Nouvelles approches physiopathologiques et innovation thérapeutique

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INSERM UMR_S 999
Pulmonary Hypertension: Pathophysiology and Novel Therapies

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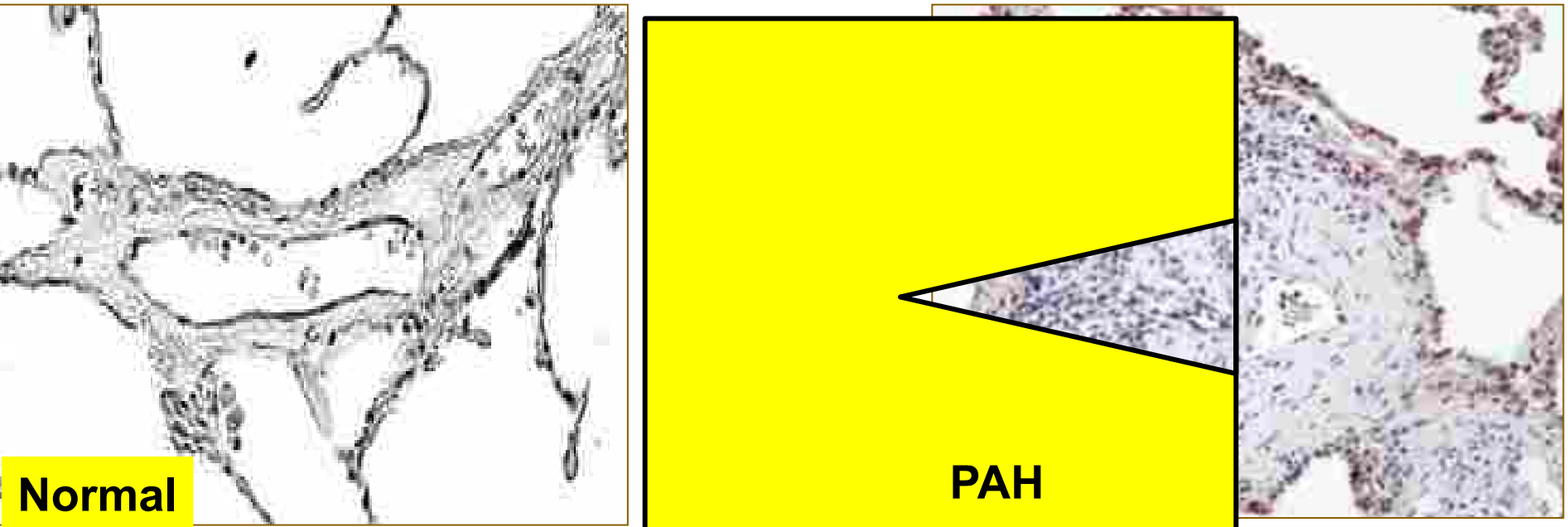
TORINO

Pulmonary Arterial Hypertension

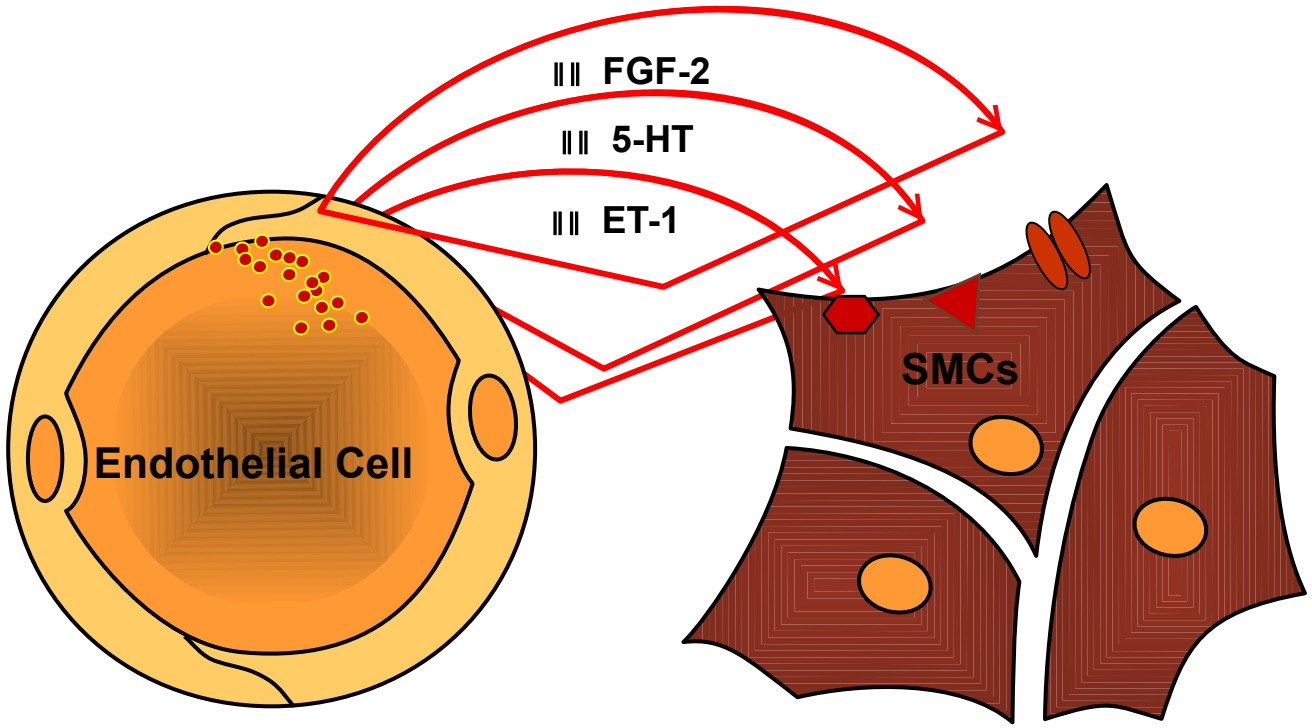
a severe pulmonary vascular disease

- ***Definition*** **: chronic precapillary pulmonary hypertension**
- ***Cause*** **: progressive structural remodeling of the small pulmonary arteries**
- ***Consequence*** **: right heart failure and death**



