Comprendre le monde, construire l'avenir

5ème colloque annuel de l'ITMO PMN
Vers de nouveaux concepts

Hypertension Artérielle Pulmonaire (HTAP) :

Vers une nouvelle voie pour lutter contre le remodelage vasculaire pulmonaire

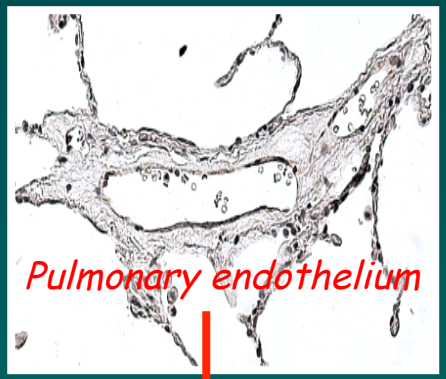
Christophe GUIGNABERT
CR1 INSERM

Research group: "Cellular and molecular bases of pulmonary endothelial dysfunction in PAH"

INSERM UMR_S 999 – Univ. Paris Sud – Université Paris-Saclay
" Pulmonary Hypertension: Physiopathology and Novel Therapies "
Directeur : Pr Marc Humbert

La Circulation Pulmonaire : spécificités structurelles et fonctionnelles

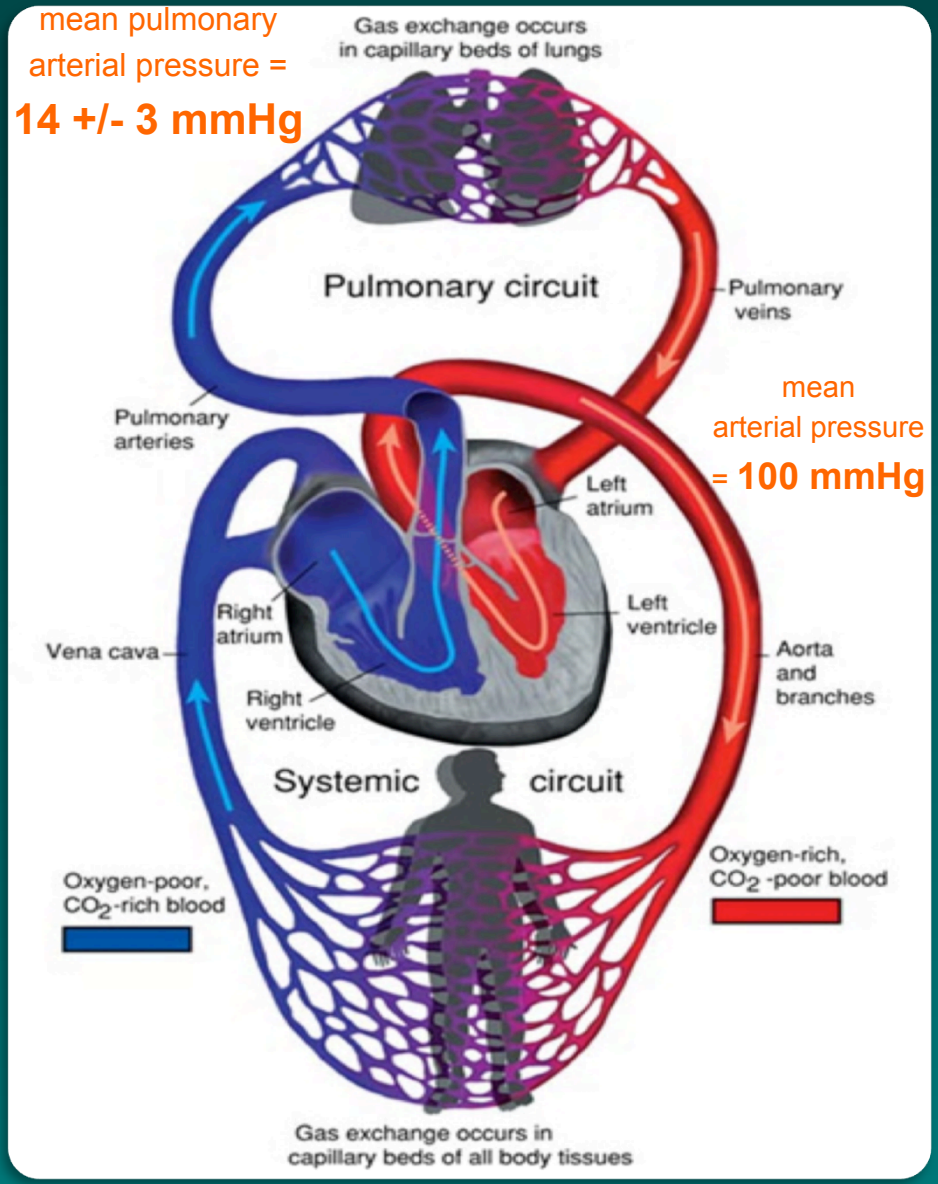
① The pulmonary circulation is a high flow, low-resistance, low-pressure system



- ☑ a high compliance of pulmonary pre-capillary arterioles characterized by a thin media
- ☑ a high capacity to recruit vessels available

- ✓ Vasoconstrictors (i.e. ET-1, 5-HT, AngII)
- ✓ Vasodilators (i.e. NO, PGI2)
- ✓ Activators and inhibitors of SMC growth and migration
- ✓ Pro- and anti-thrombotic mediators
- ✓ Pro- and anti-inflammatory signals

Remodelage vasculaire pumonaire



Classification Clinique de l'Hypertension Pulmonaire :

5TH WORLD SYMPOSIUM ON PULMONARY HYPERTENSION

Pulmonary hypertension (PH) is defined by a mean pulmonary artery pressure **≥ 25 mmHg** at rest, measured during right heart catheterization.

- Consequences: Right ventricular hypertrophy
  Right heart failure
  Dyspnea, disability, syncope, death

1. Pulmonary arterial hypertension

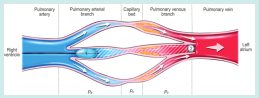
1.1 Idiopathic
1.2 Heritable
  1.2.1 BMPR2 mutation
  1.2.2 Other mutations
1.3 Drugs and toxins induced

PAH
Pulmonary artery wedge pressure (PAWP) **≤ 15 mmHg**

1.4 Associated with:
  1.4.1 Connective tissue disease
  1.4.2 Human immunodeficiency virus (HIV) infection
  1.4.3 Portal hypertension
  1.4.4 Congenital heart disease (Table 6)
  1.4.5 Schistosomiasis

1'. Pulmonary veno-occlusive disease and/or pulmonary capillary haemangiomatosis

PVOD or/and PCH



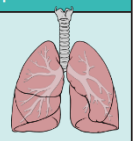
1'.1 Idiopathic
1'.2 Heritable
  1'.2.1 EIF2AK4 mutation
  1'.2.2 Other mutations
1'.3 Drugs, toxins and radiation induced
1'.4 Associated with:
  1'.4.1 Connective tissue disease
  1'.4.2 HIV infection

1''. Persistent pulmonary hypertension of the newborn

2. Pulmonary hypertension due to left heart disease

2.1 Left ventricular systolic dysfunction
2.2 Left ventricular diastolic dysfunction
2.3 Valvular disease
2.4 Congenital/acquired left heart inflow/outflow tract obstruction and congenital cardiomyopathies
2.5 Congenital/acquired pulmonary veins stenosis

3. Pulmonary hypertension due to lung diseases and/or hypoxia



3.1 Chronic obstructive pulmonary disease
3.2 Interstitial lung disease
3.3 Other pulmonary diseases with mixed restrictive and obstructive pattern
3.4 Sleep-disordered breathing
3.5 Alveolar hypoventilation disorders
3.6 Chronic exposure to high altitude
3.7 Developmental lung diseases (Web Table III)

4. Chronic thromboembolic pulmonary hypertension and other pulmonary artery obstructions

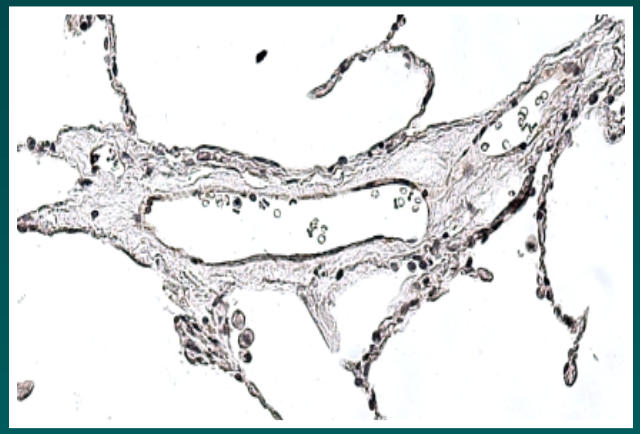
4.1 Chronic thromboembolic pulmonary hypertension
4.2 Other pulmonary artery obstructions
  4.2.1 Angiosarcoma
  4.2.2 Other intravascular tumors
  4.2.3 Arteritis
  4.2.4 Congenital pulmonary arteries stenoses
  4.2.5 Parasites (hydatidosis)

