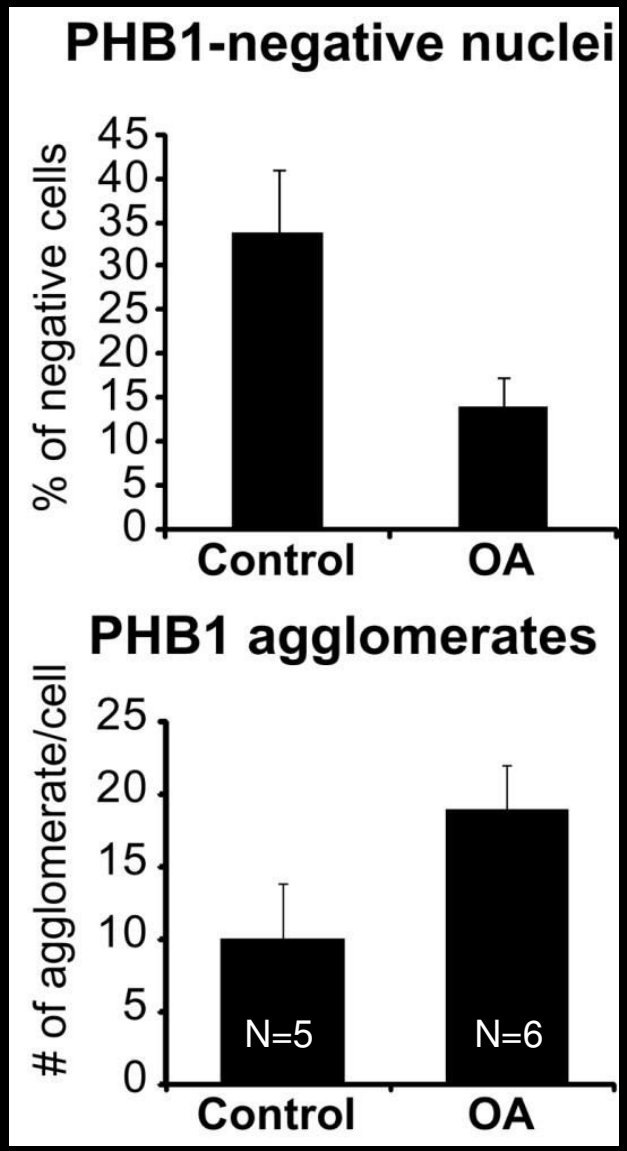
irreversible lesions / late stage

Kraus VB, et al., Application of biomarkers in the development of drugs intended for the treatment of osteoarthritis. Osteoarthritis and Cartilage (2011)

CLINICAL DATA

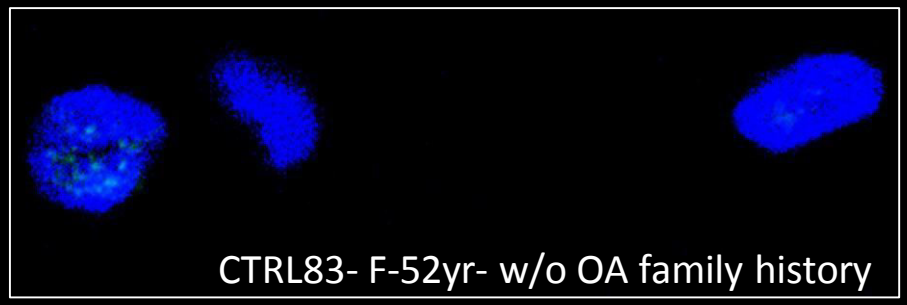
OA Blood Test Validation (1)



