Computational discovery and preclinical validation of therapeutic leads with novel MOAs for systemic lupus erythematosus

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Introduction

- Systemic Lupus Erythematosus (SLE) is a heterogeneous, systemic disease that affects millions of patients globally with a high comorbid 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 small and biological 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 check the results.
- Highly-ranked hits with novel MOAs were selected for in vivo preclinical screening to identify leads for follow-up clinical development.

Methods

- Using twoXAR’s AI platform, an in-silico SLE disease model was built and efficacy predictions were made from a chemical library of more than 50,000 small and biological molecules.
- Nine molecules with novel mechanisms of action (not previously tested in a clinical setting) were selected as drug discovery hits.
- Hits were evaluated for in vivo efficacy using the MRL mouse model of lupus without performing chemical or PK/PD optimization.
- Cyclophosphamide, a drug used for severe inflammation flares, but with poor tolerability, was used as a reference treatment for efficacy comparison.

Discovery of Novel MOA Hits for Preclinical Lupus Efficacy Testing

- In Vivo Efficacy Study Design Using MRL Mouse Model of Lupus
- Discovery Hits Well-Tolerated: 61 Days Oral QD Dosing
- TXR-711, TXR-712 Decrease Kidney Inflammation
- TXR-711, TXR-712 Improve Lupus Disease, Including Kidney Function and Inflammation, by Many Markers

Results

- TXR-711, TXR-712 Decrease Kidney Inflammation
- TXR-711, TXR-712 Summary

Conclusions

- TXR-711, TXR-712 Have Attributes of SLE Drug Discovery Leads
- Significant efficacy in the MRL mouse model of lupus
- Efficacy compares favorably with cyclophosphamide, an optimized drug with tolerability limitations used to treat severe lupus disease flares
- TXR-711 and TXR-712 preclinical development is ongoing

Continued Development

- TXR-711, TXR-712 MOAs are different and novel for SLE
- Immediate studies:
  - Characterize drug pharmacokinetics and pharmacodynamics
  - Show efficacy reproducibility in the MRL mouse model
  - Establish PK/PD/efficacy relationships

- Rapid progression through hit validation and lead optimization
- 9 MOAs selected in an in vivo screening study:
  - 4 weeks to complete predictions, select hits, and begin in vivo screening
  - 2 leads discovered from in vivo screening data (different MOAs)
  - Attractive starting points for lead optimization

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