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Remarks today concerning
United Therapeutics may include forward-looking statements which represent United Therapeutics’ expectations or beliefs regarding future events. We caution that such statements involve risks and uncertainties that may cause actual results to differ materially from those in the forward-looking statements. Consequently, all such forward-looking statements are qualified by the cautionary language and risk factors set forth in United Therapeutics’ periodic and other reports filed with the SEC.

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RELEVANT FINANCIAL DISCLOSURES: PREVIOUS 12 MONTHS

<table>
<thead>
<tr>
<th>AFFILIATION/FINANCIAL INTEREST</th>
<th>NAME OF AFFILIATED ORGANIZATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>GRANT/RESEARCH SUPPORT</td>
<td>Actelion, Bayer, United Therapeutics (UT), Arena, Reata</td>
</tr>
<tr>
<td>CONSULTANT</td>
<td>Actelion, Bayer, UT, Reata, Gilead, V-Wave Medical</td>
</tr>
<tr>
<td>ROYALTY</td>
<td>None</td>
</tr>
</tbody>
</table>
1982 HEART & LUNG TRANSPLANT

Friday, November 19, 1982

He Has New Heart, Lungs

 PITTSBURGH (AP) — A 29-year-old Baptist minister from South Carolina who underwent a heart and lung transplant operation left the hospital Thursday plans for a relaxing shower and a fancy restaurant. I feel great. I'm on top of the world," the Rev. Gary Lundy said, adding, "I can run a mile or anything, all rather weak." Lundy said he has been "pretty well confined to hospital" room or the hallway. So I'm looking forward to just getting out and doing things whenever I want. Going out to dinner sounds very appealing." The S.C. minister underwent the 9-hour operation in September, becoming the ninth person to undergo the rare heart and lung transplant operation.
SENIOR ASSISTANT RESIDENT LECTURE
August 1, 1985

PULMONARY ARTERIAL HYPERTENSION:
WHERE DO WE STAND IN 1985?

Victor Tapson, MD
SAR
WHAT IS PAH?\textsuperscript{1,2}

» Mean pulmonary artery pressure $> 25$ mmHg

» PCWP $\leq 15$ mmHg

» Increased pressure load on right ventricle

» Eventual right-sided heart failure and death
WHAT IS PAH?¹,²

» Mean pulmonary artery pressure > 25 mmHg
» PCWP ≤ 15 mmHg
» Increased pressure load on right ventricle
» Eventual right-sided heart failure and death

HEALTHY VESSEL

DISEASED VESSEL

100 microns (µm)
(Human hair = 15 µm to 180 µm)
WHAT IS PAH?\textsuperscript{1,2}

» Mean pulmonary artery pressure $> 25$ mmHg

» PCWP $\leq 15$ mmHg

» Increased pressure load on right ventricle

» Eventual right-sided heart failure and death

**HEALTHY VESSEL**

100 microns ($\mu$m)

(Human hair = 15 $\mu$m to 180 $\mu$m)

**DISEASED VESSEL**
WHAT DO YOU NEED TO KNOW IN ORDER TO INITIATE PH THERAPY?

CAUSE OF PH

SEVERITY OF PH
PULMONARY HYPERTENSION

CAUSE OF PH

SEVERITY OF PH
CLINICAL CLASSIFICATION OF PH
WORLD SYMPOSIUM PH – NICE, FRANCE, 2013

1 PULMONARY ARTERIAL HYPERTENSION

1. Idiopathic PAH
2. Heritable PAH
   2.1. BMPR2
   2.2. ALK-1, ENG, SMAD9, CAV1, KCNK3
   2.3. Unknown
3. Drug and toxin induced
4. Associated with:
   4.1. Connective tissue disease
   4.2. HIV infection
   4.3. Portal hypertension
   4.4. Congenital heart diseases
   4.5. Schistosomiasis
1’ PVOD and/or PCH
1” Persistent PH of the newborn (PPHN)

2 PH DUE TO LEFT HEART DISEASE

2.1. Left ventricular systolic dysfunction
2.2. Left ventricular diastolic dysfunction
2.3. Valvular disease
2.4. Congenital/acquired LH inflow/outflow tract obstruction and congenital CMs