5. Pulmonary hypertension with unclear and/or multifactorial mechanisms

5.1 Haematological disorders: chronic haemolytic anaemia, myeloproliferative disorders, splenectomy
5.2 Systemic disorders: sarcoidosis, pulmonary histiocytosis, lymphangioleiomyomatosis, neurofibromatosis
5.3 Metabolic disorders: glycogen storage disease, Gaucher disease, thyroid disorders
5.4 Others: pulmonary tumoral thrombotic microangiopathy, fibrosing mediastinitis, chronic renal failure (with/without dialysis), segmental pulmonary hypertension

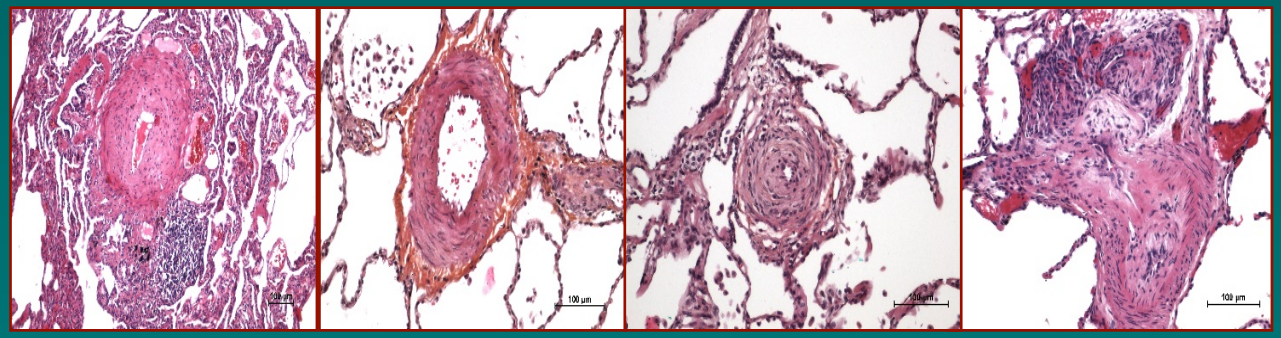
Galiè N *et al* Eur Respir J 2015.
Simonneau G *et al* J Am Coll Cardiol. 2013.

Remodelage vasculaire pulmonaire associé à l'Hypertension Artérielle Pulmonaire (HTAP)



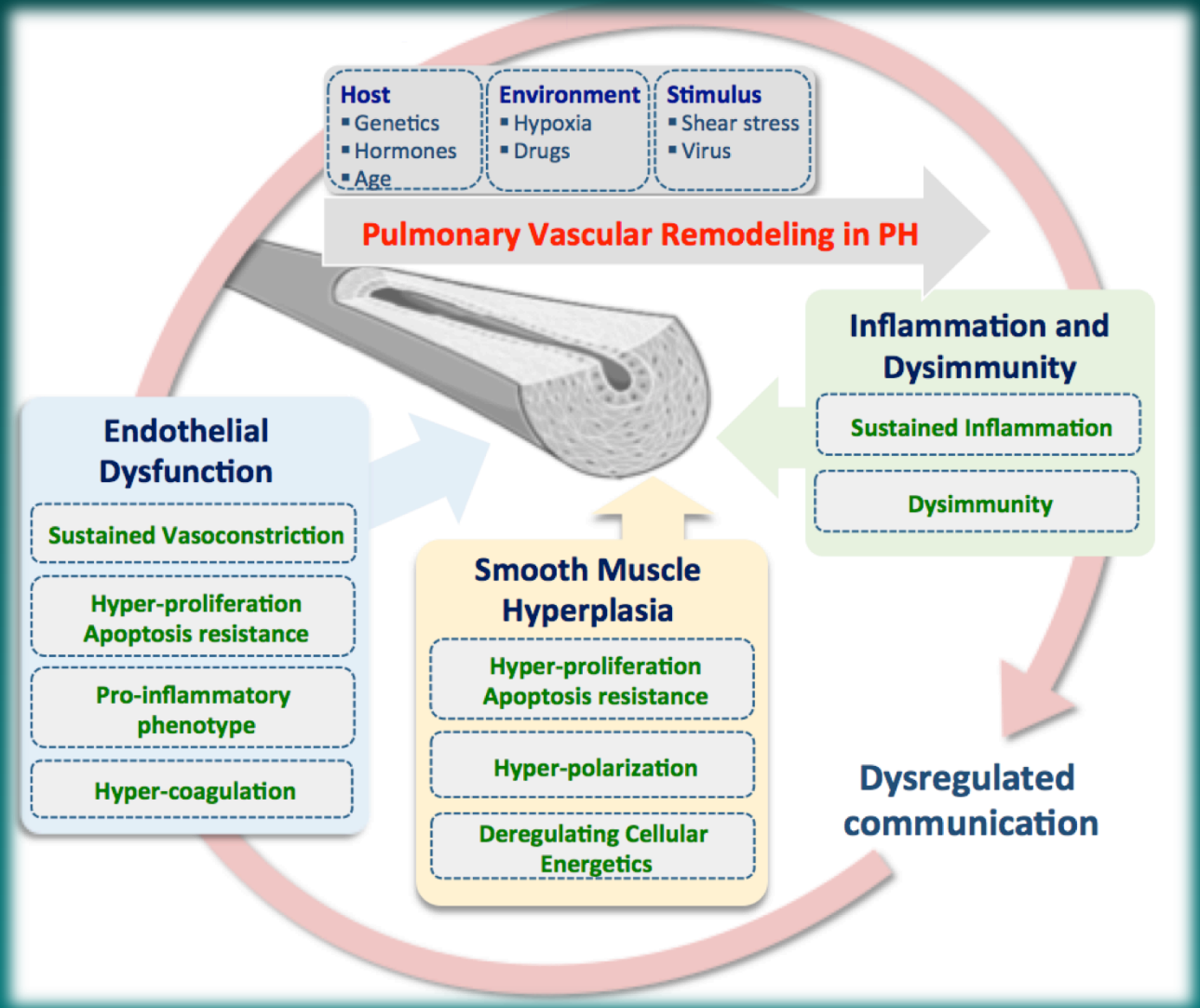
Lymphoid follicles in remodeled arteries	Hypertrophy/ hyperplasia of the media	Concentric intimal fibrosis	Plexiform lesions

