Malic Enzyme 1 (ME1) Inhibitors for Pancreatic and Gastrointestinal Cancers

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<table>
<thead>
<tr>
<th>Background &amp; Unmet Need</th>
<th>Technology Overview</th>
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<td>• Pancreatic ductal adenocarcinoma (PDAC) is an extremely aggressive cancer with a 5-year survival rate of only 10% and no effective therapies</td>
<td><strong>The Technology</strong>: A small-molecule inhibitor of ME1, AS1134900, for treatment of PDAC and gastrointestinal cancers</td>
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<td>• PDAC, among other cancer types, frequently exhibits loss of tumor suppressor SMAD4, which is often associated with co-deletion of the nearby housekeeping enzyme, malic enzyme 2 (ME2)</td>
<td>• AS1134900 was identified from a proprietary chemical library (Astellas Pharma) through a diaphorase/resazurin-coupled assay for measuring ME1 enzymatic activity</td>
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<td>• This SMAD4/ME2 co-deletion is observed in ~20% of PDAC and &gt;6% of gastrointestinal cancers</td>
<td>• AS1134900 inhibits ME1 activity by allosteric binding and doesn’t have cross reactivity for ME2</td>
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<td>• Malic Enzyme 1 (ME1) and ME2 belong to the same family of enzymes, which are involved in several essential metabolic processes and are likely to be functionally redundant</td>
<td>• <strong>PoC Data</strong>: Validated inhibition of ME1 activity (IC50 = 0.73 ( \mu )M)</td>
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<td>• Deletion of ME1 in ME2-null tumors may confer synthetic lethality, making it a good target for selective killing of ME2-null pancreatic cancers</td>
<td>• ME1 inhibition in ME2-null pancreatic cancer cells and xenograft tumors leads to profound growth inhibition</td>
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<td>• Unmet Need: Inhibitors of ME1 for treatment of PDAC and other ME2-null cancers</td>
<td>• ME1 knockout in adult mice leads to enhanced CD8+ T cells and their infiltrations to tumors, suggesting potential synergy with immunotherapy</td>
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Inventors:
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- Mengrou Shan
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Patents:
PCT Application Filed

Publications:

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Cornell Reference:
- D-9968
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Technology Applications

• Treatment of patients with ME2-null PDAC
• Treatment of patients with other ME2-null gastrointestinal cancers, such as colon, esophagus, biliary, and stomach cancer

Technology Advantages

• Inhibitor is specific for ME1 and does not have cross reactivity for ME2
• Potential synergy for ME1 inhibitors in combination of with checkpoint blockade therapy
• ME2 expression may be a biomarker for patient selection in ME1 inhibitor therapy
• Off-target toxicity of ME1 deletion was not observed in genetic models

Supporting Data / Figures

Figure 1: Top: Structure of ME1 inhibitor and Diaphorase/resazurin-coupled ME1 assay used to identify the inhibitor Bottom: Inhibition of ME1 and ME2 activities by AS1134900.

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Figure 2: ME1 inhibition in ME2 null pancreatic cancer cells (Left) and pancreatic patient-derived xenograft tumors (Right) via shRNA leads to profound growth inhibition.

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