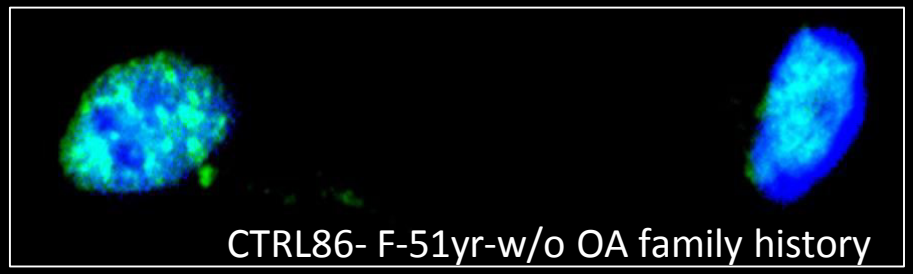


CLINICAL DATA

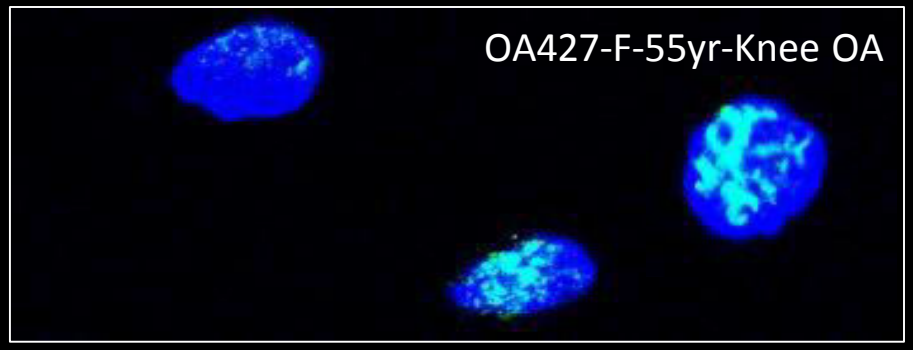
OA Blood Test Validation (2)



44% of cells negative for PHB1 signal, among positive cells-avg of 5.6 nuclear aggregates/cell



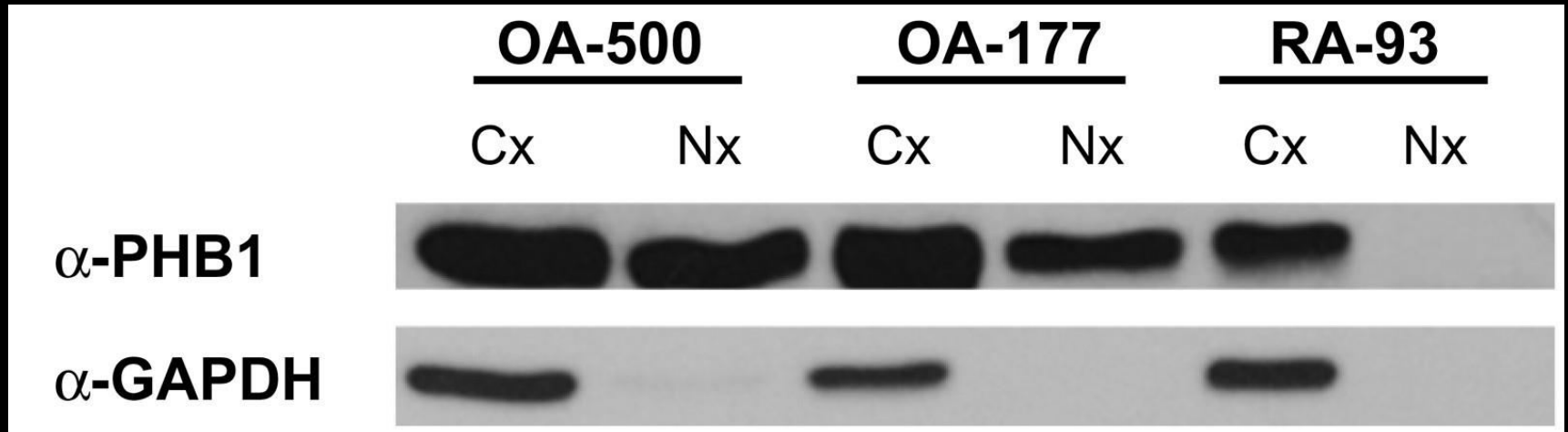
28% of cells negative for PHB1 signal, among positive cells-avg of 7.1 nuclear aggregates/cell



9.5% of cells negative for PHB1 signal, among positive cell-avg of 10.8 nuclear aggregates/cell

CLINICAL DATA

OA Blood Test Validation (3)