PAH Pulmonary arteries



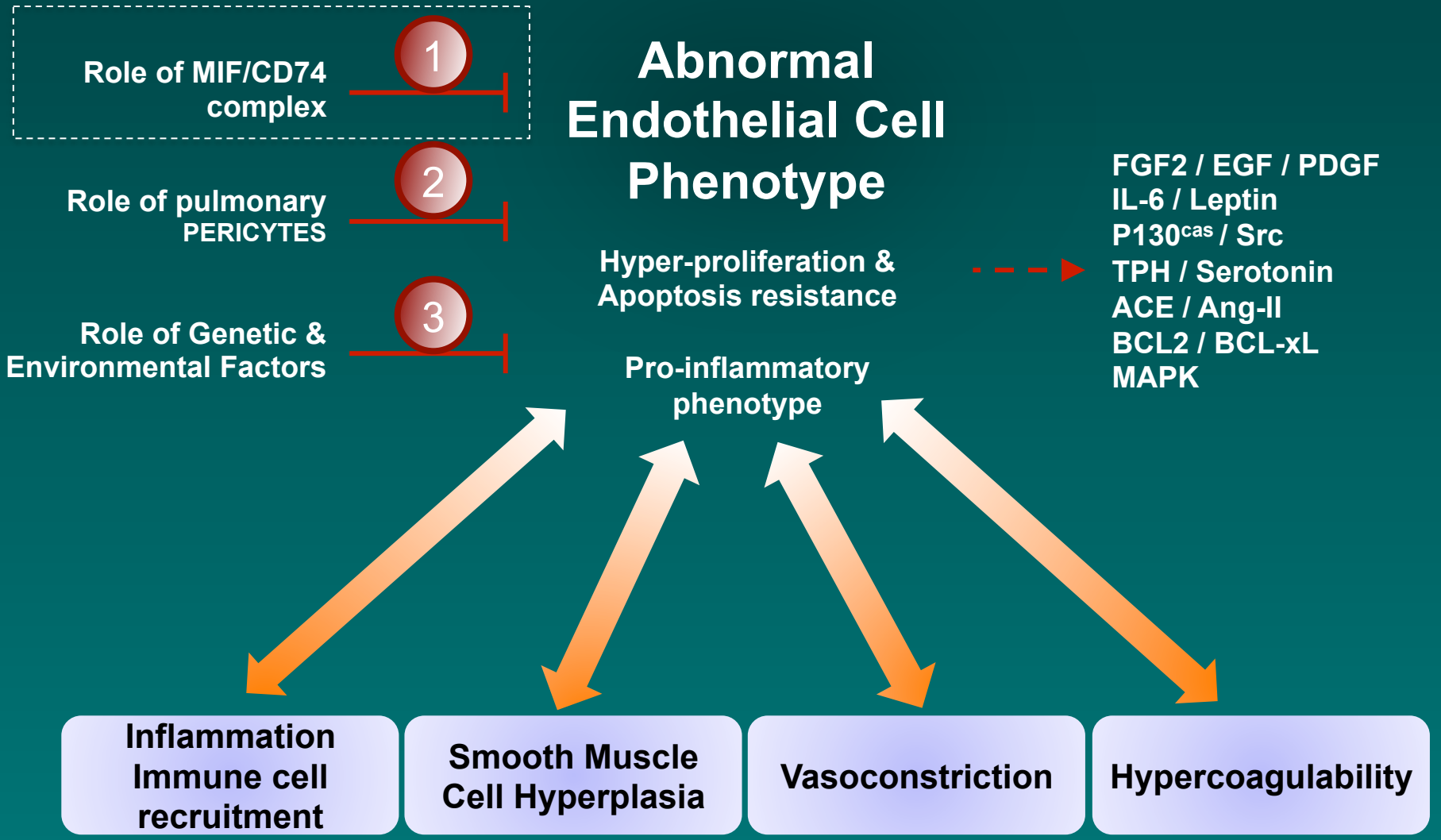
Guignabert C. and Dorfmüller P, Semin Respir Crit Care Med, 2013.

Composantes du remodelage vasculaire pulmonaire associé à l'Hypertension Artérielle Pulmonaire (HTAP)



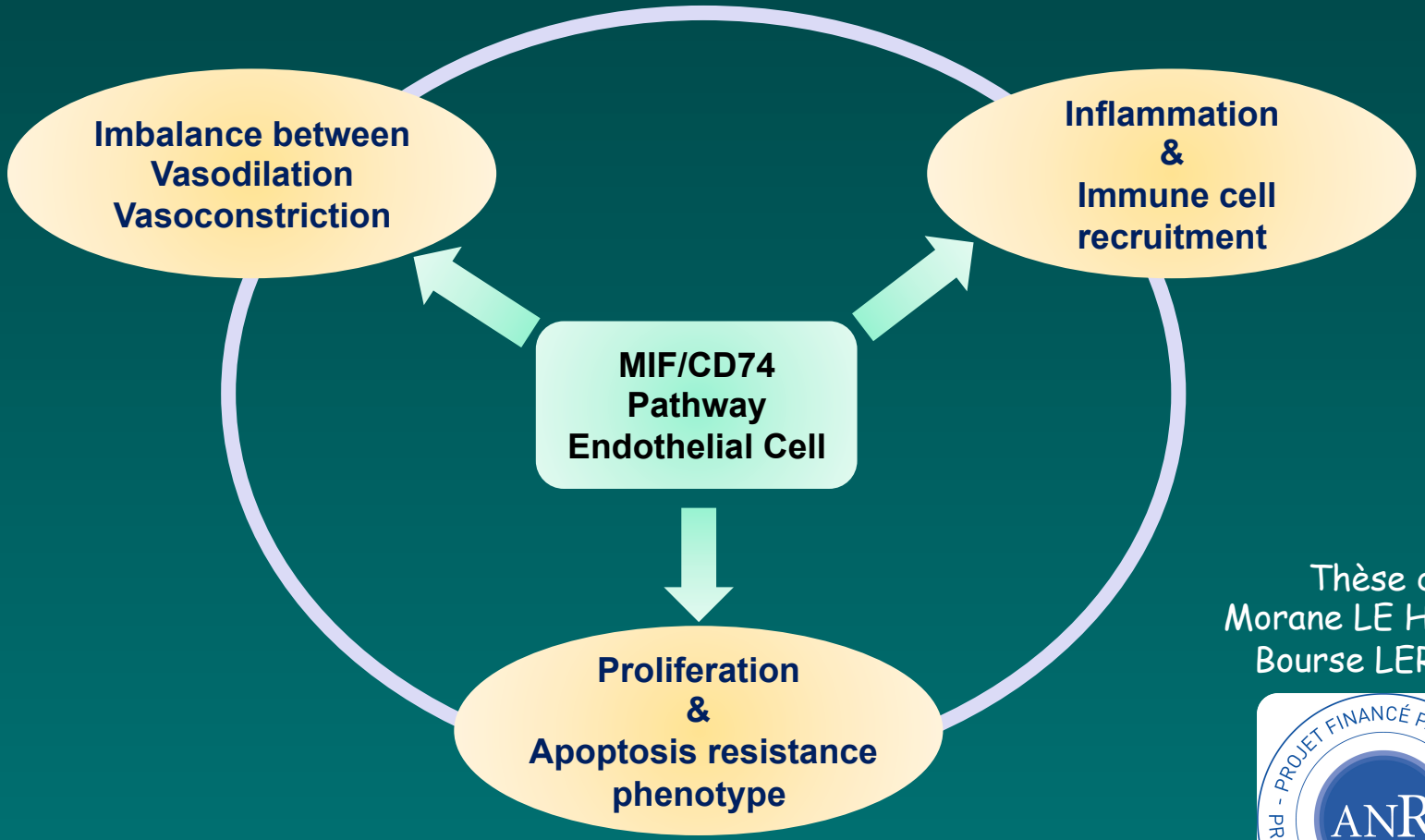
Guignabert C, Tu L, Girerd B, Ricard N, Huertas A, Montani D, Humbert M. Chest 2015.

Groupe "Bases cellulaires et moléculaires de la dysfonction endothéliale pulmonaire HTAP"



ANR JCJC "EPINE" : Rôle de la voie MIF/CD74 dans l'HTAP

à l'interface entre Inflammation et Dysfonction endothéliale



Thèse de
Morane LE HIRESS
Bourse LERMIT

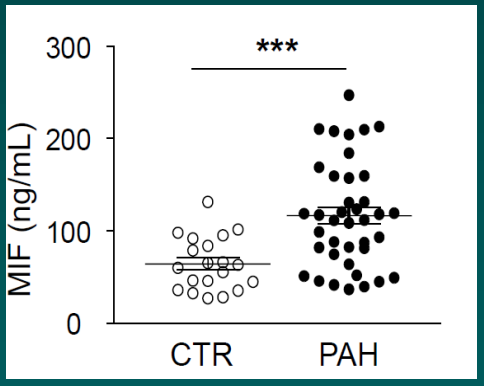
PROJET FINANCÉ PAR L'ANR - PROJECT FUNDED BY THE ANR
ANR
ANR-12-JSV1-0004-01

1

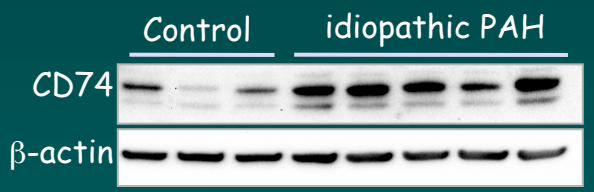
ANR JCJC "EPINE" : Rôle de la voie MIF/CD74 dans l'HTAP

à l'interface entre Inflammation et Dysfonction endothéliale

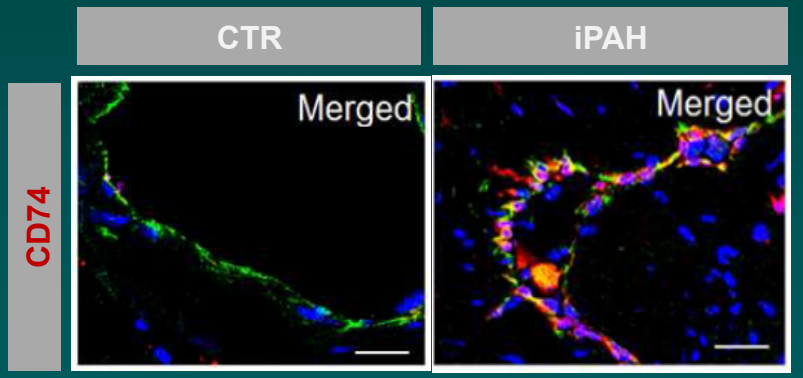
Serum MIF protein level:

