ACTRIIA-Fc Rebalances Activin/GDF and BMP9 Signaling to Attenuate Experimental Pulmonary Hypertension

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SCIENTIFIC 210
SESSIONS 18
Mutations of Heritable PAH syndromes implicate loss of BMP function in pulmonary vascular disease

BMPRII  BMPR2  HPAH
ALK1    ACVRL1  HHT2-HPAH
ENG     ENG     HHT1
SMAD4   SMAD4   JP-HT
SMAD9   SMAD9   HPAH
BMP9    GDF2     HHT5
PAH is characterized by deficient BMP signaling and exaggerated TGFβ/activin signaling

- Genetics implicates deficient BMP9-BMPRII-ALK1-ENG-SMAD1/5/9 axis
- Non-genetic forms of PAH exhibit deficient BMP, and exaggerated TGFβ/activin signaling
- Pattern recapitulated in multiple animal models of PH
- Approved therapies appear to improve this balance
What is the impact of selective activin/GDF blockade in pulmonary arterial hypertension?

**Hypothesis:**
Blockade of activin ligands attenuates pulmonary vascular remodeling by rebalancing SMAD1/5/9 vs. SMAD2/3 signaling.
Impact of ACTRIIA-Fc prophylaxis in MCT rats

Sprague Dawley Rat

Vehicle (saline)
ACTRIIA-Fc (10 mg/kg, S.C. 2x weekly)
Sildenafil (30 mg/kg, P.O. 2x daily)

Right heart catheterization
Fulton’s Index
PV Histology

MCT (60 mg/kg, S.C.)

4 weeks

mPAP

RV/(LV+S)

MWT

Vehicle
ACTRIIA-FC
Sildenafil

MCT (4 weeks)

Percent of vessels

Medial wall thickness index (%)
Impact of ACTRIIA-Fc prophylaxis in SU-Hx rats

Sprague Dawley Rat

Vehicle (saline)
ACTRIIA-Fc (10 mg/kg, S.C. 2x weekly)
Sildenafil (30 mg/kg, P.O. 2x daily)

SU5416 (200 mg/kg, S.C.)
+ Hypoxia

4 weeks

Right heart catheterization
Fulton’s Index
PV Histology

mPAP

RV/(LV+S)

MWT

SU-Hx (4 weeks)

mPAP (mmHg) (9) (10) (10)

RV/(LV+S) (10) (10) (10)

Medial wall thickness index (%)

0 10 20 30 40

Vehicle ACTRIIA-FC Sildenafil

0.0 0.2 0.4 0.6 0.8

0 20 40 60

Vehicle ACTRIIA-FC Sildenafil

0.1 1.0

27.4 69.3** 31.6

72.5 29.3** 67.4

1.4*

29.3**

67.4

0 10 20 30 40

Vehicle ACTRIIA-FC Sildenafil

0 10 20 30 40

Vehicle ACTRIIA-FC Sildenafil

0 10 20 30 40

Vehicle ACTRIIA-FC Sildenafil
Impact of ACTRIIA-Fc on progression of established PH in MCT rats

Sprague Dawley Rat

MCT (40 mg/kg, S.C.)

ACTRIIA-Fc
(1, 3, 10 mg/kg 2x/weekly)

4 weeks
2 weeks

Right heart catheterization
Fulton’s Index
PV Histology

RVSP

RV/(LV+S)

one-way ANOVA dose trend p = 0.012

MCT 1 mg/kg 3 mg/kg 10 mg/kg

MCT + ACTRIIA-Fc

one-way ANOVA trend p=0.0003

MCT (6 weeks)

Medial wall thickness index (%)

50
40
30
20
10
0

MCT 1 3 10

Non-muscularized
Partially muscularized
Fully muscularized

p<0.05

0
10
20
30
40

MCT 1 3 10

ACTRIIA-Fc (mg/kg twice weekly)
Impact of ACTRIIA-Fc on progression of established PH in SU-Hx rats

RVSP
one-way ANOVA dose trend $p = 0.03$

RV/(LV+S)
one-way ANOVA dose trend $p = 0.05$

SU-Hx (3 weeks) → ACTRIIA-Fc (1, 3, 10 mg/kg twice weekly) → Nx (3 weeks) → Right heart catheterization Fulton’s Index PV Histology

SU-Hx + ACTRIIA-Fc

Sprague Dawley Rat

$\begin{align*}
\text{RVSP} & \quad \text{RV/(LV+S)} \\
\text{SU-Hx} & \quad \text{SU-Hx} \\
1 \text{ mg/kg} & \quad 1 \text{ mg/kg} \\
3 \text{ mg/kg} & \quad 3 \text{ mg/kg} \\
10 \text{ mg/kg} & \quad 10 \text{ mg/kg}
\end{align*}$

SU-Hx + ACTRIIA-Fc

Pai-1

$mRNA$ level
(Compared to control)

---

$\begin{align*}
\text{Percent of vessels} & \\
\text{Non-muscularized} & \quad \text{Partially muscularized} & \quad \text{Completely Muscularized} \\
\text{SU-Hx} & \quad \text{SU-Hx} + 1 \text{ mg/kg} & \quad \text{SU-Hx} + 10 \text{ mg/kg}
\end{align*}$

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*one-way ANOVA trend $p = 0.01$
Impact of ACTRIIA-Fc in SU-Hx rats with angio-obliterative lesions

SU-Hx (3 wks) → Nx (2 wks) → Treatment (4 wks)

Vehicle (saline)
ACTRIIA-Fc (5 mg/kg, S.C. 2x weekly)
Sildenafil (30 mg/kg, P.O. 2x daily)