3 PH DUE TO LUNG DISEASES AND/OR HYPOXIA

3.1. Chronic obstructive pulmonary disease (COPD)
3.2. Interstitial lung disease
3.3. Pulm diseases with mixed restriction/obstruction
3.4. Sleep-disordered breathing
3.5. Alveolar hypoventilation disorders
3.6. Chronic exposure to high altitude
3.7. Developmental lung diseases

4 CHRONIC THROMBOEMBOLIC PH (CTEPH)

5 PH WITH UNCLEAR MULTIFACTORIAL MECHANISMS

5.1. Hematologic disorders: chronic hemolytic anemia, myeloproliferative disorders, splenectomy
5.2. Systemic disorders: sarcoidosis, pulmonary histiocytosis, LAM
5.3. Metabolic disorders: glycogen storage disease, Gaucher disease, thyroid disorders
5.4. Others: tumoral obstruction, fibrosing mediastinitis, chronic renal failure, segmental PH
PULMONARY HYPERTENSION
V/Q SCAN

In PAH-Queri,

42.7% of patients with proven PH did not get a VQ scan...
SCLERODERMA & PH

[Images of fingers with skin changes, typical of scleroderma and PH]
Clinical Features and Outcomes of Patients with Sarcoidosis Associated Pulmonary Hypertension at a Tertiary Care Center, Using Pulmonary Vasodilator Medications

Talal Dahhan, Kishan Parikh, Nicole F. Ruopp, Victor Poon, Gina-Maria Pomann, Terry Fortin, Victor F. Tapson, Sudarshan Rajagopal

312 SARC OIDOSIS PATIENTS

95 WITH PH
WHY DO PATIENTS WITH PAH DIE?

Chronic RV failure
PROGRESSION OF RV FINDINGS IN PAH

NORMAL

COMPENSATED PAH

↑ THICKNESS

DECOMPENSATED PAH

↑↑S
THE RV AND ITS CRUCIAL ROLE IN THE PROGNOSIS OF PAH

“If you have PAH and your RV is fine, relax and have fun, wine and dine. Make plans way ahead, you’re not going to be dead. As long as that chamber’s sublime.”

VFT
PAH PROGRESSION

- **Pre-symptomatic/Compensated**
  - Cardiac Output (CO)
  - Pulmonary Arterial Pressure (PAP)

- **Symptomatic/ Decompensating**
  - Declining Cardiac Output
  - Rising Pulmonary Arterial Pressure

- **Declining/ Decompensated**
  - Right Heart Dysfunction
  - Right Heart Failure

*Time*

**PAH Progression**

- **Right Heart Failure**
PULMONARY HYPERTENSION

TREATMENT
MOLECULAR PATHOLOGY: IMBALANCE OF VASOACTIVE MEDIATORS

PROSTACYCLIN PATHWAY
Arachidonic acid \rightleftharpoons COX \rightarrow Prostaglandins \downarrow \text{Prostacyclin (PGL$_2$)} \rightarrow AC \rightarrow cAMP

PROSTACYCLIN PATHWAY

VASODILATION AND ANTIPROLIFERATION

NO/SGC/CGMP PATHWAY
L-Arginine \rightarrow NOS \rightarrow L-Citruline \downarrow \text{NO} \rightarrow sGC \rightarrow cGMP

NO/SGC/CGMP PATHWAY

VASODILATION AND ANTIPROLIFERATION

ENDOTHELIN PATHWAY
Pro-endothelin \rightarrow ECE \rightarrow Fragments \uparrow \text{Endothelin} \rightarrow \text{Endothelin-receptor antagonists} \rightarrow \uparrow \text{ET-A receptor} \rightarrow \uparrow \text{ET-B receptor}

ENDOTHELIN PATHWAY

VASOCONSTRICTION AND PROLIFERATION

↓ | Downregulation in PH

↑ | Upregulation in PH

Smooth muscle

\text{PDE5 inhibitor}
A comparison of continuous intravenous epoprostenol (prostacyclin) with conventional therapy for primary pulmonary hypertension.


