DES de Pneumologie Ile-de-France

Séminaire "Maladies vasculaires pulmonaires chroniques"

Physiopathologie de l'HTAP :

Le rôle critique de la CE pulmonaire dans la paroi vasculaire

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

Classification clinique de l'hypertension pulmonaire (HTP): Nice, France - 2013

Pulmonary hypertension 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

PAH
Pulmonary artery wedge pressure (PAWP) ≤ 15 mmHg

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

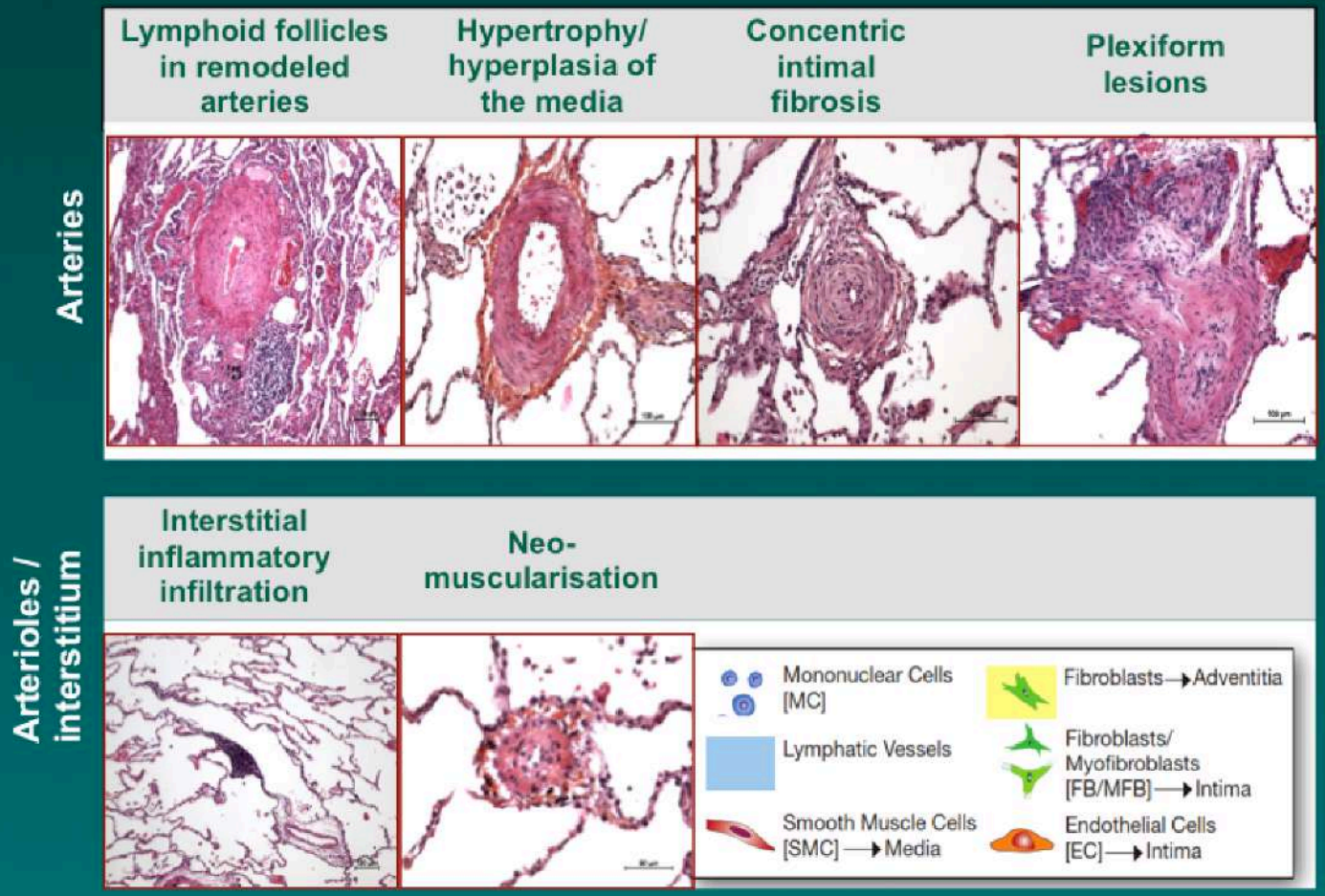
4.1 Chronic thromboembolic pulmonary hypertension
4.2 Other pulmonary artery obstructions
4.2.1 Angiosarcoma
4.2.2 Other intravascular tumors
4.2.3 Arteritis
4.2.4 Congenital pulmonary arteries stenoses
4.2.5 Parasites (hydatidosis)

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)



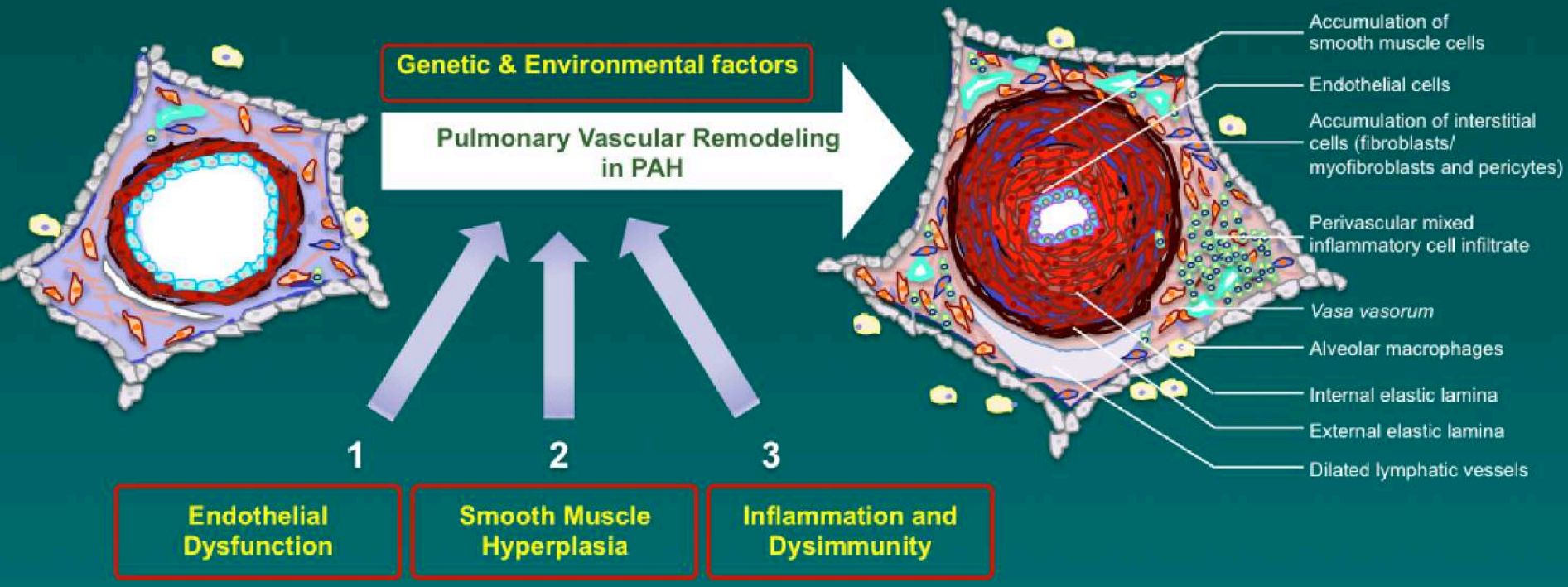
Observations in explanted human lungs

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

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

Healthy subject:
mean PAP= 14 ± 3 mmHg

PAH patient:
mean PAP ≥ 25 mmHg



Guignabert C et al., The ESC Textbook of Cardiovascular Medicine 3rd edition, 2017.
Guignabert C et al., Chest 2015.

Facteurs génétiques prédisposants à l'hypertension artérielle pulmonaire

Harrison RE, J Med Genet. 2003
Abdalla SA, Eur Respir J, 2004
Chaouat A, Thorax, 2004

