

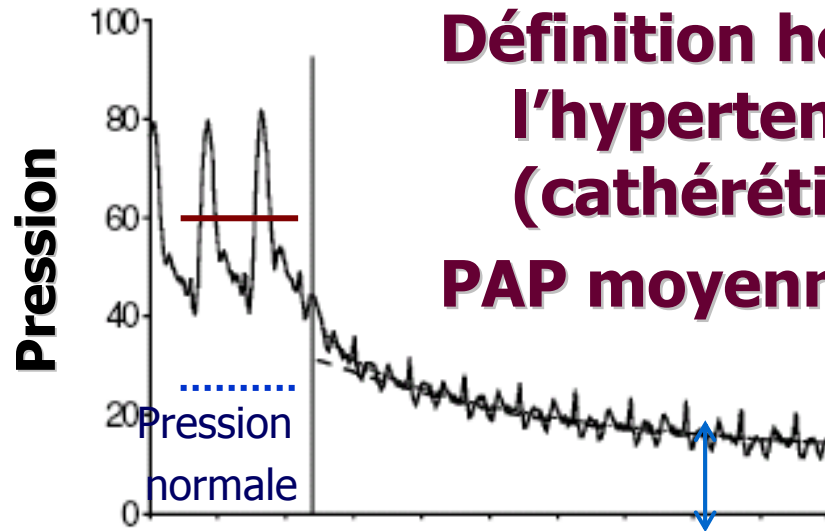
Aspects physiopathologiques de l'hypertension artérielle pulmonaire

Luc Mouthon

Internal Medicine department, Hôpital Cochin, Paris, France
& French National Center for Necrotizing vasculitis and systemic Sclerosis
Paris Descartes University, Faculty of Medicine, Cochin Institute, INSERM U1016,
CNRS UMR 8104, Paris, France;



HTAP: définition



Définition hémodynamique de l'hypertension pulmonaire (cathérétisme droit)

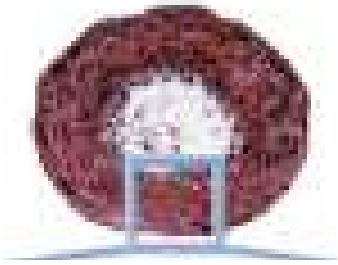
PAP moyenne > 25 mmHg au repos

Définition hémodynamique de l'hypertension artérielle pulmonaire (cathérétisme droit):

- PAP moyenne > 25 mmHg au repos

Et

- Pression capillaire pulmonaire < 15 mmHg au repos

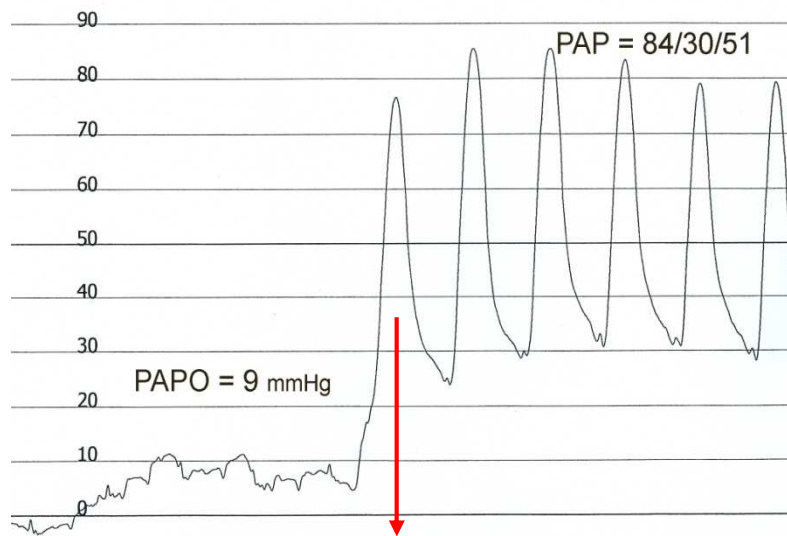


HTP pré et post capillaire

Définition

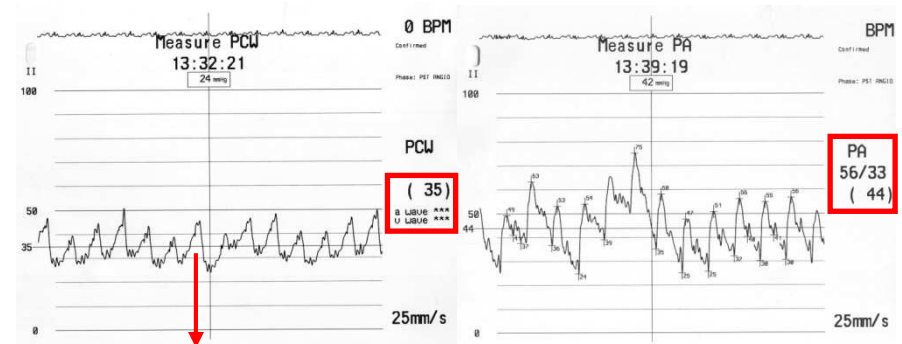


HTP pré capillaire



- $PAPm \geq 25 \text{ mmHg}^1$
- $PAPO \leq 15 \text{ mmHg}^1$
- $PAPd - PAPO > 10 \text{ mmHg}^2$

HTP post capillaire passive



- $PAPm \geq 25 \text{ mmHg}^1$
- $PAPO > 15 \text{ mmHg}^1$
- $GTP \leq 12 \text{ mmHg}^1$
- $PAPd - PAPO \leq 10 \text{ mmHg}^2$

1. Galiè N et al. *Eur Respir J* 2009
2. Chemla D et al. *Eur Respir J* 2002

Updated clinical classification of pulmonary hypertension

(4th PH World Conference – Dana Point, CA – Feb 2008)

1. Pulmonary Arterial Hypertension

- 1.1. Idiopathic PAH
- 1.2. Heritable
 - 1.2.1. BMPR2
 - 1.2.2. ALK1, endoglin (with or w/o HHT)
 - 1.2.3. Unknown
- 1.3. Drugs and toxins induced
- 1.4. Associated with:
 - 1.4.1. Connective tissue diseases
 - 1.4.2. HIV infection
 - 1.4.3. Portal hypertension
 - 1.4.4. Congenital heart diseases
 - 1.4.5. Schistosomiasis
 - 1.4.6. Chronic haemolytic anemia
- 1.5. Persistent PH of the newborn

1'. PVOD and PCH

2. PH due to left heart diseases

- 2.1. Systolic dysfunction
- 2.2. Diastolic dysfunction
- 2.3. Valvular disease

3. PH due to lung diseases and/or hypoxia

- 3.1. COPD
- 3.2. Interstitial lung diseases
- 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 abnormalities

4. Chronic Thromboembolic PH (CTEPH)

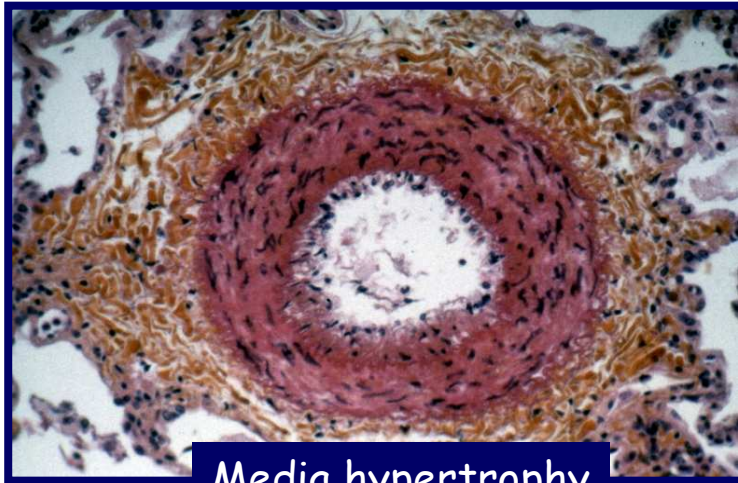
5. PH with unclear and/or multifactorial mechanisms

- 5.1. Haematological disorders : myeloproliferative disorders splenectomy.
- 5.2. Systemic disorders, Sarcoidosis, pulmonary Langerhans cell histiocytosis, LAM, neurofibromatosis, vasculitis
- 5.3. Metabolic disorders : Glycogen storage disease, Gaucher disease, Thyroid disorders
- 5.4. Others : tumoral obstruction, fibrosing mediastinitis, chronic renal failure on dialysis.