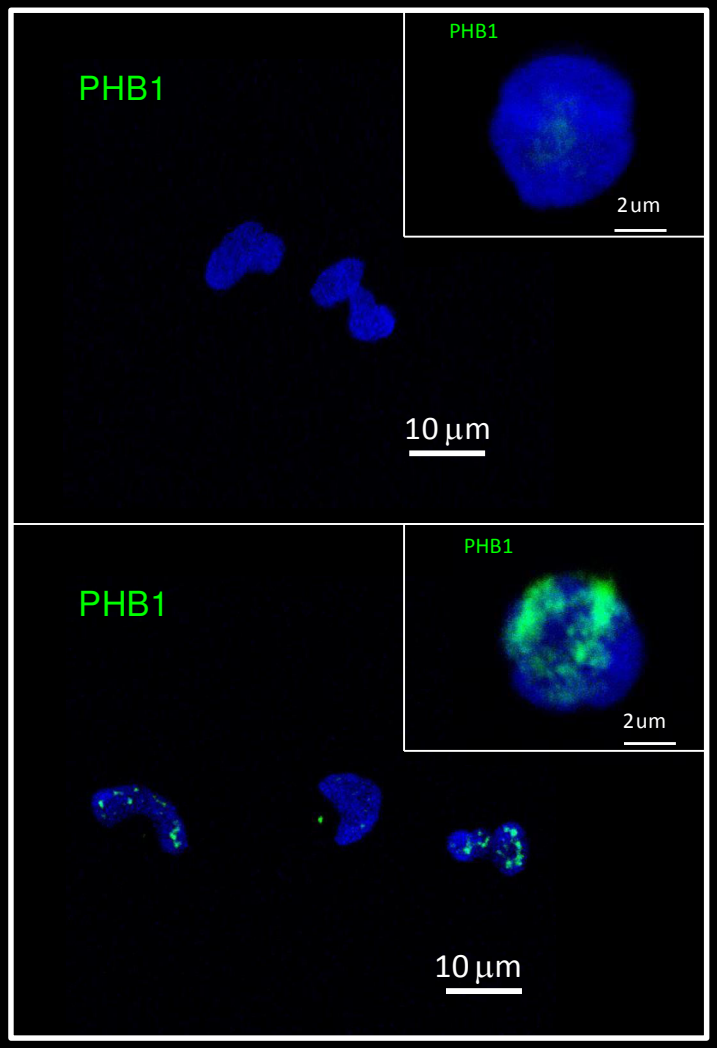


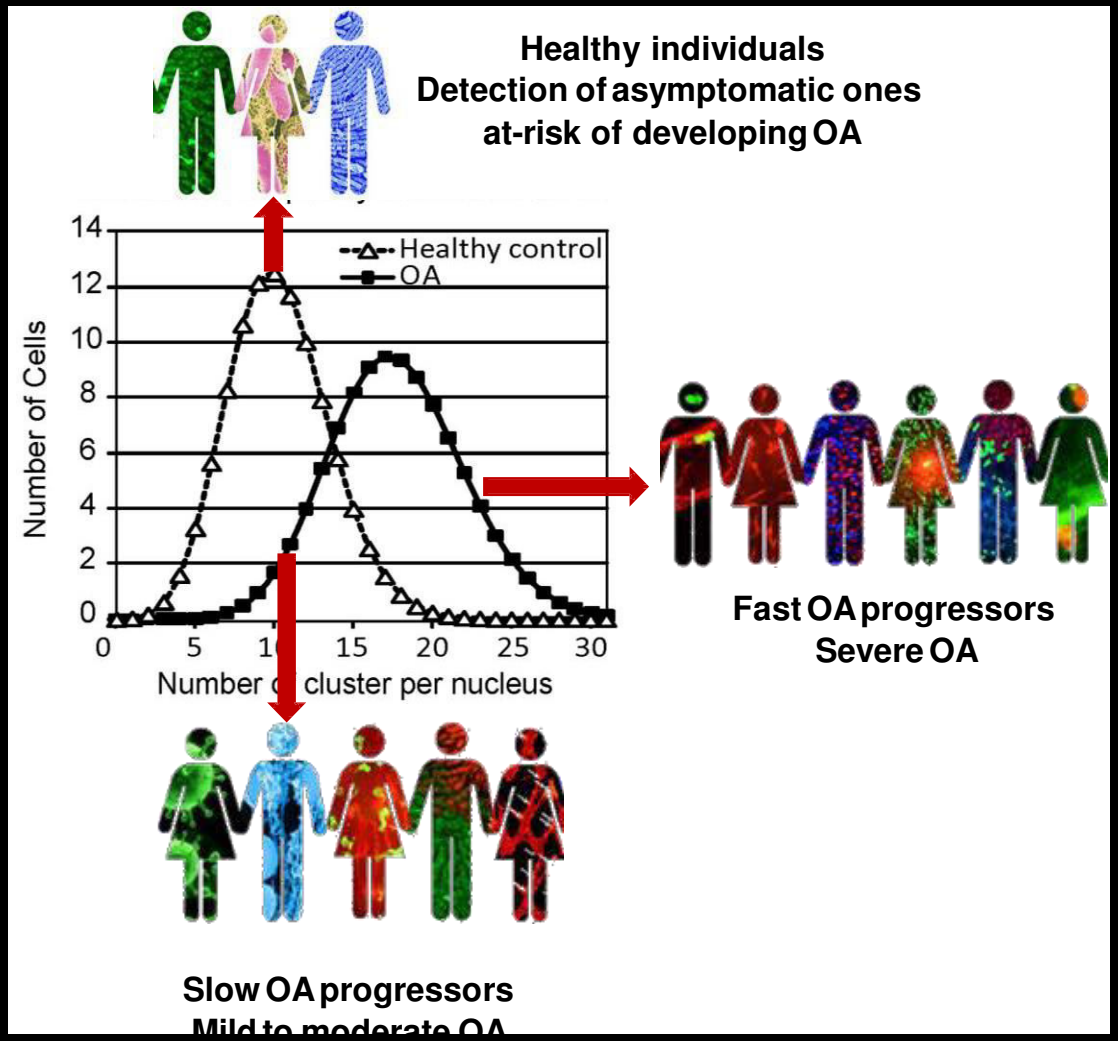
AGE	68	78	75
Gender	F	F	F
Severity	Advanced	Surgery	RA