ECHO
Right heart catheterization
Fulton's Index
PV Histology

Sprague Dawley Rat

Control
SU-Hx
5 weeks
9 weeks
ACTRIIA-Fc

0
50
100
150
RVSP (mmHg)

0
0.2
0.4
0.6
0.8
RV/(LV+S)

0
0.5
1.0
1.5
2.0
ED RV wall thickness (mm)

0
10
20
30
40
50
PAT (ms)

0
1
2
3
4
TAPSE (mm)

Non-muscularized
Partially muscularized
Fully muscularized

Percent of vessels

Wall thickness index (%)

% occluded vessel
ACTRIIA-Fc selectively inhibits Activin/GDF signaling and phenotypic switch in SMC
**GDF11 inhibits BMP9 signaling; ACTRIIA-Fc enhances BMP9 signaling in ECs**

<table>
<thead>
<tr>
<th>BMP2</th>
<th>BMP4</th>
<th>BMP6</th>
<th>BMP7</th>
<th>BMP12</th>
<th>BMP9</th>
<th>BMP10</th>
<th>GDF8</th>
<th>GDF11</th>
<th>activin A</th>
<th>activin B</th>
<th>activin AC</th>
<th>TGFβ1</th>
<th>TGFβ3</th>
<th>TGFβ2</th>
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**HPMVEC**

<table>
<thead>
<tr>
<th>Control</th>
<th>BMP9</th>
<th>GDF8</th>
<th>GDF11</th>
<th>Act A + BMP9</th>
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**p-SMAD1/5 (RLU)**

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**p-SMAD1/5 (RLU)**

<table>
<thead>
<tr>
<th>Control</th>
<th>BMP9 10 pg/ml</th>
<th>BMP9 50 pg/ml</th>
<th>BMP9 250 pg/ml</th>
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Comparison of ACTRIIA-Fc to approved therapies in PH models

<table>
<thead>
<tr>
<th>Agent</th>
<th>% Reduction in mPAP</th>
<th>% Reduction in RVH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bosentan</td>
<td>21</td>
<td>30</td>
</tr>
<tr>
<td>Sildenafil</td>
<td>24</td>
<td>18</td>
</tr>
<tr>
<td>Beraprost NP</td>
<td>25</td>
<td>28</td>
</tr>
<tr>
<td>ACTRIIA-Fc</td>
<td>56</td>
<td>47</td>
</tr>
</tbody>
</table>

**Monocrotaline (Prevention)**

<table>
<thead>
<tr>
<th>Agent</th>
<th>% Reduction in mPAP</th>
<th>% Reduction in RVH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Macitentan</td>
<td>36</td>
<td>31</td>
</tr>
<tr>
<td>Sildenafil</td>
<td>22</td>
<td>10</td>
</tr>
<tr>
<td>Beraprost NP</td>
<td>27</td>
<td>32</td>
</tr>
<tr>
<td>ACTRIIA-Fc</td>
<td>51</td>
<td>54</td>
</tr>
</tbody>
</table>

**SU-Hx (Prevention)**

<table>
<thead>
<tr>
<th>Agent</th>
<th>% Reduction in mPAP</th>
<th>% Reduction in RVH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sildenafil</td>
<td>10</td>
<td>19</td>
</tr>
<tr>
<td>Riociguat</td>
<td>10</td>
<td>20</td>
</tr>
<tr>
<td>Tadalafil + Macitentan</td>
<td>28</td>
<td>28</td>
</tr>
<tr>
<td>ACTRIIA-Fc</td>
<td>33</td>
<td>30</td>
</tr>
</tbody>
</table>

**SU-Hx (Therapeutic)**

2. Akagi et al J Cardiovasc Pharmacol 2016; 67; 290-298; Beraprost NP 150 µg/kg
3. Shinohara et al Am J Physiol Lung Cell Mol Physiol 2015; Macitentan 30 mg/kg/d
4. RAP-011 and Sildenafil (60 mg/kg/d) were tested in same study
5. Right ventricular systolic pressure

   Sildenafil 50 mg/kg/d; Riociguat 10 mg/kg/d
   Tadalafil 10 mg/kg/d; Macitentan 30 mg/kg/d
3. Current study; 10 mg/kg twice weekly
Summary

1. ACTRIIA-Fc is a mechanism-targeted, non-vasodilator PAH therapy that inhibits neo-intimal and medial remodeling.

2. ACTRIIA-Fc inhibits signaling of activins/GDFs and may augment BMP9; multiple mechanisms of action and cellular targets being considered.

3. Human clinical experience includes nearly 400 patients across 13 trials for muscle wasting and anemia.

4. Well tolerated at 0.3, 0.7, and 1.5 mg/kg in human subjects, corresponding to human equivalent doses of 1.8, 4.2 and 10 mg/kg in rats, overlapping with efficacious rat doses.

5. PULSAR, a Phase 2 study of Sotatercept for PAH began enrolling June 2018.
Acknowledgements

Yu Lab - BWH Cardiology
Paul Yu, M.D., Ph.D.
Brian Yang, Ph.D.
Geoff Bocobo, B.S.
Teresa Dinter, B.S.
Po-Sheng Chen, M.D.
Megan McNeil, B.S.
Zachary Augur, B.S.
Stephanie Kim, B.S.
Luca Troncone, Ph.D.
Ivana Nikolic, M.D.

University of Cambridge
Nicholas Morrell, M.D.
Mark Southwood, M.D.

Acceleron Pharma
Ravindra Kumar, Ph.D.
R. Scott Pearsall, Ph.D.
Gang Li, Ph.D.
Sachindra Joshi, Ph.D.
Dianne S. Sako, B.S.

Funding
Gilead Sciences Research Scholars Program
NHLBI R01-HL131910
NHLBI R42-HL132742
B-BIC DRIVE GRANT
Fondation Leducq