HYPERTENSION ARTERIELLE PULMONAIRE

Anatomopathologie

- Prolifération des cellules musculaires lisses et des cellules endothéliales



Media hypertrophy



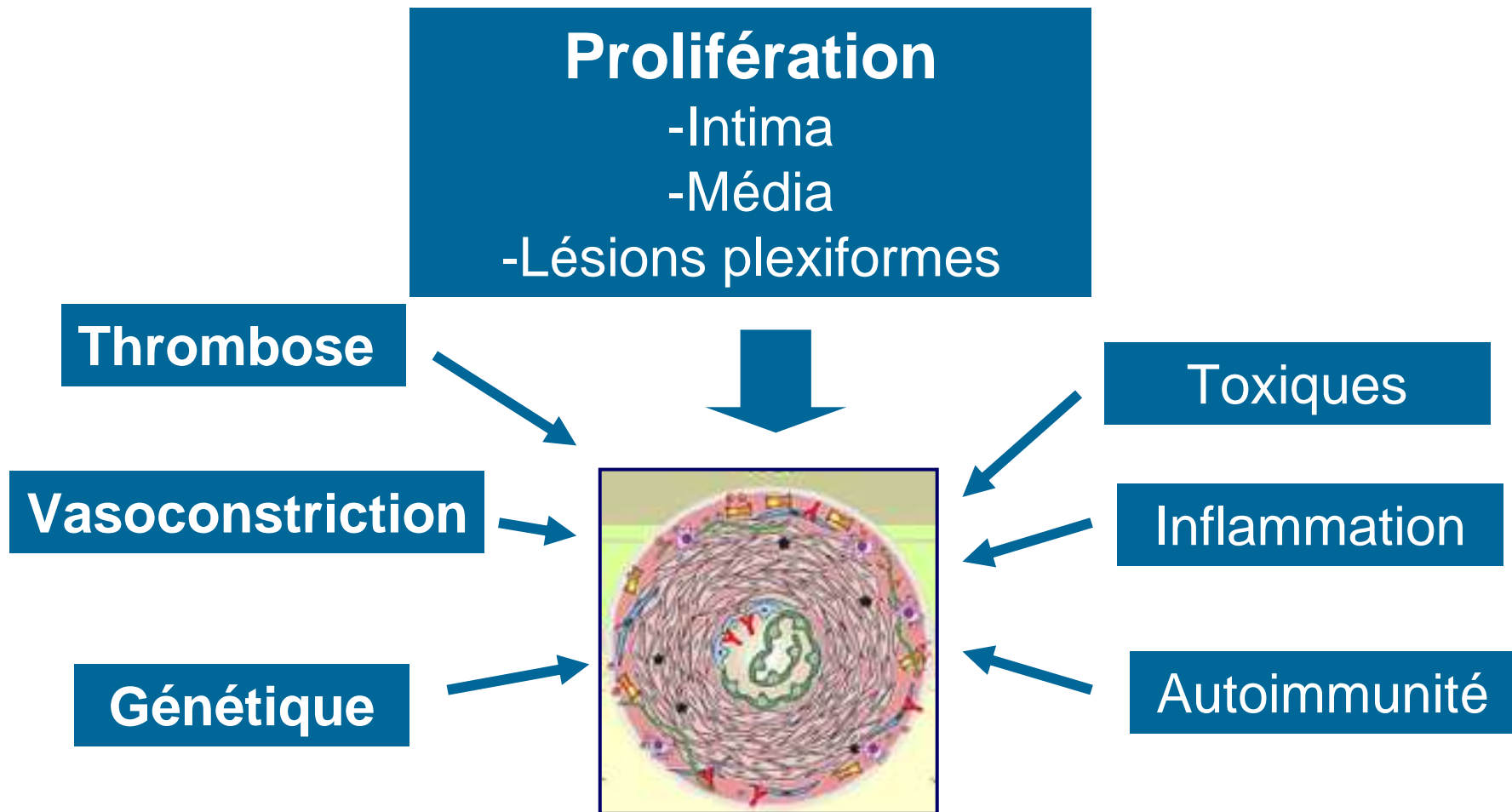
Intimal proliferation / thickening



Plexiform lesions

Courtesy of Marc Humbert

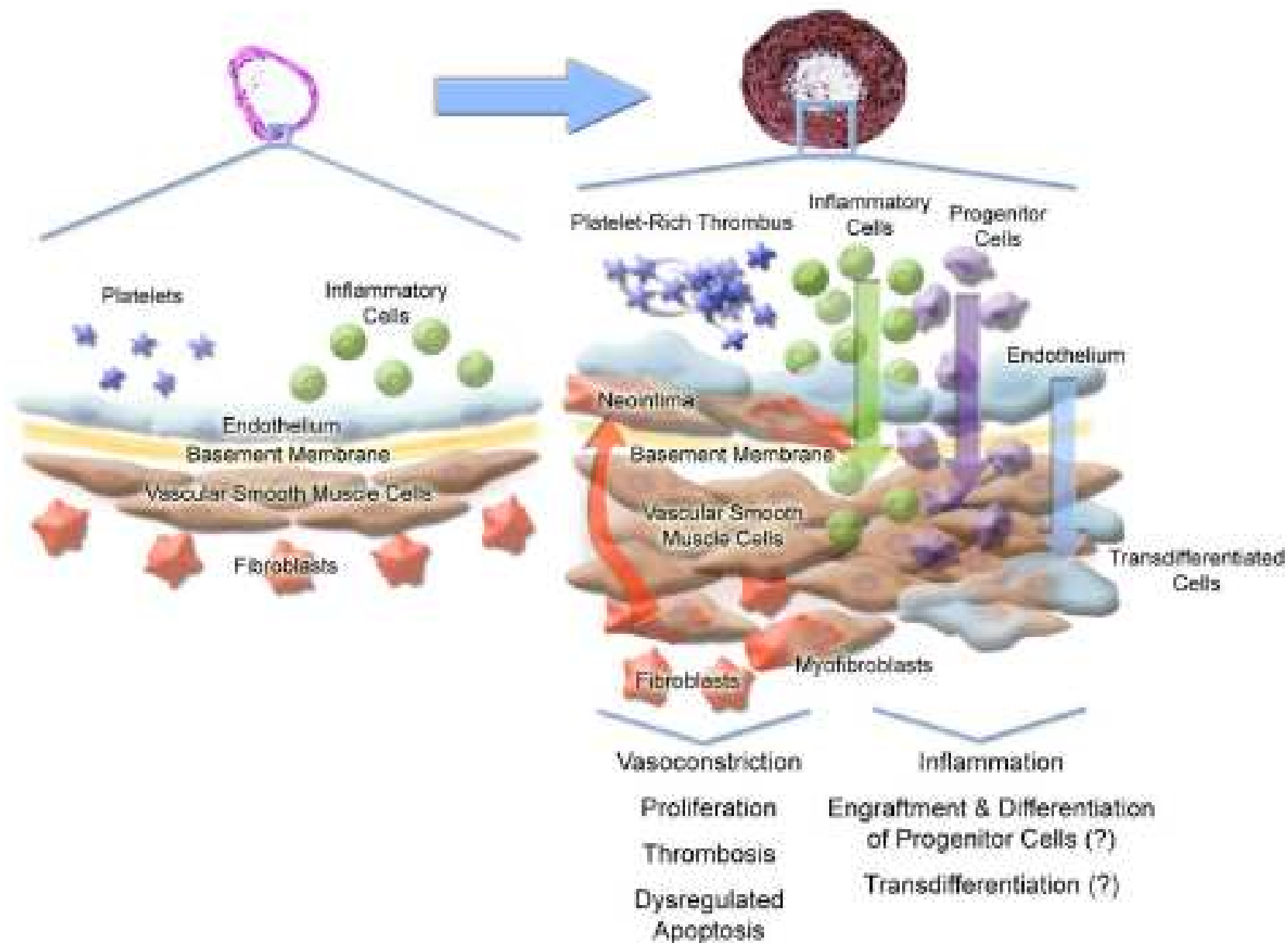
HTAP: principaux mécanismes en cause



