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

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twoXAR Pharmaceuticals Discovered with AI

Introduction

- Systemic Lupus Erythematosus (SLE) is a heterogeneous, systemic disease that affects millions of patients globally with a 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 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 quality check the results.
- Highly-ranked hits with novel MOAs were 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

- 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 lupus clinical trial) 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

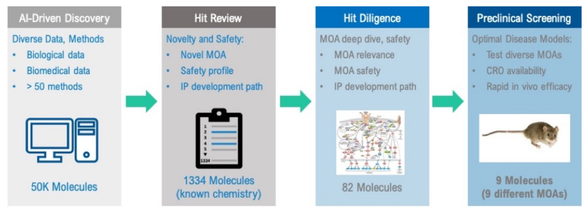


Figure 1: twoXAR's AI-driven drug discovery approach. An *in-silico* SLE disease model was constructed using complex data sets from SLE patients. Biological data examples include gene expression, micro-RNA, and GWAS data. Biomedical data includes health record data. The computational process integrated disease features with chemical features from a large library of drug and drug-like molecules to produce a rank-ordered list of molecules with predicted efficacy for treatment of lupus. Predictions were reviewed in two steps to select 9 hits with novel MOAs for evaluation in a preclinical *in vivo* efficacy screening study.

In Vivo Efficacy Study Design Using MRL Mouse Model of Lupus

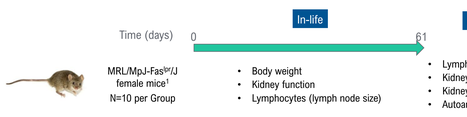


Figure 2: Nine molecules predicted to have efficacy in SLE were evaluated in the MRL/MpJ-Fas^{lpr}/J SLE mouse model. Each treatment group include 10 mice. All 9 discovery hits were dosed once-daily (QD) for 61 days by oral gavage. The reference or positive control group was treated with cyclophosphamide. Lymph node and kidney tissues were collected at study termination for efficacy assessment. Body weight was measured weekly to monitor drug tolerability.

Results

Discovery Hits Well-Tolerated: 61 Days Oral QD Dosing

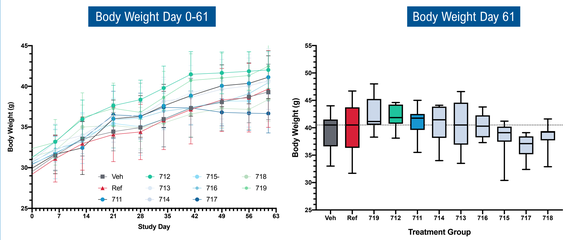


Figure 3: Discovery hits were well tolerated when dosed once-daily for 61 days by oral gavage. Weekly body weight measurements of MRL mice during the in-life phase provides a method to assess drug tolerability. Left panel: Mean body weight during the entire 61-day period of the in-life study phase. Right panel: Body weight distributions on day 61 at study termination.

TXR-711, TXR-712 Decrease Kidney, Lymph Node Weight

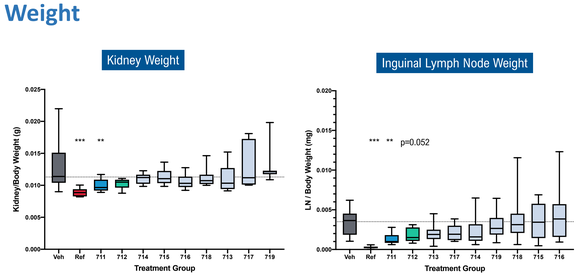
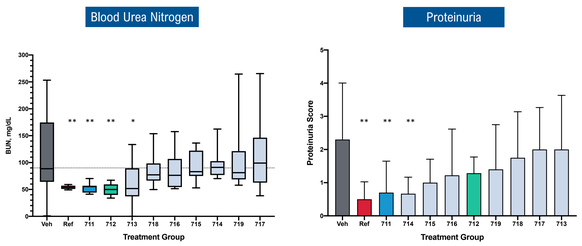