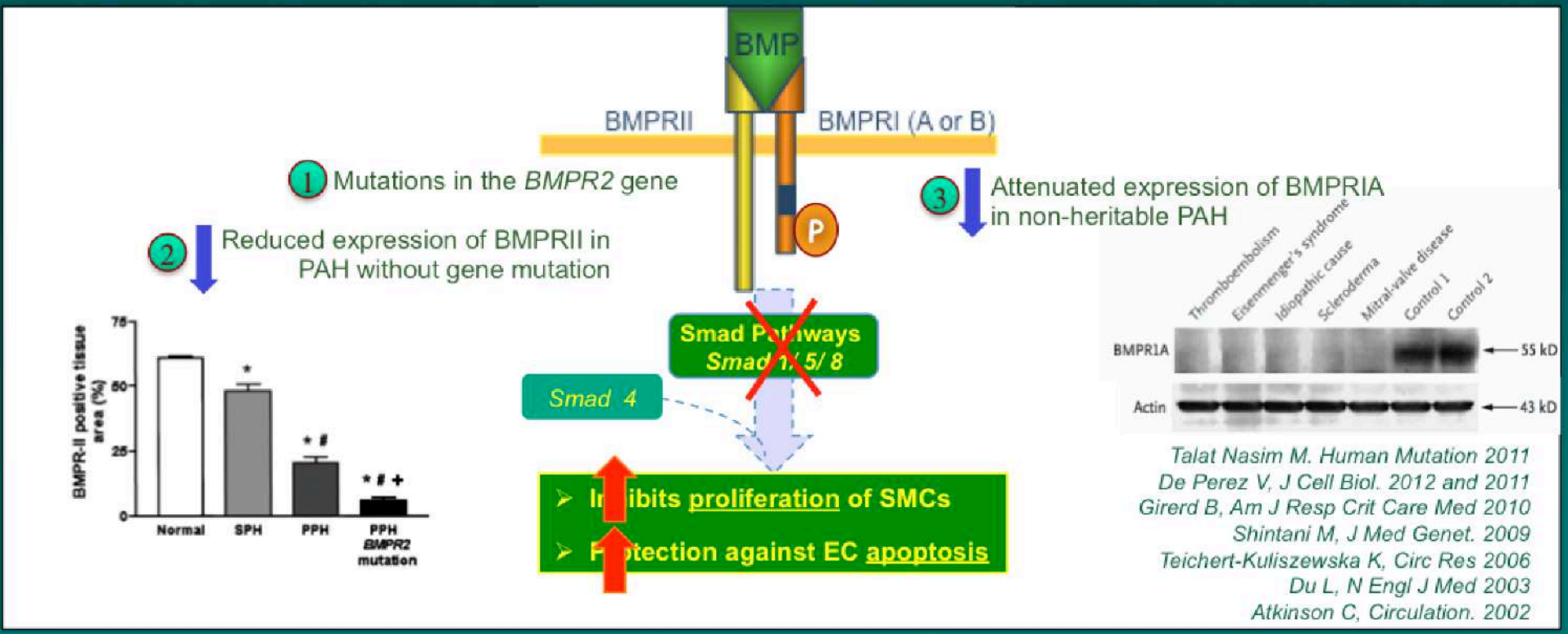
Austin ED, Circ Cardiovasc Genet, 2012

BMPR2 (70-80%) | **ACVRL1** **ENG** | **SMAD9** | **CAV1** | **KCNK3** **locus close to CBLN2**

Deng Z, Am J Hum Genet, 2000
Lane KB, Nat Genet, 2000

Shinati M, J Med Genet, 2009

Ma L, N Engl J Med, 2013
Germain M, Nat Genet, 2013



Talat Nasim M. Human Mutation 2011
De Perez V, J Cell Biol. 2012 and 2011
Girerd B, Am J Resp Crit Care Med 2010
Shintani M, J Med Genet. 2009
Teichert-Kuliszewska K, Circ Res 2006
Du L, N Engl J Med 2003
Atkinson C, Circulation. 2002

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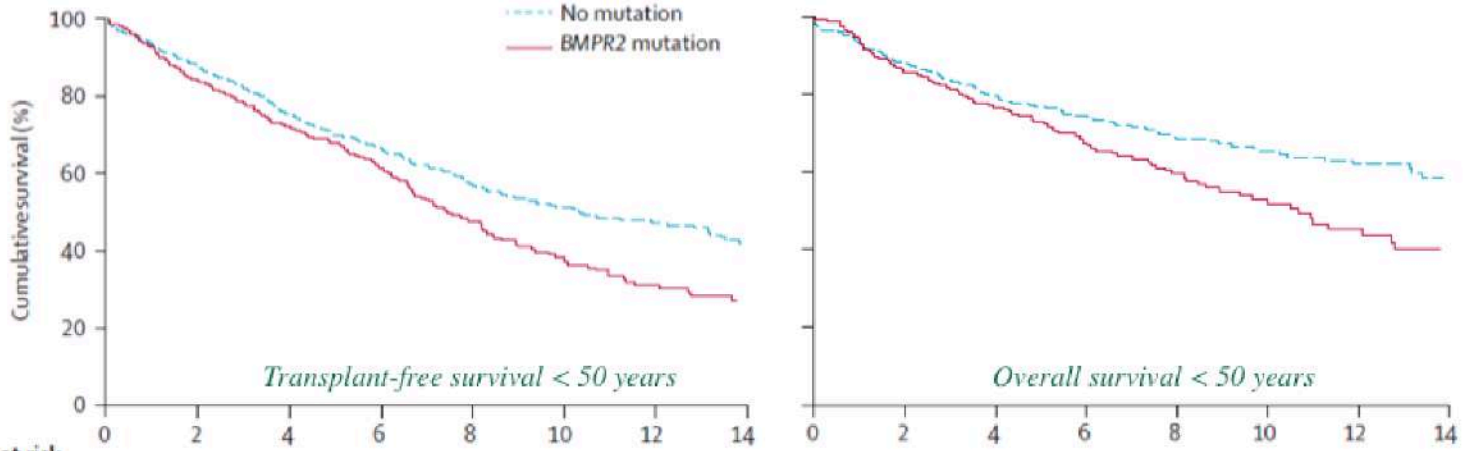
Lane KB, Nat Genet, 2000

Shinati M, J Med Genet, 2009

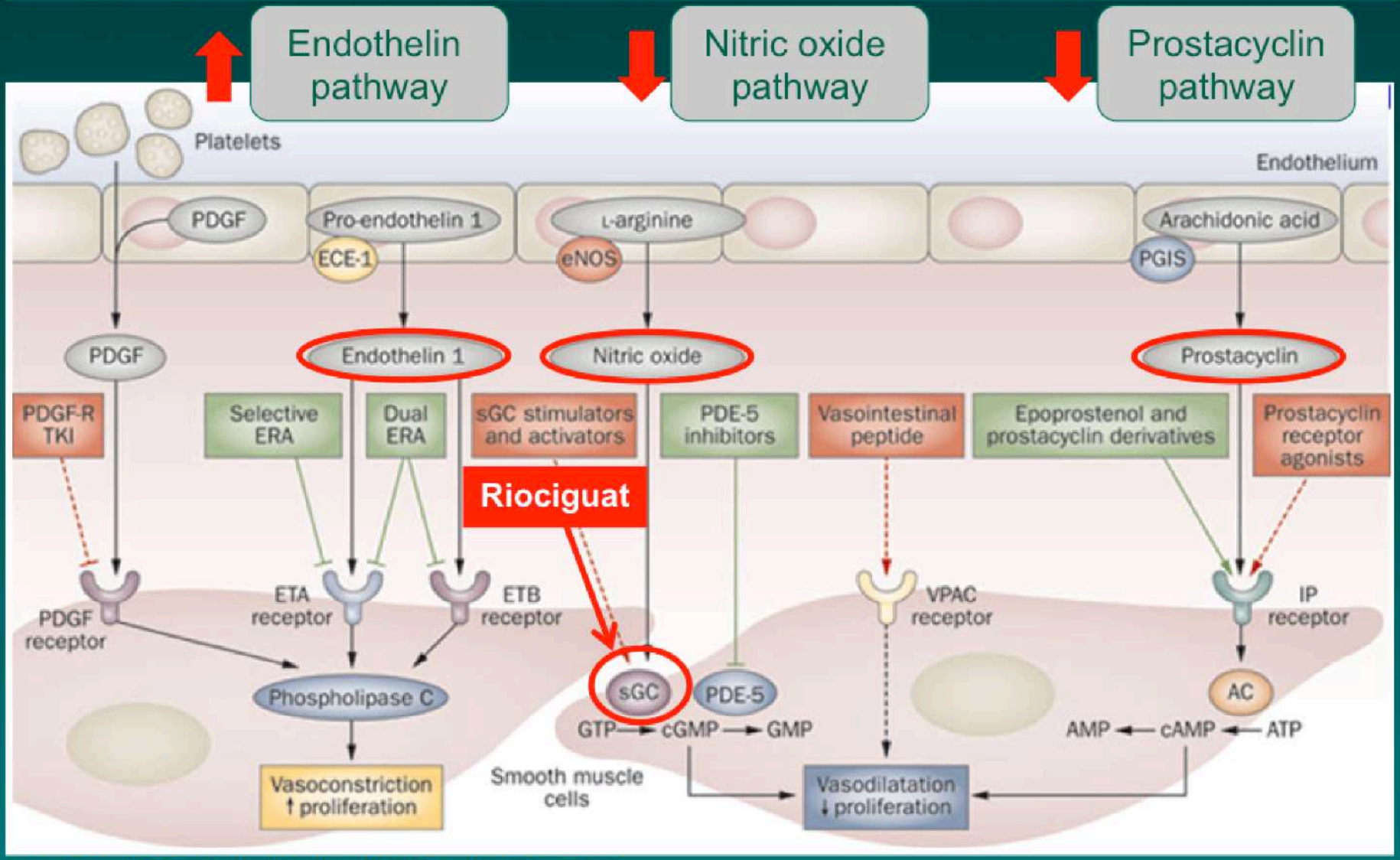
Ma L, N Engl J Med, 2013
Germain M, Nat Genet, 2013

Patients with PAH carrying a BMPR2 mutation are younger at diagnosis, have more severe disease, and have a worse prognosis than noncarriers.



