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

Lead Inventor:
Lewis C. Cantley, Ph.D.
Professor of Cell Biology, Harvard Medical School
Former Director of the Sandra and Edward Meyer Cancer Center, Weill Cornell Medical College
Former Professor of Cancer Biology in Medicine, Weill Cornell Medical College

Developed in collaboration with the University of Michigan and Astellas Pharma, Inc.

Business Development Contact:
Jeffrey James
Associate Director, Business Development and Licensing
(646) 962-4194
jaj268@cornell.edu
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Background & Unmet Need

- Pancreatic ductal adenocarcinoma (PDAC) is an extremely aggressive cancer with a 5-year survival rate of only 10% and no effective therapies
- 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)
- This SMAD4/ME2 co-deletion is observed in ~20% of PDAC and >6% of gastrointestinal cancers
- 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
- Deletion of ME1 in ME2-null tumors may confer synthetic lethality, making it a good target for selective killing of ME2-null pancreatic cancers
- Unmet Need: Inhibitors of ME1 for treatment of PDAC and other ME2-null cancers

Technology Overview

- The Technology: A small-molecule inhibitor of ME1, AS1134900, for treatment of PDAC and gastrointestinal cancers
- AS1134900 was identified from a proprietary chemical library (Astellas Pharma) through a diaphorase/resazurin-coupled assay for measuring ME1 enzymatic activity
- AS1134900 inhibits ME1 activity by allosteric binding and doesn’t have cross reactivity for ME2
- PoC Data: Validated inhibition of ME1 activity (IC50 = 0.73μM)
- ME1 inhibition in ME2-null pancreatic cancer cells and xenograft tumors leads to profound growth inhibition
- ME1 knockout in adult mice leads to enhanced CD8+ T cells and their infiltrations to tumors, suggesting potential synergy with immunotherapy

Inventors:
- Lewis Cantley
- Costas Lyssiotis
- Mengrou Shan
- Lin Lin
- Osamu Kaneko
- Akio Kamikawa

Patents:
- PCT Application Filed

Publications:

Biz Dev Contact:
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  jaj268@cornell.edu

Cornell Reference:
- D-9968
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 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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