EIGHT PATIENTS DIED DURING THE 12-WEEK STUDY.
ALL WERE IN THE CONVENTIONAL-THERAPY GROUP.
(P = 0.003)
Inhaled treprostinil (Tyvaso)
Thermostable epoprostenol (Veletri)
ambrisentan (Letairis)
Inhaled treprostinil (Tyvaso)
Sildenafil (Revatio)
Tadalafil (Adcirca)
CCB, anticoagulation, digitalis, diuretics
IV eprostenol (Flolan)
SC treprostinil (Remodulin)
IV treprostinil (Remodulin)
sildenafil (Revatio)
tadalafil (Adcirca)
Inhaled iloprost (Ventavis)
ambrisentan (Letairis)
Inhaled treprostinil (Tyvaso)
Thermostable epoprostenol (Veletri)
EVOLUTION OF PAH THERAPY
PROSTACYCLIN THERAPY

Continuous Subcutaneous Infusion of Treprostinil, a Prostacyclin Analogue, in Patients with Pulmonary Arterial Hypertension
A Double-blind, Randomized, Placebo-controlled Trial


2002 American Journal of Respiratory and Critical Care Medicine

12-week, D-B, P-C, multicenter trial
470 patients with PAH

→ Exercise capacity improved with treprostinil and was unchanged with placebo ($p = 0.006$)

→ Improvement was greater in sicker patients and was dose-related, but independent of PAH etiology

→ Treprostinil significantly improved dyspnea, signs and symptoms of PH, and hemodynamics
### EVOLUTION OF PAH THERAPY

#### Prostacyclin analogues

<table>
<thead>
<tr>
<th>STUDY ID</th>
<th>Year</th>
<th>RR (95% CI)</th>
<th>% WEIGHT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rubin</td>
<td>1990</td>
<td>0.36 (0.04, 3.00)</td>
<td>4.90</td>
</tr>
<tr>
<td>Barst</td>
<td>1996</td>
<td>0.06 (0.00, 0.96)</td>
<td>2.74</td>
</tr>
<tr>
<td>Badesch</td>
<td>2000</td>
<td>0.79 (0.22, 2.77)</td>
<td>13.72</td>
</tr>
<tr>
<td>Simonneau</td>
<td>2002</td>
<td>0.92 (0.38, 2.21)</td>
<td>28.03</td>
</tr>
<tr>
<td>Galiè</td>
<td>2002</td>
<td>1.00 (0.36, 2.77)</td>
<td>2.80</td>
</tr>
<tr>
<td>Uttschewski</td>
<td>2002</td>
<td>0.25 (0.03, 2.22)</td>
<td>4.62</td>
</tr>
<tr>
<td>Barst</td>
<td>2003</td>
<td>0.47 (0.04, 1.19)</td>
<td>3.08</td>
</tr>
<tr>
<td>McLaughlin</td>
<td>2010</td>
<td>0.35 (0.01, 8.45)</td>
<td>2.14</td>
</tr>
<tr>
<td>McLaughlin</td>
<td>2006</td>
<td>(Excluded)</td>
<td>0.00</td>
</tr>
<tr>
<td>Hooper</td>
<td>2006</td>
<td>(Excluded)</td>
<td>0.00</td>
</tr>
</tbody>
</table>

Subtotal (I²=0.0%, P=0.682) 0.62 (0.34, 1.12) 62.91

#### Endothelin receptor antagonists

<table>
<thead>
<tr>
<th>STUDY ID</th>
<th>Year</th>
<th>RR (95% CI)</th>
<th>% WEIGHT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rubin</td>
<td>2002</td>
<td>0.24 (0.02, 2.60)</td>
<td>3.84</td>
</tr>
<tr>
<td>Barst</td>
<td>2004</td>
<td>1.54 (0.06, 37.19)</td>
<td>2.15</td>
</tr>
<tr>
<td>Galiè</td>
<td>2008</td>
<td>0.99 (0.06, 15.58)</td>
<td>2.87</td>
</tr>
<tr>
<td>Channick</td>
<td>2001</td>
<td>(Excluded)</td>
<td>0.00</td>
</tr>
<tr>
<td>Galiè</td>
<td>2006</td>
<td>(Excluded)</td>
<td>0.00</td>
</tr>
<tr>
<td>Barst</td>
<td>2006</td>
<td>(Excluded)</td>
<td>0.00</td>
</tr>
</tbody>
</table>

