TL1A Inhibition is Efficacious in Mouse Models of Collagen-Induced Arthritis (CIA) and Imiquimod-Induced (IMQ) Psoriasis

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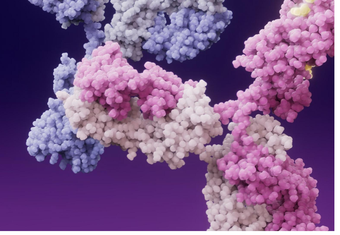

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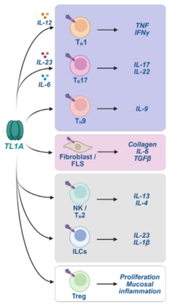
Background and Objectives



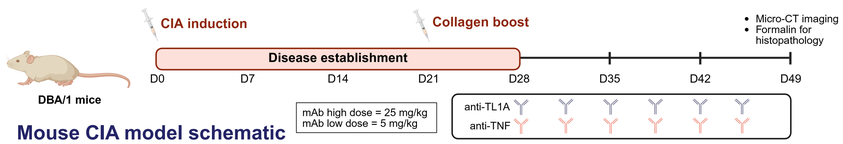
- TNF-like protein 1A (**TL1A**) is a **pro-inflammatory** and **pro-fibrotic cytokine** that is **upregulated** in patients with **rheumatic diseases**[1-5].
- TL1A inhibition has shown promising results in Phase 2 studies of patients with **Crohn's disease (CD) and ulcerative colitis (UC)** and is under investigation in additional immune-mediated conditions.
- Spyre Therapeutics is developing **SPY072**, a **half-life extended** investigational antibody targeting TL1A, as a potential treatment for patients with **RA, PsA, and axSpA**[6].

Objectives: To compare the biological activity of anti-TL1A in mouse models of rheumatoid arthritis (CIA) and psoriasis (IMQ) to positive controls adalimumab (anti-TNF; CIA and IMQ) and an anti-IL-23 (IMQ).

Methods

Collagen-induced arthritis (CIA) model

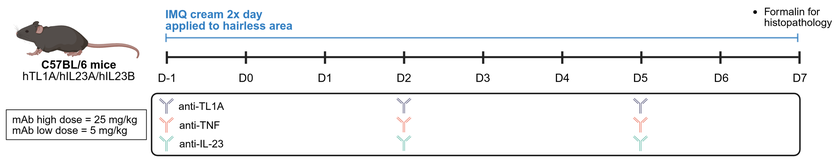
In the CIA model, disease was established by dosing DBA/1 mice (n=10/group) with a bovine type II collagen emulsion (SC) on study D0 and D21. Anti-TL1A and anti-TNF (adalimumab) antibodies were injected IP twice weekly at 25 mg/kg and 5 mg/kg starting at the first sign of symptoms (D28). Arthritis score and hind paw thickness were measured on D21 and twice weekly from D28 until the end of the study (D49). At study conclusion, right hind paw imaging was performed via micro-computed tomography (micro-CT). The left hind paw was placed in formalin for histopathology scoring.



Mouse CIA model schematic

Imiquimod (IMQ) psoriasis model

In the IMQ model, female C57BL/6 transgenic mice (n=8/group) expressing human TL1A and IL-23 had their hair removed on study D2. On study D0-D7, IMQ cream or petrolatum (healthy control) was applied to the hairless skin. Anti-TL1A, -IL-23, and -TNF (adalimumab) were dosed IV on study D-1, 2 and 5 at 25 mg/kg or 5 mg/kg. A Psoriasis Area and Severity Index (PASI) score was measured daily based upon skin erythema, scaling, and thickness. At study conclusion, skin tissue was collected and placed in formalin for subsequent histopathology scoring.



Mouse IMQ model schematic

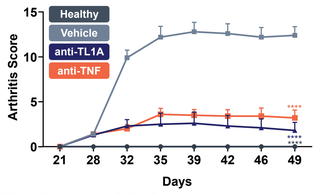
Results

Collagen-induced arthritis (CIA) model

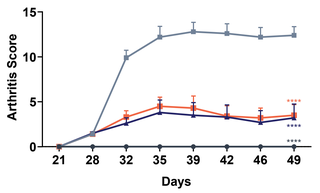
Anti-TL1A and anti-TNF treatments result in comparable improvements in multiple measures of disease:

1. Arthritis score

High doses (25 mg/kg)

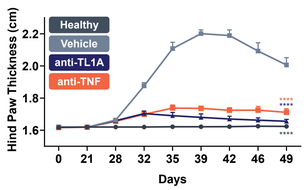


Low doses (5 mg/kg)

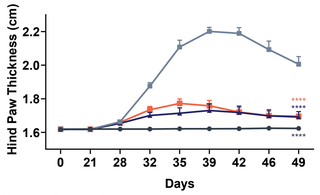


2. Hind paw thickness

High doses (25 mg/kg)