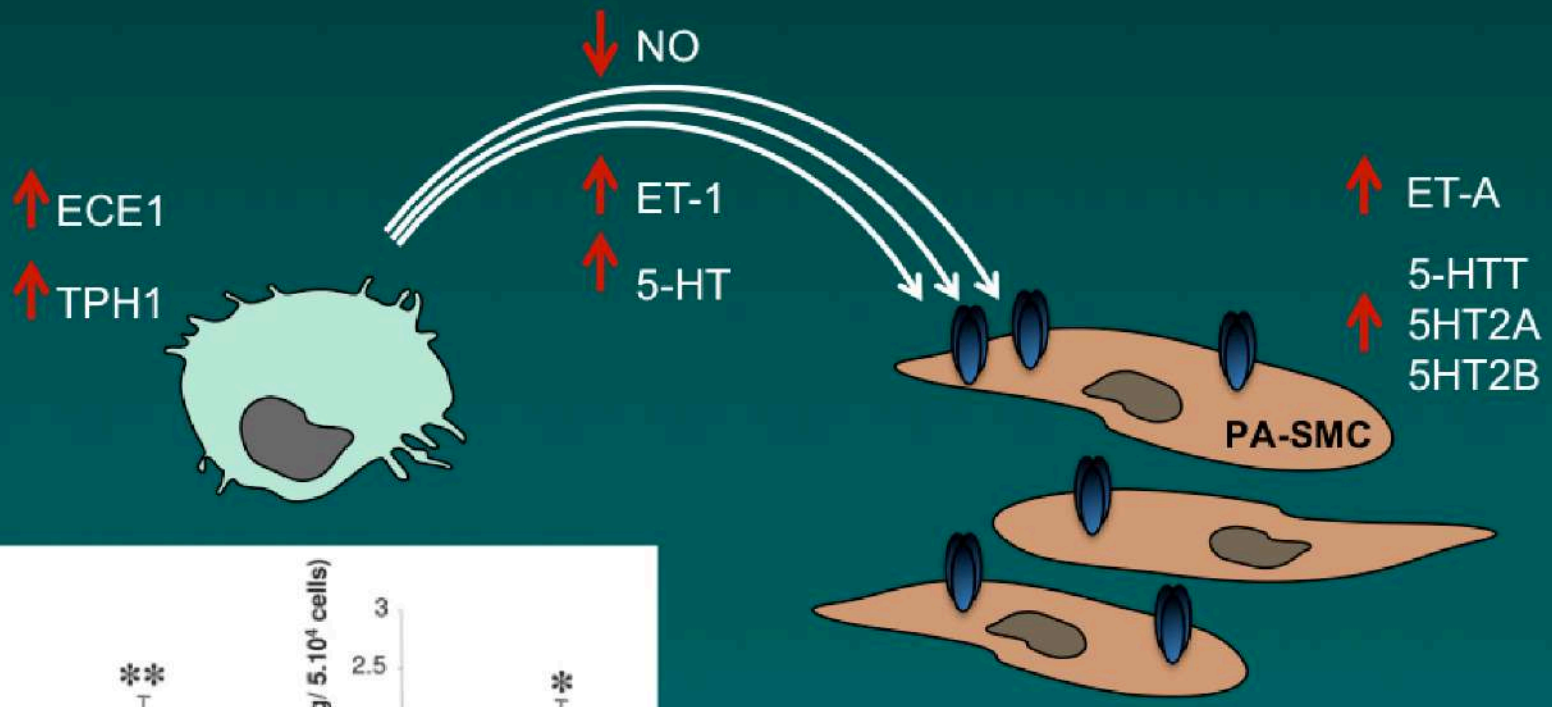
Evans JDW et al. Lancet Respir Med 2016

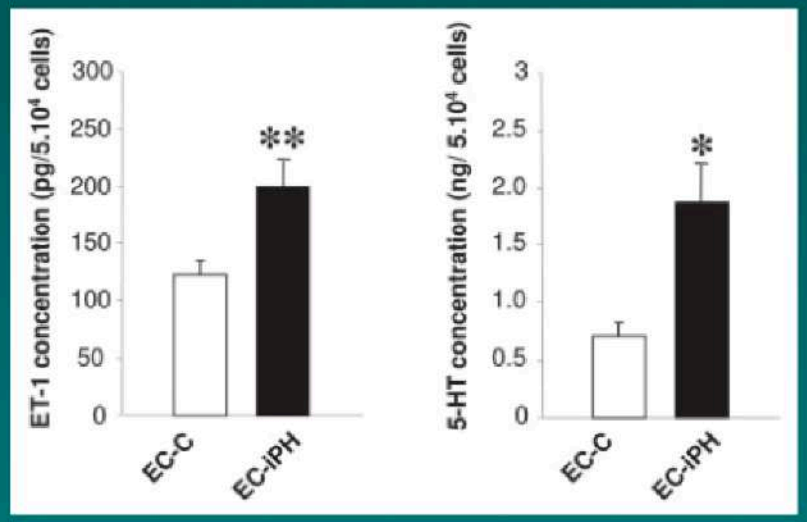
La cellule endothéliale pulmonaire régule la tonicité des artères pulmonaires



Humbert M, JACC 2004 ; Humbert M, N Engl J Med. 2004 ;
O'Callaghan DS, Nat Rev Cardiol. 2011; Ghofrani HA,N Engl J Med. 2013,

Altération dans la communication CE-CML au cours du développement d'HTAP





Eddahibi et al. Circulation 2006.
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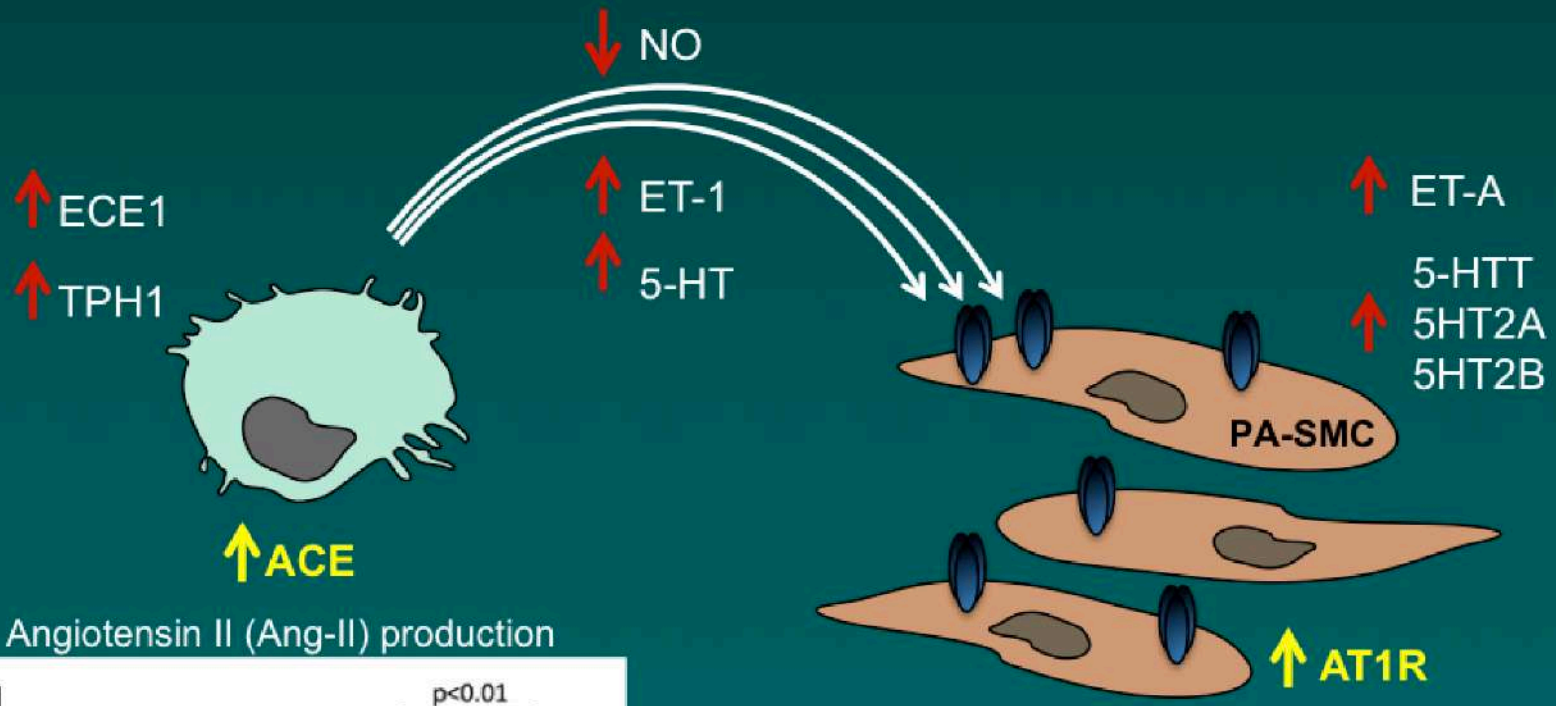
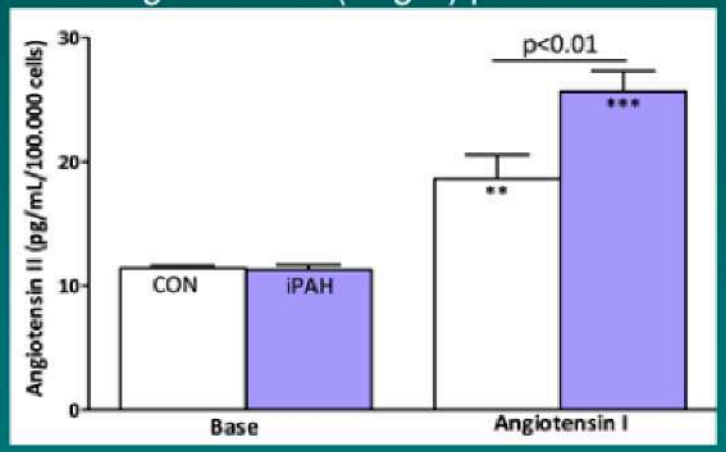
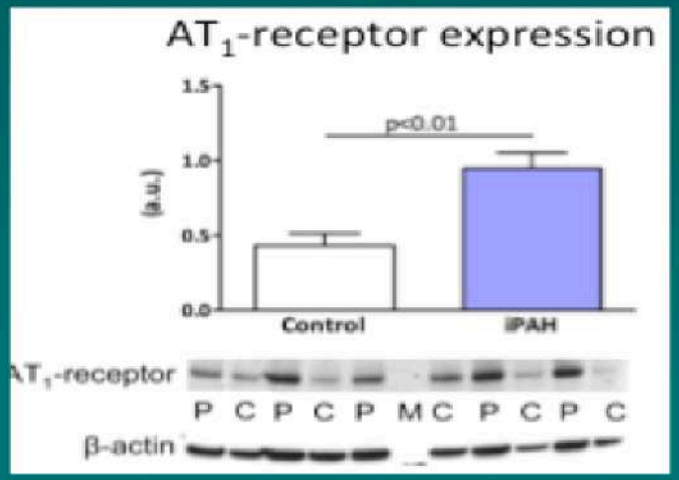