Pulmonary Arterial Hypertension
a rare, but not an orphan disease

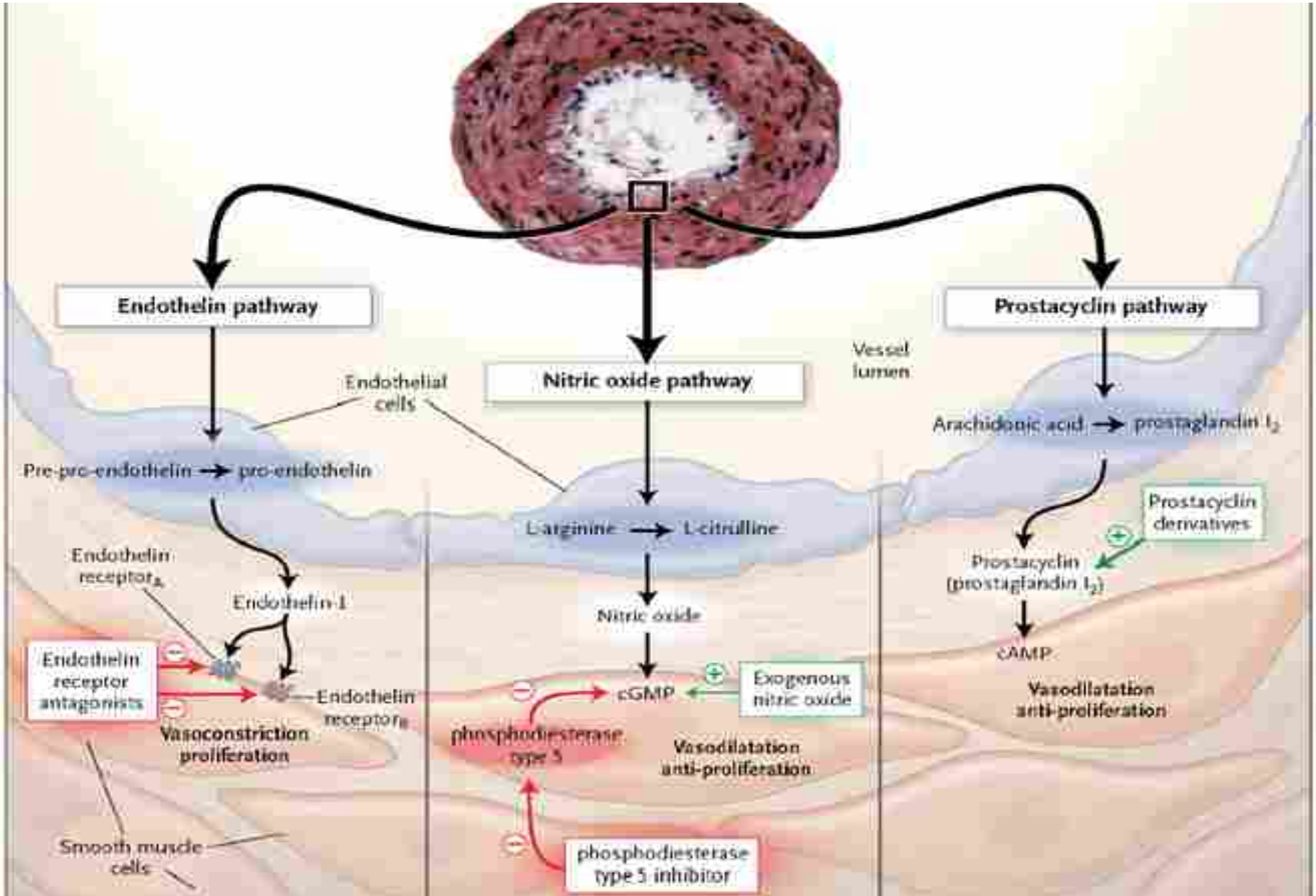
- ***Rare*** **: prevalence 15-50 / million (incidence 6/million/yr)**
- ***Pathophysiology*** **: pulmonary artery endothelial cell dysfunction…**
- ***Drugs*** **: 10 agents approved in the last 15 years (orphan drug status)**
- ***Lung / heart-lung transplantation :*** **if refractory to medical therapy**



Inserm

Université Paris Sud
Faculté de Médecine

Targeting 3 major dysfunctional pathways in PAH



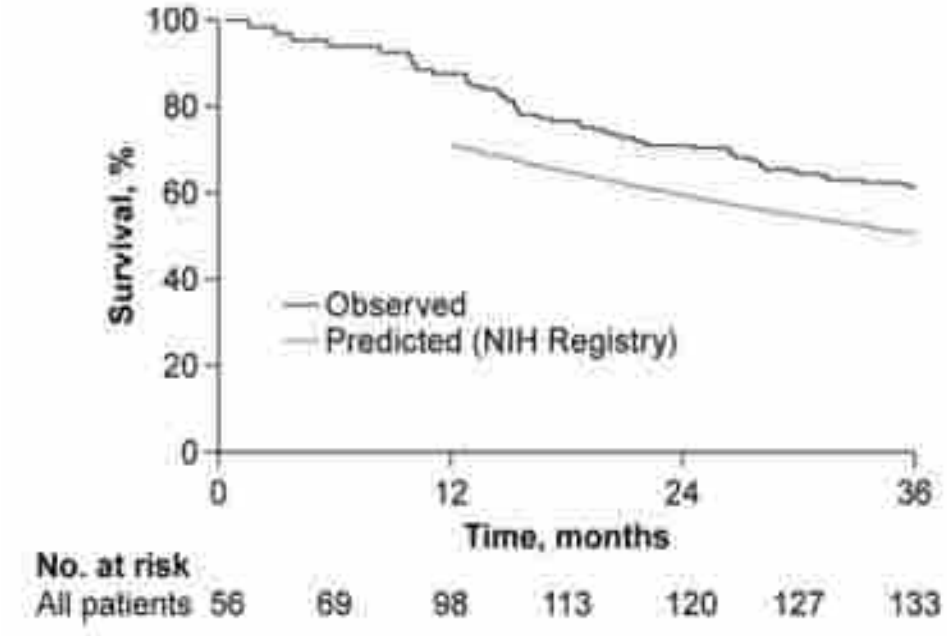
Humbert, Sitbon, Simonneau. *N Engl J Med 2004; 351:1425-36*

UNMET NEED IN THE MODERN MANAGEMENT ERA

Despite drug discovery & development PAH remains a devastating condition

Survival in Patients With Idiopathic, Familial, and Anorexigen-Associated Pulmonary Arterial Hypertension in the Modern Management Era

Marc Humbert, MD, PhD; Olivier Sitbon, MD, PhD; Ari Chaouat, MD, PhD; Michèle Bertocchi, MD; Gilbert Habib, MD; Virginie Gressin, MD; Azzedine Yaïci, MD; Emmanuel Weitzenblum, MD; Jean-François Cordier, MD; François Chabot, MD, PhD; Claire Dromer, MD; Christophe Pison, MD, PhD; Martine Reynaud-Gaubert, MD, PhD; Alain Haloun, MD; Marcel Laurent, MD; Eric Hachulla, MD, PhD; Vincent Cottin, MD, PhD; Bruno Degano, MD, PhD; Xavier Jaïs, MD; David Montani, MD, PhD; Rogério Souza, MD, PhD; Gérald Simonneau, MD