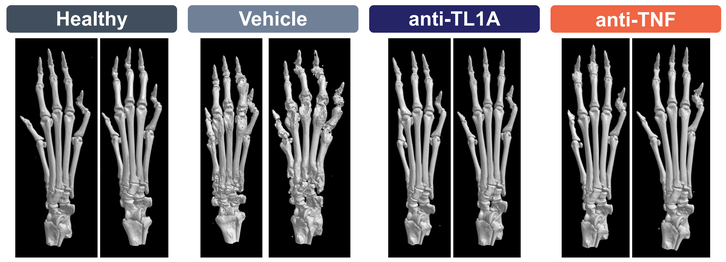


Low doses (5 mg/kg)



*N=10 per group; **** P< 0.0001 vs. vehicle control; 2-way ANOVA using Dunnett's correction for multiple comparisons.*

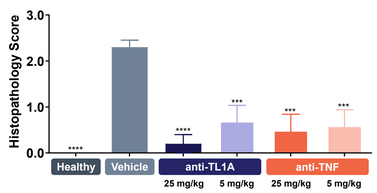
3. Micro CT imaging



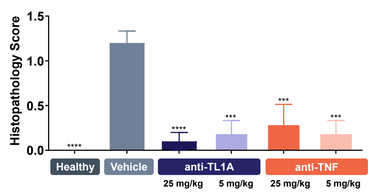
Two representative images shown per group; anti-TL1A and anti-TNF dosed at 25 mg/kg.

4. Histopathology

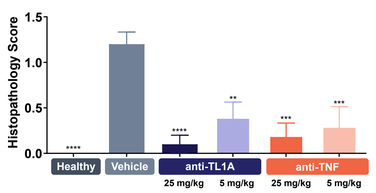
Cell infiltration



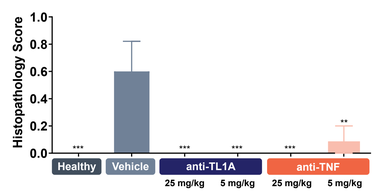
Pannus Severity



Cartilage lesion severity



Bone resorption



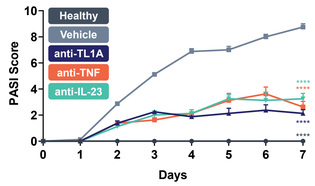
*N=10 per group; ** P<0.01, *** P< 0.001, **** P< 0.0001 vs. vehicle control; 1-way ANOVA using Dunnett's correction for multiple comparisons.*

Imiquimod (IMQ) psoriasis model

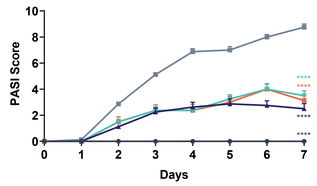
Anti-TL1A treatment results in comparable or better improvement in multiple measures of disease compared to anti-TNF and anti-IL-23 at two tested doses:

1. PASI score

Higher doses (25 mg/kg)



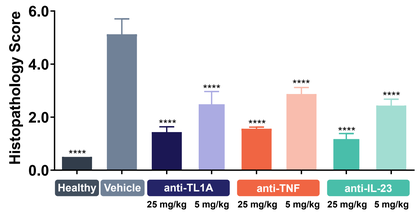
Lower doses (5 mg/kg)



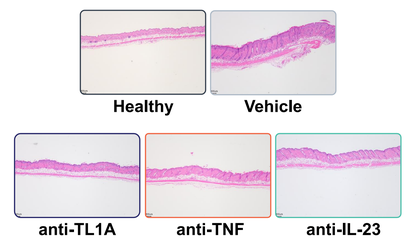
*N=8 per group; **** P< 0.0001 vs. vehicle control; 2-way ANOVA using Dunnett's correction for multiple comparisons.*

2. Histopathology

Changes in stratus corneum, epidermis, and dermis



Histology sections



*N=8 per group; **** P< 0.0001 vs. vehicle control; 1-way ANOVA using Dunnett's correction for multiple comparisons. 25 mg/kg dose shown for histology sections; 40X magnification.*

Conclusions

- **Anti-TL1A** and **anti-TNF** antibody treatments showed **comparable efficacy** in the **mouse CIA model** at both doses tested.
- **Anti-TL1A** showed efficacy that was **equivalent** to or **better** than **anti-IL-23** and **anti-TNF** in the **mouse IMQ psoriasis model**.
- Taken together, the data suggest that **anti-TL1A therapy** has the potential to **improve joint** (RA, PsA) and **skin** (PsA) symptoms associated with rheumatic diseases.
- These data support **clinical testing of the anti-TL1A antibody SPY072** in the ongoing **SKYWAY-RD Phase 2 basket study** in which SPY072 is being evaluated for the treatment of **RA**, **PsA**, and **axSpA** (NCT07148414).

References

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Schematics created in https://BioRender.com

Disclosures: All authors own equity in Spyre Therapeutics, Inc.