# Clinical Classification of Pulmonary Hypertension: Dana Point (2008)

1. Pulmonary arterial hypertension (PAH)
   1.1. Idiopathic PAH
   1.2. Heritable
       1.2.1. BMPR2
       1.2.2. ALK1, endoglin (with or without hereditary hemorrhagic telangiectasia)
       1.2.3. Unknown
   1.3. Drug- and toxin-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 hemolytic anemia
   1.5. Persistent pulmonary hypertension of the newborn

1’. Pulmonary veno-occlusive disease (PVOD) and/or pulmonary capillary hemangiomatosis (PCH)

2. Pulmonary hypertension owing to left heart disease
   2.1. Systolic dysfunction
   2.2. Diastolic dysfunction
   2.3. Valvular disease

3. Pulmonary hypertension owing 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 abnormalities

4. Chronic thromboembolic pulmonary hypertension (CTEPH)

5. Pulmonary hypertension with unclear multifactorial mechanisms
   5.1. Hematologic disorders: myeloproliferative disorders, splenectomy
   5.2. Systemic disorders: sarcoidosis, pulmonary Langerhans cell histiocytosis: lymphangioleiomyomatosis, 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

G. Simonneau, JACC, 2008
Pulmonary Arterial Hypertension: *idiopathic PAH & heritable PAH*

- Rare (1-2/million/year) and often Fatal disease of unknown Etiology
- Occurs either Sporadically (idiopathic PAH) or as a Familial form (heritable PAH: *BMPR2, ACVRL-1* …)
- mean Pulmonary Artery Pressure (mPAP) at rest ≥ **25mm** Hg
- Progressive structural remodeling of the pulmonary vascular bed
Pulmonary Vascular Abnormalities in Patients with IPAH

- Neo muscularization of previously non-muscular capillary-like vessels,
- Loss of precapillary arteries
- Concentric medial thickening of the distal pulmonary arteries,
- Structural wall changes in larger pulmonary arteries (100-500 µm) with neointimal formation
- Formation of Plexiform lesions (30 to 50% of the patients)

Lesions are irregularly distributed throughout both lungs.

Marlene Rabinovitch, JCI, 2008
Special Tools in Research on PAH

Animal models
- Chronic Hypoxia
- Monocrotaline
- SuHx

Biological samples
(e.g., urine, sera, or plasma)
(Hôpital Antoine Béclère, CRB Paris-Sud)
- DNAthèque
- Sérothèque

Lung specimens
(CCML, Univ. Paris-Sud)
- Tissuthèque

Transgenic mice
- SM22-5HTT+
- Tie2-PPARγ

Cell culture
- Smooth muscle cells
- Endothelial cells
Idiopathic Pulmonary Arterial Hypertension (IPAH)

- **Vasoconstriction**
- **Genetic Predisposition**
  BMPR2 and ALK-1 pathway
- **Smooth Muscle Cell Hyperplasia**
  5-HTT, Kv1.5, Growth Factors
- **Inflammatory 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
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An Imbalance Between Vasoconstrictors and Vasodilatators

An Imbalance Between Vasoconstrictors and Vasodilators

An Imbalance Between Vasoconstrictors and Vasodilators

Nitric oxide pathway

N. H. Kim, Eur Respir Rev. 2010
An Imbalance Between Vasoconstrictors and Vasodilators

Endothelin pathway

Nitric oxide pathway

Prostacyclin pathway

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BMPRII is a serine/threonine receptor kinase

BMP ligands bind to the BMP receptors BMPRI and BMPRII, and BMPRII then phosphorylates and activates BMPRI.

Phosphorylated BMPRI subsequently phosphorylates Smads, which migrates into the nucleus and activates the transcription of specific target genes.

The Smad proteins regulate promoter activity by interacting with transcriptional co-activators or co-repressors to positively or negatively control gene expression.

- BMP-2, BMP-4, and BMP-7 suppress proliferation and induce apoptosis in cultured PA-SMCs from normal subjects but not from IPAH patients.