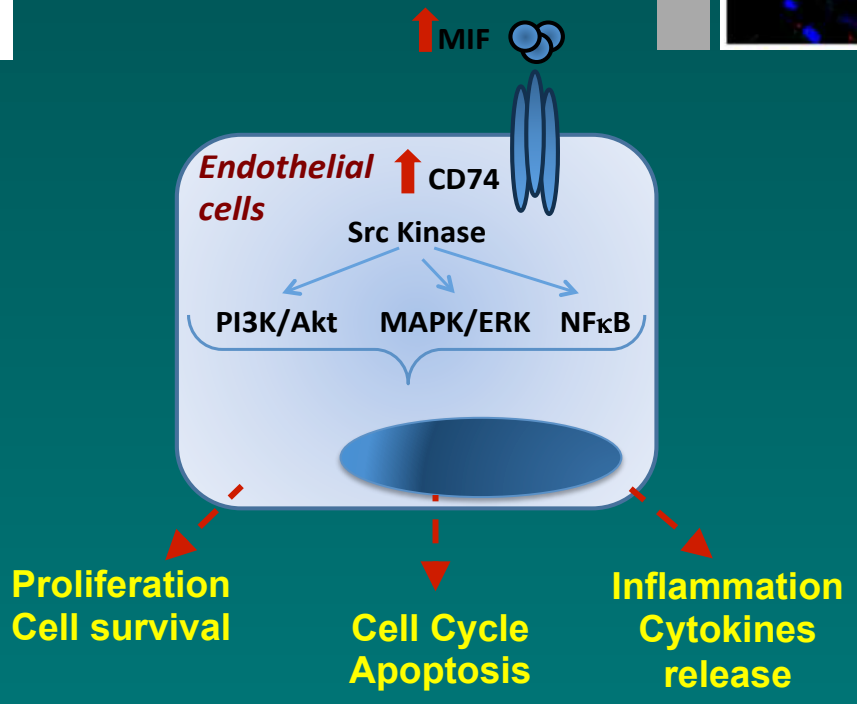


In vitro:



In situ:





Le Hiress M et al., Am J Respir Crit Care Med, 2015.

ANR JCJC "EPINE" : Rôle de la voie MIF/CD74 dans l'HTAP

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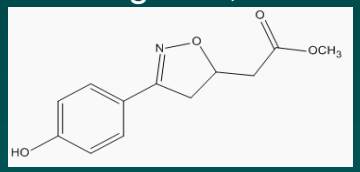
MIF-antagonist, ISO-1 (30 mg.kg^{-1}.day^{-1})



monocrotaline injection

daily i.p. administration

ISO-1 TREATMENT

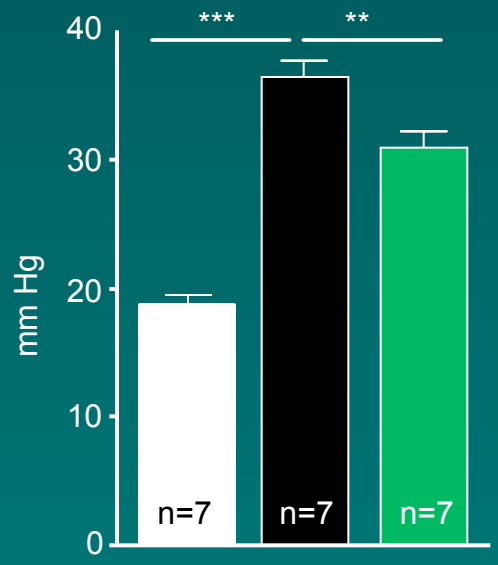
0 1 2 3 4 weeks

Vehicle

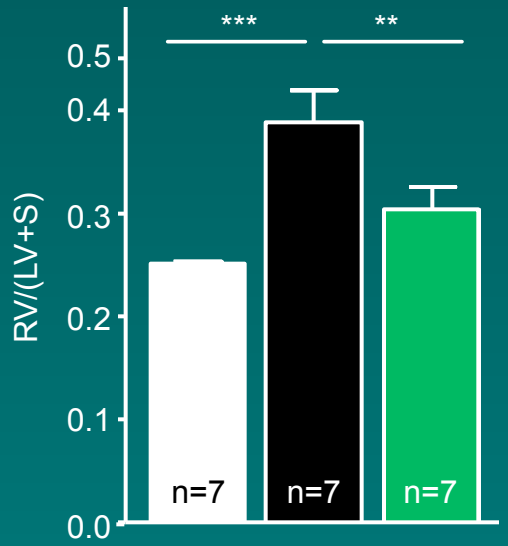
MCT

MCT + ISO-1

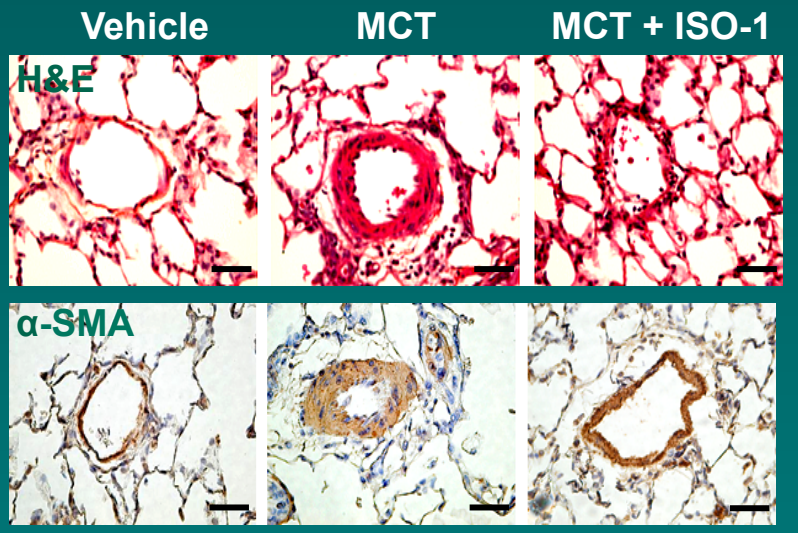
mPAP



RVH



Pulmonary Arterial Muscularization



Le Hiress M et al., Am J Respir Crit Care Med, 2015.

