Small molecule Wnt inhibitor: First-in-class therapy for atherosclerosis

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Expertise in vascular inflammation, steroid microenvironments, endothelial cells, Wnt signaling

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Cardiovascular disease prevalence continues to *increase*

<table>
<thead>
<tr>
<th>Year</th>
<th>Event</th>
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<tbody>
<tr>
<td>2030</td>
<td>Mortality will exceed 23 million deaths</td>
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<td>2021</td>
<td>Global cardiovascular drug market totaled $79 billion</td>
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<td>2015</td>
<td>17.3 million deaths, totaling more than $316B in healthcare costs and</td>
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<td>lost productivity</td>
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<td>2010</td>
<td>FDA approved nearly 30 new drugs</td>
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Besides modifiable lifestyle factors, mainstay of therapy for CVD is use of lipid-lowering agents.

Wnt signaling was identified as a key mechanistic pathway for CVD through an unbiased genomic screen in our laboratory, yet NO THERAPY targeting this pathway currently exists.
Effect of Wnt inhibition

Reversal of aortic lipid deposition by 50%
Novel mechanism

Lipid-lowering AND Restoration of fuel preference defects

Reversal of lipid deposition

Mitigation of inflammatory cytokines

PCS9i + statin $\rightarrow$ 35%-40 decrease in total chol

**Graphs showing CHOL levels, IL-6, IL-10, and CO2 released fold activity.**
Progress-to-date

Awarded $3.1 million in NIH funds to study this mechanism

IP: Patent has been issued as of June 2022; claim set allows for use of Wnt inhibitors as therapy for cardiovascular disease

Represents a first-in-class novel therapeutic
## Proposed Use of Funds

<table>
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<tr>
<th>Experimental design</th>
<th>Timeline and Milestones</th>
<th>Where</th>
<th>$$</th>
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| **Phase 1: Find novel lead compounds** | IN Cell Analyzer 2200 to assess Wnt signaling in endothelial cells treated with curated libraries of small molecules:  
  • Bioactive lipids  
  • Nuclear receptor ligands  
  • Maybridge diversity | 0-6 months  
Assessment of endpoints:  
1. Quantification of nuclear translocation of beta-catenin in endothelial cells  
2. Wnt-dependent gene expression via optimized luciferase reporter assay (in-hand) | Yale Center for Molecular Discovery, home lab | $30K |

| **Phase 2: Dose-finding range and preliminary tox study** | In vivo studies (rodent)  
  • Escalating dosing  
  • Repeated daily dosing  
  • Maximum tolerated dose | 6-18 months  
1. Morbidity and mortality observations  
2. Body weight  
3. Toxicokinetic sample collection  
4. Hematology and clinical chemistry  
5. Macroscopic tissue examination and histology | Charles River | $165k |