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

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twoXAR Pharmaceuticals Discovered with AI

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* disease model using complex patient-derived biological data combined with clinical health record data and a diverse chemical library of drug discovery molecules with associated 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.
- Highly-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 (untested in HCC or PDAC clinical trials) were selected as drug discovery hits for each disease.
- Hits were evaluated for *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

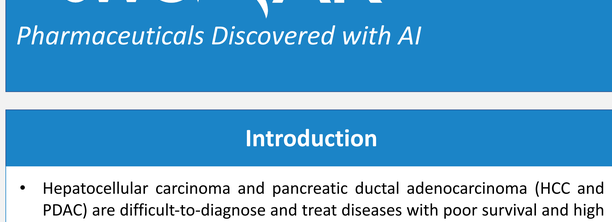


Figure 1: twoXAR's AI-driven drug discovery approach. An *in-silico* disease model was constructed using heterogeneous patient-derived data. The computational process integrated disease and chemical features to produce a rank-ordered list of molecules with predicted efficacy. Selected novel-MOA hits were evaluated in preclinical models.

Novel MOA Hit Discovery Process

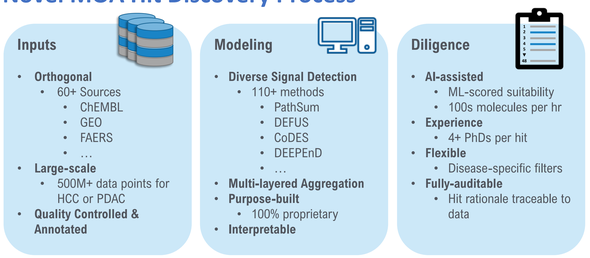


Figure 2: AI Discovery Process. (1) Large-scale data input using orthogonal biological and phenotypic data sets. (2) Data processing with >110 computational methods extract and integrate signal to produces efficacy predictions. (3) An AI-assisted process reviews and selects predictions for evaluation in preclinical models. Abbreviation: ML: Machine Learning

Results

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

HCC

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

PDAC

- Signal Transduction
- Cell metabolism
- Cell survival
- Cell proliferation

Hit Screening and Lead Optimization Workflow

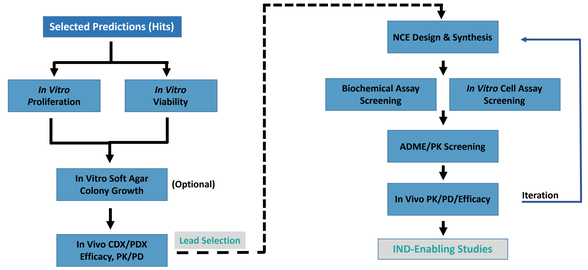


Figure 3. Hits are screened using *in vitro* phenotypic assays with HCC or PDAC tumor cell lines. Hits with IC_{50} values below 2 µm are advanced into soft agar colony growth assays or directly to *in vivo* xenograft tumor growth inhibition studies. Xenograft tumor growth inhibition data enable selection of a lead molecule for optimization and IND-enabling studies.

In Vitro Phenotypic Screening of Drug Discovery Hits

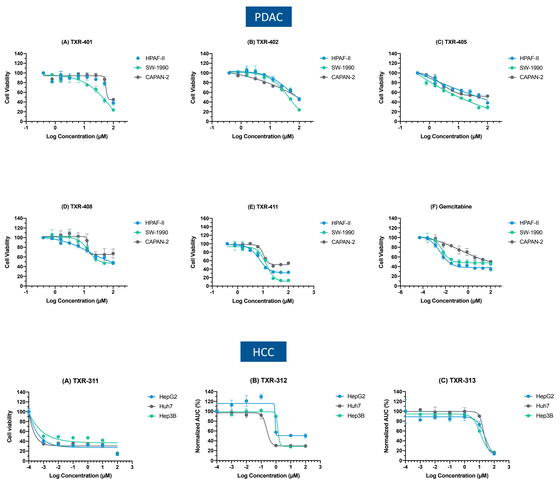


Figure 4. Dose response results from *in vitro* viability assays with PDAC or HCC tumor cell lines. 7-8 tumor cell lines were screened for each tumor type. Data shown are representative of all cell lines and hits.

