Emerging Pharmacological Treatment Approaches/Novel Pathways: Strengths, Gaps, Unmet Needs

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Disclosure Information:

- Scientific Advisory Board
  - Actelion, Bayer Healthcare, Eli Lilly, Gilead Sciences, GlaxoSmithKline, Iaria, Lung Rx, Medtronic, Novartis, Pfizer, United Therapeutics
- Speakers’ Bureau/Honoraria
  - Actelion, Gilead
- Stock Shareholder
  - None
- Other Financial or Material Support
  - None

Objectives:

- Highlight efficacy/limitations of currently available PAH drugs
- Introduce most recent understanding of disease mechanisms
- Present new molecular targets for treatment of PAH (selection of molecules from new classes of drugs)

Where have we been?

German physician Ernst von Romberg (1869) first pathologic description (autopsy case) — sclerosis of pulmonary arteries without underlying cardiac or pulmonary disease

Dana Point PH Classification

PH encompasses multiple disease subtypes

I  Pulmonary arterial hypertension (PAH)
II  Pulmonary hypertension owing to left heart disease (PH-LHD)
III Pulmonary hypertension owing to lung disease and/or hypoxemia (PH-LD/PH-OH)
IV  Chronic thromboembolic pulmonary hypertension (CTEPH)
V  Pulmonary hypertension with unclear multifactorial mechanisms

Existing treatments are indicated only for PAH

Poor Prognosis: NIH PPH Registry

Median survival: 2.8 yrs (n=194)
Pediatric pts: 10 mos
Where are we now? PAH Specific FDA-Approved Therapies

- Oral
  - Bosentan - ERA
  - Ambrisentan - ERA
  - Sildenafil - PDE 5 inhibitor
  - Tadalafil - PDE 5 inhibitor
- Continuous parenteral infusion
  - Epoprostenol - IV prostacyclin analog
  - Treprostinil - IV or SC prostacyclin analog
- Inhaled
  - Iloprost – prostacyclin analog
  - Treprostinil – prostacyclin analog

Where are we now?

- 1984 - Coumadin - improved survival PPH
- 1990 - Single lung transplant PPH
- 1992 - Responders to high-dose CCB improved survival PPH
- 1995 - IV Epoprostenol approved
- 2001 - Oral bosentan and SC treprostinil approved
- 2004 - Inhaled iloprost and IV treprostinil approved
- 2005 - Oral sildenafil approved
- 2007 - Oral ambrisentan approved
- 2009 - Present - Oral tadalafil, inhaled treprostinil, RTS epoprostenol, generic epoprostenol and IV sildenafil approved

A Meta-analysis of Randomized Controlled Trials in Pulmonary Arterial Hypertension

Where are we now? Surgical Therapies

- Atrial septostomy 1,2
  - Severe right heart failure refractory to medical therapy
  - Option when costly medical therapy not available
  - Risk of inadequate pulmonary flow and clinically significant hypoxemia
- Lung transplantation 3
  - 1, 3, and 5 year survival rates: 77%, 63%, and 54%, respectively

Compelling Evidence of Long-Term Outcomes in Pulmonary Arterial Hypertension?

A Clinical Perspective

Gomberg-Maitland, MD, MSc, 2 Christoph Dufen, PhD 1 Ronald J. Oudia, MD 1 Raymond L. Burre, MD 1

...the authors review the published research to assess the strengths and weaknesses of the data that support the long-term clinical benefit of current PAH therapies. The authors conclude that current medical therapies approved for the treatment of PAH can provide sustained benefits in hemodynamic function and exercise capacity. The cumulative evidence, in the form of meta-analysis and registry data, suggests that patients are living longer compared with untreated patients; the reasons are likely multifactorial...
Five-Year Survival from PAH Diagnosis

Benza et al. REVEAL Registry 2010 ISHLT

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PAH: the State of Limbo

Where are we going?