Subtotal (I²=0.0%, P=0.597) 0.60 (0.12, 2.86) 8.86

#### Phosphodiesterase type 5 inhibitor

<table>
<thead>
<tr>
<th>STUDY ID</th>
<th>Year</th>
<th>RR (95% CI)</th>
<th>% WEIGHT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sastry</td>
<td>2004</td>
<td>0.39 (0.01, 8.73)</td>
<td>2.27</td>
</tr>
<tr>
<td>Galiè</td>
<td>2005</td>
<td>1.01 (0.11, 9.56)</td>
<td>4.32</td>
</tr>
<tr>
<td>Galiè</td>
<td>2008</td>
<td>0.47 (0.11, 1.94)</td>
<td>12.95</td>
</tr>
<tr>
<td>Simonneau</td>
<td>2008</td>
<td>0.87 (0.00, 1.19)</td>
<td>2.48</td>
</tr>
<tr>
<td>Galiè</td>
<td>2009</td>
<td>0.51 (0.05, 5.55)</td>
<td>3.83</td>
</tr>
<tr>
<td>Singh</td>
<td>2006</td>
<td>(Excluded)</td>
<td>0.00</td>
</tr>
</tbody>
</table>

Subtotal (I²=0.0%, P=0.977) 0.60 (0.12, 2.86) 8.86

#### Thromboxane synthase inhibitor

<table>
<thead>
<tr>
<th>STUDY ID</th>
<th>Year</th>
<th>RR (95% CI)</th>
<th>% WEIGHT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Langleben</td>
<td>2002</td>
<td>1.64 (0.07, 39.30)</td>
<td>2.18</td>
</tr>
</tbody>
</table>

Subtotal (I²=0.0%, P=0.977) 1.64 (0.07, 39.30) 2.18

Heterogeneity between groups: P=0.788 Overall (I²=0.0%, P=0.908) 0.56 (0.35, 0.90) 100.00

FAVORS TREATMENTS 0.00342 292 FAVORS CONTROLS
**EVOLUTION OF PAH THERAPY**

**RECENT COMBINATION STUDIES**

- **Riociguat (Adempas)**
  - FDA-approved: 10/8/13
  - 2013: First oral prostanoid
  - FDA-approved: 12/20/13
  - Oral treprostinil (Orenitram)

- **Macitentan (Opsumit)**
  - FDA-approved: 10/18/13

- **Selexipag (Uptravi)**
  - FDA-approved: 12/21/15

- **TD-300/A inhalation device**
  - FDA-approved: 10/17/17

- **SOUTHPAW (Grp 2)**
- **INCREASE (Grp 3)**
- **PERFECT (Grp 3)**

- **RemUnity or RemoSynch?**
- **CO-254 patch (TRE pro-drug)**
EVOLUTION OF PAH THERAPY
RECENT COMBINATION STUDIES

- **Riociguat (Adempas)**
  - FDA-approved: 10/8/13
- **Macitentan (Opsumit)**
  - FDA-approved: 10/18/13
- **Selexipag (Uptravi)**
  - FDA-approved: 12/21/15
- **TD-300/A inhalation device**
- **SOUTHPAW (Grp 2)**
- **INCREASE (Grp 3)**
- **PERFECT (Grp 3)**

**Timeline:**
- **2013**
  - First oral prostanoid: FDA-approved 12/20/13
  - Oral treprostinil (Orenitram)
- **2014**
- **2017**
  - FDA-approved: 10/17/17
- **2018**
  - RemUnity or RemoSynch?
  - SC pump
  - CO-254 patch (TRE pro-drug)
AND THEN WHAT HAPPENED?

2002 | Continuous subcutaneous infusion of treprostinil, a prostacyclin analogue, in patients with pulmonary arterial hypertension: a double-blind, randomized, placebo-controlled trial.

2003 | Efficacy and Safety of Treprostinil: An Epoprostenol Analog for Primary Pulmonary Hypertension
Vallerie V. McLaughlin; Sean P. Gaine; Robyn J. Barst; Ronald J. Oudiz; Robert C. Bourge; Adana Frost; Ivan M. Robbins; Victor F. Tapson; Michael D. McGoon; David B. Badesch; Jeff Sigman; Robert Rossignol; Sheltmer D. Blackburn; Carl Arneson; Lewis J. Rubin; Stuart Rich

2006 | Long-term outcome in pulmonary arterial hypertension patients treated with subcutaneous treprostinil

2006 | Efficacy of long-term subcutaneous treprostinil sodium therapy in pulmonary hypertension
Lang I, Gomez-Sanchez M, Kneussl M, Naeije R, Escribano P, Skoro-Sajer N, Vachiery JL

2006 | Safety and efficacy of IV treprostinil for pulmonary arterial hypertension: a prospective, multicenter, open-label, 12-week trial
Tapson VF, Gomberg-Maitland M, McLaughlin VV, Benza RL, Widlitz AC, Krichman A, Barst RJ

