Discovery of Orally Bioavailable Small Molecules for Inhibition of Complement C5

22nd Congress of the European Hematology Association

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Forward Looking Statements

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Complement Component 5: A Central Target for the Therapeutic Intervention of Complement Mediated Disorders

- 188 kDa, highly abundant protein
- C5 activation by cleavage results in the formation of the C5a anaphylotoxin and C5b, which initiates MAC (membrane attack complex) formation

Therapeutic Inhibition of C5 has resulted in observed clinical benefits in multiple disorders

- Hemolytic anemia (PNH, aHUS)
- Autoimmune disorders (rMG, C3G)
Discovery of Small Molecule (SM) Inhibitors of Complement C5

- In depth understanding of C5 structural biology gained with the macrocyclic peptide RA101495 (currently in Phase 2) justified search for SM C5 inhibitors

- Knowledge-based approach resulted in successful identification of SM inhibitors with a new and unprecedented mechanism of action (differentiated from mAb)
  
  - Displayed dose-dependent inhibition of hemolysis of antibody-sensitized sheep RBCs
  - Binds to C5 and prevents cleavage into C5a and C5b as determined by ELISA from the hemolysis assay supernatant

<table>
<thead>
<tr>
<th>Compound</th>
<th>Hemolysis IC\textsubscript{50} (nM)</th>
<th>MAC ELISA IC\textsubscript{50} (nM)</th>
<th>C5a ELISA IC\textsubscript{50} (nM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Compound A</td>
<td>33</td>
<td>10</td>
<td>12</td>
</tr>
<tr>
<td>Compound B</td>
<td>17</td>
<td>16</td>
<td>14</td>
</tr>
<tr>
<td>Compound C</td>
<td>2</td>
<td>7</td>
<td>7</td>
</tr>
</tbody>
</table>
Inhibition of the classical (CP) and alternative (AP) pathway convertases demonstrated by using Weislab ELISA assays.

Consistent with the mechanism of inhibition, it is expected that the molecules will also inhibit Lectin Pathway (same convertase as Classical Pathway).

<table>
<thead>
<tr>
<th>Compound</th>
<th>Wieslab CP IC$_{50}$ (nM)</th>
<th>Wieslab AP IC$_{50}$ (nM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Compound A</td>
<td>20</td>
<td>187</td>
</tr>
<tr>
<td>Compound B</td>
<td>44</td>
<td>250</td>
</tr>
</tbody>
</table>
SM Inhibitors Offer Opportunities for Differentiation vs. mAb Approaches

- Small molecule inhibitors bind C5 with polymorphism R885H with high affinity in a dose-dependant saturable manner.

**Compound B: \( K_D \): 11 nM**

- Small molecules inhibit complement mediated hemolysis upon C5 R885H activation by the alternative pathway.

- mAbs Eculizumab and ALXN1210 are not able to bind to C5 with polymorphism R885H.

- Small molecules inhibit extrinsic (non-C5 convertase mediated) hC5 activation by plasmin (crosstalk with coagulation cascade).
Protection of Human PNH Type III Cells From Lysis by Small Molecule C5 Inhibitor

- SM inhibits complement mediated hemolysis of human PNH type III erythrocytes in a dose dependent manner

*18h incubation of PNH RBCs with 50% acidified serum. PNH RBCs provided by Dr. Jaroslaw Maciejewski
Lead Series has Drug-Like Properties and Crystallographic Data Allows Optimization via Structure-aided Design

- **Desirable properties**
  - *e.g. Compound B:* MW<500, HBD<5, HBA<10, cLogP<5, tPSA<100

- **Highly selective: no known off-target effects**
  - Good selectivity against hERG and CEREP(44) panel

- **Pharmacokinetics studies in rat show favorable oral bioavailability**
  - Up to 50% F after oral gavage dosing observed with analogs of lead series

- **Multiple High Resolution co-crystal structures of C5 bound to SM have been obtained enabling structure aided design**
  - Cryptic binding site on C5 revealed by SM (novel MOA)
  - Binding mode consistent with the activity observed across different assays

- **Ra Pharmaceuticals plans to initiate IND enabling studies supporting SM program by Q4 2017**
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