LX-101, a novel payload bearing IGF1-methotrexate conjugate, shows anti-inflammatory and anti-fibrotic effects in thyroid eye disease

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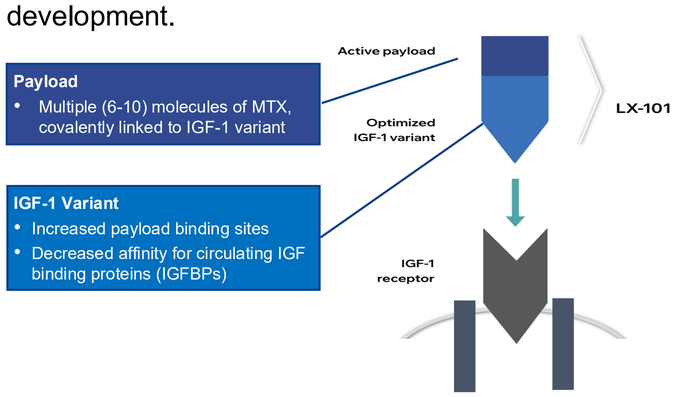
INTRODUCTION

- **Thyroid eye disease (TED)** is an autoimmune disease driven by activated orbital fibroblasts (OFs) and infiltrating T lymphocytes, leading to orbital expansion, fibrosis, disfigurement and vision impairment/loss.
- **IGF-1R** signaling plays a central role in TED and is a validated therapeutic target. However, current treatments face challenges including relapse, side effects, and limited efficacy, especially in chronic cases.
- These gaps underscore the need for **novel, targeted therapies** to improve outcomes in TED.

LX-101: Targets IGF-1R

- **LX-101** is a next-generation IGF-1R-targeted therapy delivering an autoimmune medicine, methotrexate (MTX), with high precision to cells expressing IGF-1R. MTX has a long clinical history in autoimmune diseases, including TED.
- LX-101 uses an optimized IGF-1 ligand covalently linked to MTX for targeted delivery to IGF-1R+ cells.
- In a Phase 1a oncology trial (as 765IGF-MTX), LX-101 was well-tolerated with signs of activity, and no dose-limiting toxicity was observed, supporting further clinical development.



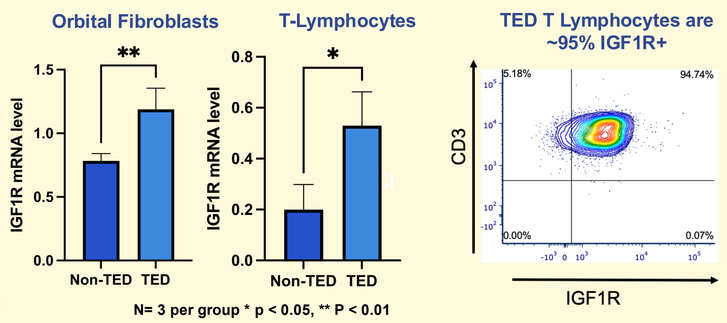
- Here, we evaluated LX-101's ability to suppress inflammation driven by IGF-1R+ T cells and OFs derived from TED patients.

METHODS

- TED-derived OFs and T cells were treated with LX-101 (0.01–2.5 µM) alone or in co-culture.
- Viability, apoptosis and cell activation were assessed. Cytokine levels were measured via ELISA, Luminex, and qPCR.
- TED OF migration was evaluated using scratch assays.