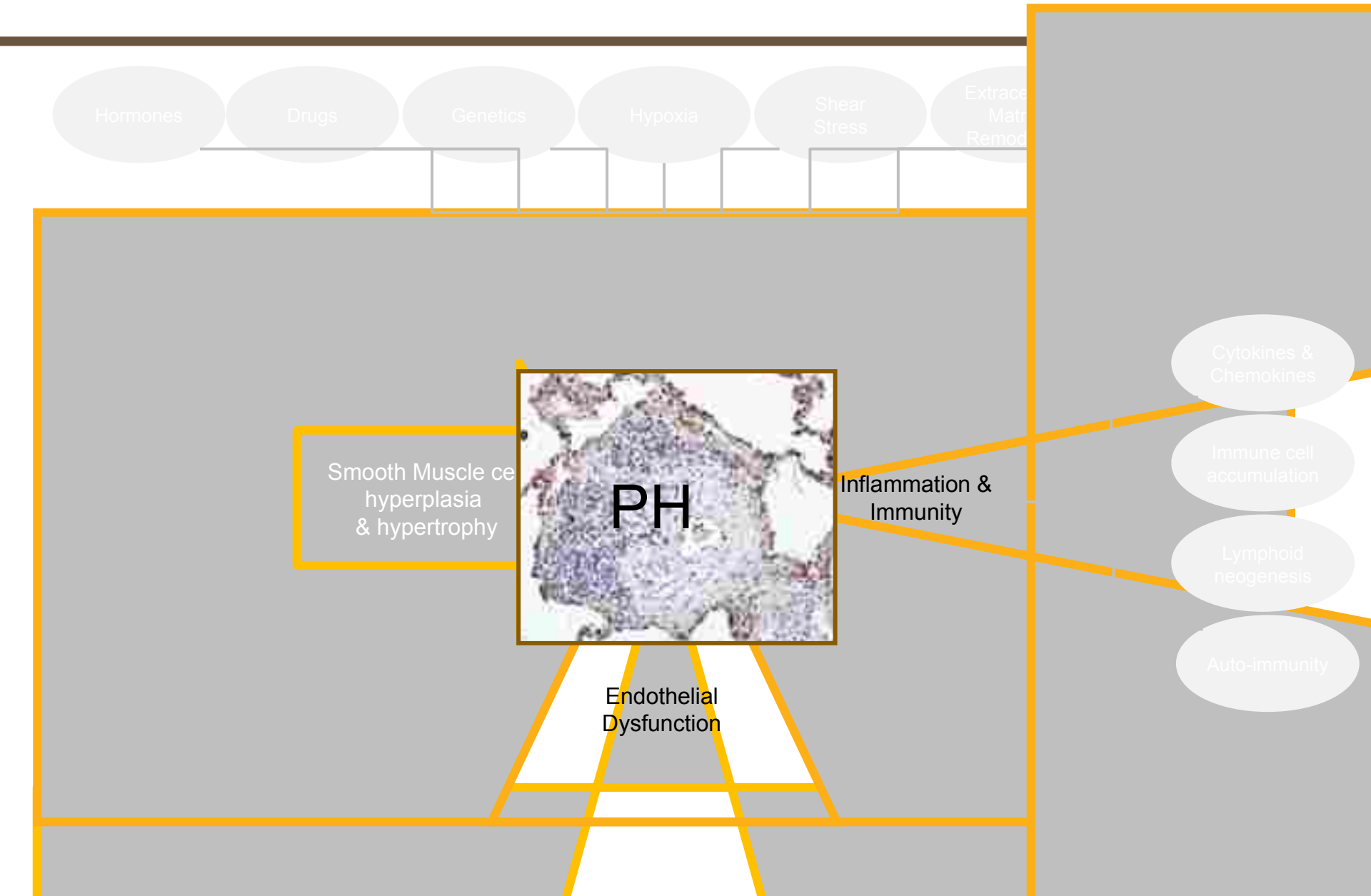


Humbert et al. Circulation 2010

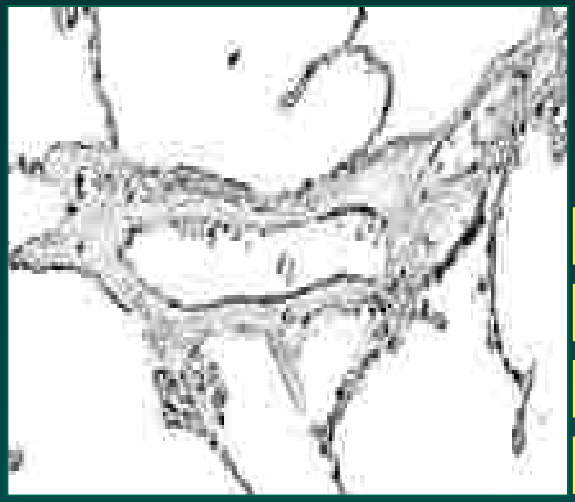
How to improve survival in PAH?

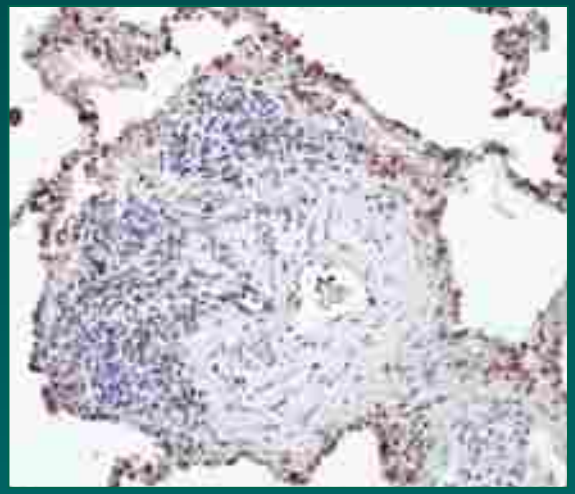
- Better assessment of disease's severity
- Better definition of treatment goals
- Early detection and early management
- Improvement in medical therapy
  - Combination therapy targeting multiple pathways
  - Novel therapies including agents targeting other pathways
- Better integration of non medical therapies (lung transplantation+++)

Pulmonary Hypertension: Pathophysiology



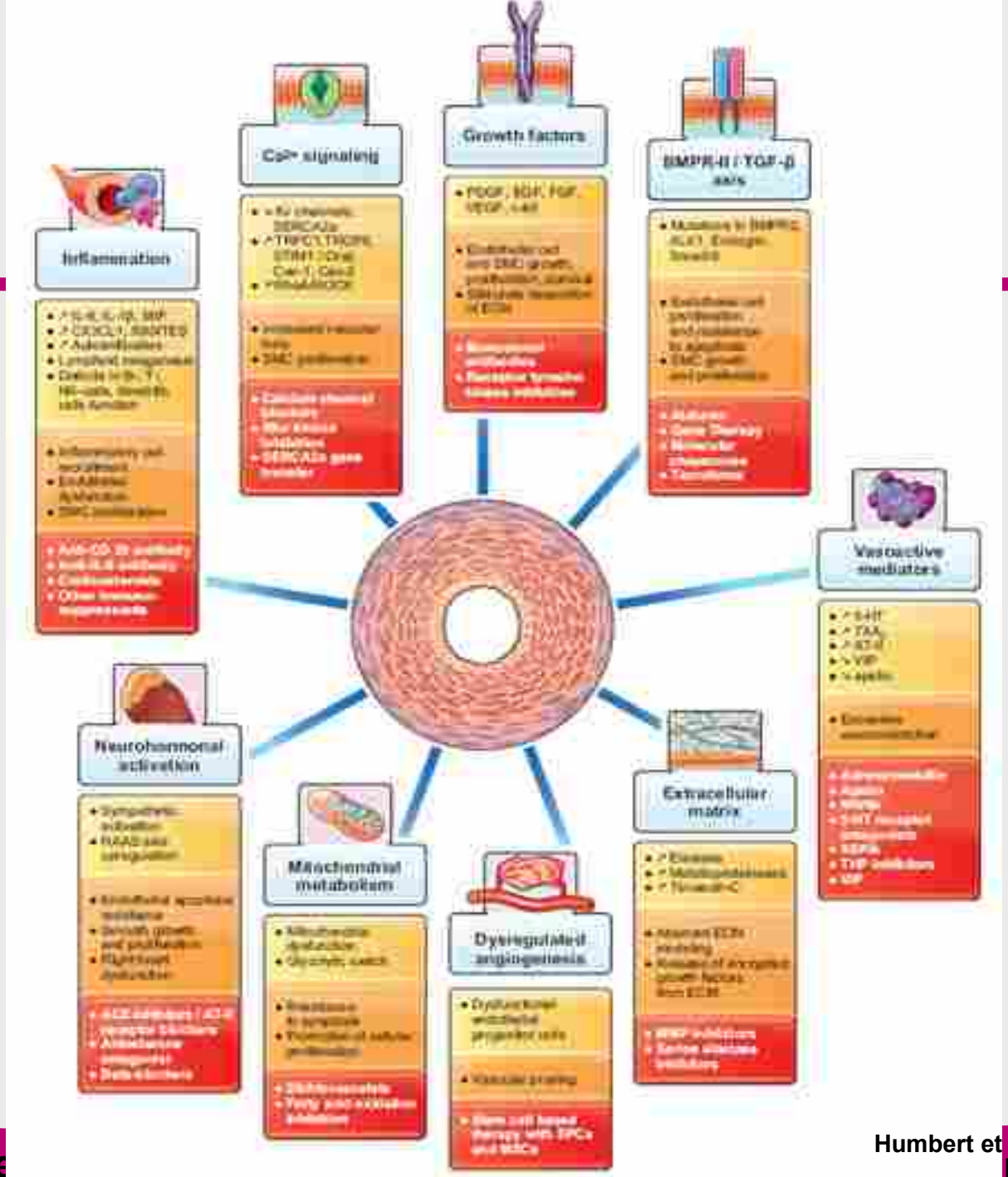
Idiopathic Pulmonary Arterial Hypertension (IPAH)



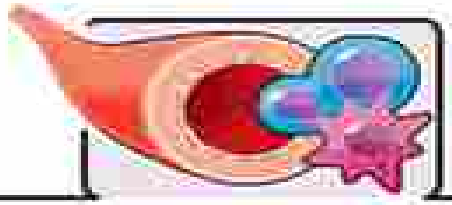


- **Vasoconstriction**
- **Genetic Predisposition**
  BMPR2 and ALK-1 pathway
- **Smooth Muscle Cell Hyperplasia**
  5-HTT, Kv1.5, Growth Factors
- **Inf ammatory cells and mediators**
  Cytokines and chemokines
  Auto-antibodies
- **Endothelial Dysfunction**
  Vaso-reactivity control (PGI2, eNOS, ET-1)
  Imbalance proliferation /apoptosis
  Cross-talk SMC/EC
- **Extracellular Matrix Deposition**
  MMP-2, MMP-9, Fibronectin, Vitronectin