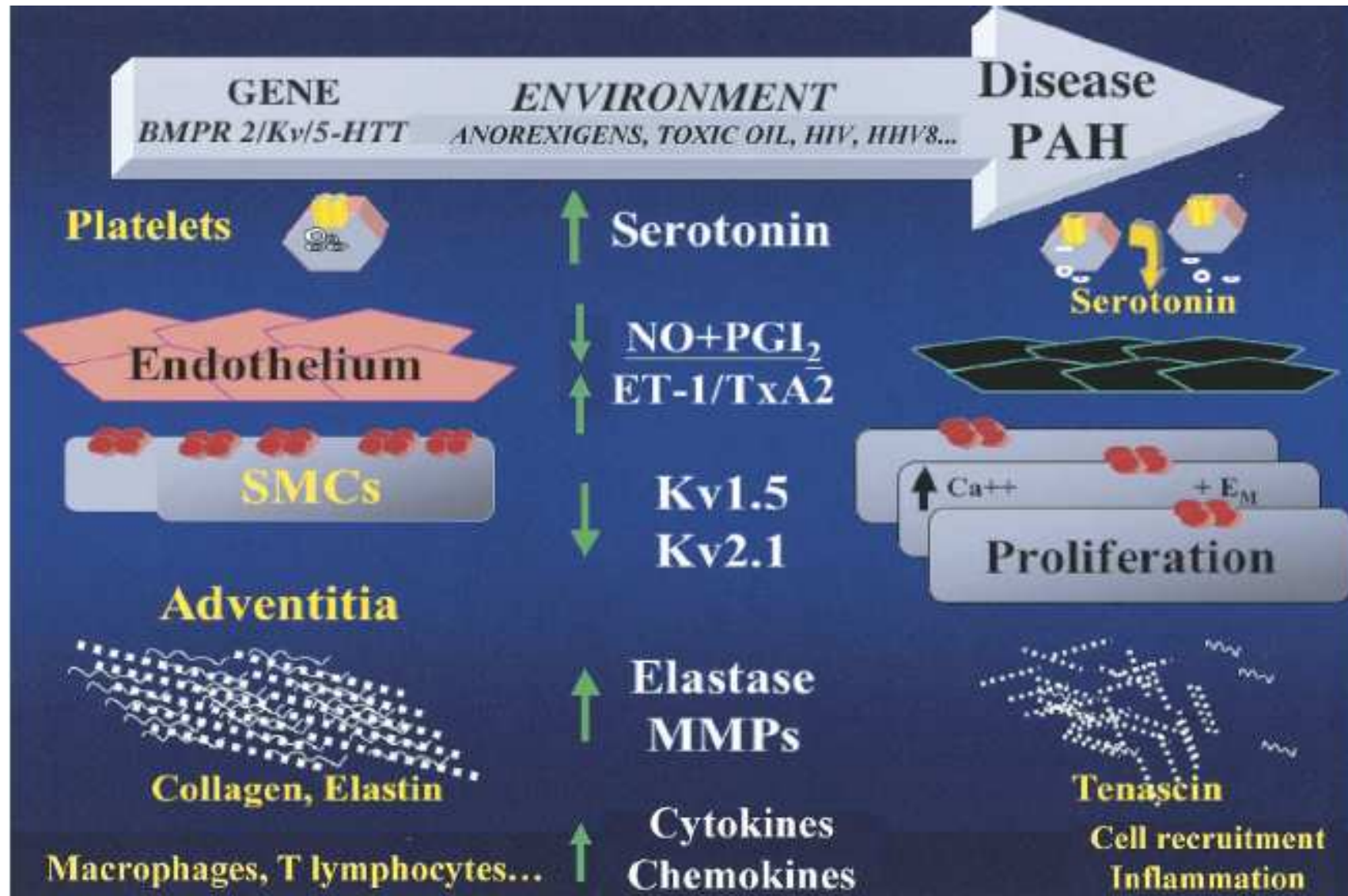
Réduction de la lumière artériolaire pulmonaire

Remodelage vasculaire

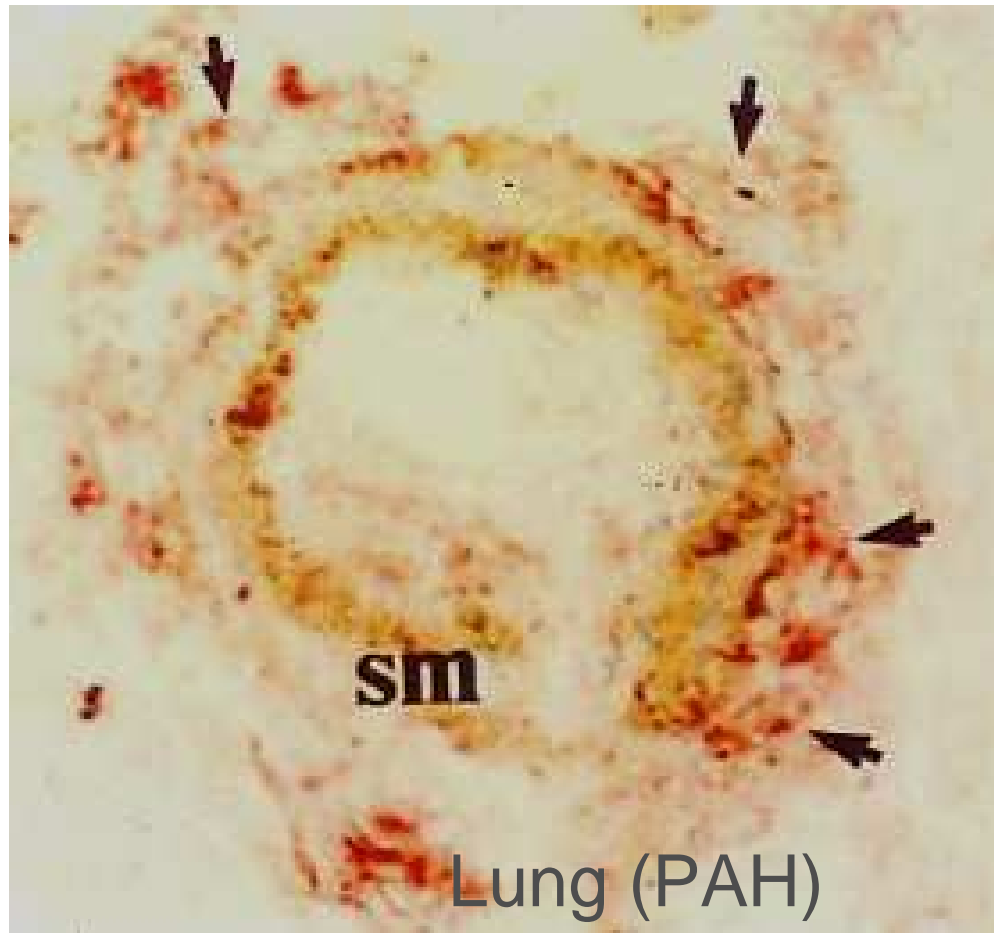
Physiopathologie de l'HTAP



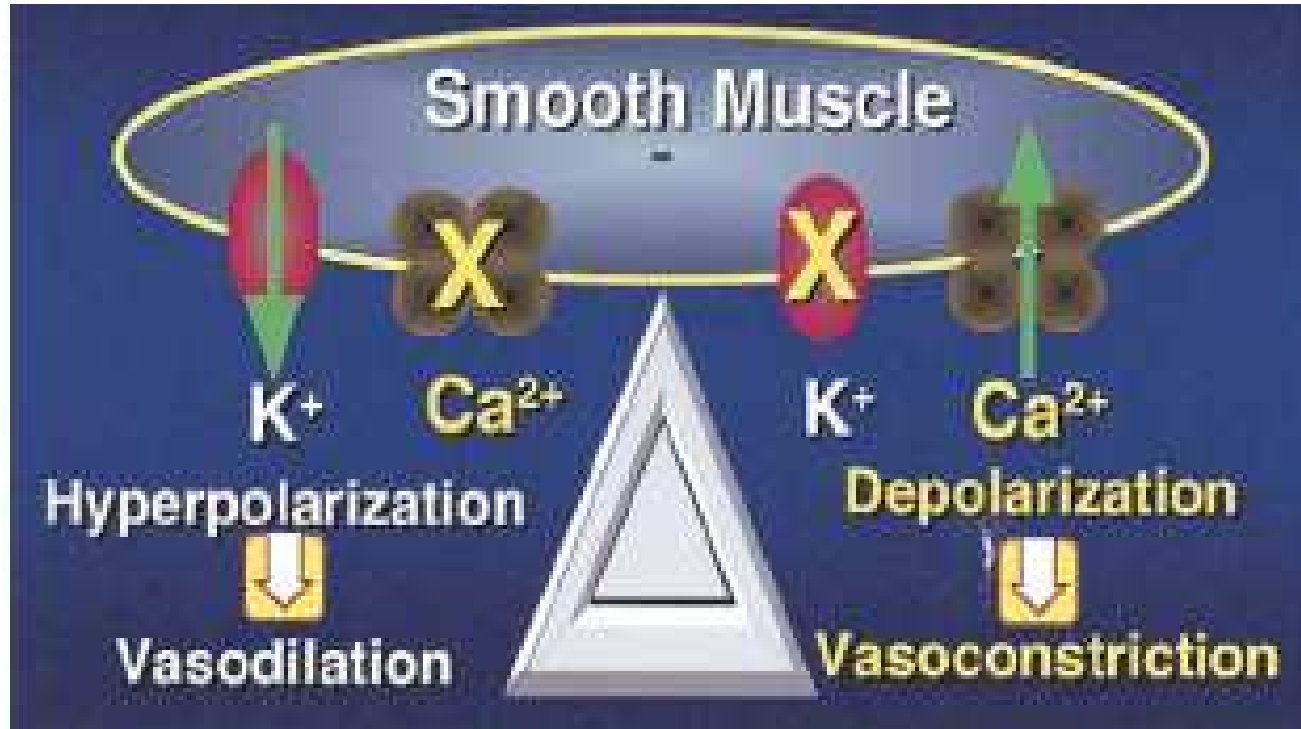
Physiopathologie de l'HTAP



Expression de l'endothéline 1 au sein des lésions de remodelage au cours de l'HTAP



