ACTRIIA-Fc rebalances BMP and activin/TGF-β signaling to attenuate experimental pulmonary hypertension

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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

vascular homeostasis     myogenic and fibrogenic differentiation
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

Atkinson L, Circ 2002
Yndestad A, J Appl Physiol 2009
Yang J, Circ Res 2010
Ogo T, Circ 2013
Long L, Nat Med 2015
Yan Y, Int J Cardiol 2016
Yung LM, AJRCCM 2016
What is the impact of selective activin/GDF blockade in pulmonary arterial hypertension?

**Hypothesis:**
Blockade of activin ligands attenuates pulmonary vascular remodeling by rebalancing SMAD1/5/8 vs. SMAD2/3 signaling.

*Primary ligands inhibited*
- SMAD 1/5/9 vascular homeostasis
- SMAD 2/3 myogenic and fibrogenic differentiation

ACTRIIA-Fc
(ACE-011/Sotatercept)

TGFBRII-Fc
Yung LM et al.
AJRCCM 2016
Impact of ACTRIIA-Fc (15 mg/kg S.C. twice weekly x 4 weeks) prophylaxis in rats treated with MCT (60 mg/kg)

MPAP

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Weight Ratio</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vehicle</td>
<td>1.4</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>ACTRIIA-Fc</td>
<td>36.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Sildenafil</td>
<td>66.9**</td>
<td>&lt;0.01</td>
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</table>

RV / LV+S

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Weight Ratio</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vehicle</td>
<td>0.9</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>ACTRIIA-Fc</td>
<td>25.8**</td>
<td>&lt;0.01</td>
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<tr>
<td>Sildenafil</td>
<td>57.9</td>
<td>&lt;0.01</td>
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</tbody>
</table>

* p ≤ 0.05 vs. control
** p ≤ 0.01 vs. control
Impact of ACTRIIA-Fc (10 mg/kg weekly x 4 weeks) prophylaxis in rats treated with SUGEN5416 (200 mg/kg) and hypoxia

**MPAP**

- Vehicle: 42 mm Hg
- ACTRIIA-Fc: 30 mm Hg
- Sildenafil: 22 mm Hg

**P** ≤ 0.001 vs. control

**RV / LV+S**

- Vehicle: 0.1
- ACTRIIA-Fc: 1.4*
- Sildenafil: 1.0

**P** ≤ 0.05 vs. control

* *p ≤ 0.05 vs. control
** *p ≤ 0.01 vs. control

**Legend:**
- Non-muscularized
- Partially muscularized
- Completely muscularized
Impact of ACTRIIA-Fc prophylaxis on PV remodeling in SU-Hx rats

SUGEN-Hypoxia

SUGEN-Hypoxia + Sildenafil

SUGEN-Hypoxia + ACTRIIA-Fc

Sugen hypoxia, lung histology (αSMA/elastin Staining)
Impact of ACTRIIA-Fc on progression of established PH in SU-Hx rats

<table>
<thead>
<tr>
<th>SU-Hx Model</th>
<th>Treatment</th>
<th>n</th>
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</thead>
<tbody>
<tr>
<td>Control</td>
<td>Vehicle</td>
<td>8</td>
</tr>
<tr>
<td>ACTRIIA-Fc</td>
<td>1 mg/kg twice weekly</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td>3 mg/kg twice weekly</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td>10 mg/kg twice weekly</td>
<td>8</td>
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</table>

Normobaric hypoxia (FIO2 = 0.10) SU5416 (20 mg/kg S.C., weekly)

SU-Hx (3 weeks) → Normoxia (3 weeks) → Echo RV function
Right heart catheterization
Fulton’s Index
PV and RV Histology
ACTRIIA-Fc attenuates PH progression in SU-Hx rats

One-way ANOVA dose trend \( p = 0.03 \)

One-way ANOVA dose trend \( p = 0.05 \)

*One-way ANOVA trend \( p = 0.05 \)
ACTRIIA-Fc attenuates intimal-medial remodeling in SU-Hx rats

One-way ANOVA trend $p = 0.05$

One-way ANOVA trend $p = 0.01$
ACTRIIA-Fc de-represses activin inhibition of BMP9 signaling

BMP Response Element (BRE-Luciferase) activity in A204 reporter cell line
Comparison of ACTRIIA-Fc to approved therapies in PH models

<table>
<thead>
<tr>
<th>Monocrotaline - Prevention</th>
<th>SUGEN-Hypoxia - Prevention</th>
<th>SUGEN-Hypoxia – Therapeutic</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Agent</strong></td>
<td><strong>% Reduction in mPAP</strong></td>
<td><strong>Agent</strong></td>
</tr>
<tr>
<td>Bosentan&lt;sup&gt;1&lt;/sup&gt;</td>
<td>21</td>
<td>Macitentan&lt;sup&gt;3&lt;/sup&gt;</td>
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<tr>
<td>Sildenafil&lt;sup&gt;4&lt;/sup&gt;</td>
<td>24</td>
<td>Sildenafil&lt;sup&gt;4&lt;/sup&gt;</td>
</tr>
<tr>
<td>Beraprost NP&lt;sup&gt;2&lt;/sup&gt;</td>
<td>25&lt;sup&gt;5&lt;/sup&gt;</td>
<td>Beraprost NP&lt;sup&gt;2&lt;/sup&gt;</td>
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<tr>
<td>ACTRIIA-Fc&lt;sup&gt;4&lt;/sup&gt;</td>
<td>56</td>
<td>ACTRIIA-Fc&lt;sup&gt;4&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

**Comparison**

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 at CorDynamics
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 potentially mechanism-targeted, non-vasodilator PAH therapy that potently inhibits neo-intimal and medial remodeling.

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

3. Sotatercept has favorable pharmacokinetics, dosed SC every three weeks.

3. Human clinical experience includes nearly 400 patients across 13 trials.

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 doses in rat models.

6. Phase 2 studies for PAH are planned.
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ACTRIIA-Fc fusion protein (RAP-011/Sotatercept) is an activin/GDF ligand trap

ACTRIIA-Fc (RAP-011/Sotatercept) traps activin A, activin B, GDF8, GDF11