2012 | First long-term experience with intravenous treprostinil administered by the implantable infusion pump LenusPro. A single-center pilot study
Regina Steringer-Mascherbauer, Venonika Eder, Charlotte Huber, Susanne Wittrich, Reinhold Fuegger, Uwe Fröschi, Hans Joachim Nesser

2012 | Oral treprostinil for the treatment of pulmonary arterial hypertension in patients on background endothelin receptor antagonist and/or phosphodiesterase type 5 inhibitor therapy (the FREEDOM-C study): a randomized controlled trial

2013 | Oral treprostinil for the treatment of pulmonary arterial hypertension in patients receiving background endothelin receptor antagonist and phosphodiesterase type 5 inhibitor therapy (the FREEDOM-C2 study): a randomized controlled trial
Tapson VF, Jing ZC, Xu KF, Pan L, Feldman J, Kiely DG, Kotlyar E

2013 | Efficacy and safety of oral treprostinil monotherapy for the treatment of pulmonary arterial hypertension: a randomized, controlled trial

2013 | One-year experience with intravenous treprostinil for pulmonary arterial hypertension
Benza RL, Tapson VF, Gomberg-Maitland M, Poms A, Barst RJ, McLaughlin VV

2015 | Long-term therapy with oral treprostinil in pulmonary arterial hypertension failed to lead to improvement in important physiologic measures: results from a single center
Chin KM, Ruggiero R, Bartolome S, Velez-Martinez M, Darsaklis K, Kingman M, Harden S, Torres F

2017 | Experience with subcutaneous treprostinil in children with pulmonary arterial hypertension
Alba Torrent Vernetta, Sandra Rovira Amigo, Ignacio Iglesias Serrano, María Morillo, Inés de Mir Messa, Silvia Gartner, Dimpna Albert Brotons, Antonio Moreno Galidó
FREEDOM-EV TOP LINE RESULTS RELEASED

**PRIMARY OBJECTIVE**  
Met on August 8, 2018

**TIME TO FIRST CLINICAL WORSENING EVENT**

» 214 patients had adjudicated clinical worsening (morbidity/mortality) event

» Majority had either FC II (63%) or III (34%) symptoms

» Orenitram generally well tolerated / safety profile c/w previous studies

Orenitram decreased the risk of a morbidity/mortality event versus placebo by 26%.
FREEDOM-EV STUDY DESIGN

- **NCT01560624** FREEDOM EV
- **N=690** SUBJECTS WITH PAH RECEIVING BACKGROUND ORAL MONOTHERAPY
- RANDOMIZE 1:1 DOUBLE-BLIND
- 152 CENTERS FROM 23 COUNTRIES

**UT-15C (TREPROSTINIL DIETHANOLAMINE)**

- **PRIMARY EFFICACY ENDPOINT**
  - TIME TO THE FIRST CLINICAL WORSENING (MORTALITY/ MORBIDITY) EVENT

- **TREATMENT PERIOD CONTINUED UNTIL THE 214TH ADJUDICATED CW EVENT**

**PLACEBO**

**382 CENTERS FROM 23 COUNTRIES**
### WHAT IS THE IDEAL TREATMENT STRATEGY?\(^8\)

<table>
<thead>
<tr>
<th>WHAT DETERMINES PROGNOSIS?</th>
<th>BETTER PROGNOSIS</th>
<th>POORER PROGNOSIS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CLINICAL RV FAILURE</strong></td>
<td>Not present</td>
<td>Present</td>
</tr>
<tr>
<td><strong>SYMPTOMS</strong></td>
<td>Gradual worsening</td>
<td>Rapid worsening</td>
</tr>
<tr>
<td><strong>FUNCTIONAL CLASS</strong></td>
<td>2 or 3</td>
<td>4</td>
</tr>
<tr>
<td><strong>6MWD</strong></td>
<td>Longer (&gt;400 m)</td>
<td>Shorter (&lt;300 m)</td>
</tr>
<tr>
<td><strong>CP EXERCISE TESTING</strong></td>
<td>Peak VO(_2) &gt;10.4</td>
<td>Peak VO(_2) &lt;10.4</td>
</tr>
<tr>
<td><strong>ECHOCARDIOGRAM</strong></td>
<td>RV near-normal size / Near-normal pumping</td>
<td>Very enlarged RV/poor pumping function</td>
</tr>
<tr>
<td><strong>HEART CATHETERIZATION</strong></td>
<td>Normal RA pressure / Normal cardiac index</td>
<td>Very high RA pressure / Very low cardiac index</td>
</tr>
<tr>
<td><strong>BNP BLOOD TEST</strong></td>
<td>Normal/barely elevated</td>
<td>Very elevated</td>
</tr>
</tbody>
</table>
### WHICH MEDICATION? WHY?

