BMP4 Inhibitors for the Treatment of Atherosclerosis

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Emory OTT Breakfast Club
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THE OPPORTUNITY
According to the American Heart Association, coronary heart disease is caused by atherosclerosis, the narrowing of the coronary arteries due to fatty build ups of plaque.

Atherosclerosis is likely to cause angina and eventually, heart attack.

Coronary heart disease caused 451,326 deaths in 2004 and is the single leading cause of death in America today.

16,000,000 people alive today have a history of heart attack, angina or both.
THE SCIENCE
Chronic **BMP4** infusion (4 wk) increases, but **Noggin** prevents, atherosclerotic lesion development in ApoE-deficient mice.

<table>
<thead>
<tr>
<th>Group</th>
<th>BMP (mg/Kg/day)</th>
<th>Nog (mg/Kg/day)</th>
<th>BMP+Nog (mg/Kg/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control (Con)</td>
<td>0.45</td>
<td>0.45</td>
<td>0.45</td>
</tr>
<tr>
<td>BMP</td>
<td>0.9</td>
<td>0.45</td>
<td>0.9+0.9</td>
</tr>
<tr>
<td>Nog</td>
<td>0.9</td>
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<tr>
<td>BMP+Nog</td>
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DEVELOPMENT
Screening:
1. LOPAC (1,280)
2. Spectrum (2,000)
3. CDL (1st) (34,561)

Screening novel library (36,934)

Continue screening CDL (64,160)

1° % inhibition < 50% 
- 352 compounds

2° IC50 < 30 μM
- Confirmatory assay: TR-FRET dose response
  - 135 compounds

IC50 < 30 μM
- Secondary assay: Luciferase dose-response test
  - 9 compounds

3° Cell-based Secondary assays, p-Smad inhibition

4° Chemistry/Cheminformatics (SAR)

4° BPM4 inhibitors

Mouse studies – BMP-dependent hypertension, flow-dependent atherosclerosis

Modification of selected BPM4 inhibitors with a medicinal chemist collaborator
A patent application has not been filed yet

An application is planned for filing in the next 3-6 months that will cover the compounds discovered in the screening process and methods of use
FUTURE PROJECTS
Test identified BMP4 inhibitors in mouse models for BMP-dependent hypertension and flow-dependent atherosclerosis

Collaborate with medicinal chemist to develop novel BMP4 inhibitors

End goal is to identify noggin-like compounds that will treat or prevent atherosclerosis