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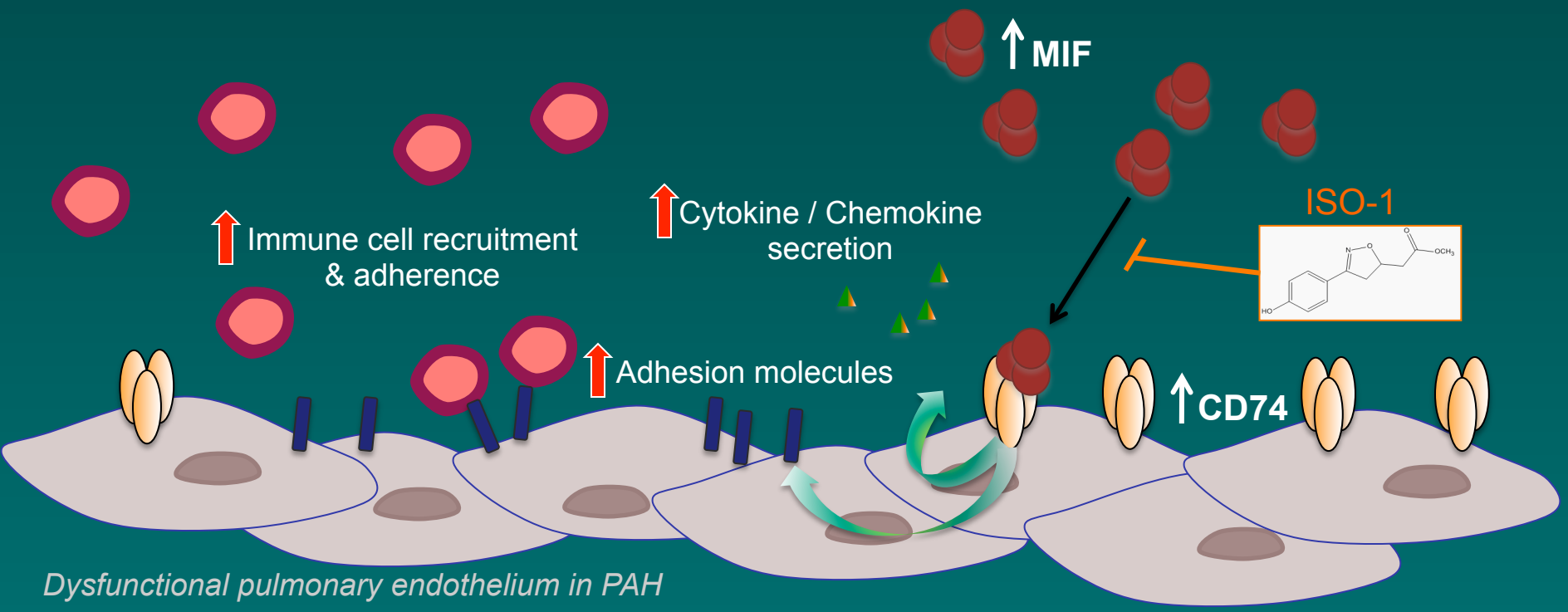
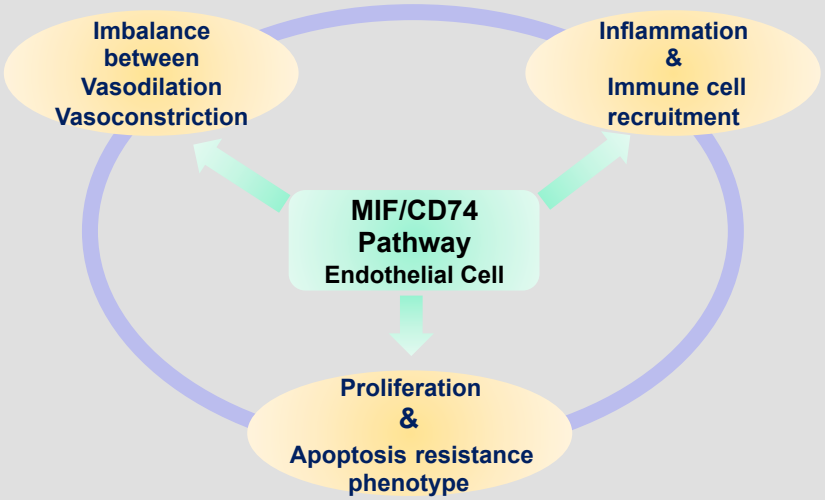
à l'interface entre Inflammation et Dysfonction endothéliale



Le Hiress M et al., Am J Respir Crit Care Med, 2015.

Vers le développement de nouveaux antagonistes de MIF

ANR "EPINE" : Endothelial-CD74 in PAH at the crossroad of Inflammation and Endothelial dysfunction



Inserm – Institut national de la santé et de la recherche médicale

Université Paris Sud

Projet financé par l'ANR – Project funded by the ANR

To evaluate new small molecule inhibitors of MIF and their ability to reduce the severity of experimental of PH:

LabEx ERMIT – Laboratoire d'Excellence en Recherche sur le Médicament et l'Innovation Thérapeutique

Mifcare

Dr. Gaël Jalce

CEO & Founder,

Paris, France

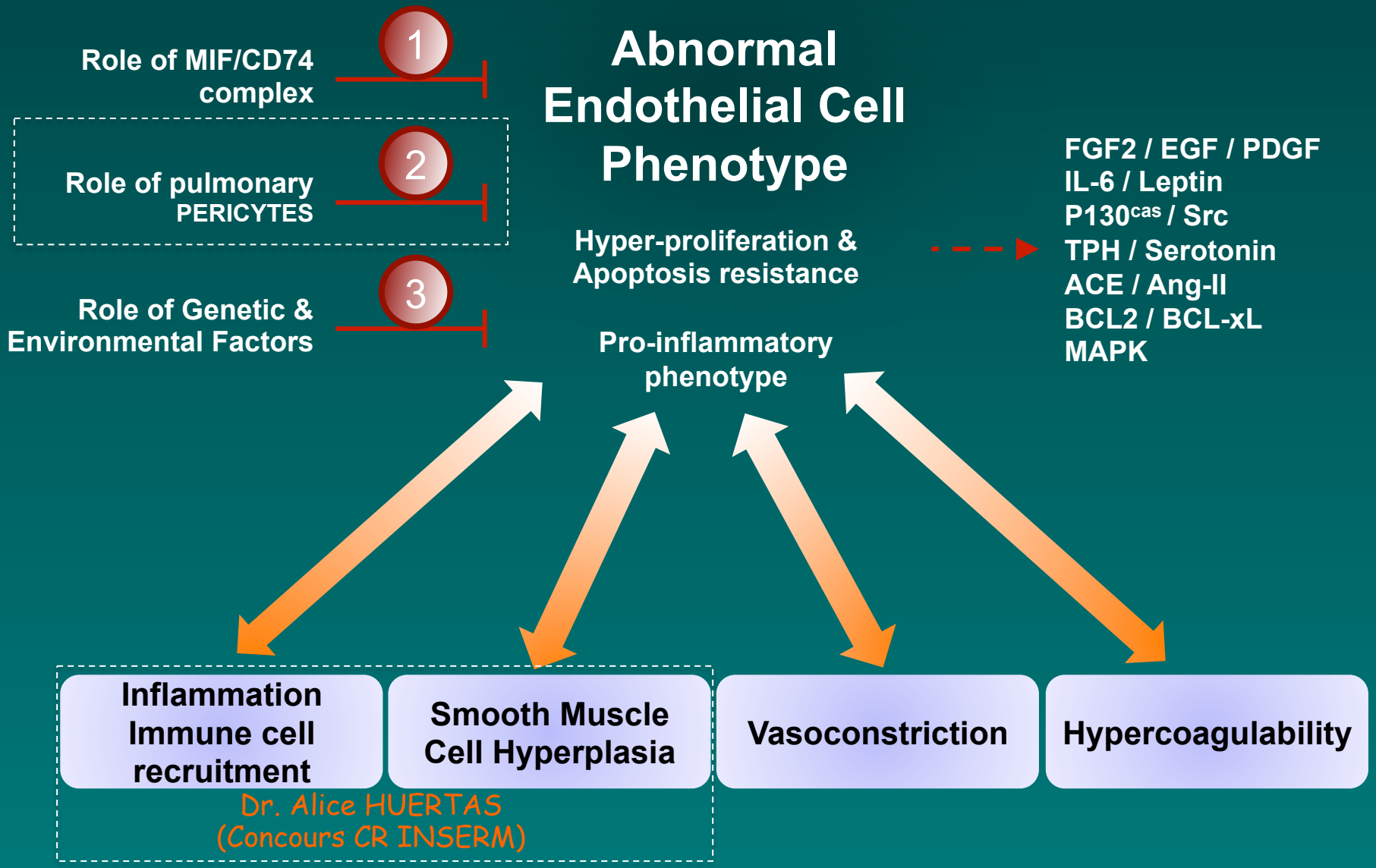
15e concours national d'aide à la création d'entreprises de technologies innovantes

Paris Biotech Santé

Le Hiress M et al., Am J Respir Crit Care Med, 2015.

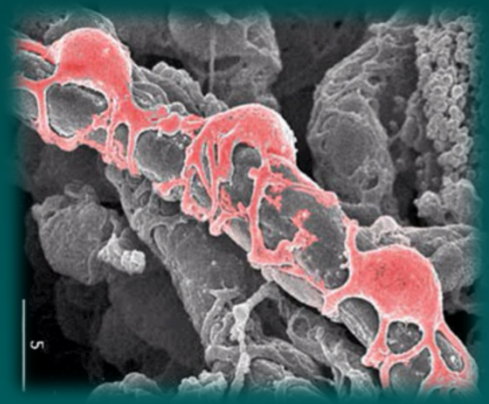
Patents: EP 2 944 310 A1 - WO 2015/173433 A1.