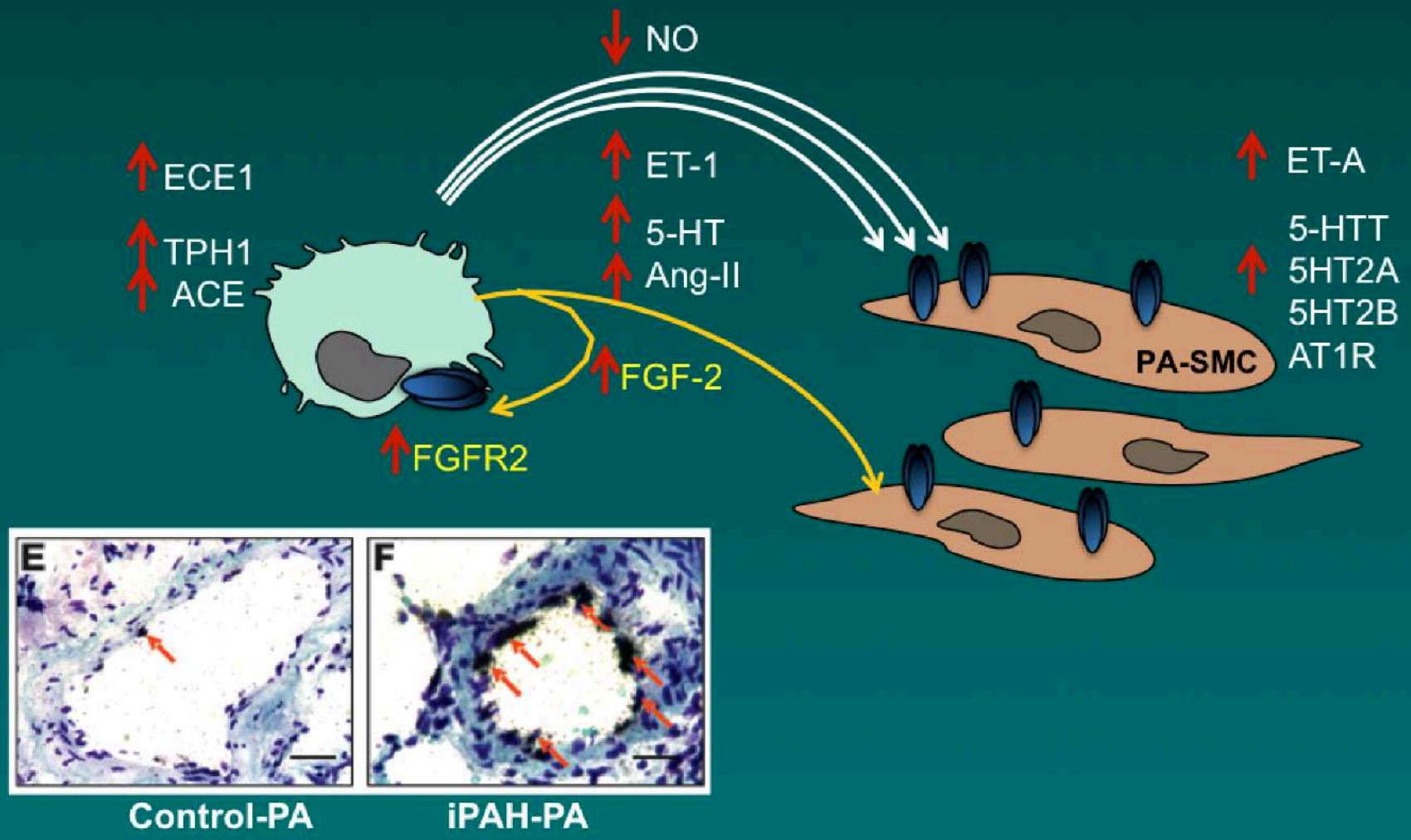
Angiotensin II (Ang-II) production



De Man et al. Am J Respir Crit Care Med. 2012



Rôle du FGF-2 dans le remodelage vasculaire pulmonaire associé à l'HTAP



Izikki et al. J Clin Invest. 2009.
Tu et al. Am J Respir Cell Mol Biol. 2011.

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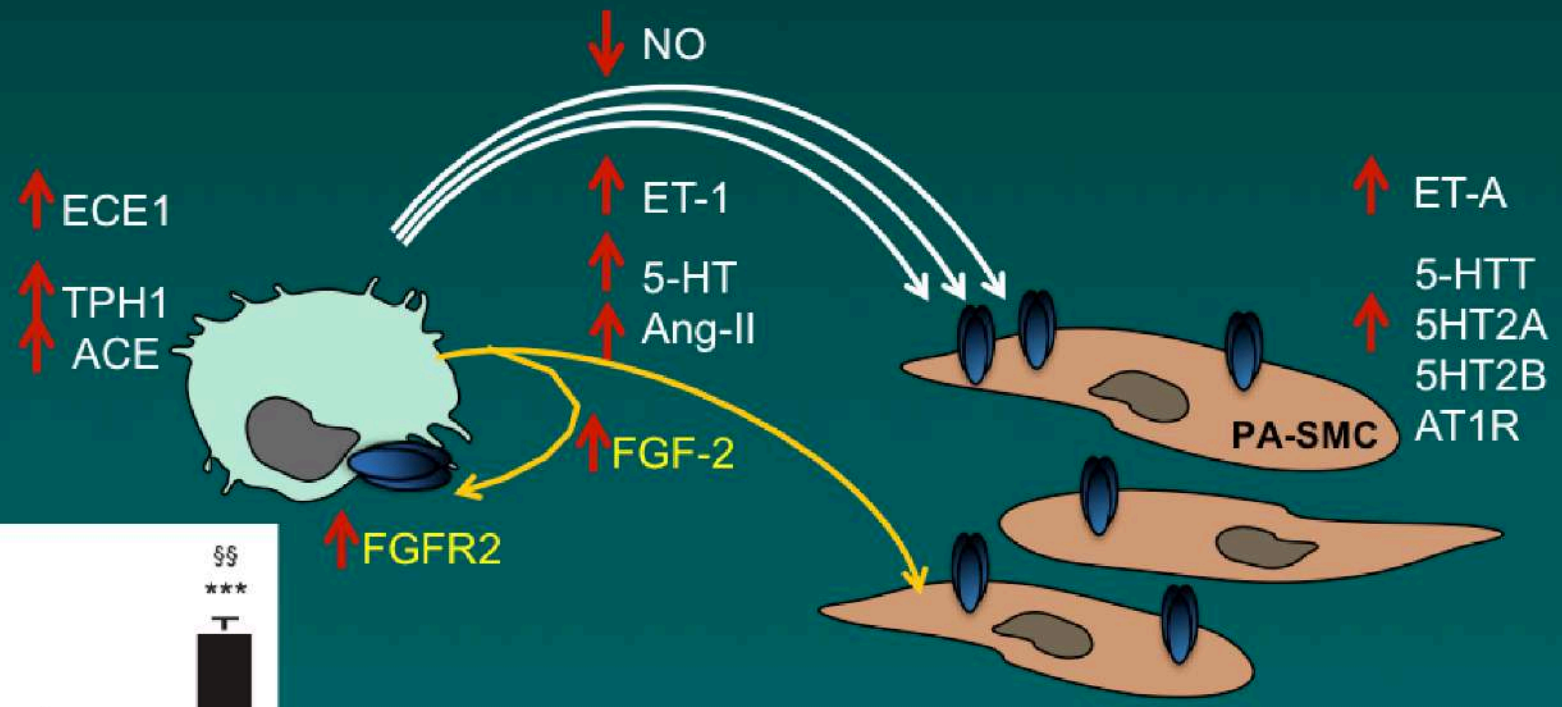
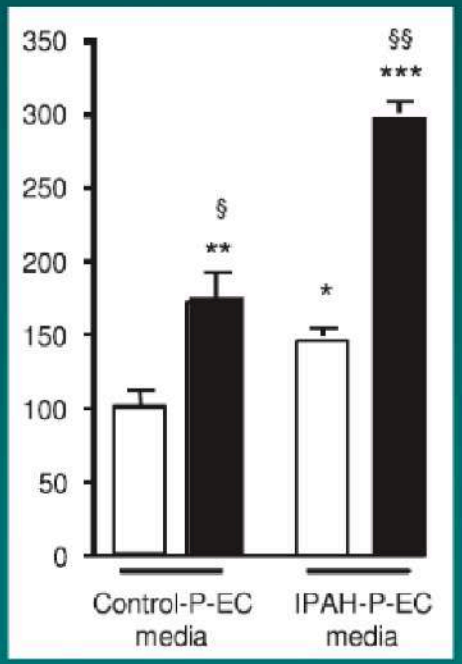




IPAH-ECs media induces
Hyperproliferation phenotype

Izikki et al. J Clin Invest. 2009.
Tu et al. Am J Respir Cell Mol Biol. 2011.

