Animal Models of Human Severe PAH

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Clinical Classification of Pulmonary Hypertension

• Group 1: Pulmonary arterial hypertension
• Group 2: PH with left heart disease
• Group 3: PH associated with lung diseases and/or hypoxemia
• Group 4: PH with chronic thrombotic and/or embolic disease
• Group 5: Miscellaneous
Group 1: Pulmonary Arterial Hypertension

Idiopathic (primary) pulmonary hypertension

Familial pulmonary hypertension (bad BMPR2)

PAH associated with
  * Connective tissue disease
  * Congenital heart disease
  * Portal hypertension
  * HIV infection
  * Drugs /toxins

Persistent pulmonary hypertension of the newborn

Pulmonary veno-occlusive disease

Pulmonary capillary hemangiomatosis

Other
Pathogenesis of PAH

Vasoconstriction + Vascular Remodeling + In Situ Thrombosis

Increased Vascular Resistance & Decreased Vascular Distensibility

Pulmonary Hypertension

RV Failure
Severe PAH Can Cause RV Dilatation and Failure

PA Normotensive

PA Hypertensive
Hypothetical: Vasoconstriction vs. Fixed Obstruction over Time/Severity of PAH

Reeves et al, ARRD 134: 342, 1986
Medial Hypertrophy in Human Severe PAH

Pre-Acinar PA

Intra-Acinar PA

Pietra et al., J Am Coll Cardiol 43: 25S, 2004
Examples of Intimal Thickening in Human Severe PAH

Concentric Laminar Thickening

Eccentric & Concentric Nonlaminar Thickening

Intra-Acinar

Pre-Acinar

Pre-Acinar

Pietra et al., J Am Coll Cardiol 43: 25S, 2004
Congestive Arteriopathy & Re-Canalized Thrombus in PAH

elastic van Gieson

Plexogenic Pulmonary Arteriopathy

More Plexiform Lesions

A

Muscle specific actin

B

Factor VIII

Intra-Acinar PAs in Reversible vs. Irreversible PAH in Patients with CHD

Reversible PAH

Irreversible PAH

Lévy et al, JACC 49: 803, 2007
Hypothetical: Vasoconstriction vs. Fixed Obstruction over Time/Severity of PAH

Reeves et al, ARRD 134: 342, 1986
Therapeutic Goal: Normalize the Pressure

How?
Reverse sustained abnormal vasoconstriction and/or abnormal ECM deposition and cell growth.

How?
A meta-analysis of trials of pulmonary hypertension: A clinical condition looking for drugs and research methodology

Alejandro Macchia, MD, a Roberto Marchioli, MD, a RosaMaria Marfisi, MS, a Marco Scarano, MS, a Giacomo Levantesi, MD, a Luigi Tavazzi, MD, b and Gianni Tognoni, MD a Chieti and Pavia, Italy

The analysis revealed a statistically insignificant 30% reduction in mortality in patients receiving experimental treatments.

More effective therapy for PAH is urgently needed.
Most Commonly Used Animal Models of PAH

- Chronically hypoxic rats (and mice)
- Monocrotaline injected rats
“Typical” PA Wall Thickening in Chronically Hypoxic Rat

Normoxic Rat

Hypoxic Rat

Bars = 50 μm

Jeffery and Wanstall, Pharmacol Ther 92: 1, 2001
Vasoconstriction Increases Medial Thickness

Maeda et al, Ann Thoracic Surg 78: 1371, 2004

\[ R = \frac{S}{\left( \sqrt{L^2 + 4\pi S} - L \right)} \]
\[ D = \frac{\left( \sqrt{L^2 + 4\pi S} - L \right)}{2\pi} \]
PH in CH Rat Is Due Largely to Rho Kinase-Mediated Vasoconstriction

Pulmonary Artery Pressure

- Normoxia
- After 3-4 weeks of Hypoxia

48 h of Normoxia + Acute Nifedipine

48 h of Normoxia + Acute Y-27632 (or Fasudil)

Nagaoka et al., AJP Lung 287: L665, 2004
Inhaled NO Does not Reverse Hypoxia- or Bleomycin-Induced PH in Neonatal Rats

**PVR**

\[\frac{1}{(PAAT/RVET)}\]

McNamara et al., AJP Lung 294: L205, 2008
Acute Rho Kinase Inhibitor Reverses Hypoxia & Bleomycin PH in Neonatal Rats

McNamara et al., AJP Lung 294: L205, 2008
No Inward Remodeling in CH Lungs

Vasodilated before Fixation

Normoxic Rat

Hypoxic Rat

Bar = 20 μm

Howell et al., J Physiol 547: 133, 2003
Little or No Reduction in Distal PA Lumen Area in MCT and CH Hypertensive Rat Lungs Vasodilated before Fixation

van Suylen et al., AJRCCM 157: 1423, 1998
The Rat Is A Poor Animal Model for The Study of Human Pulmonary Hypertension

