Miso Therapeutics

Targeting cancer cells’ Metabolic isoenzyme addiction

Vignesh Gunasekharan, PhD
Yale Cancer Center
Executive Summary

- **Unique Investment Opportunity**
  A novel way to target metabolism by blocking isoenzymes that function ‘solo’ in cancer

- **Multi-billion dollar market**
  Target, Phosphoenolpyruvate Carboxykinase 2 (PCK2) is dysregulated in multiple cancers, diabetes, and obesity (Sales prediction of > 1 billion by 2024 for one subtype of breast cancer alone)

- **Competitive edge**
  A novel target with a first homology model
  A first-in-class inhibitor
  Targeted approach

- **Industry interest**
  Partnership with Atomwise, Inc. for virtual hits screening, hit expansion, and lead optimization
  Partnership with Pfizer for drug repurposing against another target from the same pipeline

- **Development Plan**
  Lead optimization, PK/PD studies, *in vivo* testing, and metabolomics
Scientific and business leadership

Lajos Pusztai, MD DPhil
Professor of Medicine, Cancer
Director of Breast Cancer Translational Research
Chair of SWOG breast cancer research committee

Vignesh Gunasekharan, PhD
Associate Research Scientist, Cancer
Yale Cancer Center

Richard Kibbey, MD/PhD
Associate Professor of Medicine, Metabolomics
Director of Yale IOMIC Flux Core

Mostafa Ahmed, PhD
Senior Scientist
Medicinal Chemistry
Atomwise Inc.

Yulia Surovtseva, PhD
Director of Biology,
High throughput screening
YCMD

David Lewin, PhD
Director of BD, Business
Yale OCR
Scientific Background

- A novel approach: **Loss of Isoenzyme Diversity (LID)** in cancers
- Novel target- **PCK2** with no protein structure, no commercial enzyme assays, no inhibitor

Milestones:
- Created a PCK2 protein model and identified hits using a AI-based virtual platform
- Developed a high throughput enzyme screening assay and identified an active hit
- Performing hit expansion experiments
Critical and actionable target

Silencing PCK2 severely affect tumor cell proliferation both \textit{in vitro} and \textit{in vivo}.

Vincent \textit{et al}, Molecular Cell. 2015 Oct 15
Zhao \textit{et al}, Oncotarget. 2017 Oct 13

PCK2 knockout mice and rats are viable

Abulizi \textit{et al}, bioRxiv. 2020 Feb 14

PCK2 model

A.I. screening

Enzyme Screening Assay

Active hit
\( IC_{50} \) 2.4\( \mu \)M

Hit expansion

Yale Center for Molecular Discovery

Yale Cancer Center

Atomwise
Now

Stage 1 - $125,000

2 Months
Hit expansion
Med Chem study
Selectiv compounds 
with drug-like properties for filing IP

Homology model
Enzyme screening assay
Active hit

Other milestones
 Identified hit analogs
 Standardized PCK2 metabolic flux
 PCK2 knockout mouse models
 PCK2 depleted stable cell systems

Stage 2 - $175,000

8 Months
Lead optimization and In vitro testing

Stage 1 - $125,000

14 Months
PK/PD studies
In vitro and in vivo ADMET determination

Stage 2 - $175,000

19 Months
In vivo efficacy testing
PDX models
Single agent and combination

Stage 1 - $125,000

24 Months
Metabolomics
MOA determination

Stage 2 - $175,000

Other milestones
 Identified hit analogs
 Standardized PCK2 metabolic flux
 PCK2 knockout mouse models
 PCK2 depleted stable cell systems

Defined drug dosage, route of administration and safety

Inflection point
Validated compounds with defined MOA and a validated discovery platform

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