Orally Bioavailable Small Molecule CD73 Inhibitor Reverses Immunosuppression by Reduction of Adenosine Production (Abstract #1242)

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Disclosure

• Xiaohui Du is an employee of ORIC Pharmaceuticals
CD73 is required for adenosine production and linked to therapy resistance

**Therapeutic Hypothesis**
- CD73 inhibition may enhance activity of chemotherapy and immunotherapy
- Small molecule approach may differentiate in dosing regimen and tumor penetration

**CD73**
- Overexpressed across cancer types driving local elevation of adenosine
- Overexpression correlated with poor prognosis
- Mediates immunosuppression and chemoresistance via adenosine production
Surveying linker region towards exo phosphonate led to novel starting point

Müller J. Med. Chem. 2015, 58, 6248.

- Replace bisphosphonate motif to reduce overall polar surface area and charge
- Internal-capped phosphonate tolerated; linker length to exo phosphonate important
- Ether-linked phosphonic acid shows early signs of oral bioavailability
Co-crystal structure of 5 with CD73 provided possible directions for potency improvement

- Can α-substitution further improve potency?

5: IC$_{50}$ = 29 nM
\(\alpha\)-Substitution identified key functional groups to increase potency

The oxygen in \(\text{CH}_2\text{OR}\) possibly interacts with CD73.

Disubstituted analogs 21 and 22 are more potent than mono-substituted 8 and 9.

<table>
<thead>
<tr>
<th>Compound</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
<th>11</th>
<th>12</th>
<th>13</th>
<th>14</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD73 IC(_{50}) (nM)</td>
<td>11</td>
<td>18</td>
<td>2.4</td>
<td>0.96</td>
<td>28</td>
<td>559</td>
<td>108</td>
<td>193</td>
<td>387</td>
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</table>

<table>
<thead>
<tr>
<th>Compound</th>
<th>15</th>
<th>16</th>
<th>17</th>
<th>18</th>
<th>19</th>
<th>20</th>
<th>21</th>
<th>22</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD73 IC(_{50}) (nM)</td>
<td>1.3</td>
<td>&gt;5000</td>
<td>97</td>
<td>10</td>
<td>23</td>
<td>31</td>
<td>0.57</td>
<td>0.53</td>
</tr>
</tbody>
</table>
Discovery of potent and orally bioavailable CD73 Inhibitor **OP-5244**

<table>
<thead>
<tr>
<th>Compound</th>
<th>Structure</th>
<th>Biochem</th>
<th>H1568</th>
<th>EMT6</th>
<th>Mouse PO (200mg/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>IC$_{50}$ (nM)</td>
<td>EC$_{50}$ (nM)</td>
<td>EC$_{50}$ (nM)</td>
<td>AUC$_{\text{inf}}$ (µM*hr)</td>
</tr>
<tr>
<td>1</td>
<td><img src="image1.png" alt="Compound 1 Structure" /></td>
<td>0.52</td>
<td>-</td>
<td>-</td>
<td>no oral exposure</td>
</tr>
<tr>
<td>AB680*</td>
<td><img src="image2.png" alt="Compound AB680 Structure" /></td>
<td>0.86</td>
<td>3.3</td>
<td>198</td>
<td>Clinical trial (IV formulation)</td>
</tr>
<tr>
<td>23</td>
<td><img src="image3.png" alt="Compound 23 Structure" /></td>
<td>0.25</td>
<td>0.79</td>
<td>14</td>
<td>45.1</td>
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<tr>
<td>24</td>
<td><img src="image4.png" alt="Compound 24 Structure" /></td>
<td>1.0</td>
<td>10.4</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

- OP-5244 has comparable potency to bisphosphonic acid series
- OP-5244 shows good oral bioavailability in mouse

Co-crystal structures confirmed key interactions for potency improvement of **OP-5244**

- **CH₂OH/CH₂OMe H-bonds with Arg 354/395**
- **Replaced the phosphonate H-bond interactions**

**OP-5244**: $IC_{50} = 0.25$ nM
**OP-5244 fully suppresses ADO Production**

- OP-5244 inhibited ADO production from AMP in tumor cells & CD8+ T Cell (EC$_{50}$ = 0.22 nM)
- A CD73-targeted antibody incompletely inhibits AMP conversion to ADO
OP-5244 rescues immunosuppressive effects of AMP on T cells

OP-5244 rescued CD8+ T cell proliferation and cytokine (IFNγ and TNFα) production in the presence of AMP.
**OP-5244** reduces tumor size, ADO/AMP ratio and reverses immunosuppression in vivo

- OP-5244 exhibits anti-tumor effects as a single agent
- OP-5244 modulates intra-tumoral adenosine pathway
- OP-5244 activates tumor-mediated immune response

![Graphs showing tumor size, ADO/AMP modulation, and exposure of OP-5244](image)

**EMT-6 Murine Breast Cancer Model in BALB/c Mice**

- **Tumor Size**
- **ADO/AMP Modulation**
- **Exposure of OP-5244**

**E.G7-OVA Murine T Cell Lymphoma Model in C57BL6 Mice**

- **Tumor Size**
- **CD8⁺ Cytotoxic T cells**
- **CD8⁺/Treg Ratio**

- OP-5244: 15 mg/kg/day mini pump infusion
- Tumor measurement on Day 13
- Tumor adenosine, exposure measurement on Day 13
  - *, p<0.05; ****, p<0.0001 by t-test

- OP-5244: 150 mg/kg, BID x 16, PO
- Tumor measurement on Day 15
- TIL analysis on Day 16
  - *, p<0.05; **, p<0.01 by t-test

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Upcoming AACR presentations featuring ORIC-533 development candidate

- **Poster #10268**: An orally bioavailable inhibitor of CD73 reverts intratumoral immunosuppression and promotes anti-tumor responses
  - Significant single agent anti-tumor activity of ORIC-533 associates with reversed immunosuppression
- **Poster #4317**: CD73 inhibition with a novel orally bioavailable small molecule blocks adenosine production and rescues T-cells activation in high AMP conditions
Conclusions

• Designed novel orally bioavailable mono-phosphonic acid CD73 inhibitors

• Ether phosphonic acids with $\alpha,\alpha$-disubstitution gained additional interactions with CD73 and further potency enhancement
  – equipotent relative to the bisphosphonic acid series

• Small molecule CD73 inhibitor represents a potential therapeutic approach to reverse immunosuppression within the tumor microenvironment
  – **OP-5244** fully rescues T cell proliferation and cytokine production from ADO-mediated suppression *in vitro*
  – **OP-5244** reduces tumor size, modulates intra-tumoral ADO pathway and reverses immunosuppression *in vivo*
  – **OP-5244** is a prototype for further optimization/clinical candidate identification
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