Sotatercept for rebalancing BMP/TGF-beta/activin signaling in PAH

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Heritable PAH syndromes implicate the BMP9/sBMPR2/ALK1 signaling axis in pulmonary vascular disease

<table>
<thead>
<tr>
<th>Gene 1</th>
<th>Gene 2</th>
<th>HPAH</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMPRII</td>
<td>BMPR2</td>
<td>HPAH</td>
<td></td>
</tr>
<tr>
<td>ALK1</td>
<td>ACVRL1</td>
<td>HHT1-HPAH</td>
<td></td>
</tr>
<tr>
<td>ENG</td>
<td>ENG</td>
<td>HHT2-HPAH</td>
<td></td>
</tr>
<tr>
<td>SMAD4</td>
<td>SMAD4</td>
<td>JP-HT</td>
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<tr>
<td>SMAD9</td>
<td>SMAD9</td>
<td>HPAH</td>
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</tr>
<tr>
<td>BMP9</td>
<td>GDF2</td>
<td>HHT5-HPAH</td>
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</tr>
<tr>
<td>KCNK3</td>
<td>KCNK3</td>
<td>HPAH</td>
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<tr>
<td>KCNA5</td>
<td>KCNA5</td>
<td>HPAH</td>
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</tr>
<tr>
<td>EIF2AK4</td>
<td>EIF2AK4</td>
<td>PVOD/PCH</td>
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<tr>
<td>CAV1</td>
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<td>HPAH</td>
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<tr>
<td>KLF2</td>
<td>KLF2</td>
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<tr>
<td>AQP1</td>
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<td>HPAH</td>
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<tr>
<td>SOX17</td>
<td>SOX17</td>
<td>HPAH</td>
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<tr>
<td>TBX4</td>
<td>TBX4</td>
<td>HPAH</td>
<td></td>
</tr>
</tbody>
</table>

Graf et al., Nat Comm 2018
Is PAH regulated by imbalanced BMP/TGF signaling?

BMP2 BMP4 BMP6 BMP7 BMP12 BMP9 BMP10 GDF8 GDF11 activin A activin B activin AC TGFβ1 TGFβ3 TGFβ2

ALK4/5/7 inhibitors
SD-208 (Zaiman et al, AJRCCM 2008)
IN-1233 (Long et al., Circ 2009)
SB525334 (Thomas et al., AJP 2009)

BMP9
Long L et al.
Nat Med 2015

ALK4/5/7 inhibitors
SD-208
(IN-1233
SB525334

SMAD 1/5/9
vascular homeostasis

SMAD 2/3
myogenic and fibrogenic differentiation

TGFBRII-Fc
Yung LM et al, AJRCCM 2016
What is the contribution of activin/GDF signaling?

**SMAD 2/3**
myogenic and fibrogenic differentiation

**SMAD 1/5/9**
vascular homeostasis

**ALK1-Fc**
Nikolic et al. AJRCCM 2018

**ALK4/5/7 inhibitors**
- SD-208 (Zaiman et al, AJRCCM 2008)
- IN-1233 (Long et al., Circ 2009)
- SB525334 (Thomas et al., AJP 2009)

**ACTRIIA-Fc**
(ACE-011/Sotatercept)

**TGFBRII-Fc**
Yung LM et al, AJRCCM 2016

**Ivana Nikolic, MD**

**BMP2** **BMP4** **BMP6** **BMP7** **BMP12** **BMP9** **BMP10** **GDF8** **GDF11** **activin A** **activin B** **activin AC** **TGFβ1** **TGFβ3** **TGFβ2**
ACTRIIA-Fc attenuates PH progression in SU-Hx rats

**RVSP (mmHg)**

<table>
<thead>
<tr>
<th>SU-Hx</th>
<th>1</th>
<th>3</th>
<th>10</th>
</tr>
</thead>
<tbody>
<tr>
<td>60</td>
<td>40</td>
<td>20</td>
<td>0</td>
</tr>
</tbody>
</table>

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

**RV/(LV+S)**

<table>
<thead>
<tr>
<th>SU-Hx</th>
<th>1</th>
<th>3</th>
<th>10</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.5</td>
<td>0.4</td>
<td>0.3</td>
<td>0.2</td>
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</tbody>
</table>

-one-way ANOVA dose trend $p = 0.05$

**ACTRIIA-Fc (mg/kg twice weekly)**

<table>
<thead>
<tr>
<th>SU-Hx</th>
<th>1</th>
<th>3</th>
<th>10</th>
</tr>
</thead>
<tbody>
<tr>
<td>68.0</td>
<td>47.9</td>
<td>45.2</td>
<td>28.8</td>
</tr>
</tbody>
</table>

Non-muscularized
Partially muscularized
Completely Muscularized

*one-way ANOVA trend $p = 0.05$
ACTRIIA-Fc attenuates PV remodeling in SU-Hx rats

One-way ANOVA trend p = 0.05

% Fully Muscularized Vessels

ActRIIa-Fc (mg/kg twice weekly)

SU-Hx 1 3 10

(p = 0.05)

SU-Hx

1 mg/kg

SU-Hx + 1 mg/kg

SU-Hx + 3 mg/kg

SU-Hx + 10 mg/kg

Pai-1 mRNA level (Compared to control)

*
ACTRIIA-Fc inhibits Activin/GDF8/11-SMAD2/3 signaling and myogenic/fibrogenic differentiation of hPASMC

HPASMC

Control  TGFβ1  GDF8  GDF11  Activin A  BMP4

ACTRIIA-Fc  -  +  -  +  -  +  -  +  -  +

p-SMAD1 ➔
p-SMAD3 ➔

Total SMAD1

GAPDH

αSMA level (RLU)

Calponin level (RLU)
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>% Reduction in mPAP</td>
<td>% Reduction in RVH RV/(LV+S)</td>
</tr>
<tr>
<td>Bosentan^1</td>
<td>21</td>
<td>30</td>
</tr>
<tr>
<td>Sildenafil^4</td>
<td>24</td>
<td>18</td>
</tr>
<tr>
<td>Beraprost NP^2</td>
<td>25^5</td>
<td>28</td>
</tr>
<tr>
<td>ACTRIIA-Fc^4</td>
<td>56</td>
<td>47</td>
</tr>
</tbody>
</table>

2. Akagi et al. J Cardiovasc Pharmacol 2016; 67; 290-298; Beraprost NP 150 μg/kg
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 (Sotatercept) is a Phase 2 asset tested in nearly 400 patients across 13 trials with excellent tolerability for muscle wasting and anemia.

2. ACTRIIA-Fc is a potential mechanism-targeted, non-vasodilator PAH therapy with potent anti-remodeling effects.

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

4. PULSAR, a phase 2 study in PAH began enrolling June 2018.
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