Donald Heath

Cardioscience 3: 16, 1992

Chronically hypoxic & MCT injected
Animal Models of Neointimal PAH

- Left pneumonectomy + monocrotaline rat
- VEGFR blocker (SU5416) + chronic hypoxia rat
- SU5416 in athymic nude rat
- ET\textsubscript{B} receptor deficient rat + monocrotaline
- S100A4/Mts1 transgenic mouse
- SHIV-\textit{nef} infected macaques
- Aorta to lobar PA shunt in piglets
Neointimal Lesions in Distal Pulmonary Vessels of Pneumonectomized + MCT Rats

H&E

α-actin

Nishimura et al., AJRCCM 166: 1403, 2002
Plexiform-Like Lesions in Young (200 g) Pneumonectomized + MCT Rats

Bar = 100 μm

Trichrome

White et al., AJP Lung 293: L583, 2007
Increased Elastin & Tissue Factor in Remodeled PAs of Pneumonectomized + MCT Rats

White et al.,
AJP Lung 293: L583, 2007
Factor VIII-Positive Neointimal Lesions in Distal PAs of SU5416 + Hypoxia Rat

Taraseviciene-Stewart et al, AJP Lung 291: L668, 2006
Neointimal Lesions in Distal PAs of SU5416 + Hypoxia Rats

Pentachrome

Factor VIII

Rat Pulmonary Artery Remodeling in Chronic Hypoxia vs. VEGFR Inhibitor + Chronic Hypoxia

L Moreno-Vinasco et al., Physiol Genomics 33: 278, 2008
Acute Effects of iv Rho Kinase Inhibitor on PAP in Rat Models of PH/PAH
VEGFR Blocker-Injected Athymic Nude Rats Develop PAH in Denver

Athymic Control

Athymic + SU5416

Factor VIII

VEGFR2

Taraseviciene-Stewart et al., AJRCCM 175: 1280, 2007
MCT-Injected ET$_B$-Deficient Rats Develop Neointimal Lesions in Distal PAs

Ivy et al., Circ Res 111: 2988, 2005
EC & SMC Markers in Neointimal Lesions of MCT-Injected ET$_B$-Deficient Rats

Ivy et al. Circ Res 111: 2988, 2005
Pulmonary Arteriopathy in > 1.5-Year-Old S100A4/Mts1 Mice

Control
Movat pentachrome
Bar = 50 μm

S100A4/Mts1 Transgenic
H&E
α-actin

Greenway et al., Am J Pathol 164: 253, 2004
γHV68 but not Influenza Augments Pulmonary Arteriopathy in > 1-Year-Old S100A4/Mts1 Mice

Spikerkoetter et al., AJP Lung 294: L276, 2008
Characterization of PA Lesions in $\gamma$HV68-Infected S100A4/Mts1 Mice

Spiekerkoetter et al., AJP Lung 294: L276, 2008
Minimal RV Hypertrophy in γHV68-Infected S100A4/Mts1 Mice

Spiekerkoetter et al., AJP Lung 294: L276, 2008
Pulmonary Arteriopathy in SHIV-\textit{nef} Infected Macaques

SIV-\textit{nef}  \hspace{1cm} SHIV-\textit{nef}

\hspace{1cm} H&E  \hspace{1cm} H&E

Marecki et al., AJRCCM 174: 437, 2006
EC and SMC Markers in PA Lesions of SHIV-\textit{nef} Infected Macaques

Marecki et al., AJRCCM 174: 437, 2006
EC & SMC Markers in Obstructive PA Neointimal Lesion of SHIV-nef Macaque

Factor VIII

α-SMA
Anastomosis of Left Lower Lobe Pulmonary Artery to Aorta

Bousamra et al., J Thorac Cardiovasc Surg 120: 88, 2000
Pulmonary Arteriopathy in Piglets with An Aorta to Pulmonary Artery Shunt

Bousamra et al., J Thorac Cardiovasc Surg, 120: 88, 2000
Loss of HPV in Neointimal Lobes of Shunted Piglets

Bousamra et al., J Thorac Cardiovasc Surg, 120: 88, 2000
Summary: There Are Several Animal Models of Neointimal PAH

- Pneumonectomy + MCT rat
- SU5416 + chronic hypoxia rat
- SU5416 in athymic rat
- Athymic rat + chronic hypoxia
- ET$_B$ receptor deficient rat + MCT
- S100A4/Mts1 transgenic mouse + γHV68
- SHIV-\textit{nef} infected macaques
- Aorta to lobar PA shunt in piglets
Conclusion

If we are interested in learning how to reverse (or prevent) neointimal arteriopathy in human severe PAH, we probably need to study an animal model of neointimal PAH instead of the classic chronically-hypoxic and monocrotaline-injected rats.