**CD73 inhibition reverses immunosuppression and has potential as an immunomodulatory therapy in patients with multiple myeloma**

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**CD73 Mediates Immunosuppression and Therapeutic Resistance via Adenosine Production**

- Immunosuppressive adenosine generation from adenosine monophosphate (AMP) requires the activity of the cell surface ecto-5′-nucleotidase CD73
- Relapsed/refractory (r/r) multiple myeloma (MM) is adenosine rich
- Adenosine pathway components are highly expressed on MM cells and on many cell types within the MM niche
- Adenosine levels in bone marrow are significantly higher in MM patients
- High CD73 and adenosine are associated with poor prognosis and therapeutic resistance in multiple myeloma
- Plasmacytoid dendritic cells and multiple myeloma cells trigger tumor-promoting immunosuppression via CD73 pathway activation

**1. Discovery of CD73 Inhibitors that Potently Suppress Adenosine Production**

<table>
<thead>
<tr>
<th>Compound</th>
<th>Cell line activity</th>
<th>IC50 (nM)</th>
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<tbody>
<tr>
<td>OIRC-533 (clinical candidate)</td>
<td>0.1</td>
<td>0.1</td>
</tr>
<tr>
<td>OP-5558</td>
<td>0.1</td>
<td>0.1</td>
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<tr>
<td>AB680</td>
<td>1.0</td>
<td>1.0</td>
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**2. ORIC Inhibitors Restore T-cell Function More Potently than Other Adenosine Pathway Inhibitors**

**3. ORIC’s Potent AMP-competitive Inhibitors are Active in a High AMP Environment**

- ORIC inhibitors restored cell viability up to 30% in high AMP environments
- ORIC-533 was the most potent in restoring T-cell function

**4. ORIC CD73 Inhibitor Triggers Single Agent Cytotoxicity in R/R MM Cells in Assay Utilizing Entire Bone Marrow Milieu**

- ORIC-533 induced cytotoxicity in MM cells from r/r MM patients
- ORIC-533 increased MM cell cytotoxicity in MM cells from r/r MM patients

**5. ORIC Inhibitor Restored Immunosuppression Resulting in T-cell Activation and Lysis of MM Cells from Relapsed/Refractory Patients**

**6. ORIC-533 Reduces Adenosine Production in Bone Marrow from Relapsed/Refractory Patients**

- ORIC-533 inhibits CD73 activity and reduces adenosine production from r/r MM cells
- ORIC-533 in r/r MM patients reduced adenosine production

**7. Low Nanomolar ORIC-533 Targets Single Agent Cytotoxicity in R/R MM Cells in Assay Utilizing Entire Bone Marrow Milieu**

- ORIC-533 induced cytotoxicity in MM cells from r/r MM patients

**CONCLUSIONS**

- ORIC-533 exhibits potential best-in-class properties and is the first oral CD73 inhibitor to enter clinical development for multiple myeloma
- ORIC-533 is a highly potent adenosine pathway inhibitor
- Superior in potency relative to comparator adenosine pathway inhibitors, even in high AMP environments
- Capable of activating plasmacytoid dendritic cells and increasing T-cell activation
- Effective at reducing adenosine generation in BM serum from relapsed/refractory multiple myeloma patients
- Able to trigger lysis of relapsed/refractory multiple myeloma cells as a single agent in autologous ex vivo assays

**OIRC-533 Phase 1 Clinical Trial (NCT03277144) is Enrolling Patients with Multiple Myeloma**

**References**