Novel PAH targets



Humbert et al. Circulation 2014



Inflammation

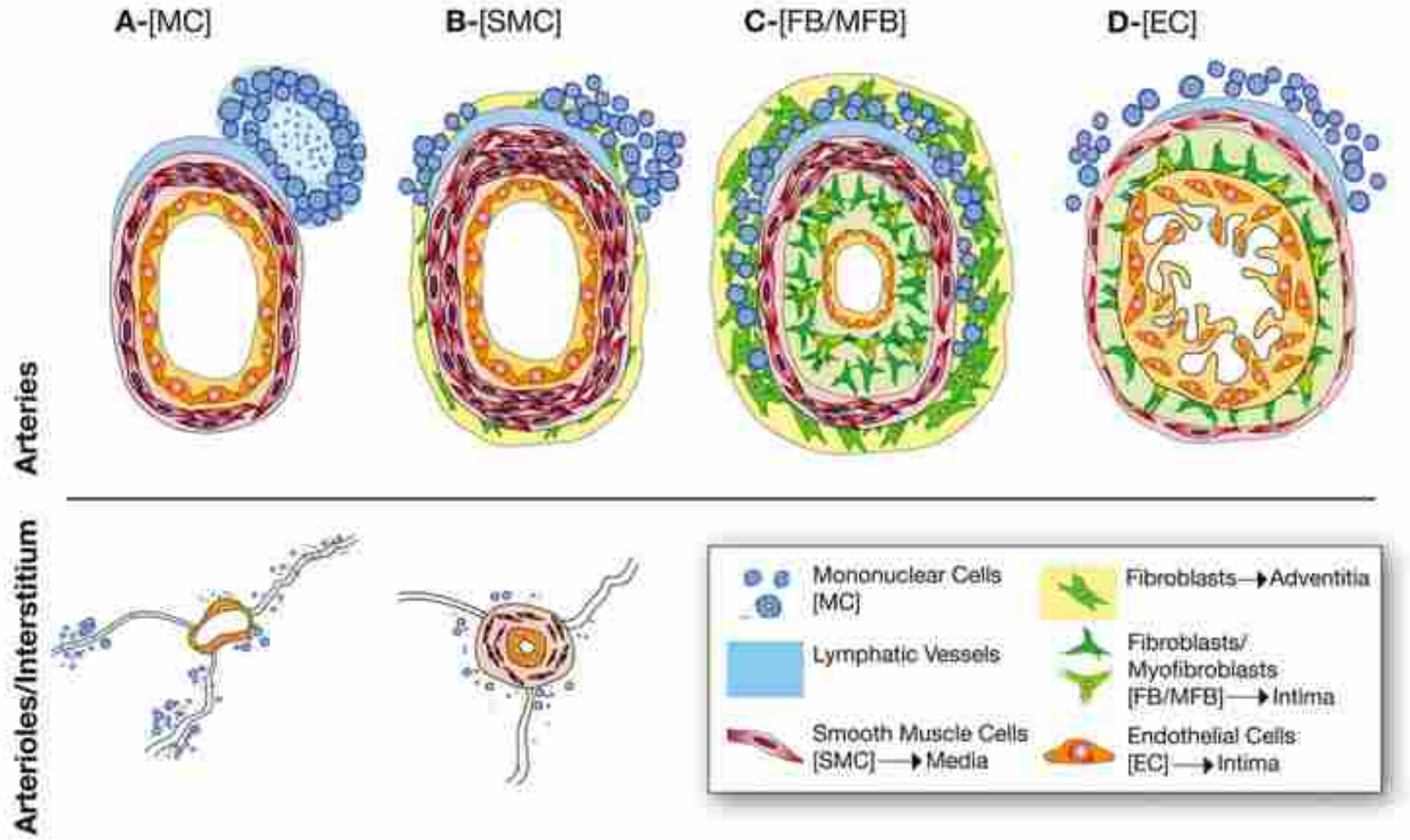
- ↗ IL-6, IL-1β, MIF
- ↗ CX3CL1, RANTES
- ↗ Autoantibodies
- Lymphoid neogenesis
- Defects in B+, T-, NK-cells, dendritic cells function

- Inflammatory cell recruitment
- Endothelial dysfunction
- SMC proliferation

- **Anti-CD 20 antibody**
- **Anti-IL-6 antibody**
- **Corticosteroids**
- **Other immuno-suppressants**

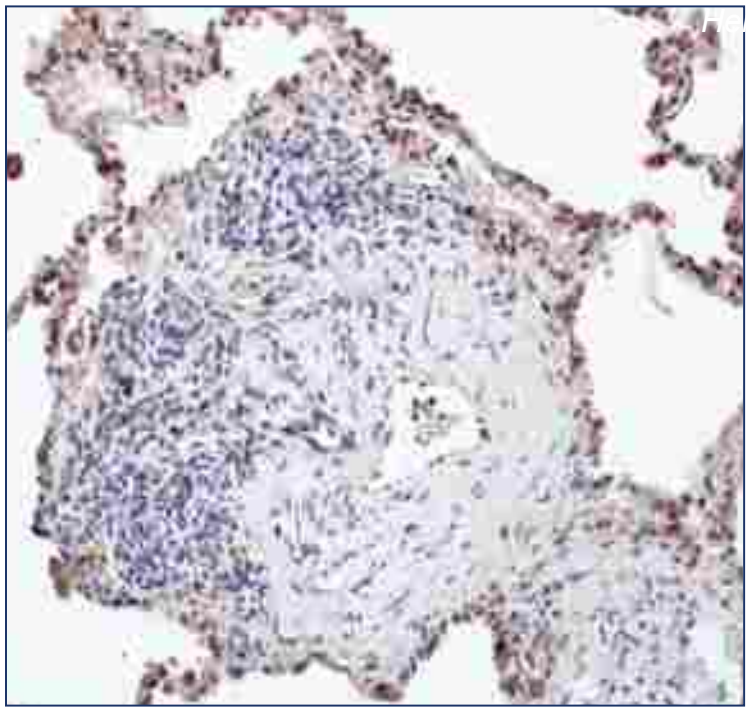
Humbert et al. Circulation 2014

Pulmonary vascular inflammation:
A common denominator of hallmark lesions of PAH



Dorfmüller & Humbert. Am J Respir Crit Care Med 2012

Increased plasma /lung cytokines & chemokines (IL-1 beta, IL-6, IL-13, MCP-1, CX3CL1, CCL5…)



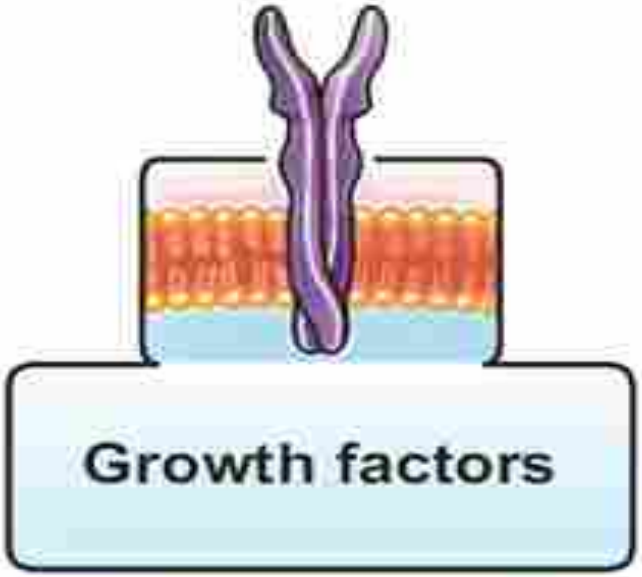
Dendritic cell recruitment and lymphoid neogenesis

