KDDF
Korea Drug Development Fund

Asset #44
Weill Cornell Medicine

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

Therapeutic Area	Oncology	**Indications**	Pancreatic and Gastrointestinal Cancers
Modality	Small Molecule	**Development Stage**	Hit To Lead or Lead Optimization

Overview

Background

- 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-mull 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

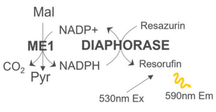
Technology Advantages

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

Key Data

Structure of ME1 inhibitor and Diaphorase/resazurin-coupled ME1 assay used to identify the inhibitor

A



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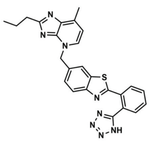
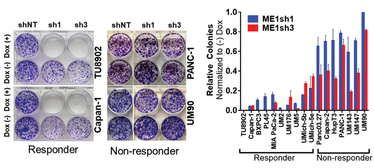


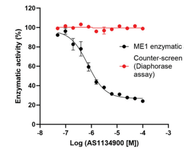
(A) Diaphorase/resazurin-coupled ME1 assay for high-throughput screening. Mal, malate; Pyr, pyruvate. (B) Structure of 6-[(7-methyl-2-propylimidazo[4,5-b]pyridin-4-yl)methyl]-2-[2-(1H-tetrazol-5-yl)phenyl]-1,3-benzothiazole (AS1134900).

E



(E) ME1 inhibition in ME2 null pancreatic cancer cells via D-9968 shRNA leads to profound growth inhibition in responder cancer lines.

C



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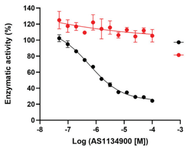
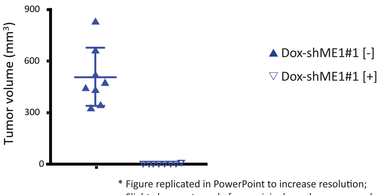


(C) Inhibition of ME1 activity by AS1134900 (black circles) and a counterscreen including only NADPH and diaphorase/resazurin in the reaction mixture (red circles). (D) Inhibition of ME1 and ME2 activities by AS1134900 (black circles, ME1; red circles, ME2).

F



* Figure replicated in PowerPoint to increase resolution; Slight changes to scale from original may have occurred.

(F) Inhibition of ME1 blocks tumor growth in pancreatic patient-derived xenografts (PDX). Final tumor volume of UM2 primary PDX tumors containing a Dox-inducible hairpin targeting MEI. Dox administration was initiated at day 7.

IP Status & Publication(s)

Intellectual Property

Patent Number
PCT/US2023/062139 (2023.02.07)

Patent Family
PCT

Publication(s)

- Yoshida, T. et al. (2022). Discovery and Characterization of a Novel Allosteric Small-Molecule Inhibitor of NADP+-Dependent Malic Enzyme 1. Biochemistry, 61(15), 1548–1553.