Preclinical identification and development of small molecule drug discovery leads with novel MOAs for non-alcoholic steatohepatitis (NASH)

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Introduction

- Non-alcoholic fatty liver disease (NAFLD) and non-alcoholic steatohepatitis (NASH) are metabolic diseases that affect millions of patients globally with a high unmet medical need.
- TwoXAR's powerful AI-driven drug discovery approach builds on silico disease model using complex patient-derived biological data combined with clinical health record data and a diverse chemical library of experimental and FDA-approved 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 vitro and/or in vivo preclinical screening to lead to optimization and clinical development.
- TwoXAR's platform preserves interpretable data-driven links to disease biology to facilitate efficient validation and optimization.

Methods

- Discovery of the novel MOAs

![Diagram showing the discovery process]

- Results

- Discovery of the novel MOAs

![Diagram showing the results]

- Conclusions

- TXR-611 and TXR-612 MOAs are unique and novel for NASH
- Immediate studies:
  - Characterize drug pharmacokinetics and pharmacodynamics
  - Show efficacy reproducibility in the CCL4 mouse model
  - Establish PK/PD efficacy relationships

- Rapid progression through discovery hit validation to lead optimization
  - 10 discovery hits with novel MOAs selected and evaluated using in vitro and in vivo NASH preclinical models
  - 15 weeks from program initiation to completion of in vivo efficacy screen

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