Perivascular inflammatory infiltrates in PAH (macrophages and T and B lymphocytes)

Production of auto-antibodies (endothelial cells, SMC, fibroblasts)

Adaptive immune responses in PAH

- The major manifestation of adaptive immune responses in PAH lies in signs of autoimmunity in the pathobiology of the disease
- Local adaptive (auto-immune) response against vascular components may develop in ectopic perivascular lymphoid follicles
- Dysregulated adaptive immunity may be favored by impaired function of regulatory cells like Treg, but also NKT and NK cells in PAH
- This impairment may be mediated by endothelium-derived mediators such as cytokines and leptin
- Identification of endothelial signals that drive and/or amplify this immune response, and of molecular targets of this response may have therapeutic implication



Growth factors

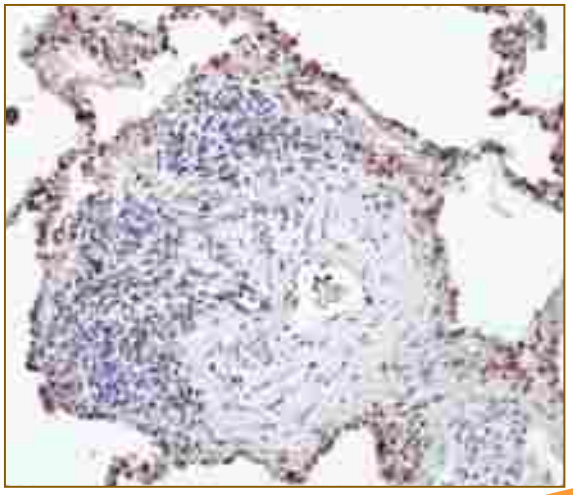
- PDGF, EGF, FGF, VEGF, c-kit

- Endothelial cell and SMC growth, proliferation, survival
- Stimulate deposition of ECM

- **Monoclonal antibodies**
- **Receptor tyrosine kinase inhibition**

Humbert et al. Circulation 2014

An Imbalance between Proliferation and Apoptosis



PROLIFERATION

APOPTOSIS
BMP Pathway

Serotonin Pathway

Kv1.5 Potassium Channels

PPAR γ

Cytokines

AUTOPHAGY
LC3

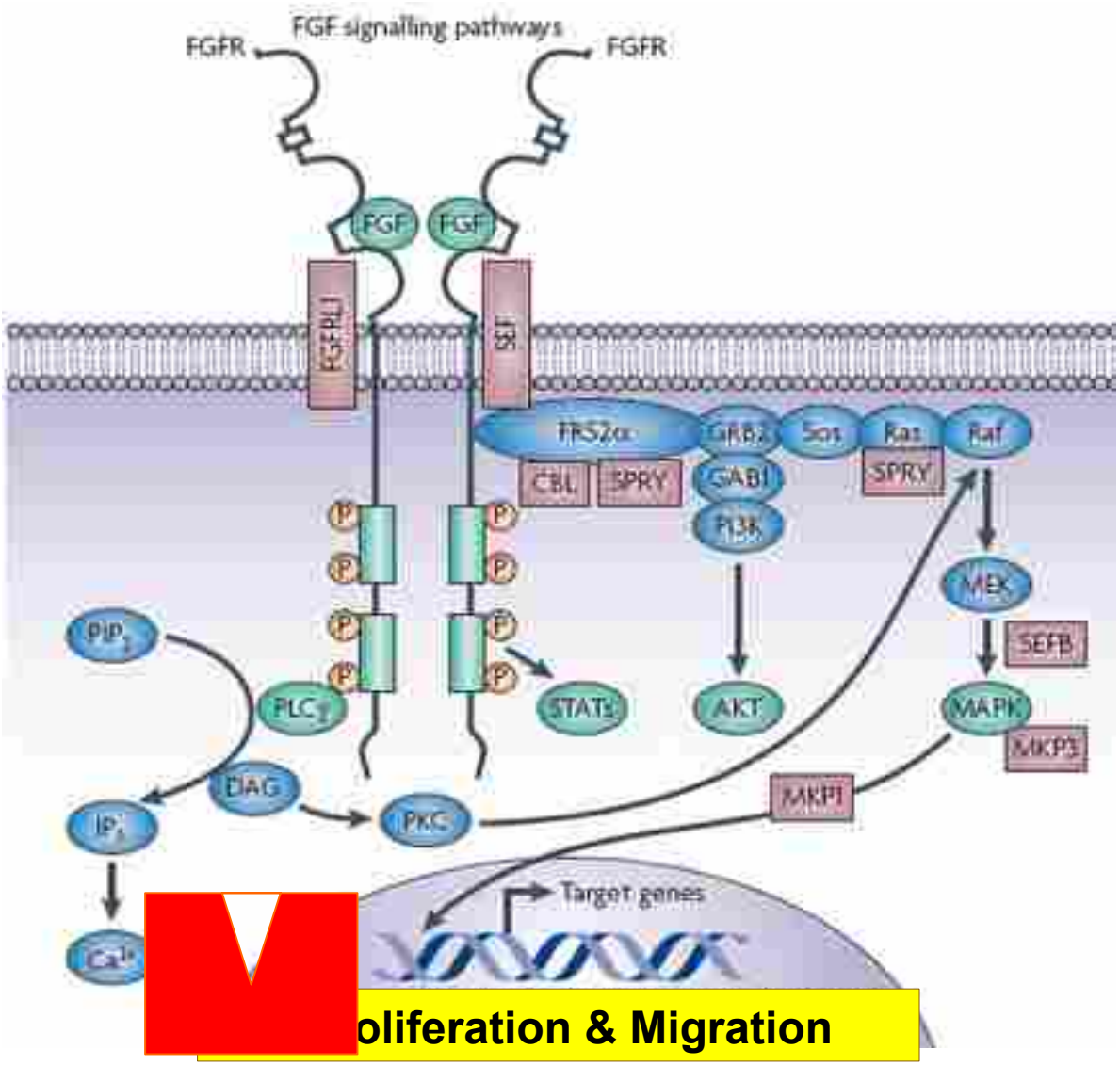
Growth Factors & RTKs
(PDGF, EGF, FGF2…)

Increased Activators of Cellular Proliferation and/or Migration : Growth factors

Epidermal Growth Factor
Receptor Blockade Mediates Smooth Muscle Cell Apoptosis and Improves Survival in Rats With Pulmonary Hypertension

Reversal of experimental pulmonary hypertension by **PDGF** inhibition

Endothelial-derived **FGF2** contributes to the progression of pulmonary hypertension in humans and rodents