RESULTS

IGF-1R Expression is Elevated in TED

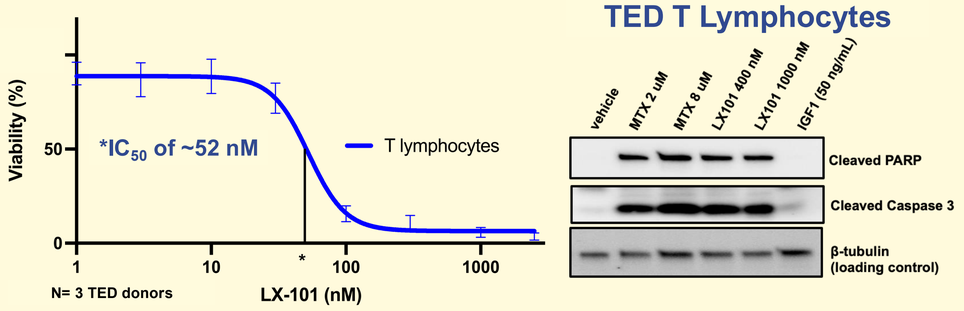


➢ **TED OFs and T lymphocytes over-express IGF-1R**

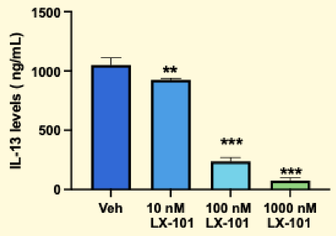
LX-101 Effectively Targets Key Pathogenic Processes in TED

Modulates Activity of IGF-1R+ T Cells

- TED T cells expanded from PBMC isolates or TED Orbital fibroblasts grown from tissue explants were treated with varying doses of LX-101 for 48 hours.



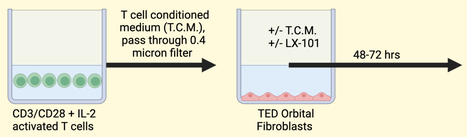
➢ **LX-101 modulates activity of IGF-1R+ T cells at a clinically achievable concentration[1]**

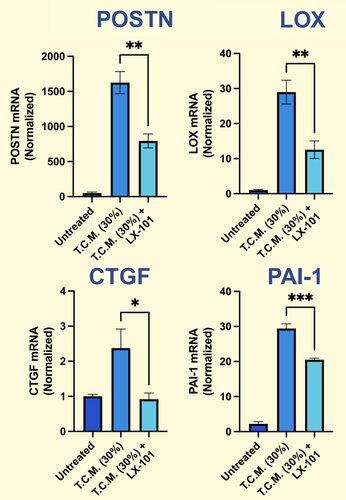


➢ **LX-101 blocks TED T cell expression of IL-13, a key mediator of TED orbital fibroblast activation**

Reduces Production of Pro-Fibrotic ECM Components

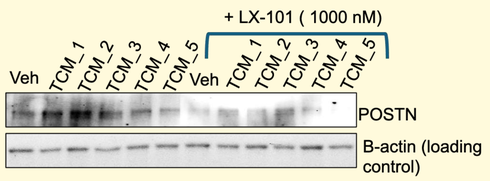
- T cell conditioned medium (TCM) activates TED orbital fibroblasts.

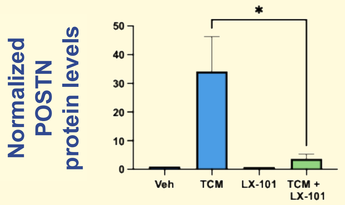




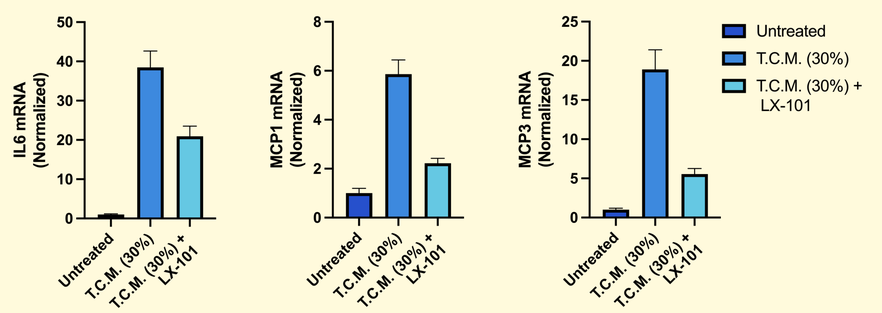
➢ **In TED OFs, TCM and IL-13 induce a pro-fibrotic phenotype, marked by increases in POSTN, LOX, CTGF, and PAI-1 (SERPINE1).**

