Computational discovery and preclinical validation of therapeutic leads with novel MOAs for hepatocellular carcinoma and pancreatic ductal adenocarcinoma

Isaac Hakim1, Mei-Sze Chau2, Wei Wei2, Li Ma2, Samuel So2, Elizabeth Noblin1, Sana Mujahid2, Aaron C. Daugherty3, and Timothy S. Heuer1
1. twoXAR Pharmaceuticals, Mountain View, CA. 2. Stanford University School of Medicine, Stanford, CA 94305

Introduction

• Hepatocellular carcinoma and pancreatic ductal adenocarcinoma (HCC and PDAC) are difficult to diagnose and treat diseases with poor survival and high unmet medical need.
• twoXAR’s powerful AI-driven drug discovery approach builds an in-silico drug discovery model using complex patient-derived biological data combined with clinical health record data and a diverse chemical library of drug discovery molecules associated with pharmacology data.
• The AI discovery output is a rank-ordered list of molecules with predicted efficacy for treatment of the disease.
• Discovery hits are reviewed to determine if drugs with known efficacy are re-discovered as a method to quality check the results.
• High-ranked hits with novel MOAs are selected for in vivo preclinical screening to identify leads for optimization and clinical development.
• twoXAR’s platform preserves interpretable data-driven links to disease biology to facilitate efficient validation and optimization studies.

Methods

• PDAC and HCC disease models were built using twoXAR’s AI platform, and efficacy predictions were made from a library with >50,000 molecules.
• 10,11 molecules with novel mechanisms of action (untreated in HCC or PDAC) clinical trials) were selected as drug discovery hits for each disease.
• Hits were evaluated in vitro and in vivo efficacy using PDAC and HCC tumor cell lines and PDX models. Dose levels were selected using published data.

Discovery of Novel MOA Hits

• Novel MOA Hit Discovery Process

Results

PDAC and HCC Drug Discovery Hits Represent Diverse MOAs Targeting Cancer-Related Biological Processes

- Signal transduction
- Cell cycle and cell division
- Cell metabolism
- Cell survival
- Cell proliferation and survival

Hit Screening and Lead Optimization Workflow

PDAC and HCC

HCC

PDAC

In Vitro Phentotypic Screening of Drug Discovery Hits

- TXR-311 Has Selective In Vitro HCC Cell Cytotoxicity

- TXR-311 Significantly Inhibits Growth of HCC PDX Tumor Models, Comparable to Sorafenib

HCC PDX Model One

- TXR-311 Continued Development

Conclusions

PDAC: In Vitro Activity at Low µM Concentrations

HCC: TXR-311 Has Attributes of a Drug Discovery Lead

- Significant efficacy in 2 HCC PDX tumor models
- Efficacy is non inferior to Sorafenib, as approved drug used as the first-line HCC standard of care to treatment

Acknowledgements and References

• The in vivo HCC-PDX mouse efficacy study was conducted by Mei-Sze Chau in Sam Sei’s laboratory at Stanford University School of Medicine.
• We thank Chassan Al-Ali and Daniel Duda for scientific discussions.
• We thank Anjali Pandey and Mark Eller at twoXAR for scientific discussions.
• Correspondence: tim@twoxar.com