La balance de tonus dans les cellules musculaires lisses d'artère pulmonaire



L'activité des canaux potassiques voltage-dépendants (Kv) dans les cellules musculaires lisses vasculaires modifie le tonus vasculaire. Au cours de l'HTAP, la perte sélective des canaux Kv (comme les Kv1.5) entraîne une dépolarisation des cellules musculaires lisses artérielles pulmonaires et une augmentation du calcium intra-cellulaire, entraînant à la fois une vasoconstriction et une

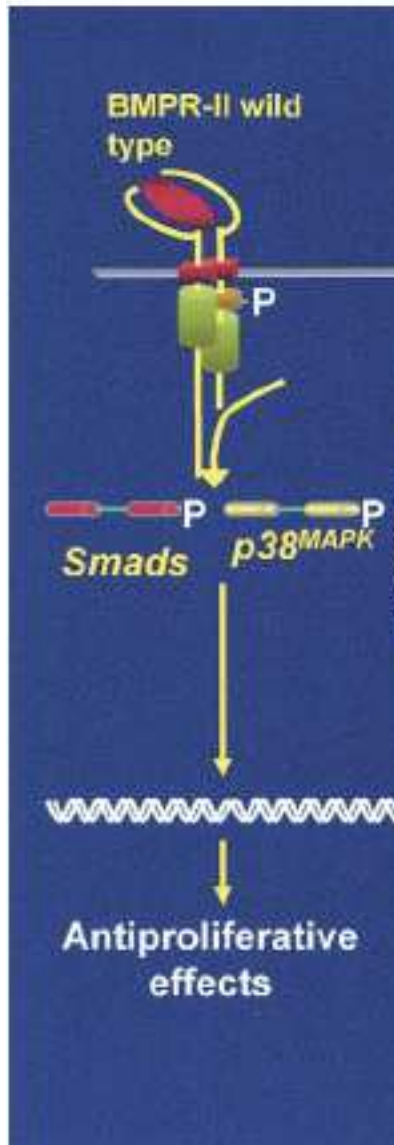
prolifération cellulaire

Humbert et al. JACC 2004

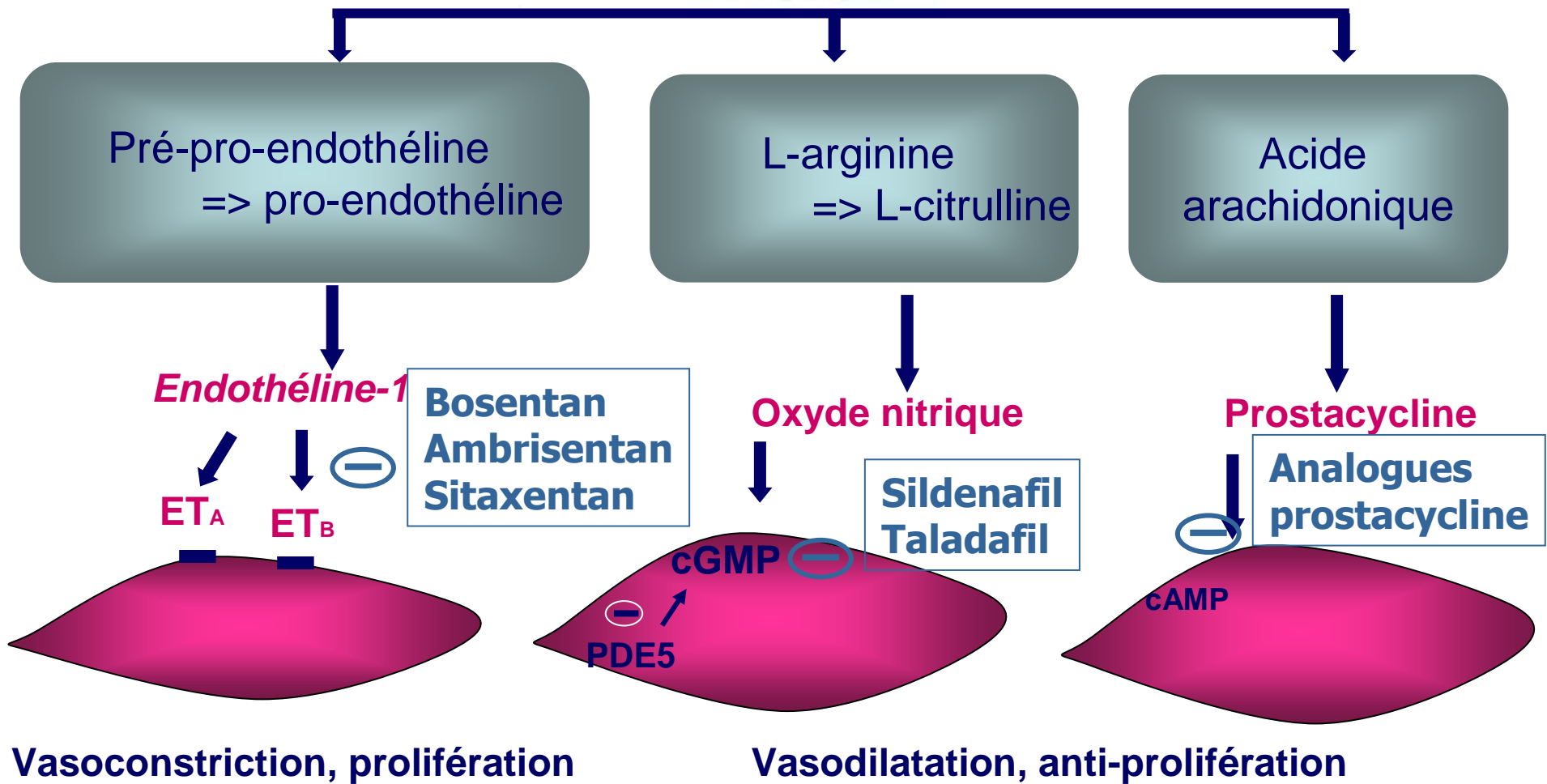
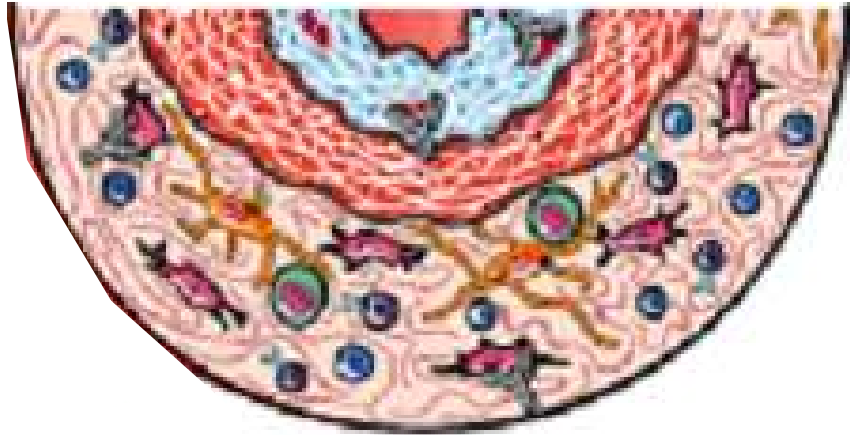
Rôle potentiel de la superfamille du TGF- β dans le remodelage vasculaire