➢ **LX-101 significantly attenuates this fibrotic response, reducing production of pro-fibrotic components, and demonstrating LX-101's anti-fibrotic activity.**





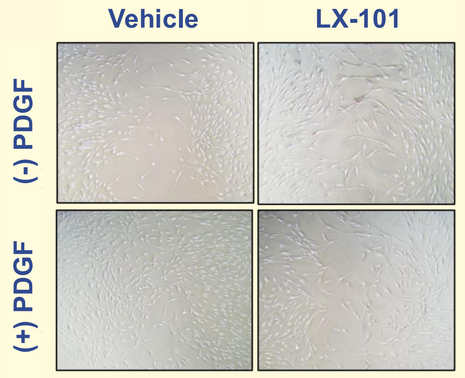
Decreases Production of Key Inflammatory Cytokines

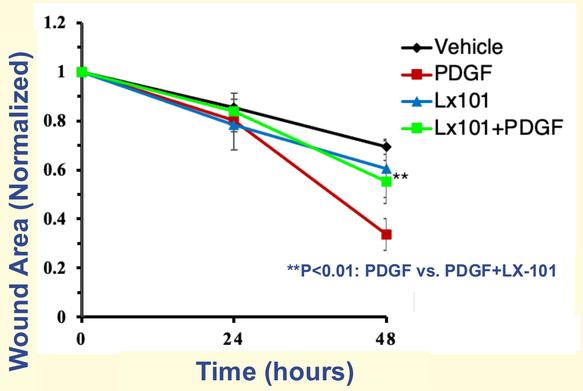


➢ **LX-101 decreases production of IL-6, MCP-1 and MCP-3, key pro-inflammatory cytokines, by TED OFs**

Inhibits Migration of TED OFs

- OFs were scratch-wounded at confluence and treated as indicated. Images were captured at 0 and 48 hours.

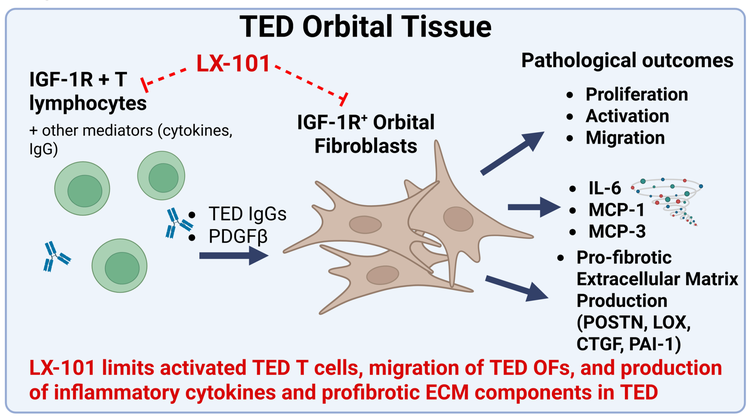




➢ **LX-101 inhibits OF migration capacity, a marker of orbital tissue expansion / fibrosis**

CONCLUSIONS

- TED is caused by inflammatory T cells and activated OFs, leading to fibrosis and vision impairment/loss.
- LX-101 effectively targets these core inflammatory processes via IGF-1R.



Key findings demonstrate that LX-101 can:

- ➢ Inhibit the migration of TED orbital fibroblasts.
- ➢ Decrease production of key inflammatory cytokines (IL-6, MCP-1, MCP-3).
- ➢ Reduce production of pro-fibrotic ECM components (POSTN, LOX, CTGF, and PAI-1),
- ➢ Modulate the activity of TED T lymphocytes.

Given these encouraging results, strong scientific rationale, and prior positive clinical experience in oncology, clinical development of LX-101 in thyroid eye disease is planned.

ACKNOWLEDGEMENTS

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Reference: [1] Venepalli et al Am J Clin Oncol 2019;42:862–869

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