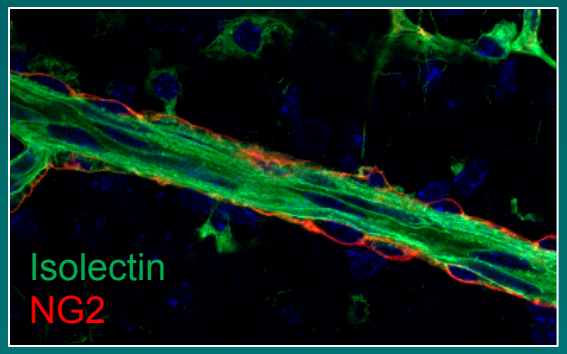
Groupe "Cellular and Molecular Bases of Pulmonary Endothelial Dysfunction in PAH"

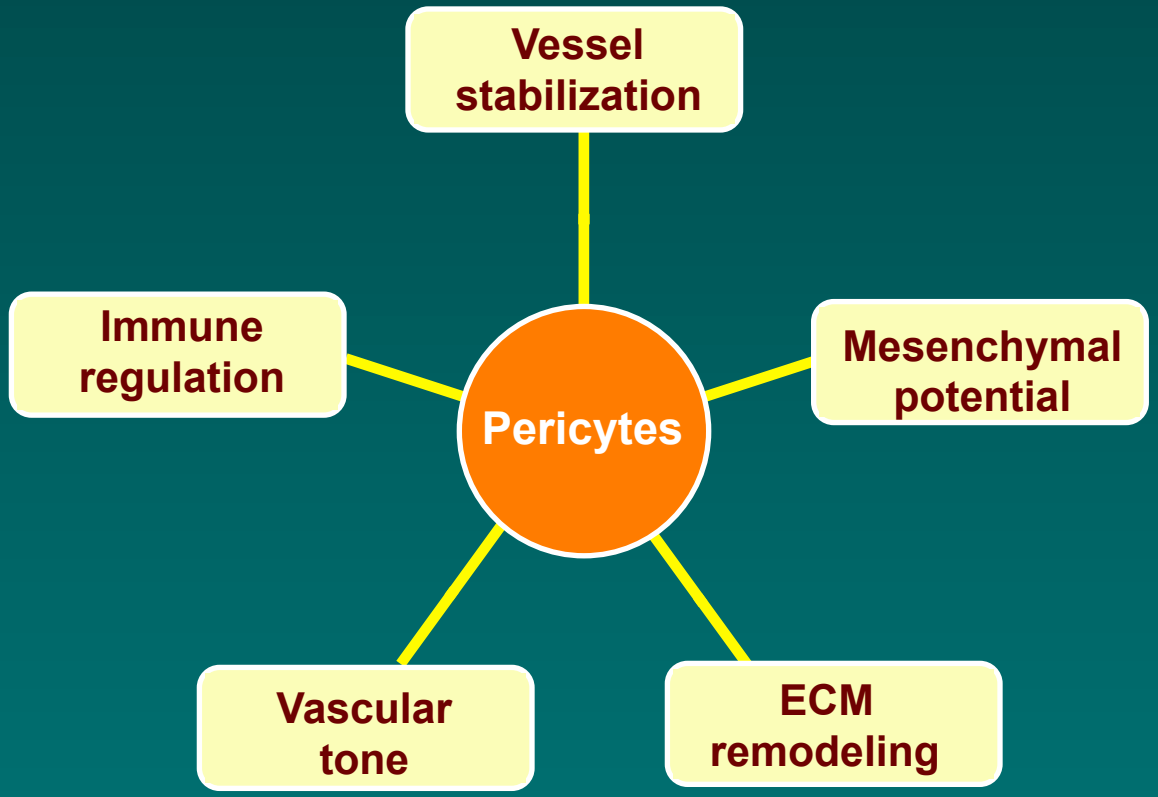


Dr. Alice HUERTAS
(Concours CR INSERM)

Rôle des péricytes pulmonaires dans l'Hypertension Artérielle Pulmonaire (HTAP)



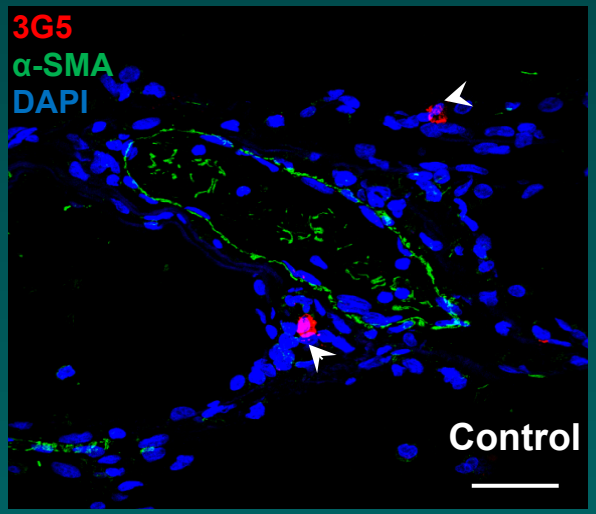


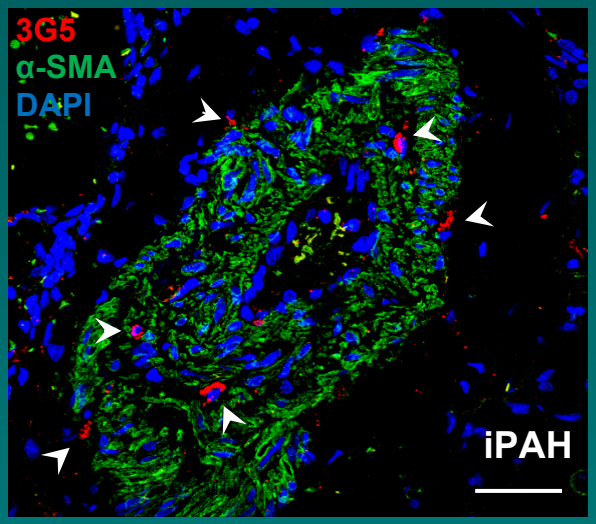


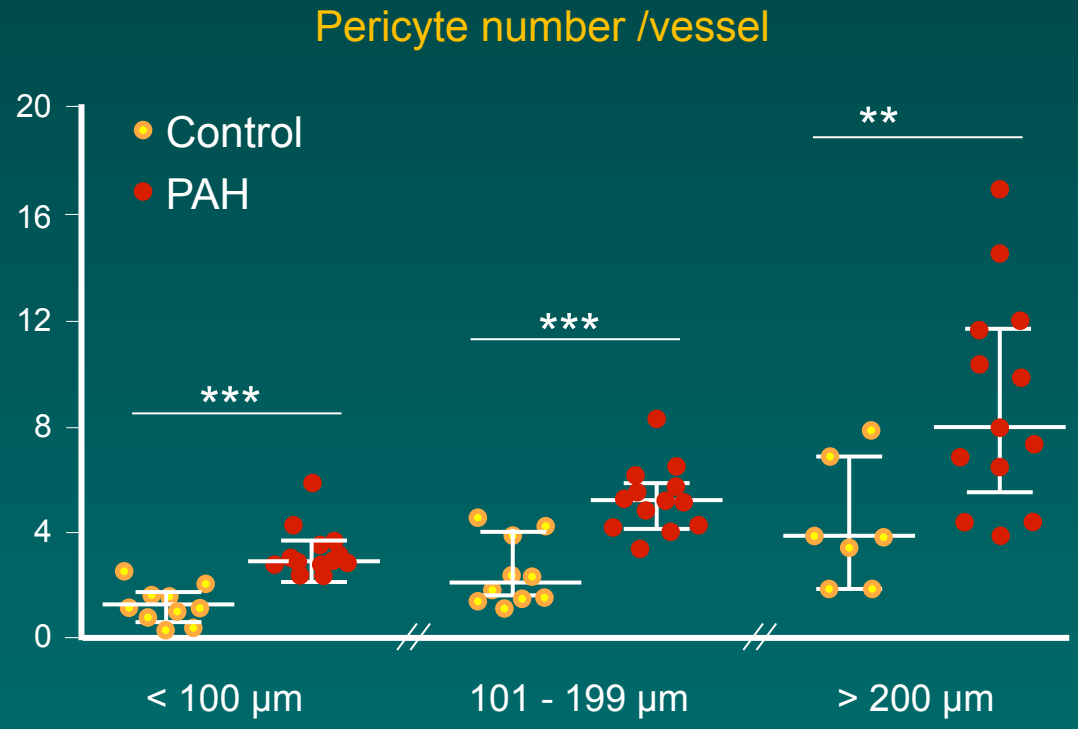
2

Rôle des péricytes pulmonaires dans l'Hypertension Artérielle Pulmonaire (HTAP)

Human lungs:



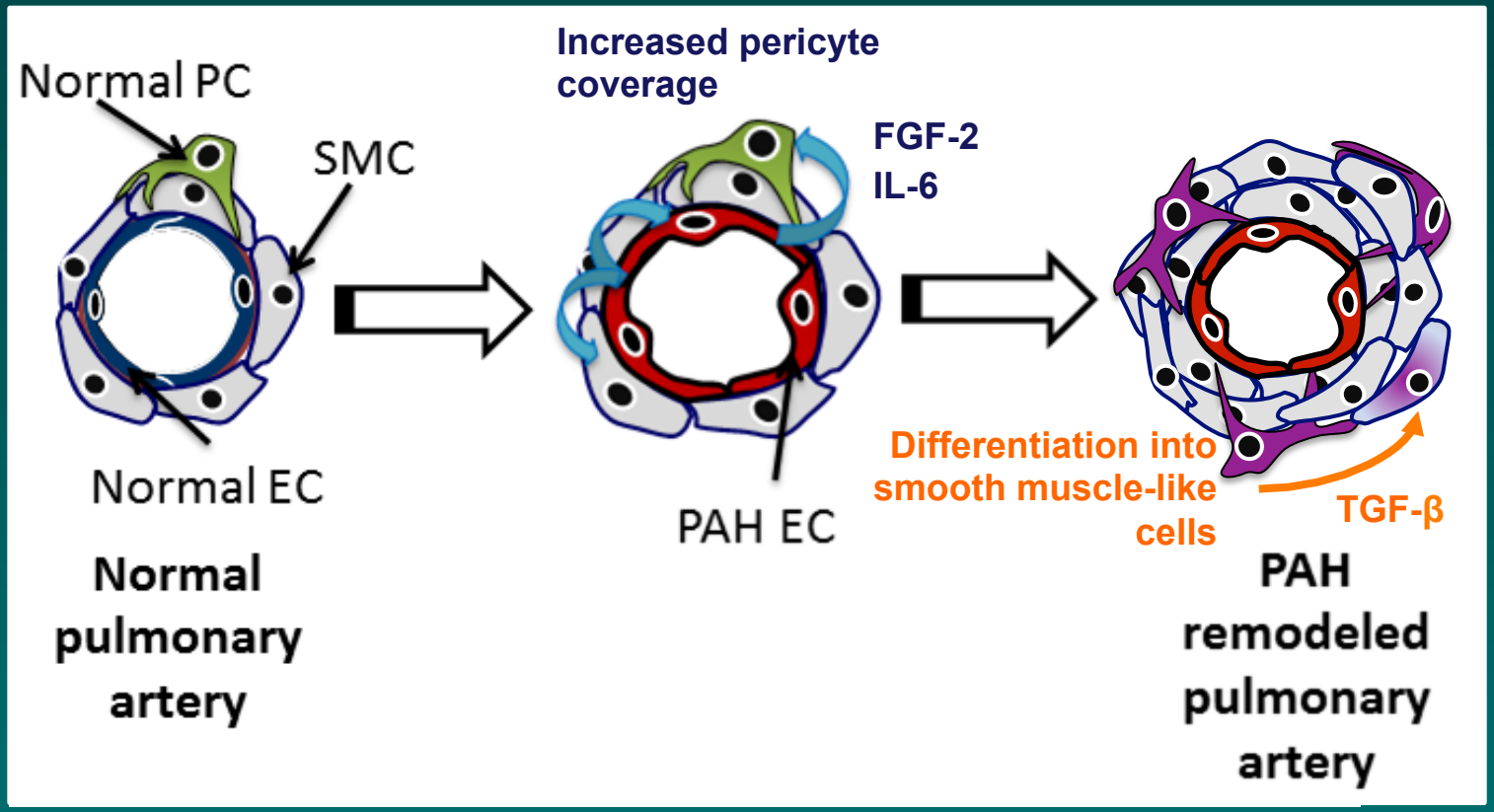




Pericyte number/vessel is increased by 2-fold in PAH lung specimens as compared to controls.

Ricard N *et al.* Circulation, 2014.

Rôle des péricytes pulmonaires dans l'Hypertension Artérielle Pulmonaire (HTAP)



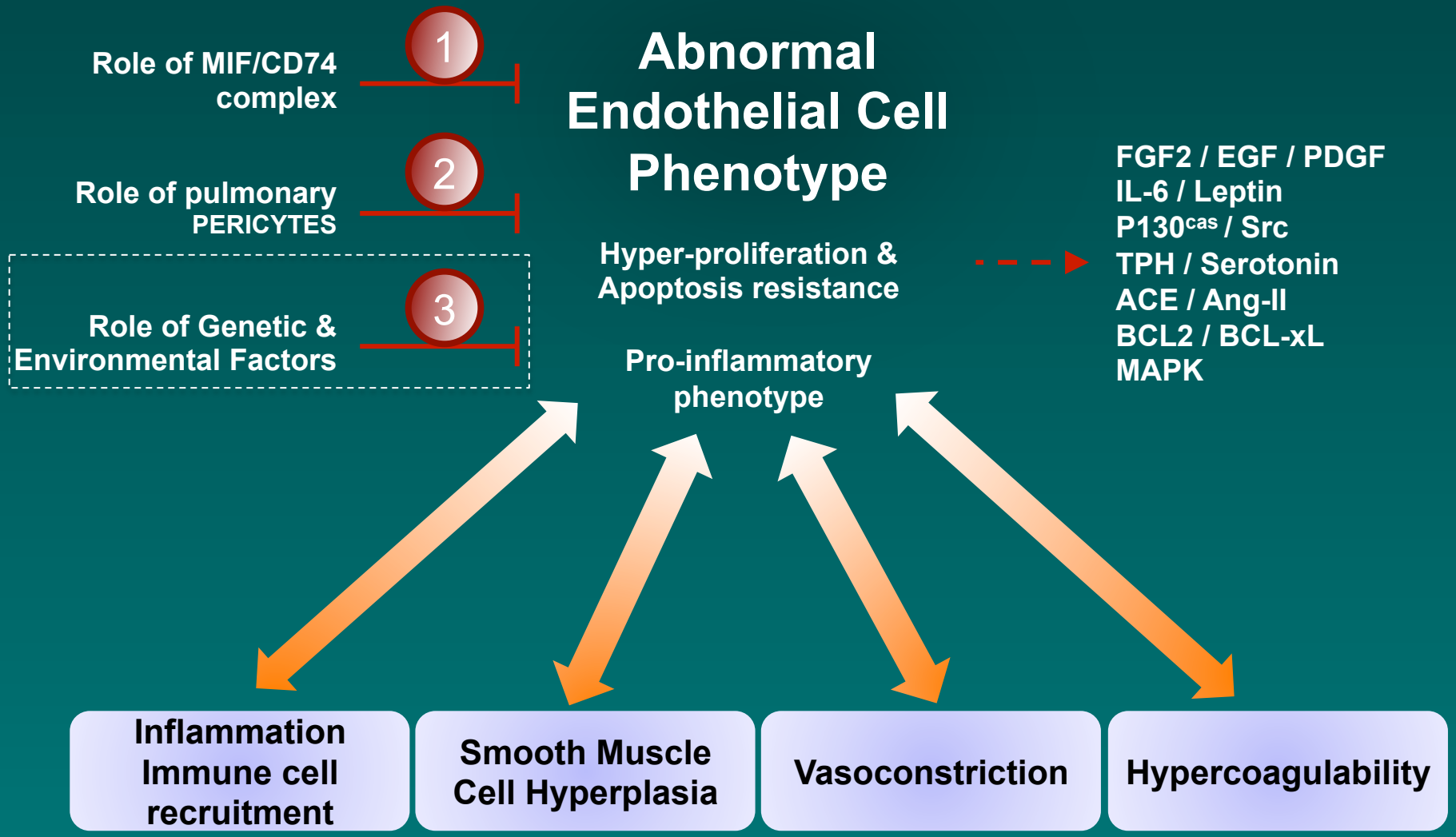
Equipe FRM 2015

FONDATION RECHERCHE MÉDICALE

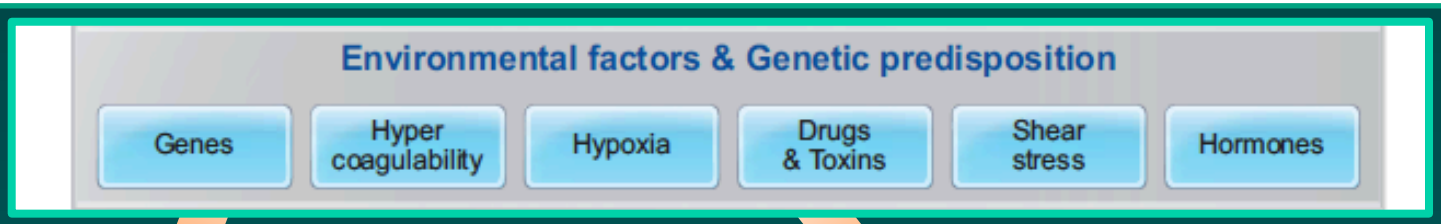
Thèse de Jennifer Bordenave (Bourse en Pneumologie - FRM)

Ricard N *et al.* Circulation, 2014.