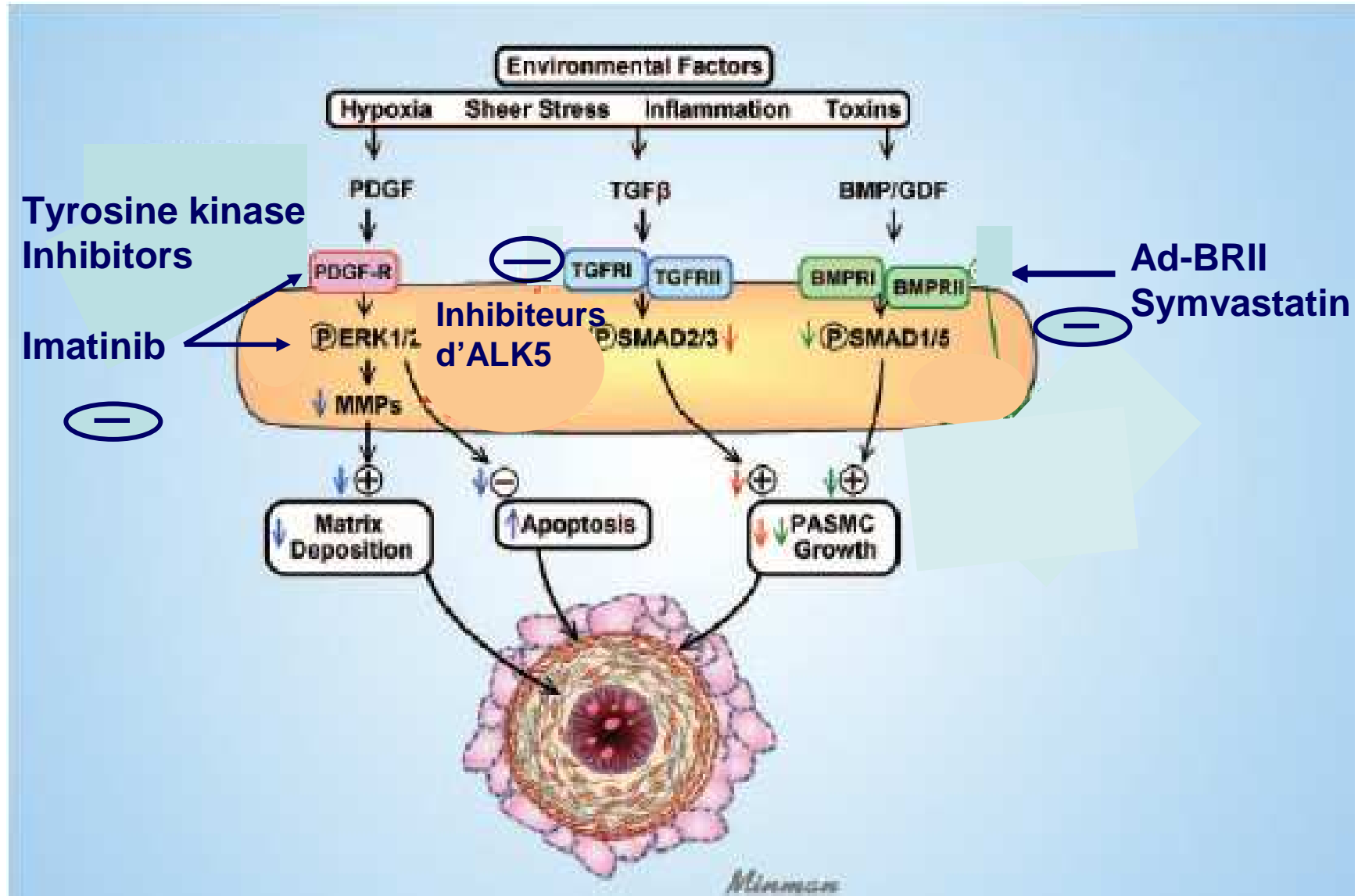
Genetics of Familial PAH



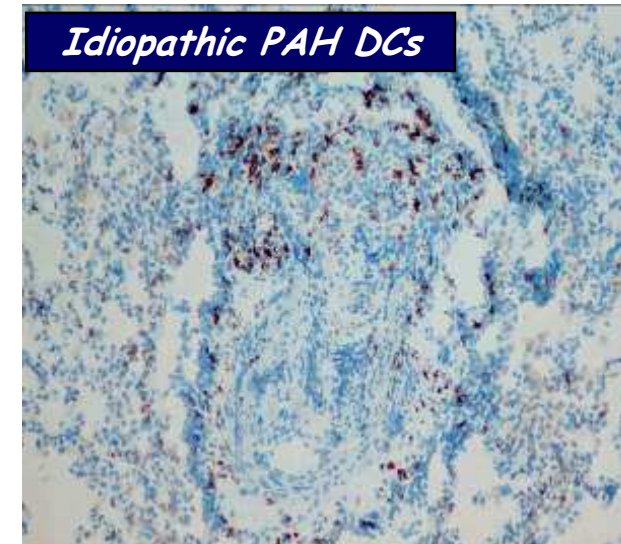
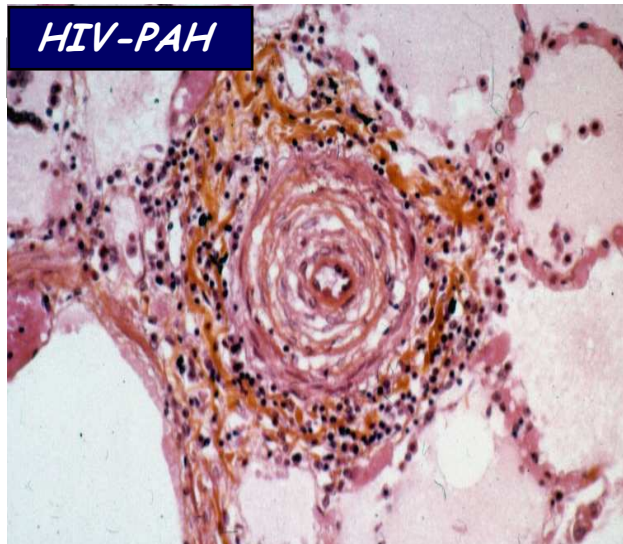
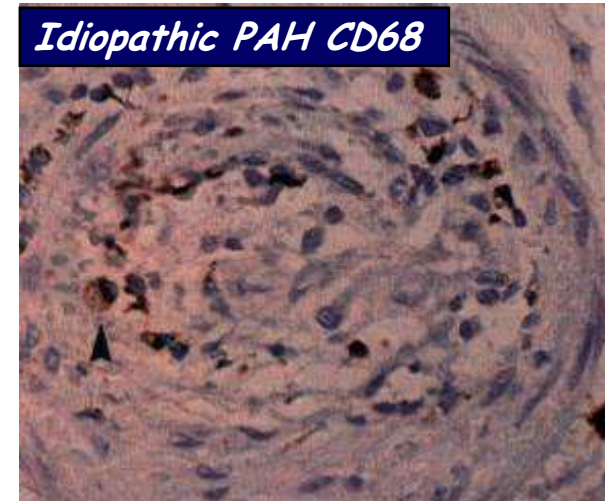
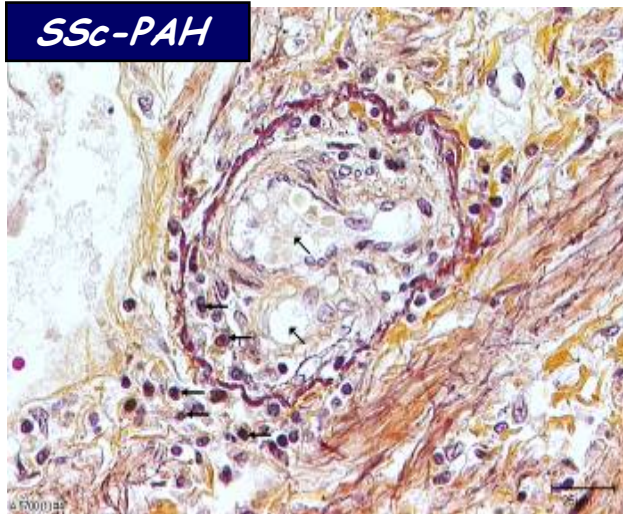
- Autosomal-dominant pattern of inheritance with reduced penetrance
- Heterozygous germline mutations in the BMPR-II in families with PAH
- mutations in the *BMPR2* gene have been found in approximately 80% of cases of familial PAH
- Patients with apparently sporadic PAH may also harbor BMPR-II mutations in 11 to 40% of cases.
- Patients with apparently sporadic PAH may also harbor BMPR-II mutations in 11 to 40% of cases.
- the expression of BMPR-II protein is markedly reduced in the lungs of patients with idiopathic PAH with no detectable mutation in BMPR-II