<table>
<thead>
<tr>
<th><strong>Parenteral therapy for the most severe</strong></th>
<th><strong>Angina / MI on nitrates, nitroglycerin?</strong></th>
<th><strong>Cannot use PDE5-I</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>IPAH vasodilator responder at RH catheterization?</strong></td>
<td><strong>Pregnant or trying to get pregnant? (!!!)</strong></td>
<td><strong>Cannot use ERA!</strong></td>
</tr>
<tr>
<td><strong>Very slow heart rate?</strong></td>
<td><strong>Low blood pressure?</strong></td>
<td><strong>Caution with PDE5-Is, riociguat</strong></td>
</tr>
<tr>
<td><strong>Liver disease?</strong></td>
<td><strong>Sinus problems?</strong></td>
<td><strong>May be exacerbated by ERAs or PDE5-Is</strong></td>
</tr>
<tr>
<td><strong>Fluid retention?</strong></td>
<td><strong>Acid reflux?</strong></td>
<td><strong>May be worse with PDE5-Is</strong></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Poor compliance with medications?</strong></th>
<th><strong>Aim for once-daily medications</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Unable to care for IV line/pump?</strong></td>
<td><strong>May need to change to oral / inhaled</strong></td>
</tr>
<tr>
<td><strong>Expense?</strong></td>
<td></td>
</tr>
</tbody>
</table>
COMBINATION THERAPY

Initial Use of Ambrisentan plus Tadalafil in Pulmonary Arterial Hypertension

WHY NOVEL THERAPIES?

PAH involves multiple pathways

Combination therapy is beneficial, the more the better

Our “strongest” therapies are very inconvenient

Some patients fail currently available therapies

Current therapies have adverse effects
PAH

MECHANISMS
BMP SIGNALING

BMP ligand
Clathrin coated pits

BMPR-II
BMPR1A/B/ALK-1
LIMK1
Tctex-1
HC

MAPK
P

Smad1/5/8
P

Smad4
P

Gene expression regulation

Transcription

P

P

P

P

P

P

P

P

P

P

P
MANY NEW POTENTIAL MECHANISMS TO EXPLORE IN PAH

ALTED METABOLISM
» Warburg Effect
» ER stress
» Channelopathies
» Altered Estrogen Metabolism
» Autophagy
» Increased HIF-1α
» Unfolded Protein Response

ENVIRONMENT
» Drugs and toxins
» Hypoxia
» Viruses

GENE MUTATIONS
» BMPR2  » KCNK3
» ALK-1  » EIF2AK4
» SMAD9  » TBX4
» Caveolin-1  » Endoglin

FIBROSIS & MATRIX
» Fibroblast
» Proliferation
» Collagen Production
» Elastase

ANGIOGENESIS
» Small vessel loss
» Impaired angiogenesis

INFLAMMATION
» Reduced Tregs
» Increased macrophage
» B Lymphocytes
» NK cells
» Tertiary Lymphoid Follicles
» Mast Cells
» Dendritic Cells
» Neutrophils
» Autoantibodies
» Cytokines

EPIGENETICS
» miRNAs
» DNA methylation

FIBROSIS & MATRIX
» Fibroblast
» Proliferation
» Collagen Production
» Elastase

ANGIOGENESIS
» Small vessel loss
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EPIGENETICS
» miRNAs
» DNA methylation
INFLAMMATION IN PAH

INFLAMMATION IN PULMONARY ARTERIAL HYPERTENSION

Laura C. Price, MBChB, S. John Wort, MBChB, PhD, Frédéric Perros, PhD, Peter Dorfmüller, MD, PhD, Alice Huertas, MD, PhD, David Montani, MD, PhD, Sylvia Cohen-Kaminsky, PhD, Marc Humbert, MD
INFLAMMATION IN PAH

"ROCK" IS A MAJOR REGULATOR OF VSMC CONTRACTION, IMPORTANT IN CONTROLLING:

- Cell migration
- Cell proliferation
- Apoptosis/survival
- Gene transcription / differentiation
STEM CELLS, ANGIOGENESIS AND OTHER THINGS...
ANGIOGENIC GENE TRANSFER

Gene transfer of angiogenic factors has been shown to be effective in preventing PAH in experimental models.