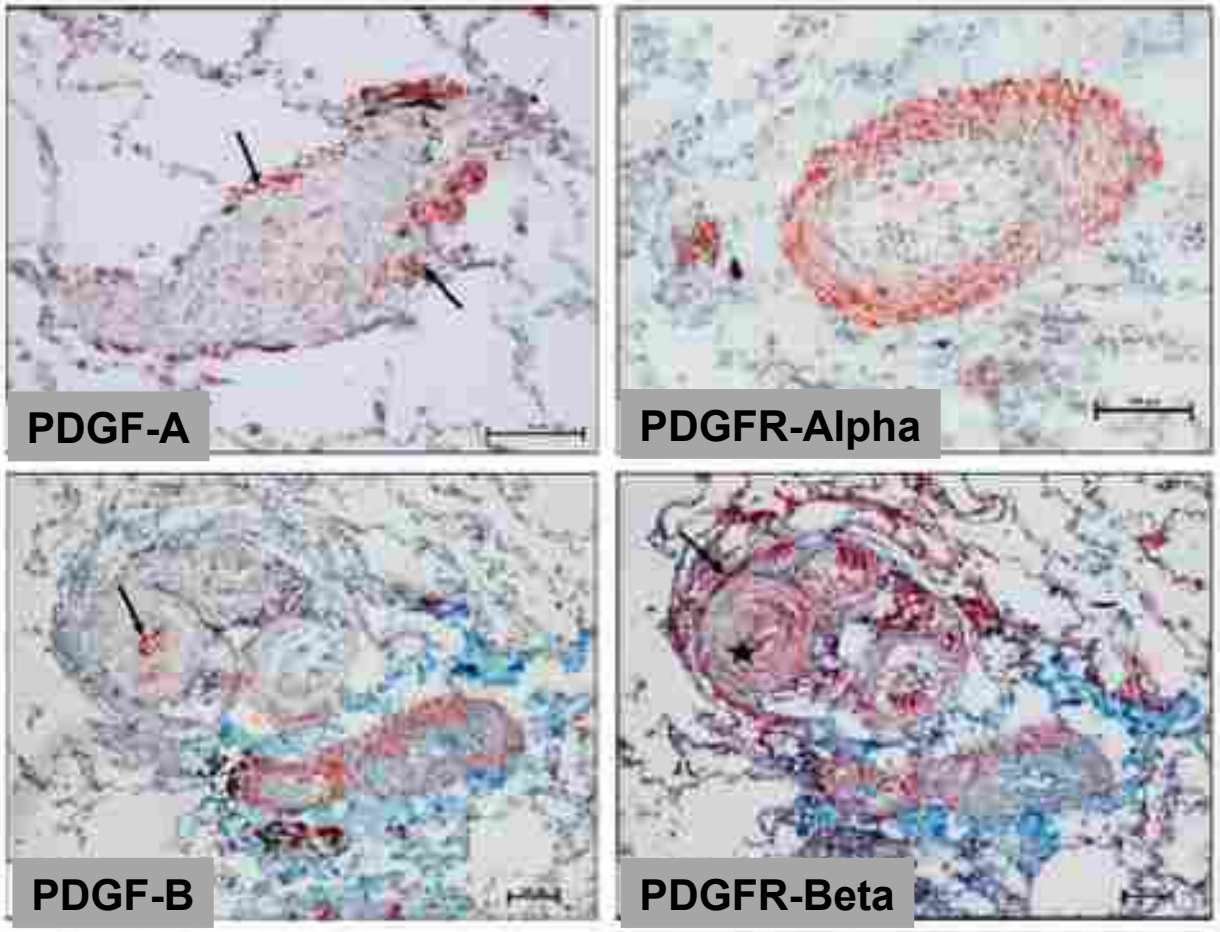


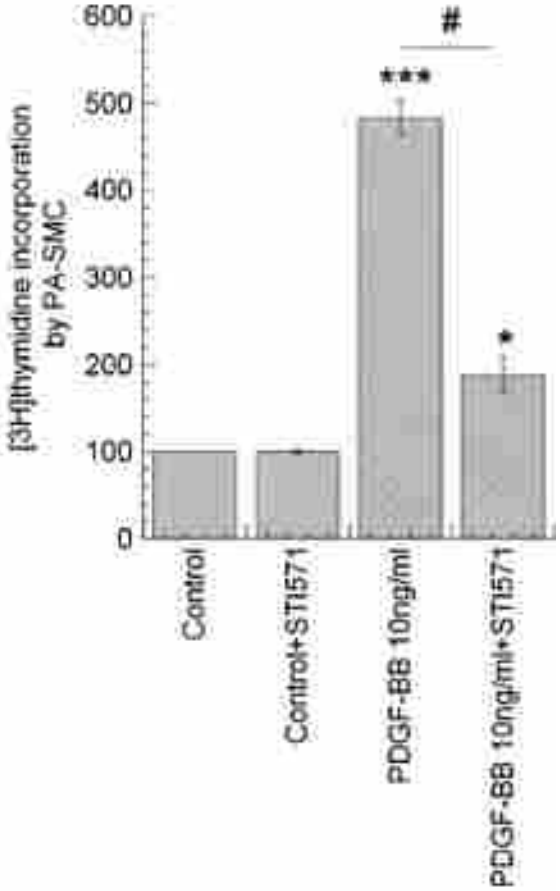
oliferation & Migration

L.Tu, AJRCMB, 2011
M. Izziki, JCI, 2009
F.Perros, AJRCCM, 2008
RT. Schermuly, JCI, 2005
SL. Merklinger, Circulation, 2005

Increased Activators of Cellular Proliferation and/or Migration : PDGF

Increased expression of PDGF and their receptors

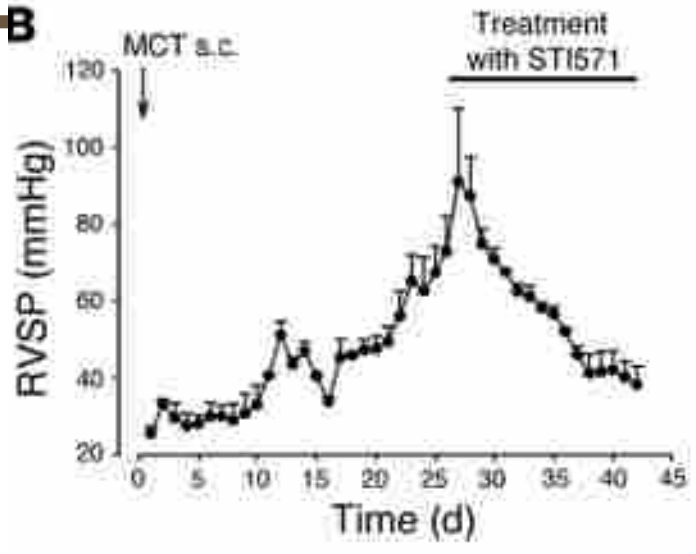


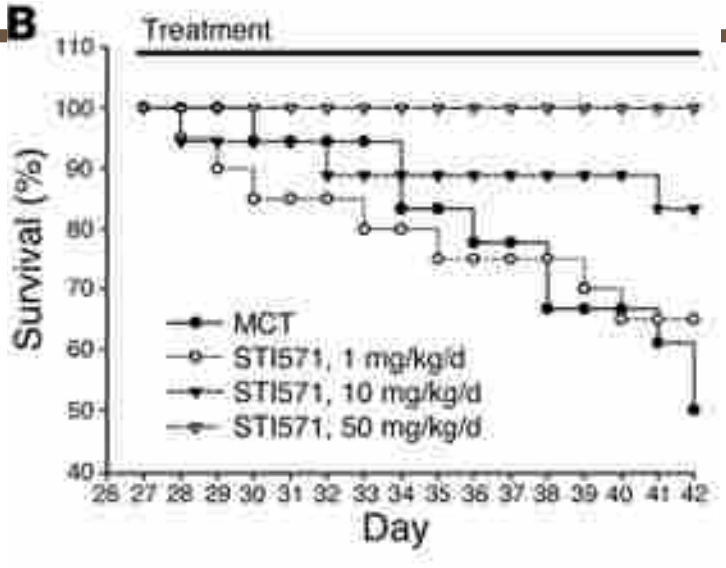


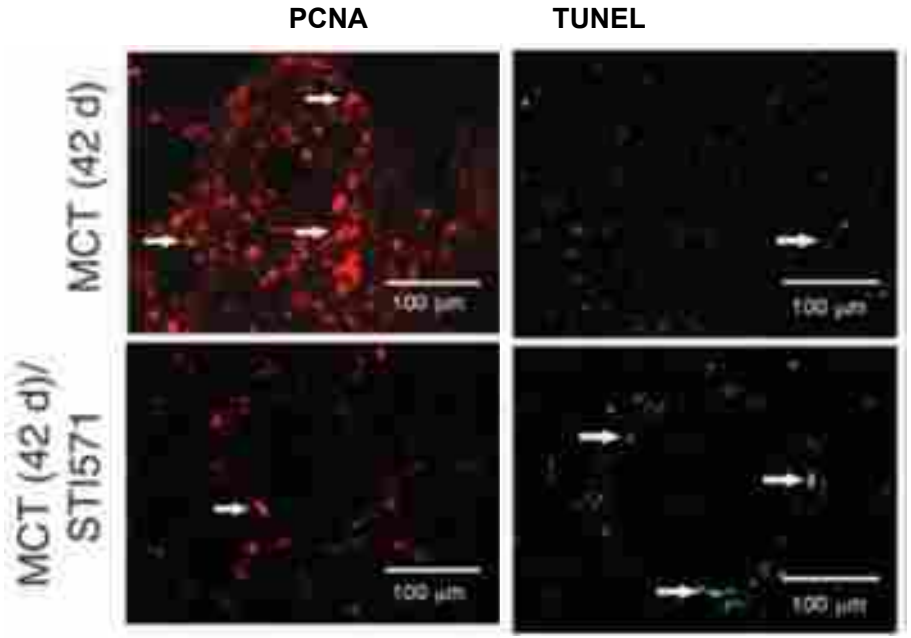
PDGF BB induces SMC proliferation

Perros, el al. Am J Resp Crit Care Med 2008

Increased Activators of Cellular Proliferation and/or Migration : PDGF







- **Imatinib reverses established PH induced by monocrotaline injection.**
- **Regression of medial hypertrophy induced by STI571 (50 mg/kg/d) was attributed to reduced SMC proliferation and increased apoptosis**
- **Clinical trial : IMPRES unfavorable efficacy/safety**