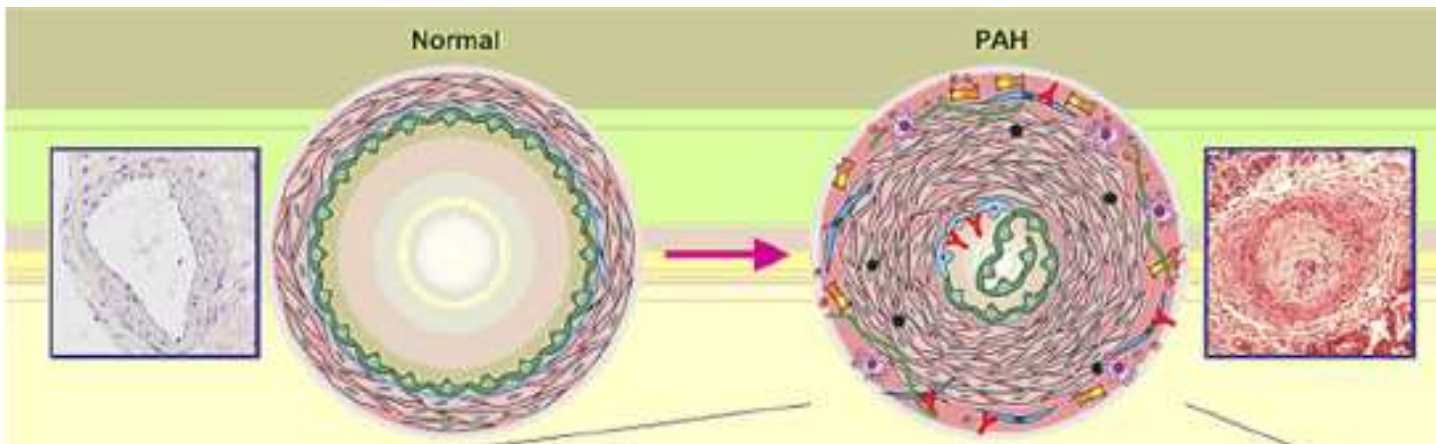
The future of treatment for PAH



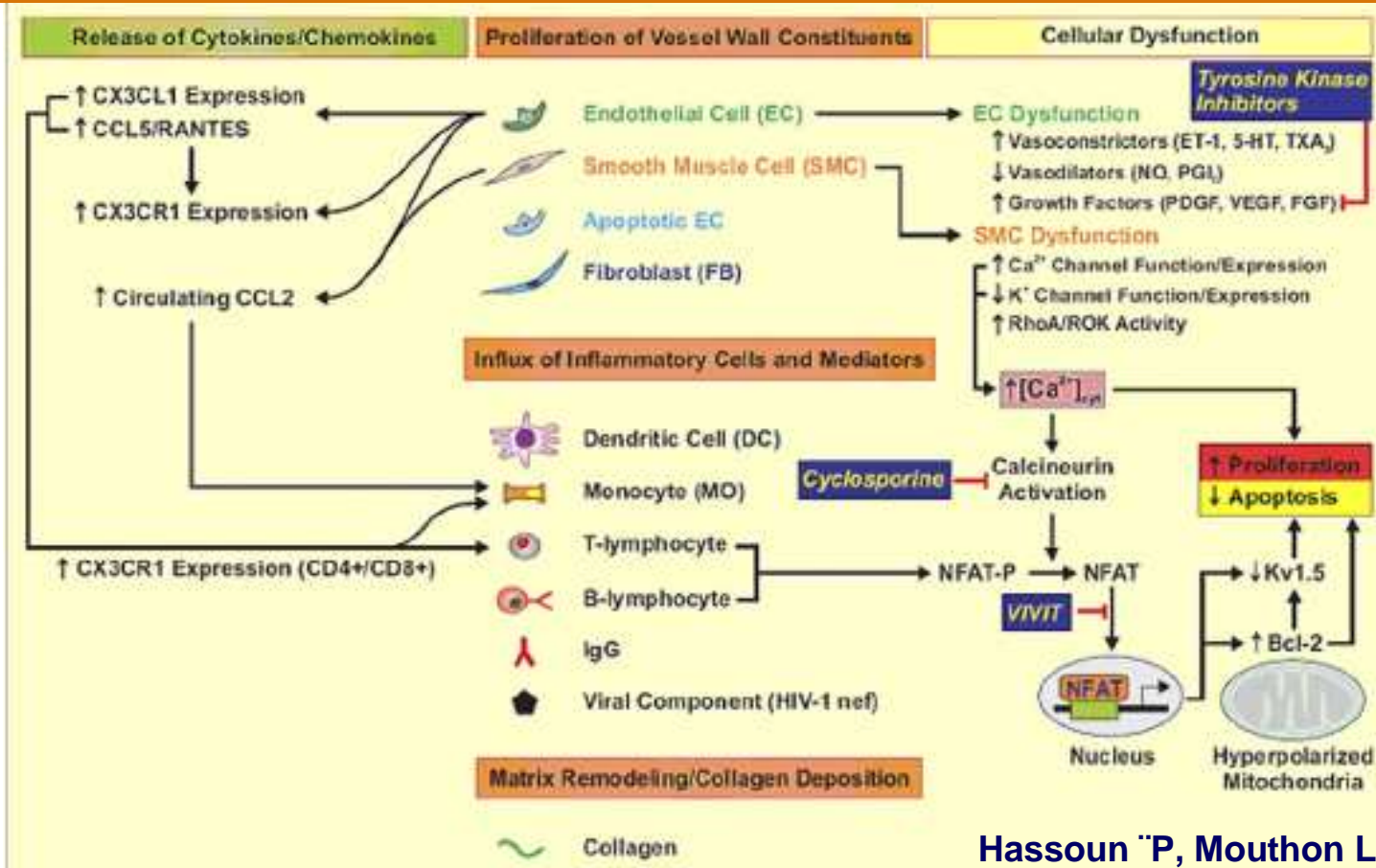
INFLAMMATORY CELLS ARE DETECTED IN PULMONARY ARTERY WALL FROM PAH PATIENTS



*Tuder et al. Am J Pathol 1994; Humbert et al. Eur Resp J 1998;
Dorfmüller et al. Human Pathol 2007 ; Perros et al. Eur Resp J 2007*



Mechanisms of inflammation-mediated remodeling



A number of patients with PAH improved with anti-inflammatory agents

- Immunosuppressive therapy in connective tissue disease associated PAH (Sanchez O et al Chest 2006)
- Immunotherapy in SLE and MCDT associated PAH (Jaïs X et al Arthritis Rheum 2008)
- Reversibility of PAH in HIV/HHV8-associated Castleman disease (Montani et al Eur Respir J 2005)
- PAH: a rare complication of primary Sjogren's syndrome (Launay D et al, (Baltimore) 2007)

Autoimmunity in PAH (I)

- **Anti-nuclear antibodies (40% IPAH vs 6% PH) “PPH is a collagen vascular disease confined to the lungs”**
- **The frequency of positive antinuclear antibody tests would place primary pulmonary hypertension between rheumatoid arthritis and scleroderma in the spectrum of collagen vascular diseases;**
- **Further studies are necessary, however, before one might expect that immunosuppressive therapy would be beneficial to these patients**

Autoimmunity in PAH (II)

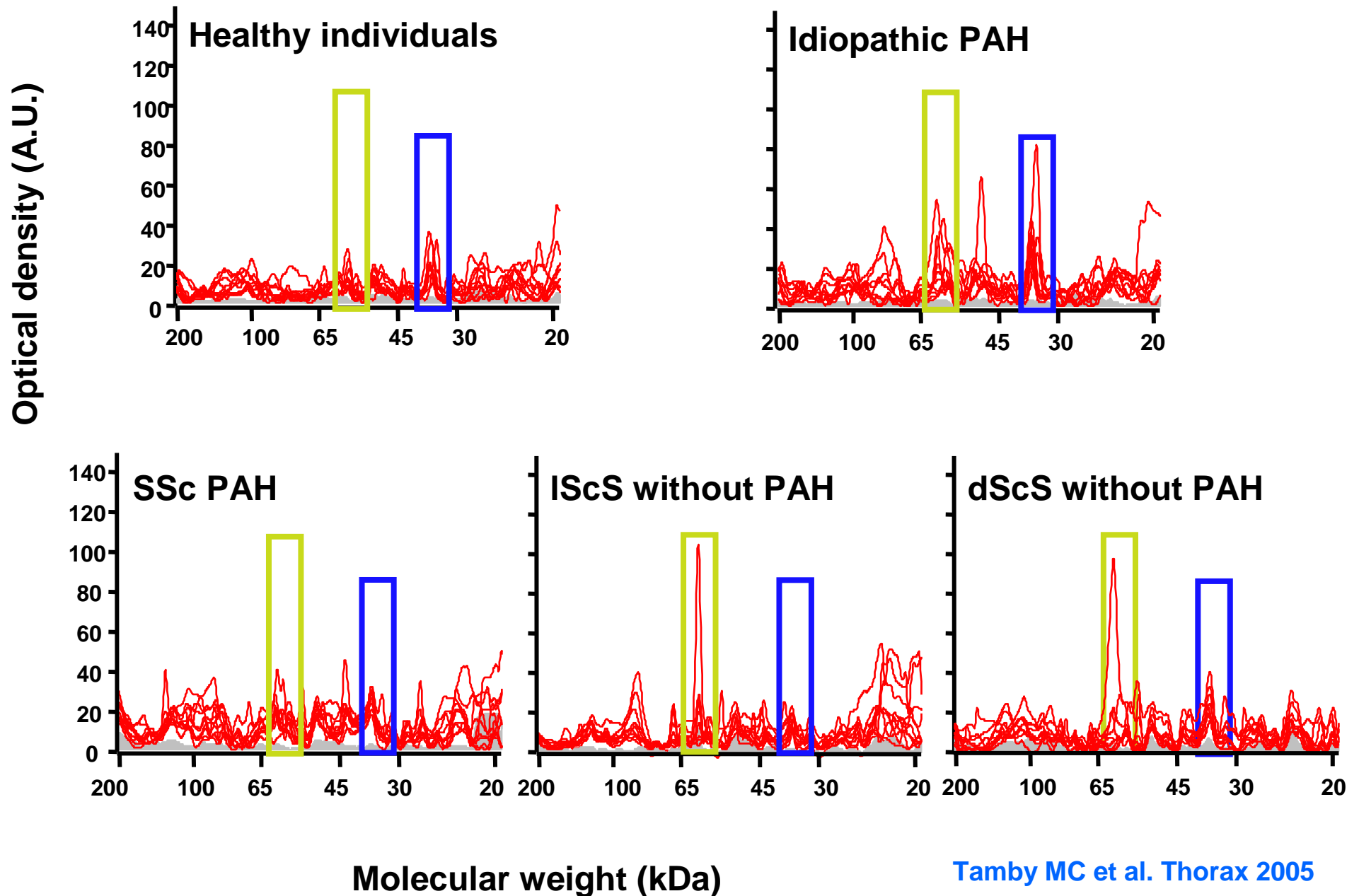
➤ Association with auto-immune diseases

- ✓ Systemic sclerosis,
- ✓ Systemic lupus erythematosus,
- ✓ MCTD,
- ✓ Sjögren's syndrome,
- ✓ Hashimoto's thyroiditis