Médiateurs inflammatoires et Hypertension Artérielle Pulmonaire (HTAP)

Circulation, 2010:

Elevated Levels of Inflammatory Cytokines Predict Survival in Idiopathic and Familial Pulmonary Arterial Hypertension

Elaine Soon, MRCP, MBBChir*; Alan M. Holmes, PhD*; Carmen M. Treacy, BSc; Natalie J. Doughty, MSc; Laura Southgate, PhD; Rajiv D. Machado, PhD; Richard C. Trembath, FMedSci; Simon Jennings, PhD; Lucy Barker, PhD; Paul Nicklin, PhD; Christoph Walker, PhD;† David C. Budd, PhD; Joanna Pepke-Zaba, PhD, FRCP; Nicholas W. Morrell, MD, FRCP

IL-6, IL-8, IL-10, IL-12

Eur Respir J 2014:

Proinflammatory cytokine levels are linked to death in pulmonary arterial hypertension

Jean-Luc Cracowski, François Chabot, José Labarère, Patrice Faure, Bruno Degano, Carole Schwebel, Ari Chaouat, Martine Reynaud-Gaubert, Claire Cracowski, Olivier Sitbon, Azzedine Yaici, Gerald Simonneau, Marc Humbert

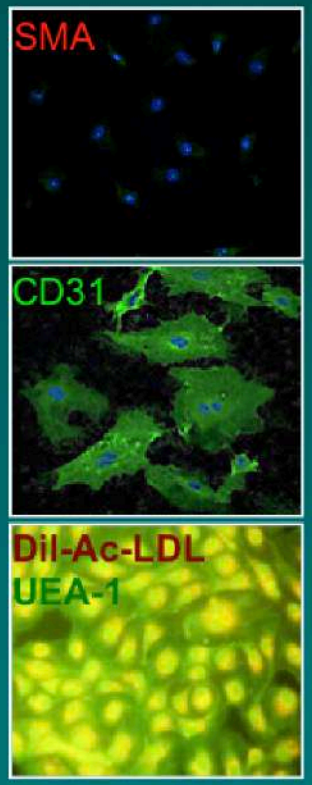
IL-1α, IL-1β, IL-6, IL-13, TNF-α

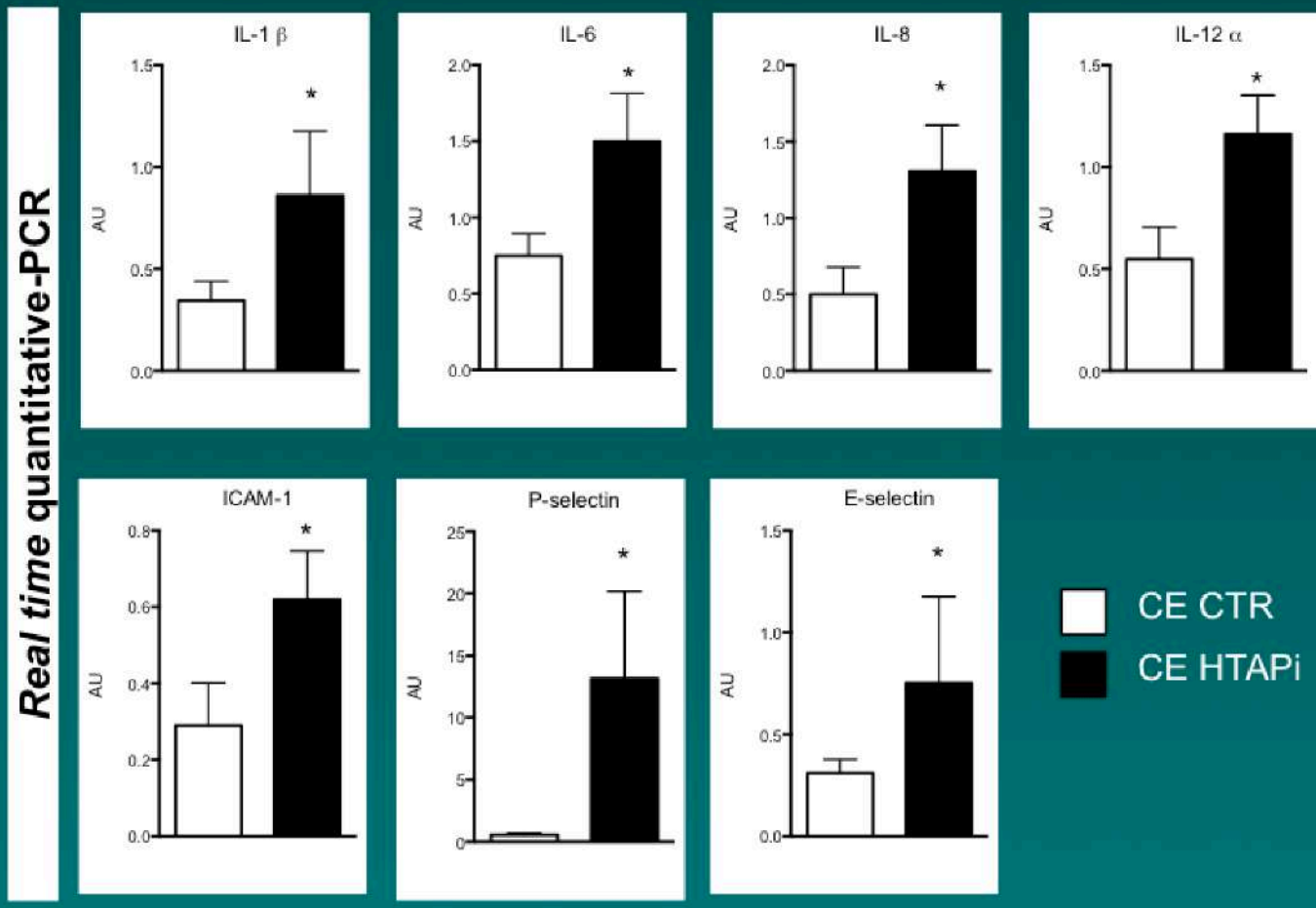
Cracowski J, Eur Respir J, 2014.
Soon E, Circulation, 2010.

Disease evolution → **Death / Survival**

La cellule endothéliale pulmonaire acquiert et maintient un phénotype pro-inflammatoire

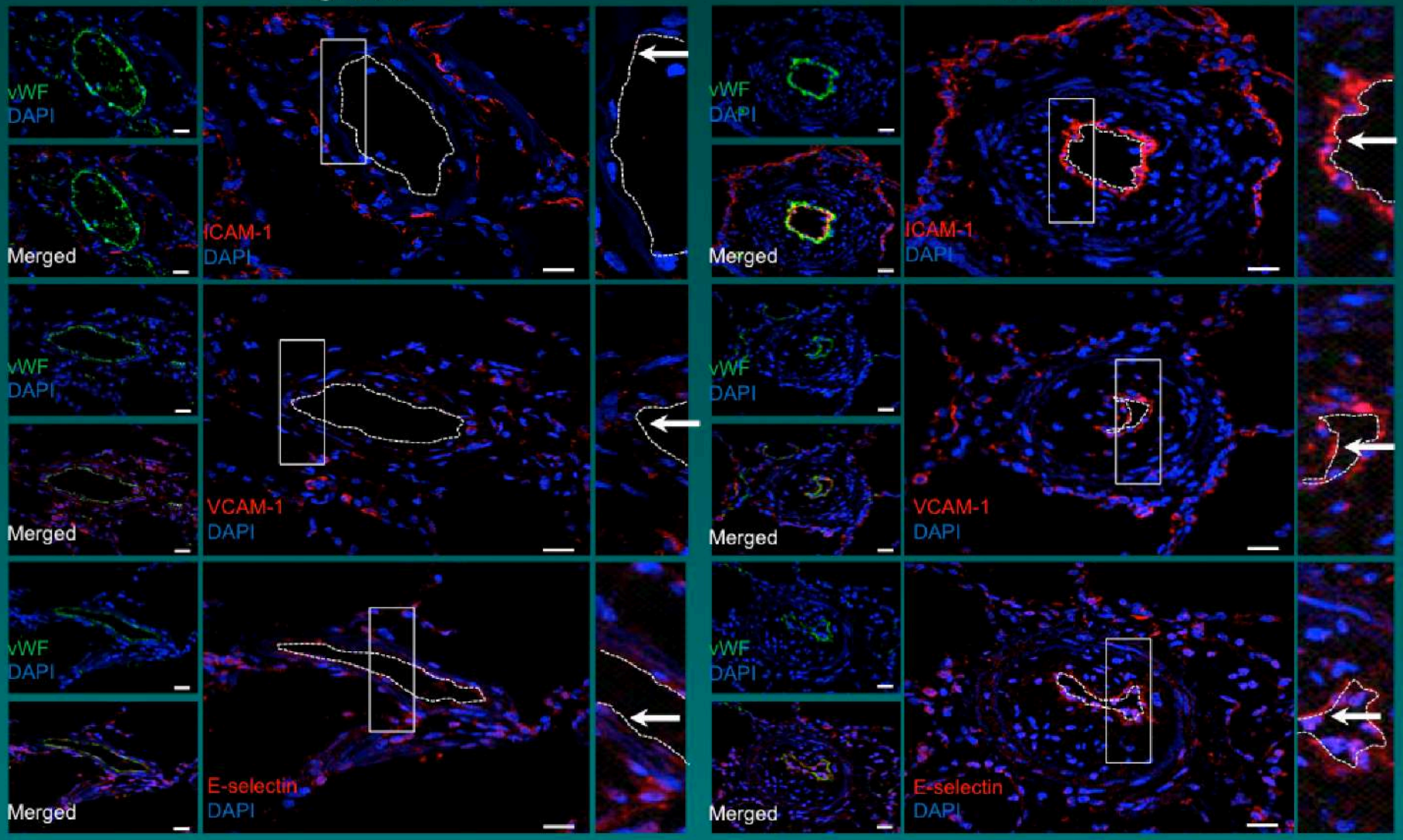
Cultures Primaires de Cellules Endothéliales Pulmonaires
(passage précoces *4-7*)





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

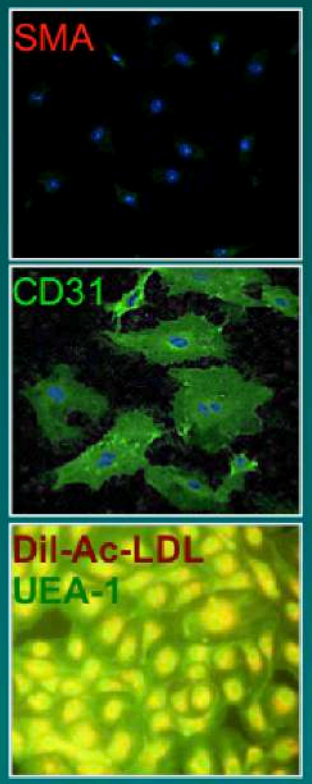
La cellule endothéliale pulmonaire acquiert et maintient un phénotype pro-inflammatoire