- Inhibits proliferation of SMCs
- Increases EC survival
Genetic Predisposing Factors:

**BMP Receptors and PAH**

*Mutated Bmpr2 in familial and sporadic PH*

*Reduced expression of BMP-RII in sporadic PH without gene mutation and in secondary PH*

*Attenuated expression of BMP-RIA in non-familial and secondary PH*

Inhibits proliferation of SMCs

Increases EC survival

SMC proliferation & EC apoptosis

**References**

M. Talat Nasim. Human Mutation 2011
B. Girerd, AJRCCM 2010
Deng et al, Am J Hum Genet 2000
Lane et al, Nat Genet 2000
Genetic Predisposing Factors: BMP Receptors and PAH

Genetic Ablation of the **Bmpr2** Gene in Pulmonary Endothelium (Tie2 BMPR2 -/-) Is Sufficient to Predispose to PH

**mPAP**

**SAP**

*Hong et al, Circulation, 2008*
Genetic Predisposing Factors:

**BMP Receptors and PAH**

- Mutated *Bmpr2* in familial and sporadic PH
- Reduced expression of BMP-RII in sporadic PH without gene mutation and in secondary PH
- Attenuated expression of BMP-RIA in non-familial and secondary PH

**Other Genetic Predisposing Factors**

- *ACVRL1 (ALK1)*
- *Endoglin*
- *Smad 1*
- *Smad 4*
- *Smad 9*

- **Smad Pathways**

- **SMC proliferation & EC apoptosis**

**References:**
- M. Talat Nasim. Human Mutation 2011
- B. Girerd, AJRCCM 2010
Genetic Predisposing Factors:

BMP Receptors and PAH

<table>
<thead>
<tr>
<th>Ligands</th>
<th>Activines – Nodals – TGFβ - BMP</th>
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<tbody>
<tr>
<td>Récepteurs</td>
<td>Type1</td>
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<tr>
<td>ALK1/ACVRL1</td>
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<tr>
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<td>ActR-2B</td>
</tr>
<tr>
<td>ALK3/BMPR1A</td>
<td>TGFBRI</td>
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<td>Smad4</td>
</tr>
<tr>
<td>Smad 2/3</td>
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Toporsian, ATVB, 2010
Jerkic, Cardiovascular res, 2011
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An Imbalance between Proliferation and Apoptosis

**PROLIFERATION**

- Serotonin Pathway
- Kv1.5 Potassium Channels
- PPAR γ
- Cytokines
- Growth Factors & RTKs (PDGF, EGF, FGF2…)

**APOPTOSIS**

- BMP Pathway

**AUTOPHAGY**

- LC3
An Imbalance between Proliferation and Apoptosis

PROLIFERATION

Serotonin Pathway

Kv1.5 Potassium Channels

PPAR γ

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LC3
The Serotonin Transporter (5-HTT) Plays a Key in PAH

5-HTT in human PAH

- 5-HTT is required for the mitogenic action of serotonin on PA-SMCS
- 5-HTT is overexpressed in PA-SMCs from patients with PH
- Overexpression of 5-HTT is associated to a higher mitogenic effect of 5-HT in cells from PH

5-HTT in experimental PAH

- Increased 5-HTT expression in the chronic-hypoxia and monocrotaline models.
- 5-HTT inhibition prevents and reverses monocrotaline-induced pulmonary hypertension in rats

Guignabert C et al, Circulation, 2005
5-HTT Inhibition Prevents Monocrotaline-Induced PH in Rats

Guignabert C et al, Circulation, 2005
5-HTT Inhibition Prevents And Reverses Monocrotaline-Induced PH in Rats

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SM22-5-HTT+ transgenic mice

Guignabert C et al, Circulation, 2005
Guignabert C et al, Circulation Research, 2006
Transgenic Mice overexpressing the 5-HTT gene in Smooth Muscle Develop PH

- We generated transgenic mice overexpressing 5-HTT under the control of the smooth muscle promoter SM22 (SM22-5-HTT+)
- SM22 : expression is restricted to smooth muscle in the adult (Moessler H et al, Development 1996)
- 5-HTT gene : human origin

**RVSP values**

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<thead>
<tr>
<th>Age</th>
<th>8 wks</th>
<th>20 wks</th>
<th>55 wks</th>
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**Fulton index**

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<th>55 wks</th>
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<tr>
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<td>20</td>
<td>30</td>
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**Muscularized pulmonary vessels**

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<th>20 wks</th>
<th>55 wks</th>
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<td>Fulton index</td>
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<td>5</td>
<td>10</td>
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</table>

Guignabert C et al, Circulation Research, 2006
Transgenic Mice overexpressing the 5-HTT gene in Smooth Muscle Develop PH

The SM22 5-HTT+ Mice

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<thead>
<tr>
<th></th>
<th>WT</th>
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Guignabert C et al, Circulation Research, 2006
An Imbalance between Proliferation and Apoptosis

- **PROLIFERATION**
  - Serotonin Pathway
  - **Kv1.5 Potassium Channels**
  - PPAR γ
  - Cytokines
  - Growth Factors & RTKs (PDGF, EGF, FGF2…)