Schermuly, et al. J Clin Invest 2005
Hoeper, et al. Circulation 2013

IMPRESsion, Sunset

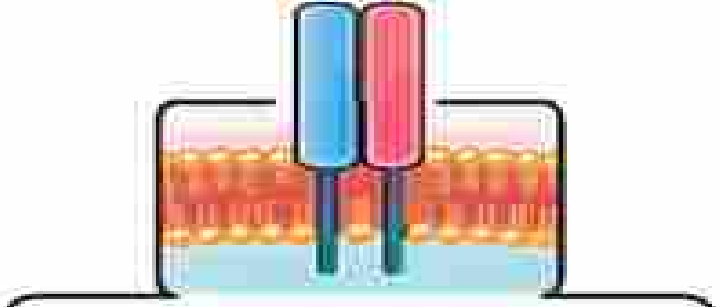
Impression, Soleil Levant
Impression, Sunrise

"There is little doubt, that the overall risks conferred with most if not all kinase inhibitors that have been proposed recently as treatments for PAH outweigh any potential benefits.

A better understanding of the pathways involved in the efficacy and safety aspects of imatinib will be paramount in the design of more targeted and better tolerated agents in the field of personalized PAH medicine.

Until then, healthcare professionals should be discouraged from offering compassionate imatinib therapy to PAH patients."

Humbert et al. Circulation 2013



BMPR-II / TGF-β axis

- Mutations in BMPR2, ALK1, Endoglin, Smad-9

- Endothelial cell proliferation and resistance to apoptosis
- SMC growth and proliferation

- **Ataluren**
- **Gene Therapy**
- **Molecular chaperones**
- **Tacrolimus**

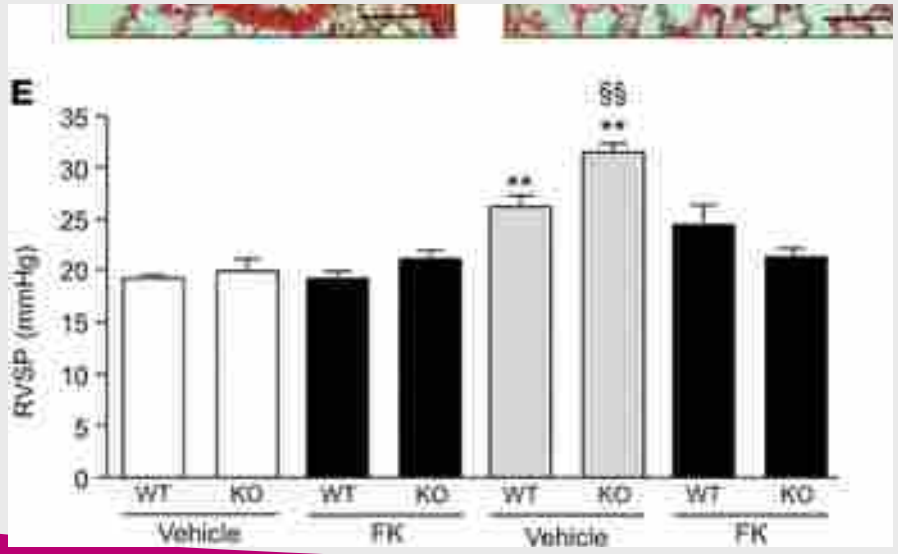
Humbert et al. Circulation 2014

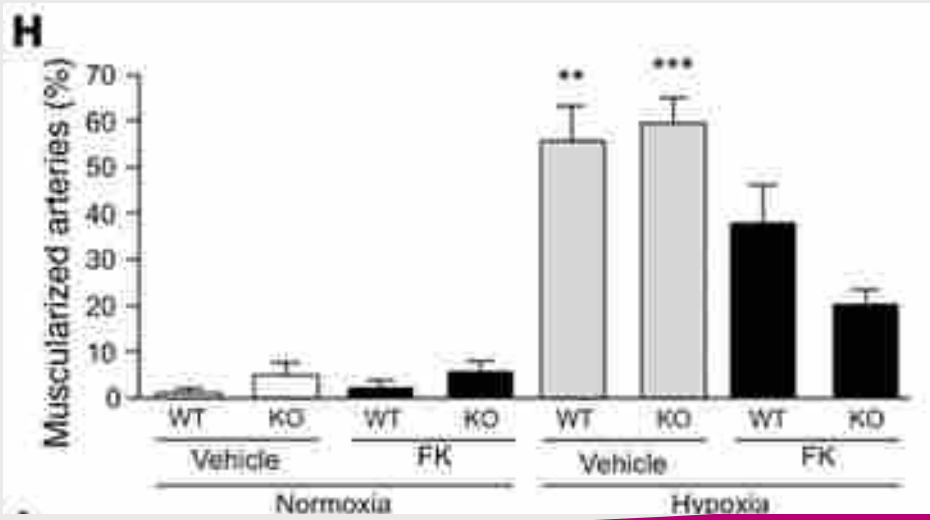
Tacrolimus in experimental PH

Research article

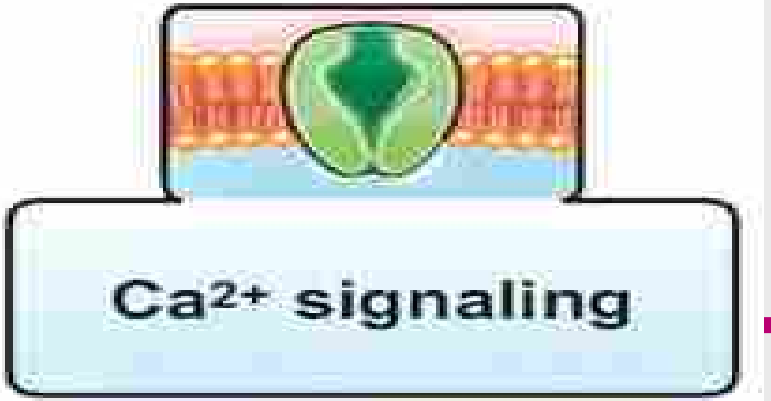
FK506 activates BMPR2, rescues endothelial dysfunction, and reverses pulmonary hypertension

Edda Spiekerkoetter,[1,2,3] Xuefei Tian,[1,2] Jie Cai,[4] Rachel K. Hopper,[1,5] Deepti Sudheendra,[1,2] Caiyun G. Li,[1,5] Nesrine El-Bizri,[1] Hirofumi Sawada,[1] Roxanna Haghighat,[5] Roshelle Chan,[5] Leila Haghighat,[5] Vinicio de Jesus Perez,[1,2,3] Lingli Wang,[1,5] Sushma Reddy,[3,5] Mingming Zhao,[5] Daniel Bernstein,[3,5] David E. Solow-Cordero,[6] Philip A. Beachy,[7] Thomas J. Wandless,[8] Peter ten Dijke,[4] and Marlene Rabinovitch[1,3,5]