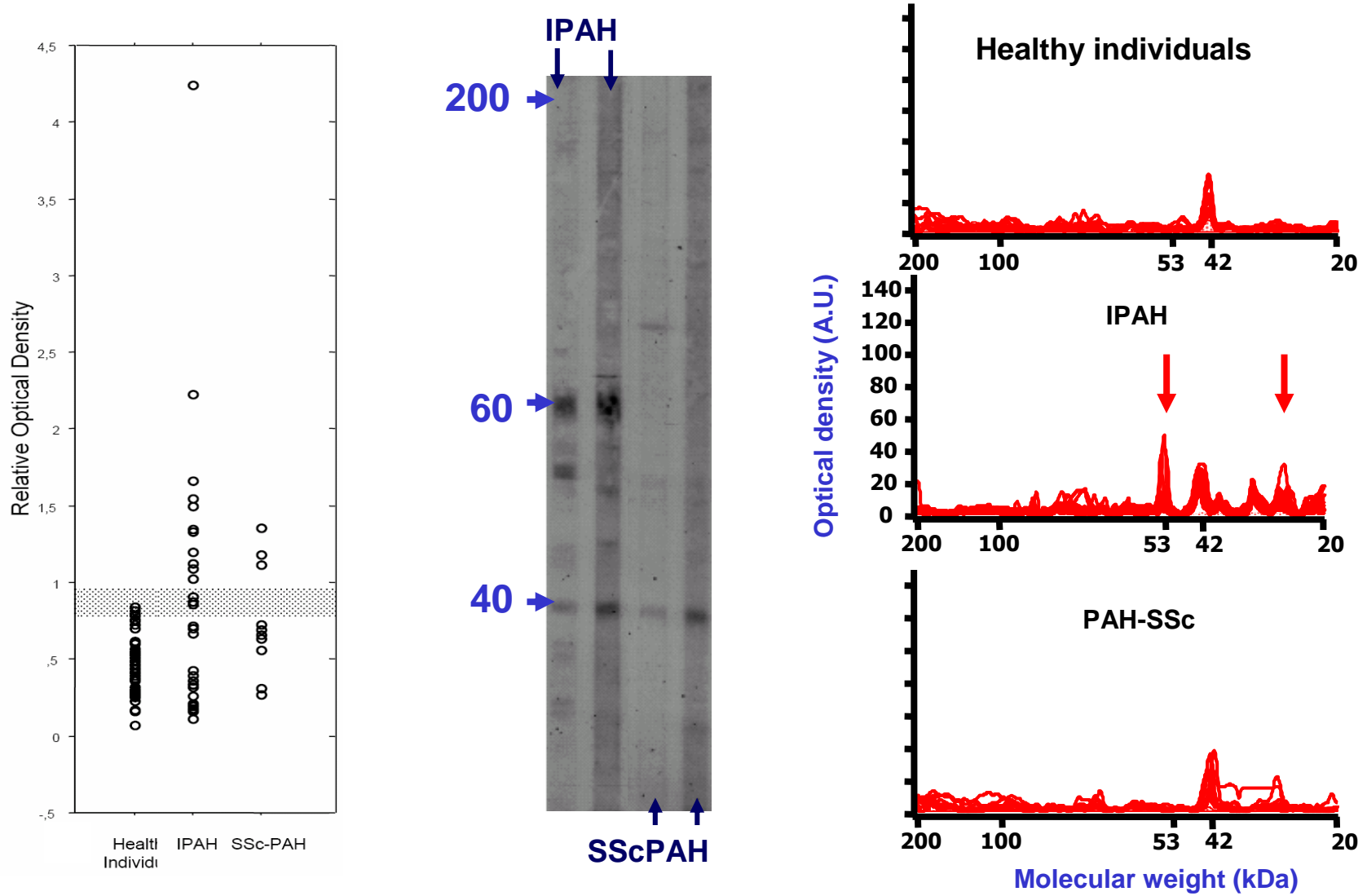
➤ Association with infections

- ✓ Viruses: HIV
- ✓ Parasitic infections (*Schistosoma*)

PAH: IgG reactivities against HUVEC



IgG anti-fibroblasts Abs Idiopathic and SSc associated PAH



Identification of target antigens of anti-fibroblast Abs in idiopathic and systemic sclerosis associated pulmonary arterial hypertension

➤ Organization of cytoskeleton and cell contraction

- ✓ Phosphatidyl inositol 3-kinase
- ✓ Vimentin
- ✓ Calumenin
- ✓ Tropomyosine 1

➤ Oxydative stress

- ✓ G6PD
- ✓ HSP27
- ✓ HSP70

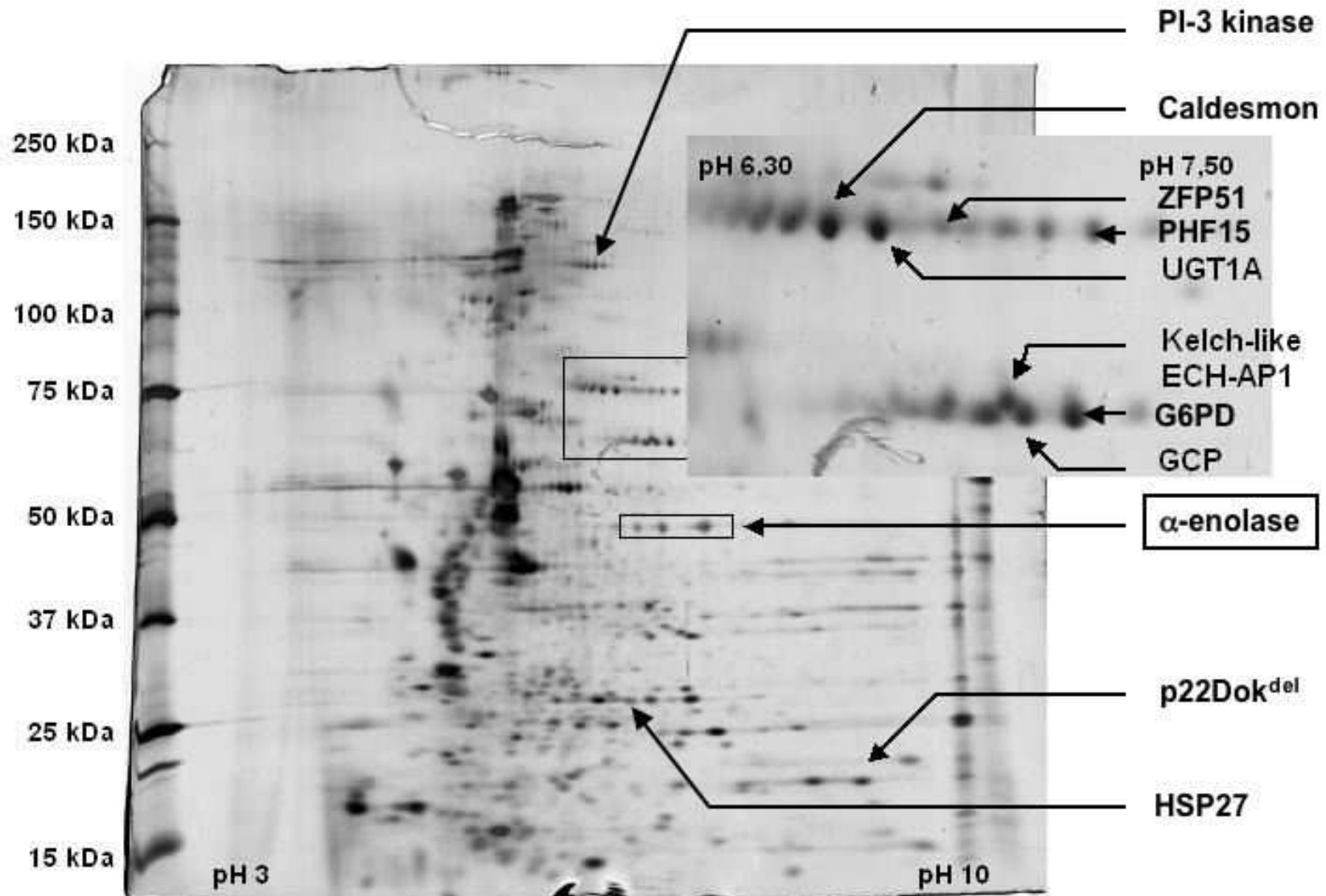
➤ Protein metabolism

- ✓ Glutaminase
- ✓ alanine-glyoxylate amino-transferase2
- ✓ glutamate carboxy-peptidase