- **APOPTOSIS**
  - BMP Pathway

- **AUTOPHAGY**
  - LC3
Voltage-gated Potassium Channel (Kv)1.5 and PAH

Kv1.5 in human PAH

- Attenuated expression and activity in pulmonary arteries of Patients with idiopathic PAH
  - Yuan et al. 1998
  - Remillard et al. 2007

Kv1.5 in experimental PAH

- Attenuated expression in various models of PH
  - McMurtry et al. 2002
  - Michelakis et al. 2008

- Kv1.5 overexpression by nebulized adenoviral therapy or oral dichloroacetate (DCA; an inducer of Kv1.5 expression) therapy improved chronic hypoxia- or monocrotaline-induced PH
  - Michelakis et al. 2002
  - Pozeg et al. 2003

SM22-5-HTT+ transgenic mice

<table>
<thead>
<tr>
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<tr>
<td><img src="image1" alt="Kv1.5" /></td>
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Guignabert C et al, FASEB Journal 2009
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Peroxisome Proliferator-Activated Receptor (PPAR)γ

- PPARγ is expressed in normal pulmonary endothelial cells but reduced in experimental and clinical PAH, particularly in plexiform lesions.

- Only a selective alteration of ECs resulting in disruption of the endothelial PPARγ signaling in mice is sufficient to cause mild PH.

- PPARγ protects the endothelium by reducing ADMA, ET-1 and inflammation.

Alastalo T-P et al, JCI 2011
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- Extracellular Matrix Deposition
  MMP-2, MMP-9, Fibronectin, Vitronectin
Number of yearly publications since 1994 obtained through a PubMed search when using the index words “inflammation” and “pulmonary hypertension”
Immunopathology in PAH

Increased cytokines et chemokines (IL-1 beta, IL-6, MCP-1, Fractalkine, CCL5, IL-13...)

Dendritic cell recruitment in lesions.

Mast Cells promote Lung vascular remodeling in PH

Lymphoid Neogenesis.

Absence of T Cells Confers Increased PAH and Vascular Remodeling

Dexamethasone Treatment reverse MCT-PH

Pulmonary Hypertension remodeling induced by a Th2 immune response

Production auto-antibodies

Treg Cells Limit Vascular Endothelial Injury and Prevent PH

F Perros, ERJ, 2007
O Sanchez, AJRCCM, 2007
M Humbert, AJRCCM, 1995
E Soon, Circulation, 2010

LC Price, ERJ, 2010

E Daley, JEM, 2008


L Tarasevicienne, AJRCCM, 2007

R Tamosiuniene, Circ Res, 2011
Immunopathology in PAH
IL-6 in the pathogenesis of PAH

Increased IL-1 and IL-6 serum concentrations in severe primary pulmonary hypertension

M Humbert, AJRCCM, 1995
E Soon, Circulation, 2010
Guignabert C et al, Circulation, 2005
IL-6 in the pathogenesis of PAH

Increased IL-1 and IL-6 serum concentrations in severe primary pulmonary hypertension

Interleukin-6 Overexpression Induces Pulmonary Hypertension

Increased serum concentration of IL-6 in MCT-PH in mice

Interleukin-6 Knock Out

M. Humbert, AJRCCM, 1995
E. Soon, Circulation, 2010
M. Kathryn Steiner, Circ Res, 2009
L. Savale, Respir res, 2009
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Cytokines

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APOPTOSIS
BMP Pathway

AUTOPHAGY
LC3
Increased Activators of Cellular Proliferation and/or Migration

RT. Schermuly, JCI, 2005
SL. Merklinger, Circulation, 2005
L.Tu, AJRCMB, 2010
M.Izziki, JCI, 2009
F.Perros, AJRCCM, 2008

Tyrosine Kinase Inhibitors (TKI)
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

L. Tu, AJRCMB, 2010
M. Izziki, JCI, 2009
F. Perros, AJRCCM, 2008
R.T. Schermuly, JCI, 2005
S.L. Merklinger, Circulation, 2005
Increased Activators of Cellular Proliferation and/or Migration: PDGF

Increased expression of PDGF and their receptors

PDGF-A

PDGF-B

PDGFR-Alpha

PDGFR-Beta

PDGF BB induces SMC proliferation

F.Perros, AJRCCM, 2008
Increased Activators of Cellular Proliferation and/or Migration: PDGF

- Imatinib reverse 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
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Abnormal Crosstalk Between Vascular Cells