“Reverse Remodeling”

Self-Perpetuating Nature of PAH

PAH remains an incurable disease
Unacceptable 5 year survival rate
Clinical disease progression continues

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Where are we going?
Molecular Pathogenesis of PAH: Potential Targets for Treatment

Where are we going?

- Tyrosine kinase inhibitors
- Soluble guanylate cyclase agonists
- Serotonin transport inhibitors
- Prostacyclin receptor agonist
- Rho-kinase inhibitors
- Vasoactive intestinal peptide
- Kv channel openers
- Rapamycin
- Endothelial progenitor cells
- Gene transfer therapy
- Inhaled nitric oxide

Tyrosine-kinase Inhibitors

- Imatinib in PAH with Inadequate Response to Established Therapy
  - 24-week, randomized, double-blind, PBO-controlled pilot
    - PAH, HPAH, APAH-CTD or APAH-repaired CHD
      - Symptomatic on ≥ 1 PAH therapies
      - ≥ 16 yrs
      - FC II-IV

Imatinib in PAH with Inadequate Response to Established Therapy

<table>
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<th>Imatinib 200 mg</th>
<th>Imatinib 400 mg</th>
<th>Placebo n=31</th>
<th>Placebo n=23</th>
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<td>Up-titration</td>
<td>Down-titration 200 mg prn</td>
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<td>Imatinib 200 mg n=28</td>
<td>Imatinib 400 mg n=19</td>
<td>Placebo</td>
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Changes in Efficacy Variables at 6 mos vs BL

- Change in PAPm (mmHg)
- Change in CO (L/min)
- Change in PVR (dyNe.sec.cm⁻⁵)
- Change in 6MW (m)

<table>
<thead>
<tr>
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<th>Placebo</th>
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<tr>
<td>Δ PAPm</td>
<td>-4.1</td>
<td>-1.8</td>
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<tr>
<td>Δ CO</td>
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<tr>
<td>Δ PVR</td>
<td>-6.5</td>
<td>3.6</td>
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<tr>
<td>Δ 6MW</td>
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</table>
Clinical Effects: Improvements in FC

![Clinical Effects Chart]

Next Target: Multi-kinase Inhibitors?

![Next Target Diagram]

Does Every Drug Work in MCT-PH?

![Does Every Drug Work Diagram]

Serotonin Mediated Effects in PAH

![Serotonin Mediated Effects Diagram]

Serotonin Transport Inhibitors

![Serotonin Transport Inhibitors Diagram]
**Serotonin Receptor Antagonist: Terguride**

- Actions:
  - Serotonin 5-HT_2a and 2b antagonist
  - Partial dopamine D_2 antagonist
  - Adrenergic antagonist
- anti-proliferative
- anti-thrombotic and anti-fibrotic
- relaxation of smooth muscle cells

**Phase 2 Clinical Trial (in progress)**

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**Prostacyclin Receptor Agonist**

- Selexipag: non-prostanoid, orally active, selective prostacyclin (IP) receptor agonist
- Phase 2 randomized 3:1, double-blind, placebo-controlled 4 month trial
- N=43 adult symptomatic PAH pts on ERA and/or PDE 5
- Efficacy endpoints include: PVR, 6MWD

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**Effects of Selexipag on PVR**

- Percentage of baseline pulmonary vascular resistance at Week 24 (Quadrant: normal)

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**Vasoactive Intestinal Peptide**

- 28 amino-acid peptide
- Neurotransmitter
- Vasodilator
- Inhibits airway and arterial smooth muscle proliferation
- VPAC-1 and 2 VIP receptors activate cAMP and cGMP second messengers

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**Reduced VIP Expression in PAH**

- VIP is one of the most abundant, biologically active peptides in human lung
- PAH patients have marked reductions of VIP in serum and lung
- VIP a potential “therapy”

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**Effects of Selexipag on 6MWD**

- Placebo (n=32)
- Selexipag (n=32)
- Placebo vs Selexipag: 6MWD increased significantly