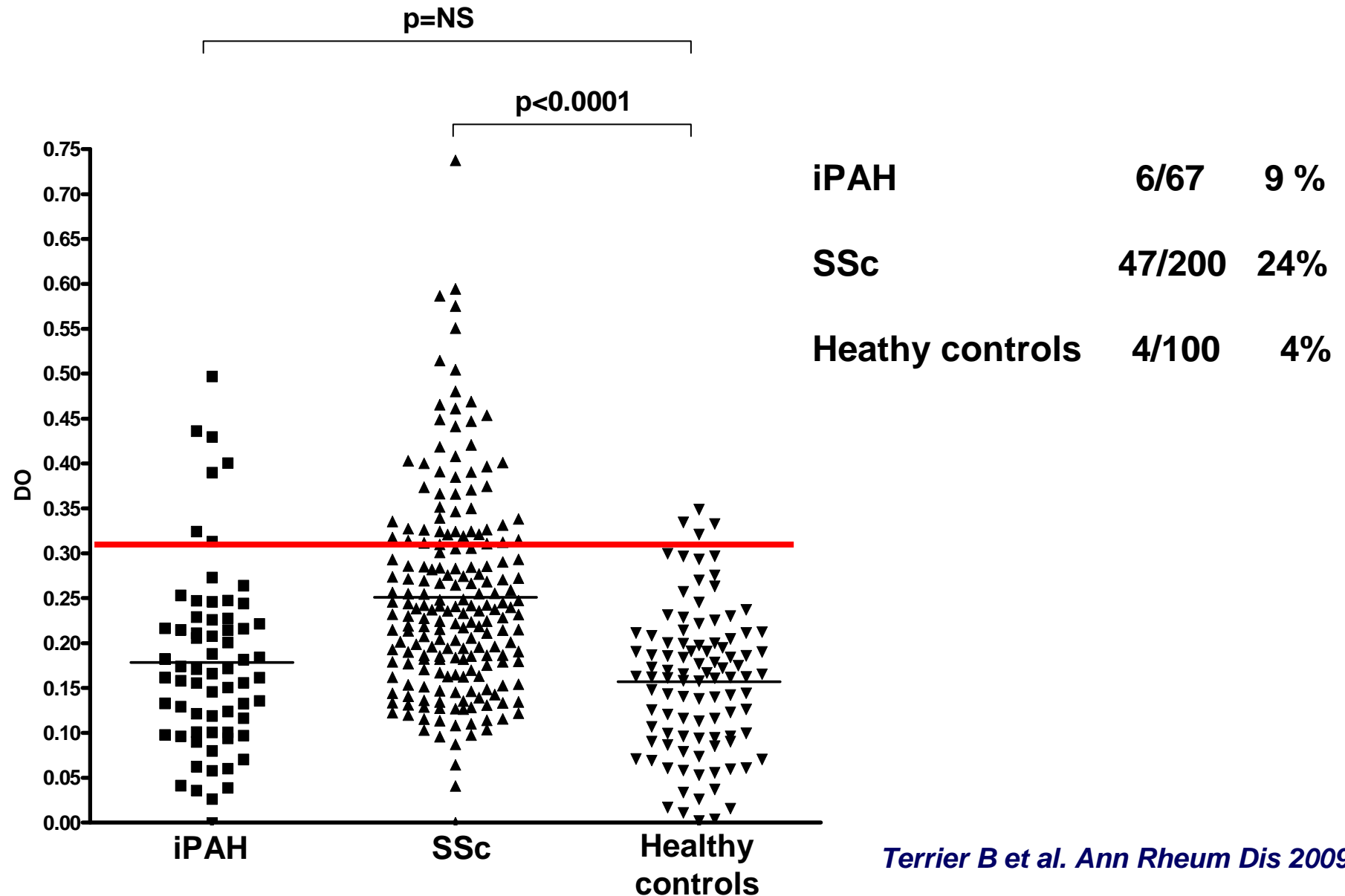
➤ Others

- ✓ death-associated protein kinase
- ✓ P61-YES
- ✓ protein Jade-2
- ✓ Kelch-like ECH
- ✓ zinc finger protein 51
- ✓ bromodomain testis-specific protein

Anti-fibroblast antibodies from systemic sclerosis patients bind to α -enolase



Anti-fibroblast antibodies from systemic sclerosis patients bind to α -enolase





Pulmonary vascular remodeling in SSc-PAH

Vascular remodeling

Intima : EC apoptosis, activation and/or proliferation
 Media: SMC hyperplasia/hypertrophy
 Adventitia: inflammatory cell recruitment, cell proliferation, and fibrosis








Intima

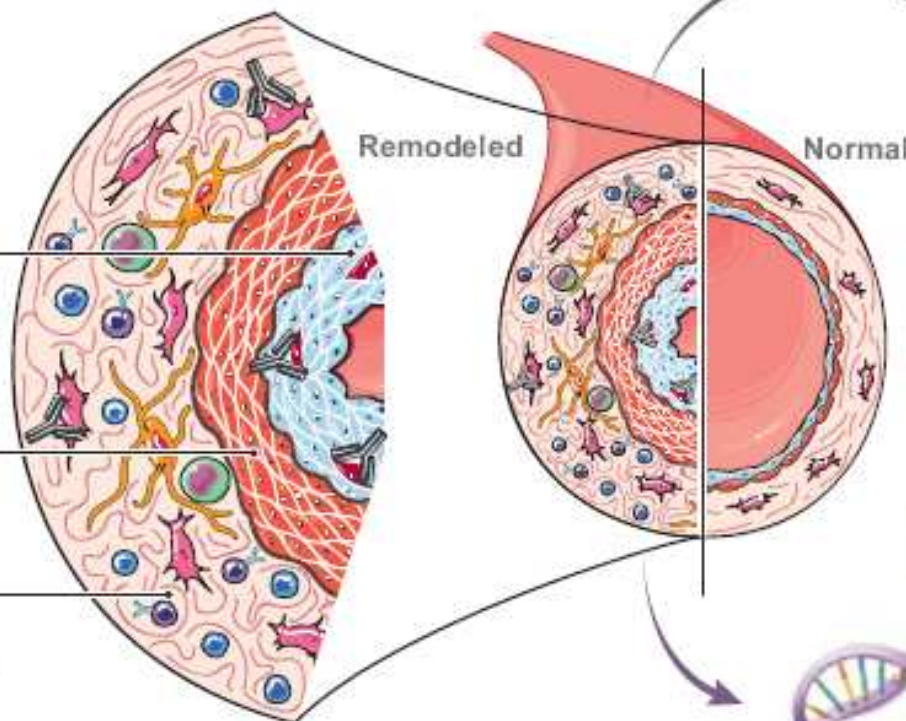
-  EC
-  Apoptotic EC

Media

-  SMC

Adventitia

-  Fb
-  Dendritic cell
-  Monocyte
-  B Lymphocyte
-  T lymphocyte
-  IgG
-  Collagen



Circulating autoantibodies

- Anti-EC
- Anti-Fb
- Anti-PDGF receptor
- Anti-Centromere
- Anti-Topoisomerase 1
- Anti-RNA-polymerase III
- Anti-Fibrillarin (U3 small nucleolar RNP)
- Anti-Th/To
- Anti-PM/Scl
- Anti-Fibrillarin 1
- Anti-Matrix Metallo Proteinase 1-3
- Anti-Nag-2

Candidate genes

- CCL2 (MCP-1)
- CD 19
- TNF alpha
- IL1 alpha
- IL10 (3-SNP haplotype)
- CTGF
- IRF5
- STAT4
- Endoglin

Conclusions (I)

- **La physiopathologie de l'HTAP est complexe et varie probablement en fonction de la pathologie associée**
- **De nombreux facteurs favorisent le remodelage vasculaires, parmi lesquels des facteurs génétiques, environnementaux, thrombotiques, inflammatoires et autoimmuns**
- **Les mutations de BMPRII sont trouvées aujourd'hui dans 10 à 40% des cas dans les formes sporadiques et 80% des cas dans les formes familiales, associées à un pronostic plus sévère**

Conclusions (II)

- **La réaction inflammatoire joue probablement un rôle important dans la physiopathologie de l'HTAP.**
- **Des autoanticorps anti-cellules endothéliales, anti-fibroblastes, anti-cellules musculaires lisses vasculaires sont présents dans le sérum de patients atteints d'HTAP.**
- **Ces autoanticorps ont pour cibles des molécules ubiquitaires qui jouent un rôle clé dans la biologie et l'homéostasie cellulaire**
- **Le traitement repose sur des médicaments vasodilatateurs ou inhibiteurs du remodelage**

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