Weill Cornell Medicine

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

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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-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 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:
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Lin Lin
Osamu Kaneko
Akio Kamikawa

Patents:
PCT Application Filed

Publications:
Yoshida et al. *Biochemistry*. 2022.

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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

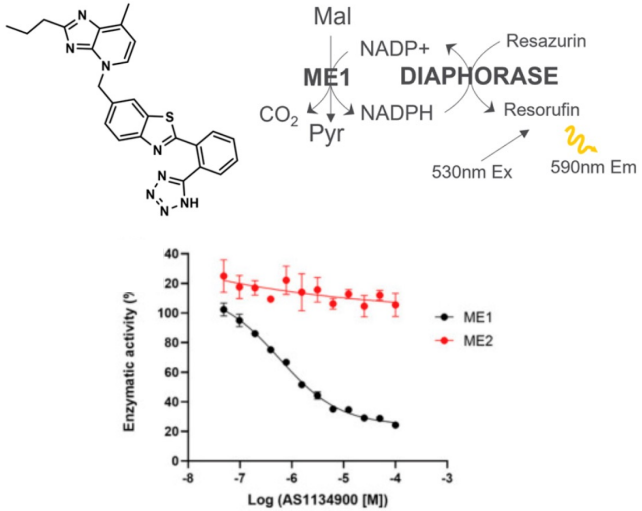

Figure 1: Top: Structure of ME1 inhibitor and Diaphorase/resazurin-coupled ME1 assay used to identify the inhibitor **Bottom:** Inhibition of ME1 and ME2 activities by AS1134900.

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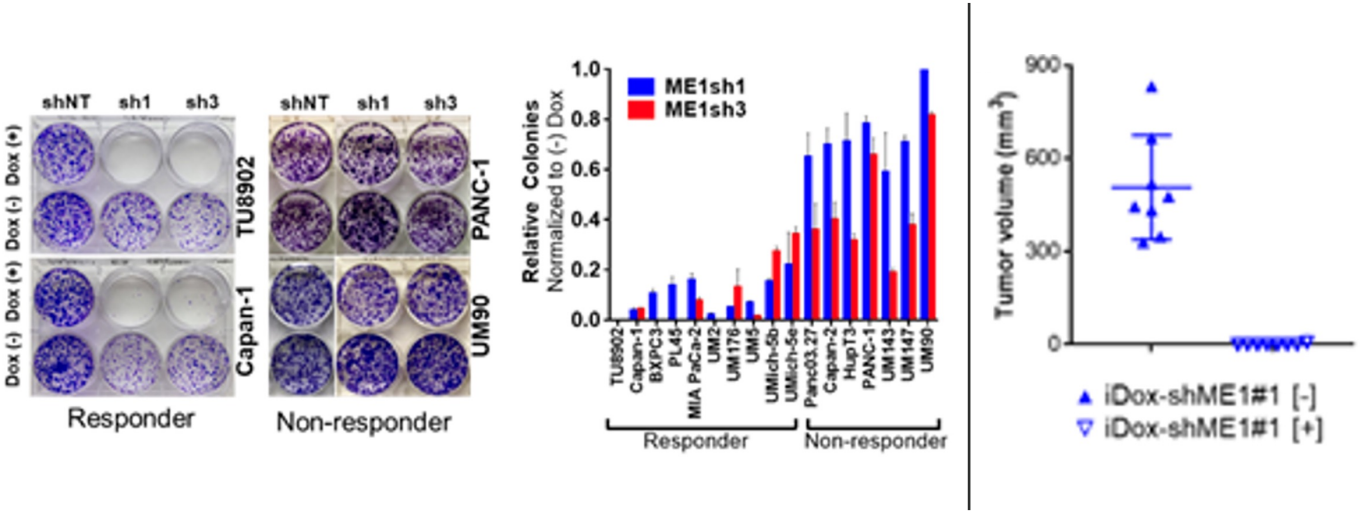

Figure 2: ME1 inhibition in ME2 null pancreatic cancer cells (**Left**) and pancreatic patient-derived xenograft tumors (**Right**) via shRNA leads to profound growth inhibition.

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