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

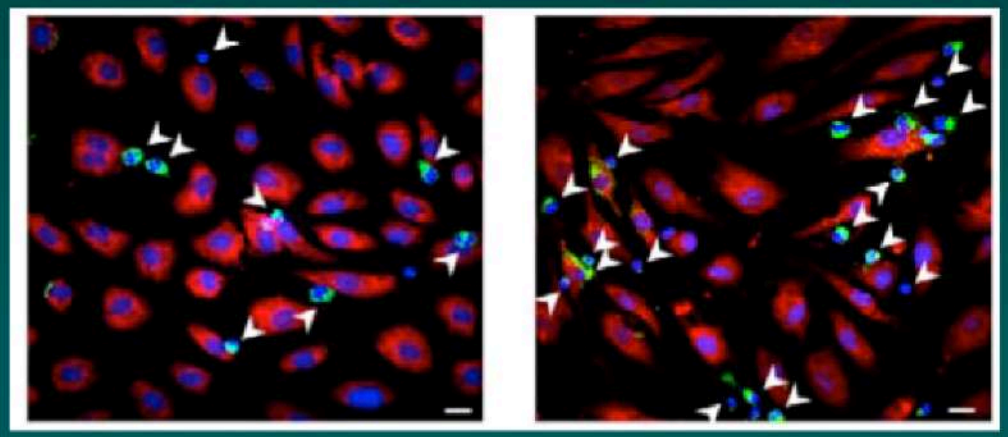
La cellule endothéliale pulmonaire acquiert et maintient un phénotype pro-inflammatoire

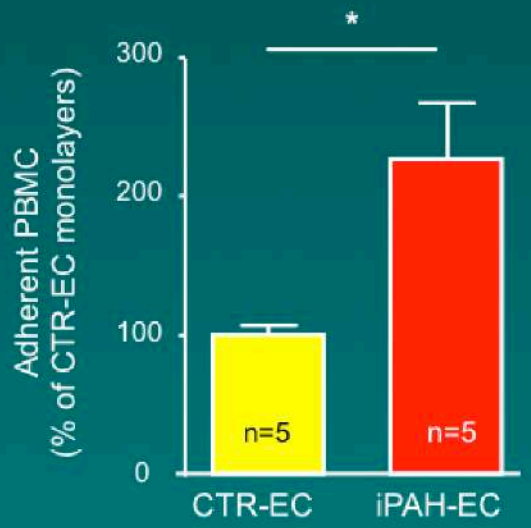
Primary cultures of Human Pulmonary Endothelial Cells
(passages 4-7)



CTR-EC
confluent monolayer

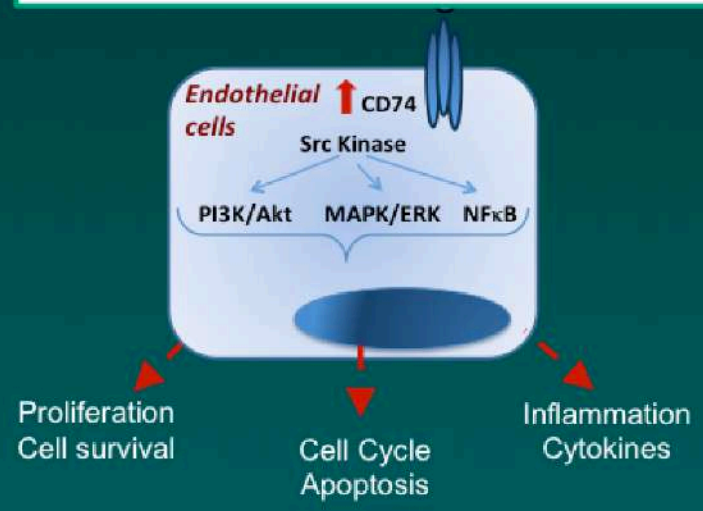
iPAH-EC
confluent monolayer

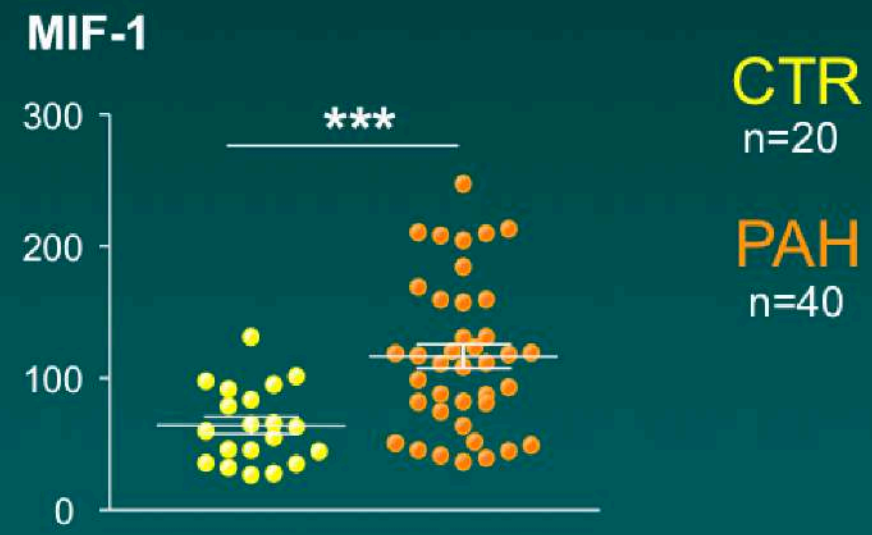


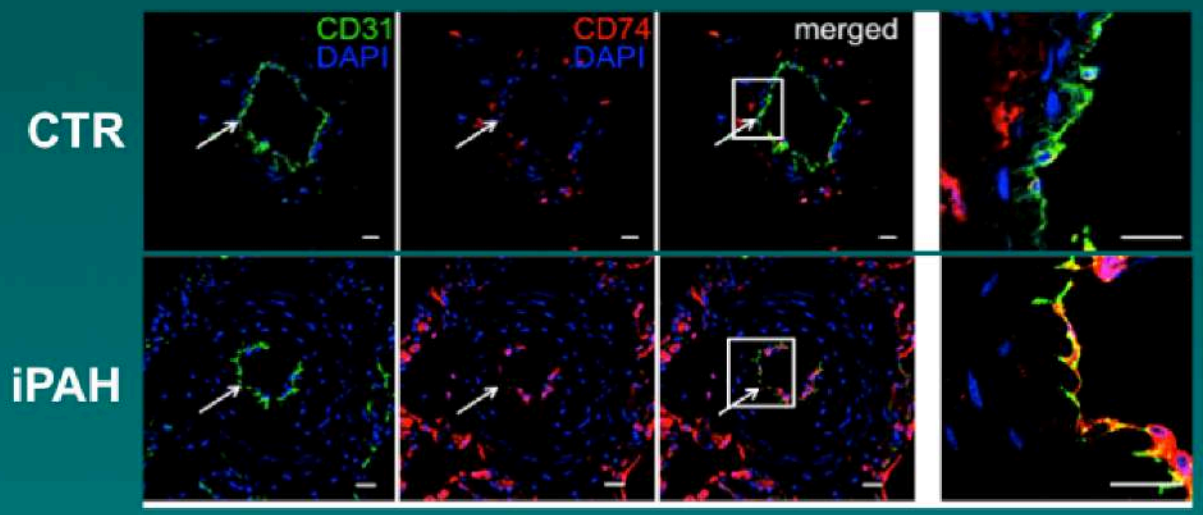


Le Hiress et al. Am J Respir Crit Care Med. 2015.

