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

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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.
What is Osteoarthritis?

- Pain
- Cartilage degeneration
- Cartilage regeneration

...worsens with further progression
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
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**
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 -
PITX1 is essential for bone and cartilage development

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

A

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960 bp

233 bp
Nuclear PHB1 inhibits Pltx1 expression

PROHIBITIN

A molecule for all seasons?
Nuclear PHB1 is increased in OA

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

### DISCOVERY
Nuclear PHB1 is increased in OA

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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
CLINICAL DATA

OA Blood Test Validation (1)

PHB1-negative nuclei

PHB1 agglomerates

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<tr>
<td># of agglomerates/cell</td>
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N=5  N=6
44% of cells negative for PHB1 signal, among positive cells-avg of 5.6 nuclear aggregates/cell

CTRL83- F-52yr- w/o OA family history

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

CTRL86- F-51yr- w/o OA family history

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

OA427-F-55yr-Knee OA
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)

Healthy individuals
Detection of asymptomatic ones at-risk of developing OA

Fast OA progressors
Severe OA

Slow OA progressors
Mild to moderate OA
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

Cythia Picard
Martin Pellicelli
Dr. Jean-Francois Lavoie
Dr. Patrick Lavigne
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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