Blocking Adenosine Production with ORIC-533, a CD73 Inhibitor with Best-In-Class Properties, Reverses Immunosuppression in High-AMP Environments
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1. ORIC-533 is a Highly Potent and Selective Inhibitor of CD73

![Diagram of CD73 Mediates Immunosuppression and Therapeutic Resistance via Adenosine Production]

2. ORIC-533 is Active in a High AMP Environment

A. AMP in Human Primary CRC Tumors

![Graph: AMP levels in primary tumors reach up to 500μM]

B. CD8+ T Cell Proliferation at 1mM AMP

![Graph: Cytokine Production at 1mM AMP]

C. Cytokine Production at 1mM AMP

3. ORIC-533, But Not A2R Antagonists, Rescues CD8+ Cytokine Secretion in Moderate AMP

![Graph: ORIC-533 Potently Rescues CD8+ Cytokine Production at 6 μM AMP]

4. ORIC-533 Rescues Immune Cell Activation in Mixed Lymphocyte Reaction in High AMP

![Graph: ORIC-533 Potently Rescues CD8+ Cytokine Production at 25 μM AMP Level Which is Commonly Found in Tumors]

CONCLUSIONS

ORIC-533 is a novel CD73 inhibitor with potential best-in-class properties in reversing immunosuppression with:
- picomolar potency and high selectivity in biochemical assays
- evidence of complete CD8+ T-cell functional rescue at low nanomolar concentrations across a range of AMP environments from low to high AMP (6 μM-1 mM AMP)
- the ability to revert immunosuppression in elevated AMP contexts found in the tumor microenvironment, in contrast to adenosine receptor antagonists and other CD73 inhibitors
- the capacity to rescue activation of AMP-suppressed CD4+ T cells co-cultured with allogeneic immature dendritic cells

ORIC-533 IND filing anticipated in first half of 2021

AACR Annual Meeting, April 10-15, 2021
Abstract #LB-163