Le facteur MIF (*Macrophage migration inhibitory factor*) dans l'HTAP humaine

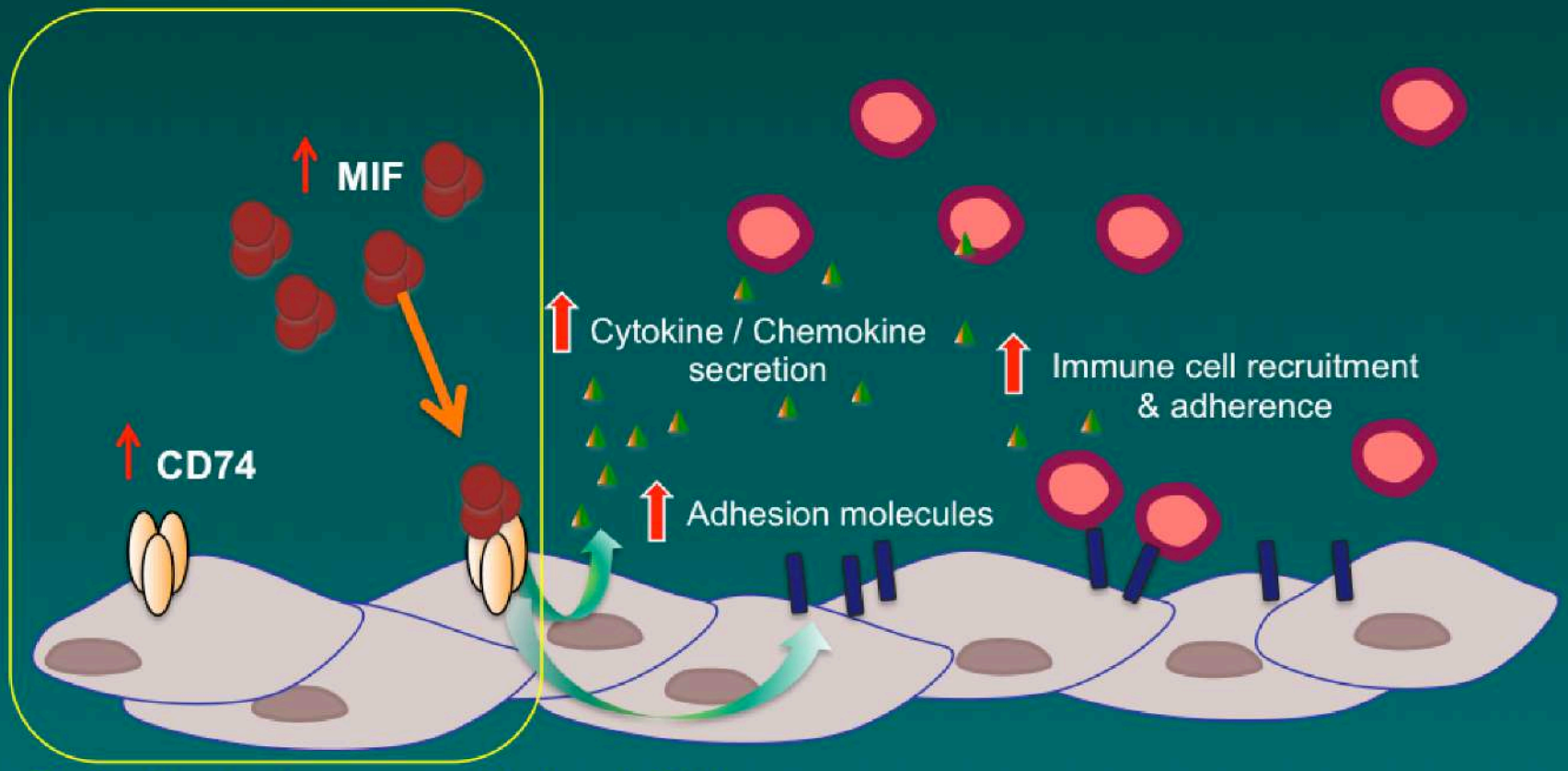






Le Hiress et al. Am J Respir Crit Care Med. 2015.

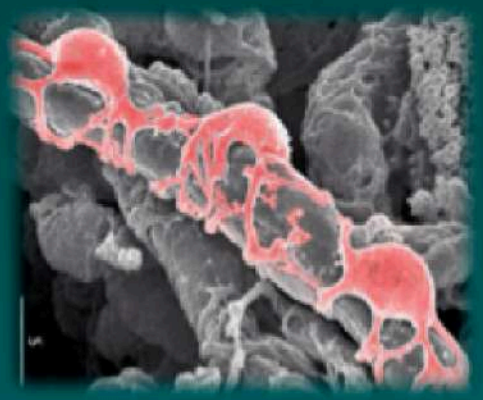
L'axe MIF-CD74 contribue à l'acquisition et à la maintenance du phénotype pro-inflammatoire des CE pulmonaires HTAP

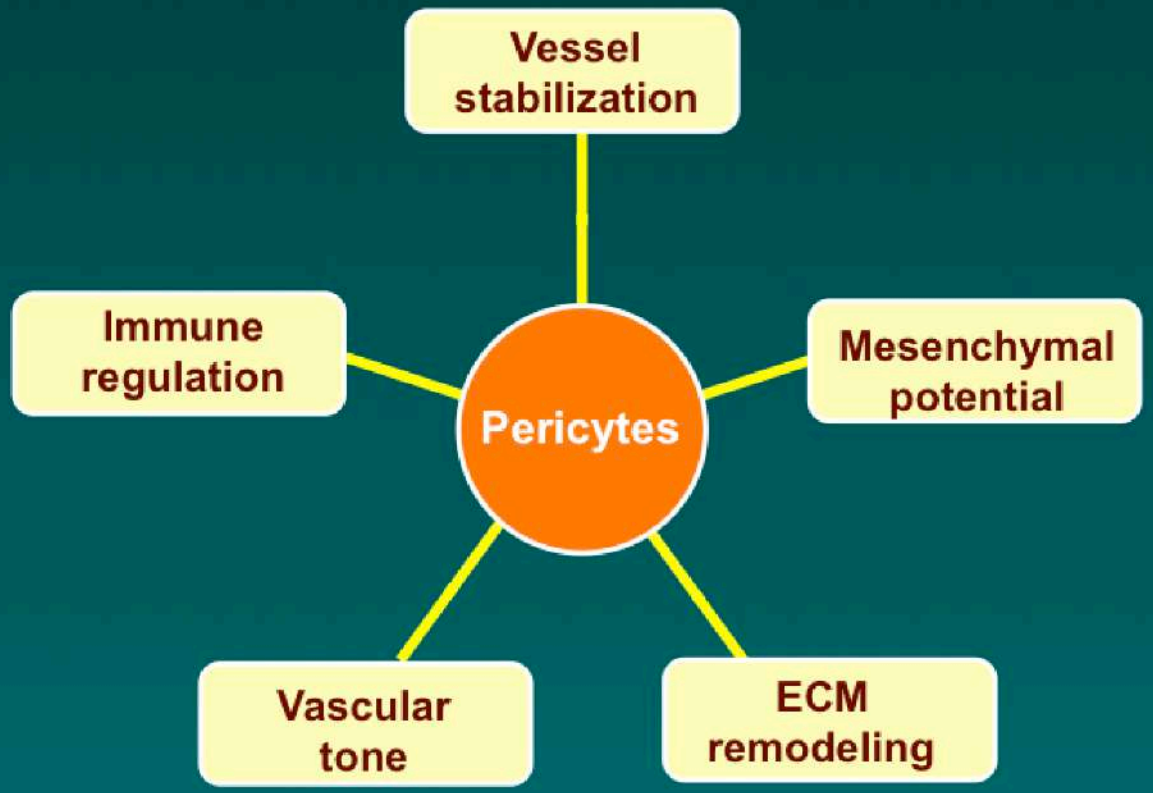


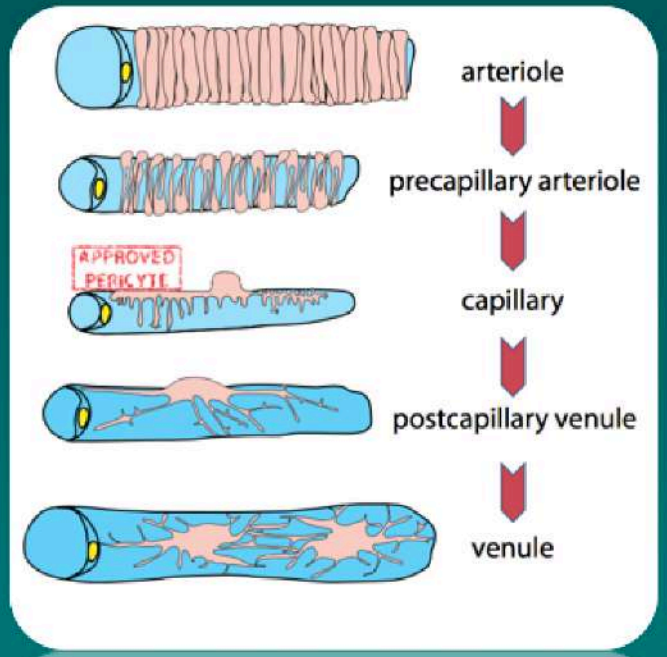
Dysfunctional pulmonary endothelium in PAH

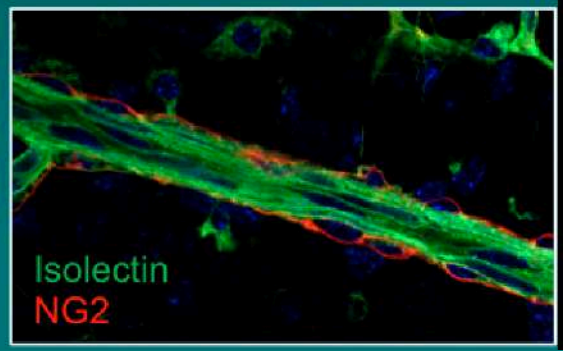
Le Hiress et al. Am J Respir Crit Care Med. 2015.