TXR-311 Has Selective *In Vitro* HCC Cell Cytotoxicity

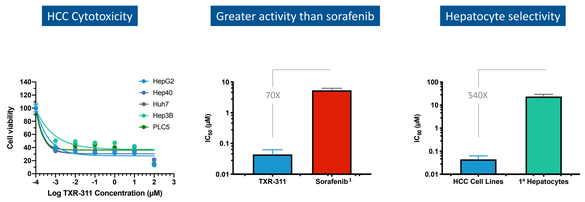
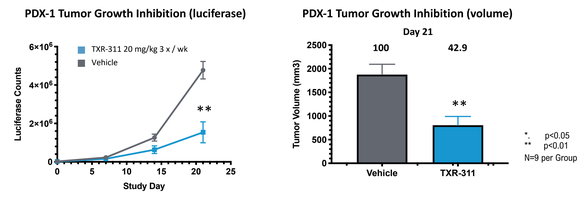


Figure 5: TXR-311 has a low nM IC_{50} value for inhibition of HCC tumor cell viability and is highly selective for tumor cells compared to normal primary hepatocytes. Sorafenib data used for comparison is taken from Liu et al. 2006.Cancer Research *66 (24): 11851-858.*

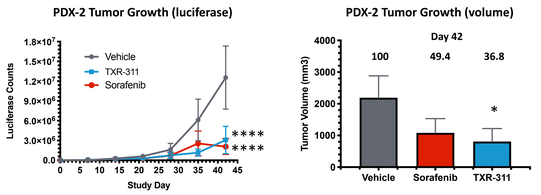
TXR-311 HCC PDX Efficacy Summary

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

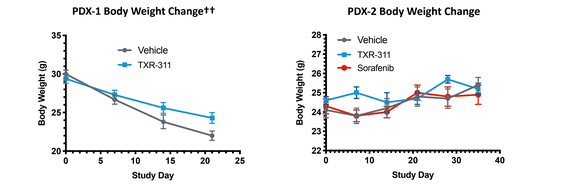
HCC PDX Model One



HCC PDX Model Two



Body Weight - Tolerability



Conclusions

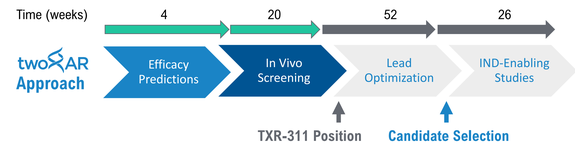
PDAC: *In Vitro* Activity at Low µM Concentrations
HCC: TXR-311 Has Attributes of a Drug Discovery Lead

Body Weight	Good Tolerability
In Vitro HCC Cytotoxicity	Greater activity and selectivity than sorafenib
In Vivo HCC PDX Efficacy	Significantly inhibits growth of multiple HCC PDX models
Efficacy ≥ to SOC	*In vivo* efficacy comparable to sorafenib without dose optimization
Optimization Starting Point	Good oral bioavailability, PK, and ADME properties

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

TXR-311 Continued Development

- TXR-311 MOA is novel for HCC
- Immediate studies:
  - Characterize drug pharmacokinetics and pharmacodynamics
  - Establish PK/PD/efficacy relationships



- Rapid progression through hit validation to lead optimization
  - 10 MOAs selected and evaluated in *in vitro* and *in vivo* screening studies
  - 4 weeks to complete predictions, select hits, and begin *in vivo* screening
  - Lead discovered from *in vivo* PDX efficacy screening data
  - Attractive starting point for lead optimization

Acknowledgements and References

- The *in vivo* HCC PDX mouse efficacy study was conducted by Mei-Sze Chua in Sam So's laboratory at Stanford University School of Medicine.
- We thank Ghassan Abou-Alfa and Daniel Duda for scientific discussions.
- We thank Anjali Pandey and Mark Eller at twoXAR for scientific discussions.
- Liu et al. 2006.Cancer Research *66 (24): 11851-858.* Sorafenib Blocks the RAF/MEK/ERK Pathway, Inhibits Tumor Angiogenesis, and Induces Tumor Cell Apoptosis in Hepatocellular Carcinoma Model PLC/PRF/5
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