NO appears to be a critical mediator of angiogenesis...

Microvascular Regeneration in Established Pulmonary Hypertension by Angiogenic Gene Transfer

Yidan D. Zhao, David W. Courtman, Doug S. Ng, Malcolm J. Robb, Yupu P. Deng, Judy Trogadis, Robin N. N. Han, and Duncan J. Stewart

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**AIM**

To evaluate the ability of cardiosphere-derived cells (cardiac progenitor cells with potent anti-inflammatory and immunomodulatory properties), to attenuate hemodynamic and morphometric remodeling of the RV and pulmonary arterioles in rats with established monocrotaline (MCT)-induced PAH.

**RESULTS**

In CDC rats at day 35:

- RSVP fell (-38%; \( p<0.001 \))
- RV hypertrophy decreased (-26%; \( p<0.01 \))
- Pulmonary arteriolar wall thickness greater in sham rats
- Pulmonary arteriolar wall thickness reduced in CDC animals
- Macrophage population was increased in Sham animals compared to CTL (\( P<0.001 \)), but markedly reduced in CDC rats.

**ALPHA TRIAL UNDERWAY!**
THE FUTURE
FUTURE DIRECTIONS IN PAH

CLINICAL ADVANCES IN PH CONTINUE:

- Computer modeling of pulmonary vasculature and RV
- New drug therapy
- Computer modeling of pulmonary vasculature and RV
- Pharmacogenomics
- Inflammation
- Next Generation Delivery System
- Epigenetics / apoptosis - Cancer lessons applied to PAH
- Endothelial progenitor cells
- Inflammation
- Next Generation Delivery System
- Cardiac regeneration / angiogenesis
- Organ manufacturing
NOVEL METHODS IN PH PHENOTYPING IN THE AGE OF PRECISION MEDICINE

The model illustrates the specific tools used to collect human samples/data from patients to help better understand pulmonary vascular disease.
WHAT CAN WE DO BETTER?
WE NEED TO DO BETTER!\textsuperscript{13}

Time in Months from Initial Symptoms: All Patients

- N = 2917, Presentation to MD for Evaluation: 1.9 months
- N = 2934, Patient First Told They had PH: 6.3 months
- N = 2936, Diagnostic RHC: 13.5 months
- N = 2935, First Visit to PAH Clinic: 14.1 months
- N = 2936, Date of Enrollment: 51.8 months
32% of FC III/IV patients were either not treated or on monotherapy.

- **Dual Therapy**: 22%
- **Triple Therapy**: 45%
- **No Therapy**: 5%
- **Monotherapy**: 27%

Functional class measured within 6 months of death.
NEXT GENERATION DELIVERY

PARENTERAL

IV
GREATER MOBILITY

SUBQ
PAIN FREE
SUBQ

INHALED
ADVANCED
FORMULATION
TECHNOLOGY

GREATER CONVENIENCE FOR GREATER OUTCOME
» Current PAH therapy **impacts on three pathways**

» There is no clear first choice re: initial drug class

» **Specific therapeutic goals** should be considered in PAH

» Agents of different classes can be combined

» **Upfront combination therapy** should be considered

» Severely ill patients need parenteral prostanoid therapy
## CONCLUSIONS

- **Inflammation** appears to be an important target.
- Survival is improving but **deaths** still occur.
- The cancer analogy has **tremendous implications**.
- Multiple therapeutic pathways for PAH have **proven effective**.
- A number of **new approaches** are forthcoming.
- Oral, inhaled, SC, IV, therapies are **now available**.
CONCLUSIONS

» Now, an implantable pump has been approved

» Patients are still dying of PAH

» The mortality of PAH has decreased over the past two decades

» New therapeutic approaches to PAH are forthcoming
“Yet there is already plenty of evidence to show that we are in much danger of losing our clinical heritage and of pinning too much faith in figures thrown up by machines. Medicine must suffer if this tendency is not checked.”

Paul Wood 1950
(1907 – 1962)
REFERENCES

THANK YOU