Nuclear accumulation of PHB1 in PBMCs is associated with OA but not with RA or aging. Western blot showing a strong nuclear accumulation of PHB1 in two OA patients, while in a RA individual of 75-years nuclear PHB1 was not detected in blood cells. Cx = cytoplasmic fraction; Nx= nuclear fraction

CLINICAL DATA

OA Blood Test Validation (4)

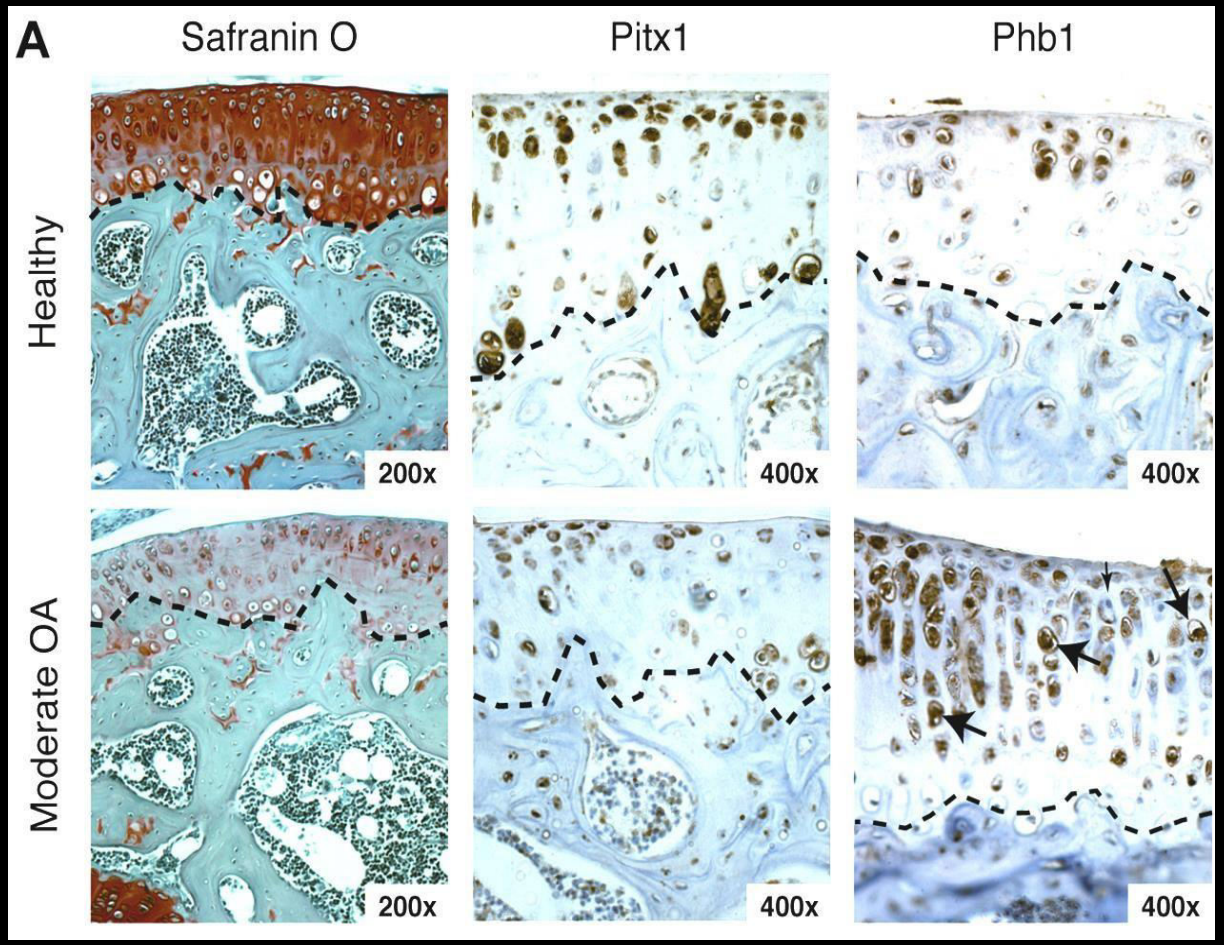


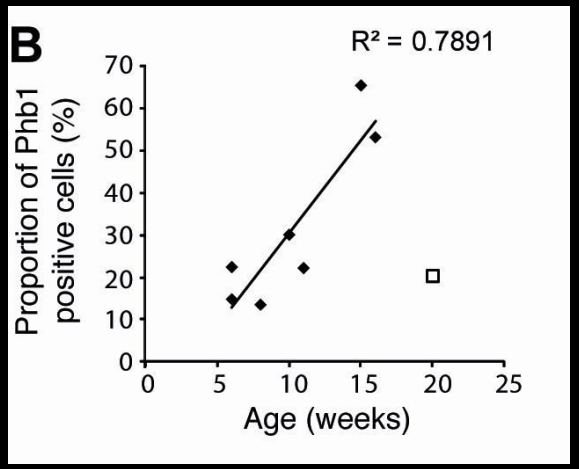


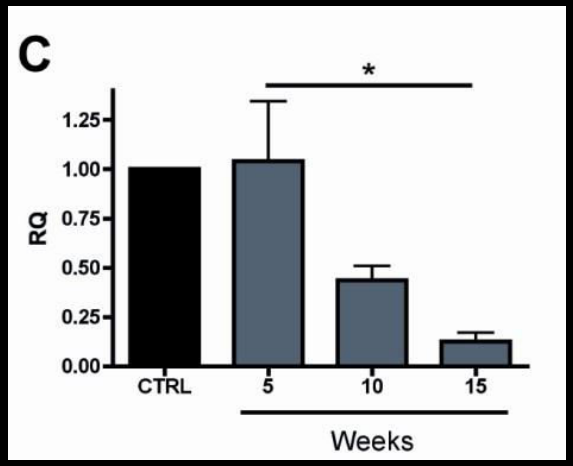
OA ANIMAL MODEL

Validation of Proof of Concept

Picard, Pellicelli *et al.* 2013, Arthritis Rheum. 65(4): 993-1003







Pixt1 expression is decreased as nuclear Phb1 levels increase and proteoglycans content diminishes in OA mouse model

OA ANIMAL MODEL

Preclinical Validation of HSJ2013



+ HSJ2013



untreated



STR/ort mice

Summary

1. Breakthrough solution for early OA detection before the first symptoms;
2. The technological platforms (IFA) required for detection of PHB1 are among the most validated ones and do not represent technical challenges;
3. Global market of 500 million potential OA diagnosed patients but not as competitive as other IVD fields such as cancer and infectious diseases;
4. PHB1 is not only a specific OA biomarker but also a druggable target.

Acknowledgements



Cyhthia Picard



Dr. Jean-Francois Lavoie



Dr. Patrick Lavigne



Martin Pellicelli



Saadallah Bouhanik



Lauriane Bernard

Team Biomarkers welcomes you all to the next chapter – 7th International Conference on Biomarkers & Clinical Research scheduled for Nov 28-30, 2016 in Baltimore, USA

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