Spiekerkoetter et al. J Clin Invest



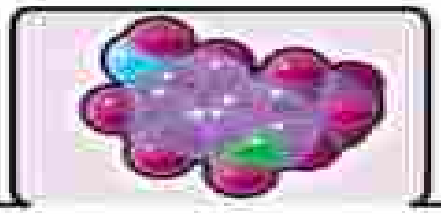
Ca^{2+} signaling

- ↘ Kv channels, SERCA2a
- ↗ TRPC1, TRCP6, STIM1 / Orai, Cav-1, Cav-2
- ↗ RhoA/ROCK

- Increased vascular tone
- SMC proliferation

- Calcium channel blockers
- Rho kinase inhibition
- SERCA2a gene transfer

Humbert et al. Circulation 2014



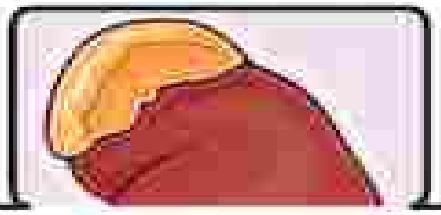
Vasoactive mediators

- ↗ 5-HT
- ↗ TXA_2
- ↗ AT-II
- ↘ VIP
- ↘ apelin

- Excessive vasoconstriction

- Adrenomedullin
- Apelin
- Nitrite
- 5-HT receptor antagonists
- SSRIs
- THP inhibitors
- VIP

Humbert et al. Circulation 2014



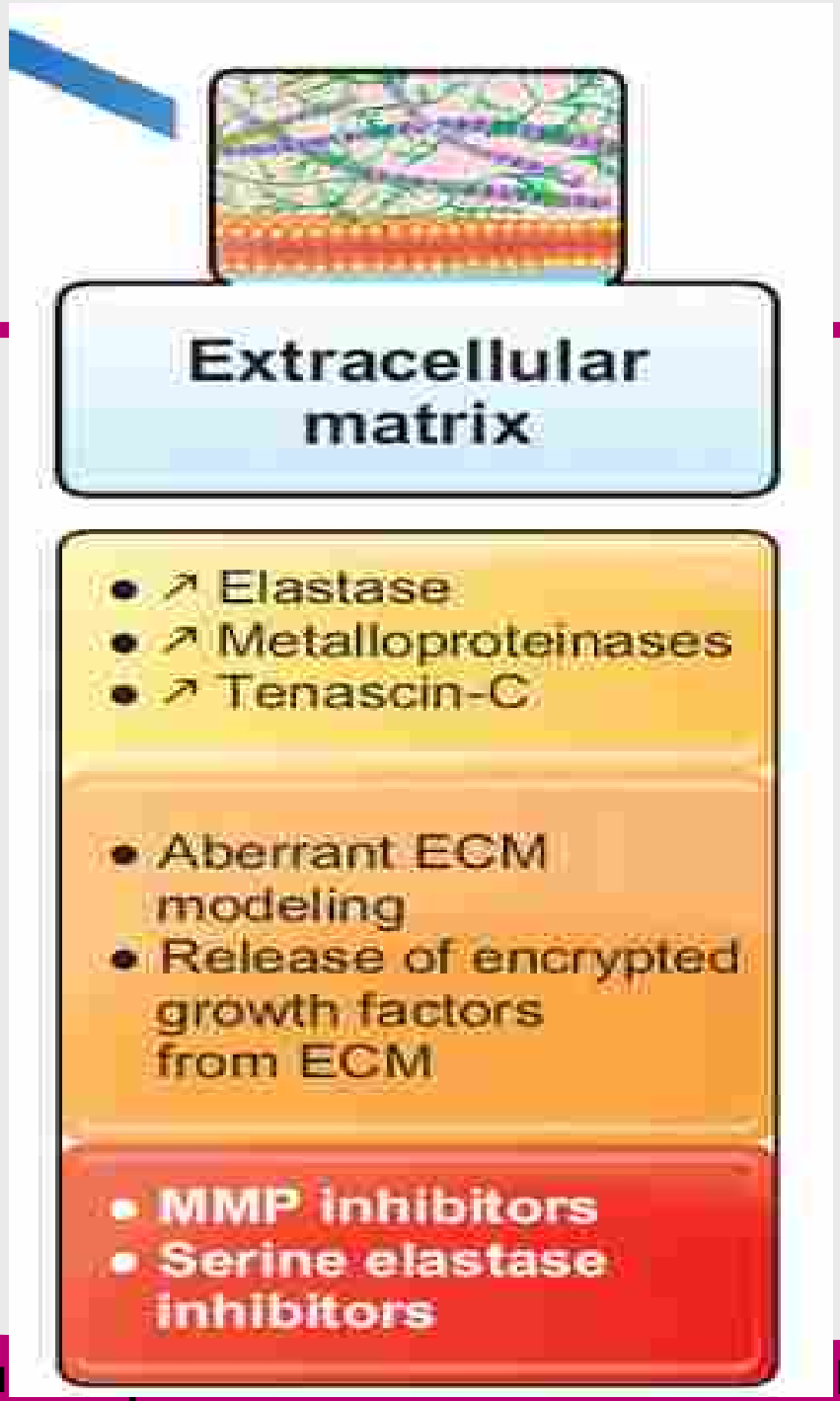
Neurohormonal activation

- Sympathetic activation
- RAAS axis upregulation

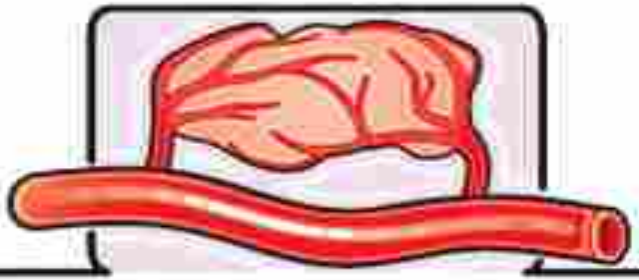
- Endothelial apoptosis resistance
- Smooth growth and proliferation
- Right heart dysfunction

- ACE inhibitors / AT-II receptor blockers
- Aldosterone antagonist
- Beta-blockers

Humbert et al. Circulation 2014



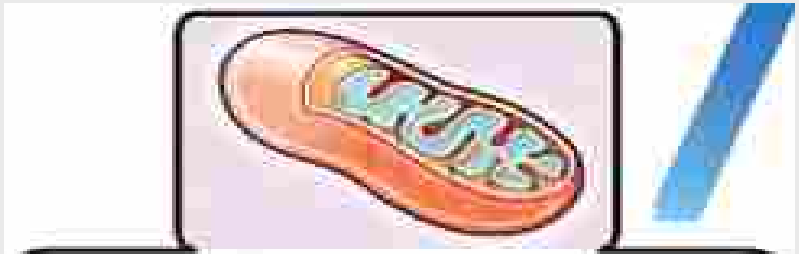
Humbert et al. Circulation 2014



Dysregulated angiogenesis

- Dysfunctional endothelial progenitor cells
- Vascular pruning
- **Stem cell based therapy with EPCs and MSCs**

Humbert et al. Circulation 2014



Mitochondrial metabolism

- Mitochondrial dysfunction
- Glycolytic switch

- Resistance to apoptosis
- Promotion of cellular proliferation

- **Dichloroacetate**
- **Fatty acid oxidation inhibition**

Humbert et al. Circulation 2014

CONCLUSION
Translational Research in PAH
Challenges and Opportunities

- Pulmonary hypertension is a fast growing field of cardio-pulmonary medicine
- 10 drugs approved targeting 3 major pathways of endothelial dysfunction
- Strong translational research has identified a large number of novel targets. A major challenge in a rare disease will be to prioritize drug discovery and development in a rare disease with a major unmet need
  - **Inflammation**
  - **Growth factors**
  - **BMPR2/TGF beta signaling**
  - **Calcium signaling**
  - **Vasoactive peptides**
  - **Neurohormonal activation**
  - **Extracellular matrix**
  - **Dysregulated angiogenesis**
  - **Mitochondrial metabolism**