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**Normal PAH**

- Normal vs PAH: Reduced VIP expression

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**Pharmacological Actions**

- Serotonin 5-HT_2a and 2b antagonists
- Partial dopamine D_2 antagonists
- Adrenergic antagonists
- Anti-proliferative
- Anti-thrombotic and anti-fibrotic
- Relaxation of smooth muscle cells

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**Clinical Trials**

- Phase 2 Clinical Trial (in progress)

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**Selexipag et al 2010**

**Simonneau et al 2010**

**Simonneau et al 2010**

**Petkov et al JCI 2003**
**Change in 6MWD with inhaled VIP in PAH**

- Petkov et al. JCI 2003
- Open label uncontrolled study

**Rho-kinase Inhibitors**


- Rho-Kinase Inhibition in MCT PH Model

**Augmentation of Kv Channels**

- Hypoxia inhibits ≥ voltage-gated potassium channels (Kv) in PASMCs
- Opens voltage-gated calcium channels, increasing cytosolic Ca²⁺ and initiating constriction
- Kv1.5 or Kv2.1 channels down-regulated in the PASMC in hypoxic-PH rat model and in IPAH
- Anorexigens and serotonin block Kv channels
- Dichloroacetate (DCA) increases expression/function of Kv2.1 channels and decreases remodeling and PVR in hypoxic- PH rat model

**Rapamycin**

- Clinical applications: drug-eluting coronary stents, immuno-suppression in transplantation medicine, possible role in LAM
- Anti-proliferative and anti-remodeling properties
- Rapamycin in hypoxic-PH mouse model
  - Blocks cellular proliferative response to hypoxia
  - Decreases RVH and cardio-myocyte diameter

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Rho-Kinase Inhibition in MCT PH Model

![Graph showing Rho-kinase inhibition](Image)

Augmentation of Kv Channels

![Graph showing augmentation of Kv channels](Image)

Rapamycin

![Graph showing rapamycin effects](Image)
**Endothelial Progenitor Cells**

- Pro-angiogenic cells - repair and regenerate vasculature
- Pilot study (N=31) in China
  - Randomized to conventional therapy or conventional therapy plus EPC infusion
  - Baseline and 12 week assessment
  - 6MWD improved 42 m in EPC group vs conventional therapy alone
  - Non-significant improvement in hemodynamics
  - No SAEs reported

**Myocardial Remodeling**

**Conclusions**

- PAH remains incurable
- Current treatment based on vasodilators
- Improvements in symptoms, exercise capacity, and prognosis
- Upfront combination treatments with may offer potential
- Importance to lower PVR as much as possible
Conclusions

• **Future treatments** address proliferative “pseudo-malignant” nature of PAH
• TK represents promising target to reverse remodeling
• sGC stimulators potential for PAH
  – individual dose titration
  – combination with PDE5i to be studied
• Inhaled nitric oxide
• Agents from new drug classes emerging:
  - 5-HT antagonists
  - Prostacyclin receptor agonists
  - Rho-kinase inhibitors

Further out on the Horizon....

• Therapies targeting the RV alone
  – Cellular cardio myoplasty via cell transplant for cardiac repair
• Gene Therapy
  – First human gene therapy trial underway \(\rightarrow\) endothelial progenitor cells over expressing NOS
  – Delivery of adenoviral vectors with BMPR2 gene to vascular endothelium in PH rat model \(\rightarrow\) reduced cell proliferation and hypoxic pulmonary hypertension
  – Direct gene transfer into skeletal muscle and liver of rat PH model (prostacyclin synthase) modulates pulmonary vascular response

Summary

• Complex molecular/genetic network involved in pathobiology of PAH
• Potential therapies under investigation at various stages of animal/human study
• Difficulty in defining each individual patient’s disease makes it difficult to apply therapy uniformly
• Future: distribution of treatment effects
  Individualized therapy?

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2 Zhao et al. Circ Res. 2005
4 Tahara et al. Hum Gene Ther. 2004