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



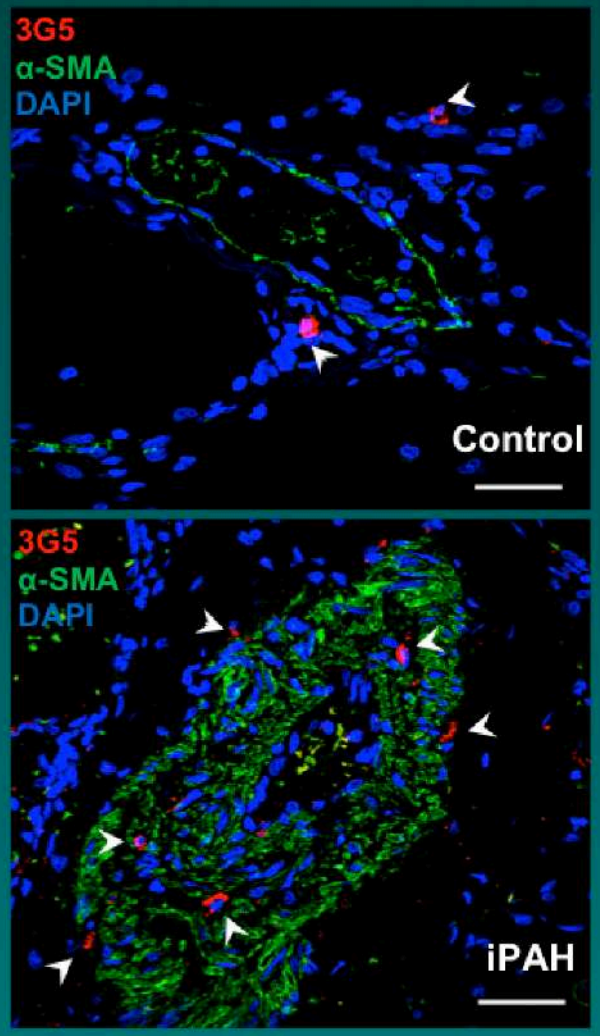


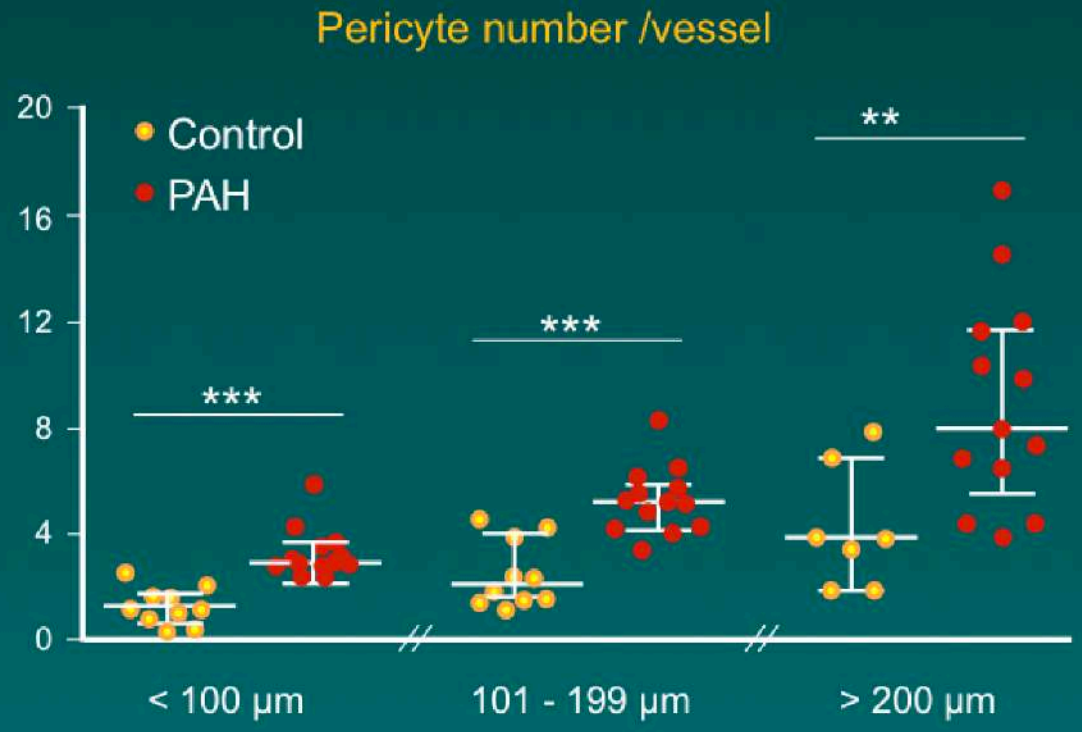




Rôle des péricytes pulmonaires dans l'Hypertension Artérielle Pulmonaire (HTAP)

Human lungs:





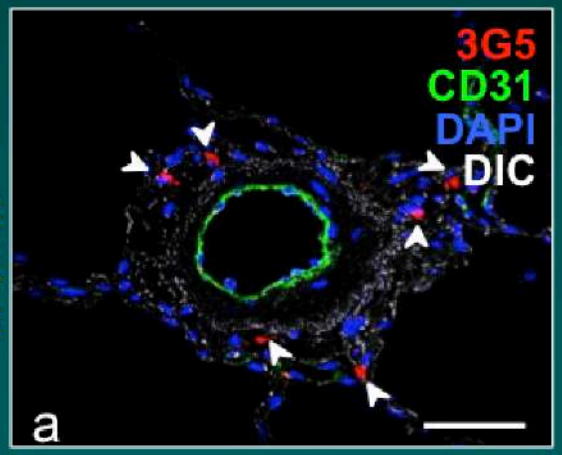
Pericyte number/vessel is increased by 2-fold in PAH lung specimens as compared to controls.

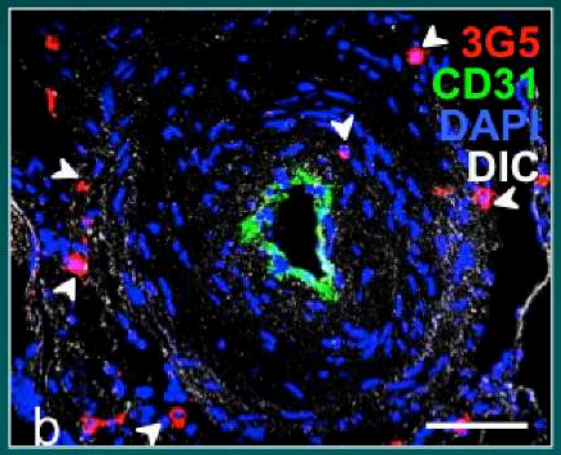
Ricard et al. Circulation 2014

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

Human lungs:

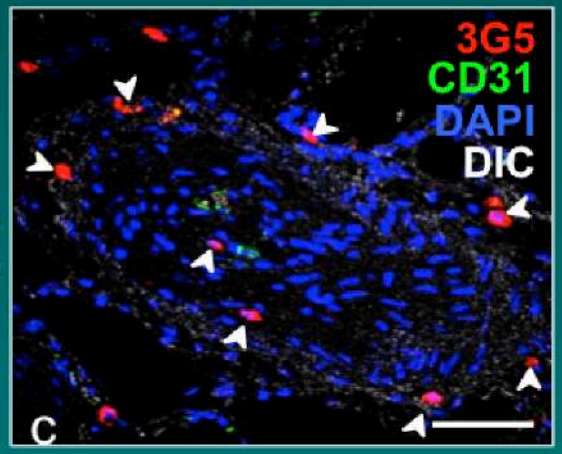
Mild pulmonary vascular remodeling

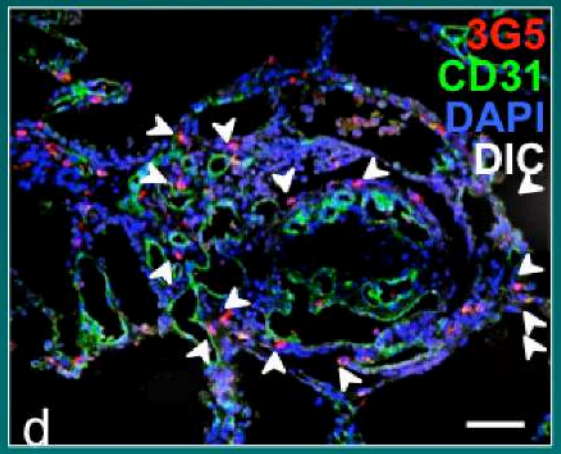




Hypertrophy/ hyperplasia of the media

Occluded lesion





Plexiform lesions

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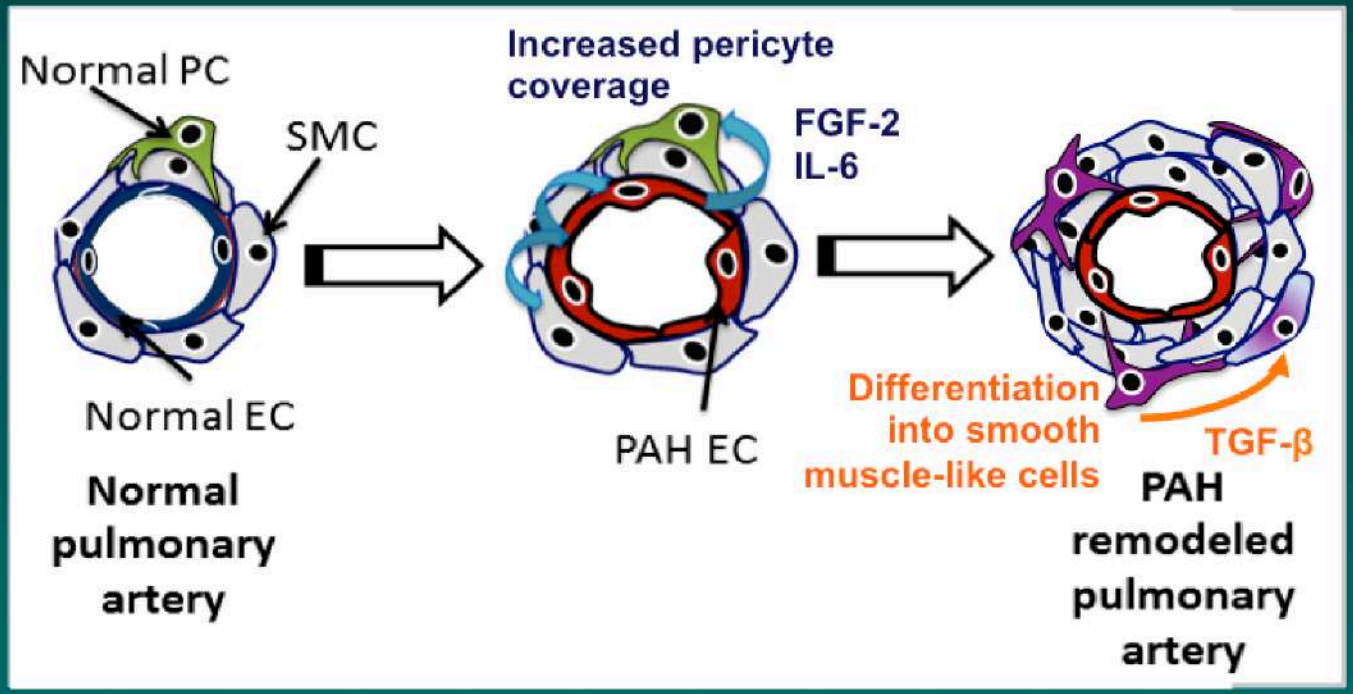
Nouveaux concepts :
Péricytes & Remodelage vasculaire pulmonaire ?



Ricard et al. Circulation 2014

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Physiopathology and Novel Therapies

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Jennifer Bordenave (PhD student)

Dr. Ly Tu (Ph.D, Res. Eng.)
Raphaël Thuillet (Eng.)
Amélie Cumont (Tech.)

Paul-Benoit Poble (MSc)
Noé Bagur (Pharm.D)

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RECHERCHE EN SANTÉ RESPIRATOIRE
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