Groupe "Bases cellulaires et moléculaires de la dysfonction endothéliale pulmonaire HTAP"



Rôle des Facteurs Génétiques et Environnementaux pour le remodelage vasculaire pulmonaire HTAP :

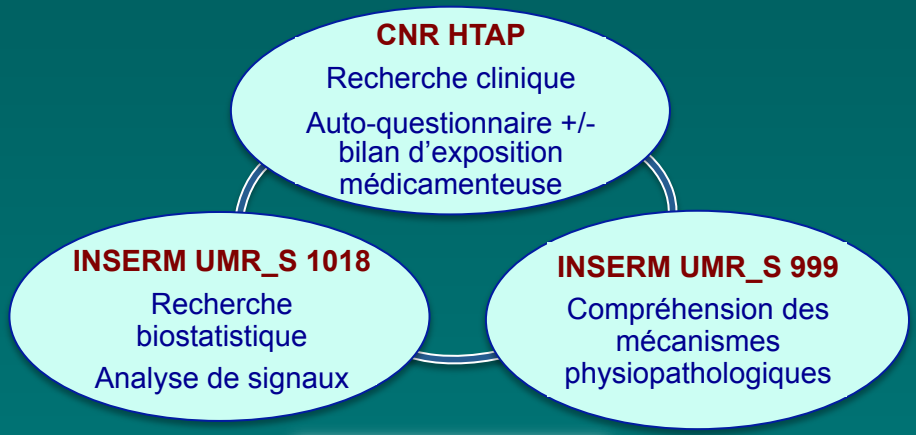


Thèse du
Dr. Maria-Rosa GHIGNA
Pathologiste

Bone Morphogenetic Protein Receptor type 2 (BMPR2) gene mutations affect the structure and function of the pulmonary arterial bed

Thèse du
Carole PHAN

« VIGIAPATH »



RECHERCHE EN SANTÉ RESPIRATOIRE
FONDS DE DOTATION

FÉDÉRATION ANTADIR

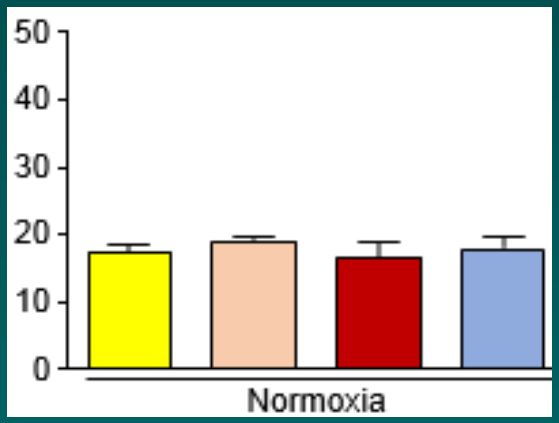
ansm
Agence nationale de sécurité du médicament et des produits de santé

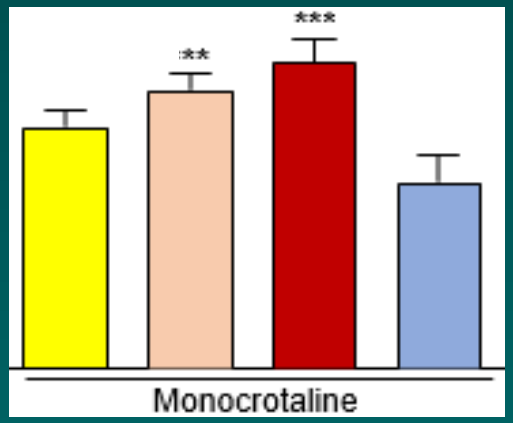
3

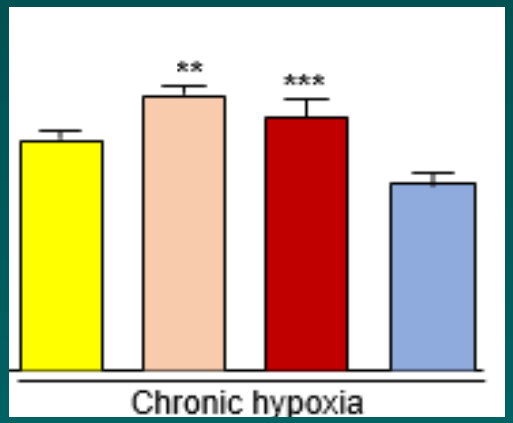
Rôle des Facteurs Génétiques et Environnementaux pour le remodelage vasculaire pulmonaire HTAP :

Vehicle
Dasatinib 1 mg/kg
Dasatinib 10 mg/kg
Imatinib 20 mg/kg

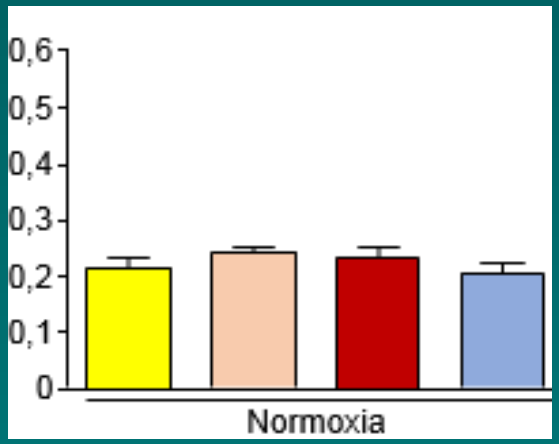
mPAP (mm Hg)

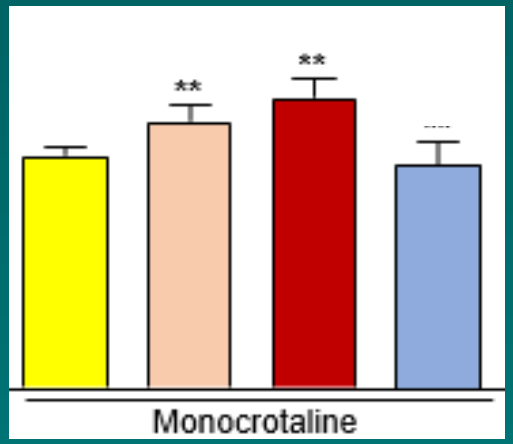


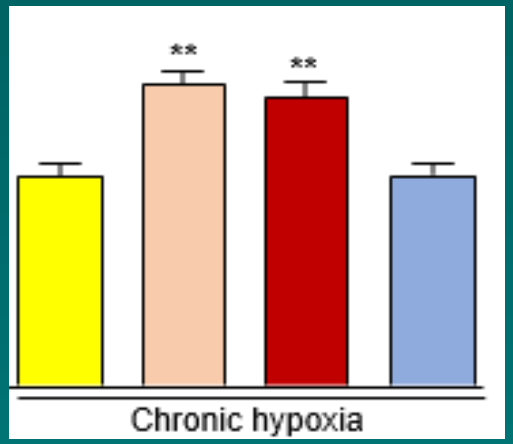




Fulton Index (%)







Phan C *et al. (soumis)*

Remerciements

Merci pour votre Attention !

INSERM UMR_S 999

« Hypertension Pulmonaire »

Physiopathologie et Innovation Thérapeutique

- Pr. Marc Humbert
- Pr. Gérald Simonneau
- Pr. Philippe Dartevelle
- Pr. Elie Fadel
- Pr. Olivier Sitbon
- Pr. Peter Dorfmüller
- Pr. Olaf Mercier
- Dr. David Montani
- Dr. Sylvia Cohen-Kaminsky
- Dr. Frédéric Perros
- Dr. Andrei Seferian
- Dr. Caroline Sattler

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Yuichi Tamura *(MD, Post-doc)*
Nicolas Ricard *(Post-Doc)*
Morane Le Hiress *(Post-doc)*

Ly Tu *(Research Engineer)*
Raphaël Thuillet *(Engineer)*
Maria-Rosa Ghigna *(MD, Ph.D)*
Carole Phan *(Ph.D)*
Jennifer Bordenave *(Ph.D)*