FGF-2

5-HT

ET-1

Endothelial Cell

SMCs

in situ Hybridization

Tu L et al, American Journal of Respiratory Cell and Molecular Biology, 2010
Abnormal Crosstalk Between Vascular Cells

**AUTOCRINE ACTION**
- EC Proliferation
- Apoptosis resistance

**PARACRINE ACTION**
- SMC Proliferation

Tu L et al, American Journal of Respiratory Cell and Molecular Biology, 2010
**In Situ** Balance Between Proliferation/Apoptosis

**Distal Pulmonary Arteries**

**Control-Patients**

- PCNA
- vWF
- DAPI

**IPAH-Patients**

- PCNA
- vWF
- DAPI

**EC PCNA+ (%)**

- **Paas-Ctr**
- **Paas-IPAH**

**EC TUNEL+ (%)**

- **Control**
- **Patients**

Tu L et al, AJRCMB, 2010

50 µm
Cultured P-ECs From IPAH Patients:

**↑ Proliferation**

<table>
<thead>
<tr>
<th>Condition</th>
<th>BrdU Incorporation (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Basal Condition</td>
<td>0</td>
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</tbody>
</table>
| 2.5% Fetal Calf Serum | 100 ± 10*
| 5% Fetal Calf Serum | 150 ± 15** |
| 10% Fetal Calf Serum | 225 ± 22*** |

**↓ Sensitivity to Apoptotic Induction**

<table>
<thead>
<tr>
<th>Serum Deprivation</th>
<th>AnnexinV+/%</th>
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<tr>
<td>Basal Condition</td>
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<tr>
<td>24 h Serum Deprivation</td>
<td>5 ± 1*</td>
</tr>
<tr>
<td>48 h Serum Deprivation</td>
<td>10 ± 2**</td>
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</table>

Tu L et al, AJRCMB, 2010
Cultured P-ECs From IPAH Patients:

**↑ Proliferation**

The MAPK pathways

**↓ Sensitivity to Apoptotic Induction**

anti-apoptotic factors

<table>
<thead>
<tr>
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<td>ERK2</td>
<td><img src="ERK2.png" alt="Image" /></td>
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</tr>
</tbody>
</table>

Phospho-ERK1/2 : ERK2 ratio (U.A)

<table>
<thead>
<tr>
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<th>Control-ECs</th>
<th>IPAH-ECs</th>
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</table>

Bax:BCL2 ratio (U.A)

Tu L et al, AJRCMB, 2010
Overview of Endothelial Dysfunction

- Hypoxia
- Hormones
- Epigenetics
- Drugs

- Inflammation
  - Immune cell recruitment
  - Cytokines & Chemokines

- Hypercoagulability
  - Shear Stress

- Endothelial Cell
  - BMP signaling pathway
  - Mutation
  - Chromosome abnormalities
  - Alterations of cellular bioenergetics
  - Hyper-proliferation & Apoptosis resistance

- Smooth Muscle Cell Hyperplasia

- Vaso-constriction

- Cross-talk
- Vaso-active molecules
Conclusions

- It is clear that PAH has a **multifactorial pathobiology**, and it is unlikely that one factor or gene mutation will explain all forms and cases of PAH.
Conclusions

- It is clear that PAH has a multifactorial pathobiology, and it is unlikely that one factor or gene mutation will explain all forms and cases of PAH.

- Our improved understanding of additional pathways in this condition will presumably lead to the development of novel therapeutic strategies in the near future.

The Pathogenesis of PAH: a complex network of interactions
Acknowledgements

INSEIRM UMR 999
« Pulmonary Hypertension »
Physiopathology and Novel Therapies

Marc Humbert
Gerald Simonneau
Philippe Dartevelle
Elie Fadel
David Montani
Olivier Sitbon
Andrei Seferian
Laurent Savale
Olaf Mercier
Sylvia Cohen-Kaminsky
Jean-François De La Favriere
Saadia Eddahibi
Frédéric Perros
Alice Huertas
Barbara Girerd
Ly Tu
Marie-Camille Chaumais
Inès Aniambossou
Carole Phan

Thank you for your attention…
An Imbalance Between Vasoconstrictors and Vasodilatators

Riociguat
An Imbalance between Proliferation and Apoptosis

PROLIFERATION

Serotonin Pathway
Kv1.5 Potassium Channels
PPAR γ
Cytokines
Growth Factors
(PDGF, EGF, FGF2…)

APOPTOSIS
BMP Pathway

AUTOPHAGY
LC3