Figure 4: Discovery hits demonstrated efficacy as measured by kidney and lymph node weight. TXR-711 and TXR-712 demonstrated the strongest efficacy by these measures. Decreases in kidney and lymph node weight by TXR-711 achieved significance with a p-value < 0.01. TXR-712 achieved near statistical significance. Tissues were collected and weighed at study termination (Day 61) and normalized to total mouse body weight. Left panel: Kidney weight reflects fibrosis and inflammation. Right panel: Lymph node weight reflects lymphocyte proliferation and inflammation. N=10 per Group. Significance: * p<0.05 ** p<0.01. *** p<0.001

TXR-711, TXR-712 Improve Kidney Function



Score	mg/dL
0	None
1	1-29
2	30-99
3	100-299
4	300-1999
5	≥2000

Figure 5: Discovery hits demonstrated efficacy in measures of kidney function. TXR-711 and TXR-712 demonstrate strongest efficacy in BUN reduction (p<0.01). TXR-711 also demonstrates strongest reduction in proteinuria (p<0.01). Left panel: Blood urea nitrogen (BUN). Right panel: Proteinuria. Proteinuria data analysis used a scoring system to dampen the variability associated sample collection challenges. The scoring system is shown on the bottom right, with a scale of 0 to 5.

TXR-711, TXR-712 Decrease Kidney Inflammation

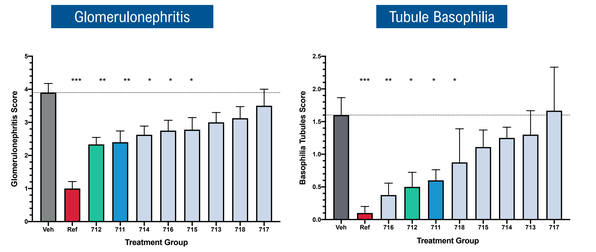
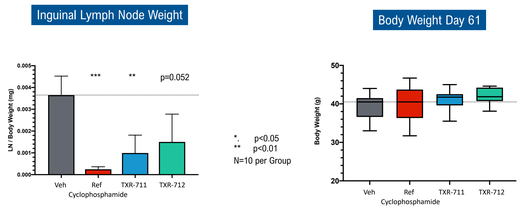


Figure 6: Discovery hits reduce kidney inflammation measured by kidney histology features. TXR-711 and TXR-712 demonstrated the strongest efficacy by assessing glomerulonephritis (p<0.01) and strong effects in reducing basophil infiltration (p<0.05). Left panel: Glomerulonephritis. Right panel: Tubule basophilia.

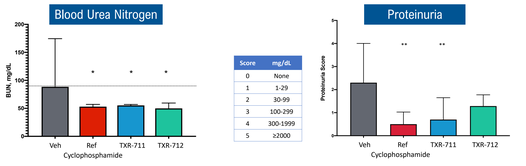
TXR-711, TXR-712 Summary

TXR-711, TXR-712 Improve Lupus Disease, Including Kidney Function and Inflammation, by Many Markers

Inflammation and Tolerability



Kidney Function



Score	mg/dL
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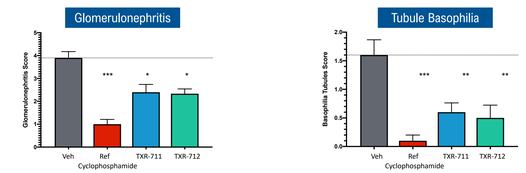
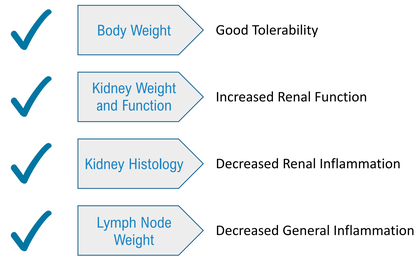
Kidney Inflammation



Conclusions

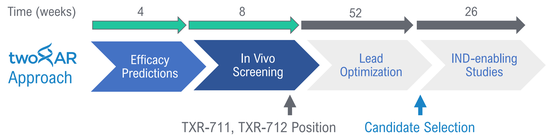
TXR-711, TXR-712 Have Attributes of SLE Drug Discovery Leads



- 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 and and evaluated 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

Acknowledgements and References

- The in vivo MRL mouse efficacy study was conducted by Crown Biosciences, (Joshua Wollam Study Director).
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- We thank Anjali Pandey and Mark Eller at twoXAR for scientific discussions.

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