# TL1A Expression is Upregulated in Rheumatic Diseases and Anti-TL1A Antibody Reduces Disease Symptoms and Pathological Changes in Rat Collagen-Induced Arthritis

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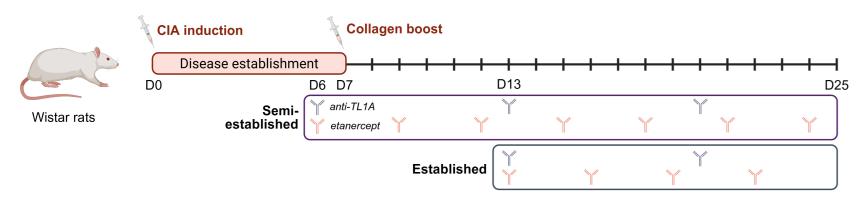
### Background

- | IL-12 | TNF | IFNy | IFNy | IL-17 | IL-22 | IL-6 | TnH7 | IL-9 | IL-9 | IL-13 | IL-13 | IL-4 | TnH2 | IL-13 | IL-4 | IL-23 | IL-16 | IL-16
- TL1A is a cytokine that activates T cell subtypes and fibroblast-like synoviocytes.
  - Variants in the TL1A gene are associated with rheumatoid arthritis (RA), psoriatic arthritis (PsA), and axial spondyloarthritis (axSpA), and TL1A expression is increased in each<sup>1-4</sup>.
  - 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.

#### Methods

- Gene expression data from published RA, axSpA, and PsA studies deposited in NCBI GEO were merged and queried to assess TL1A expression in healthy controls (HC) and in those with rheumatic diseases.
- Anti-TL1A and etanercept (anti-TNF) antibodies were studied in the rat collagen-induced arthritis (CIA) model. Female Wistar rats were injected with a bovine type II collagen emulsion on days 0 and 7. Anti-TL1A antibody was injected (IV) once weekly. Etanercept was injected (IP) every 3 days. Treatment began on day 6 for the semi-established model and on day 13 for the established model. The study concluded on day 25 (Figure 1).

Figure 1: Rat CIA model schematic

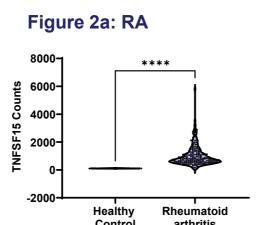


 Body weight, hind paw volume and arthritis scores were measured twice per week. At study conclusion, X-ray images of the hind paws were taken and scored. Decalcified hind paw sections were scored by a blinded pathologist.

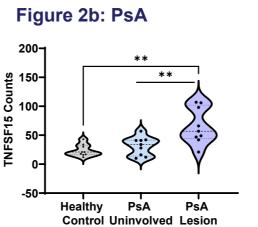
#### References

- 1. Yuan, Z. et al. Gene polymorphisms and serum levels of TL1A in patients with rheumatoid arthritis. J. Cell. Physiol. 234, 11760–11767 (2019).
- 2. Wang, N.-G. et al. Genetic analysis of TNFST15 variants in ankylosing spondylitis. Int. J. Clin. Exp. Pathol. 8, 15210–5 (2015).
- Képíró, L. et al. Genetic risk and protective factors of TNFSF15 gene variants detected using single nucleotide polymorphisms in Hungarians with psoriasis and psoriatic arthritis. Hum. Immunol. 75, 159–162 (2014).
- 4. Bull, M. J. et al. The Death Receptor 3–TNF-like protein 1A pathway drives adverse bone pathology in inflammatory arthritis. J. Exp. Med. 205, 2457–2464 (2008).
- 5. RA-MAP Consortium. RA-MAP, molecular immunological landscapes in early rheumatoid arthritis and healthy vaccine recipients. Sci Data 9(1):196 (2022).
- Johnsson, H. et al. Cutaneous lesions in psoriatic arthritis are enriched in chemokine transcriptomic pathways. Arthritis Res. Ther. 25(1):73 (2023).
  Li, S. et al. Sex dimorphism of IL-17-secreting peripheral blood mononuclear cells in ankylosing spondylitis based on bioinformatics analysis and machine learning. BMC Musculoskel Disord. 25(1):490 (2024)

# TL1A is upregulated in RA, PsA, and axSpA relative to healthy controls



Spyre analysis of RA-MAP; whole blood mircroarray; N=192 RA, 30 HC; \*\*\*\* P ≤0.0001; unpaired t-test.



Spyre analysis of Johnsson et al.; skin biopsy bulk RNA-seq; N=9 per cohort; \*\* P≤0.01; one-way ANOVA.

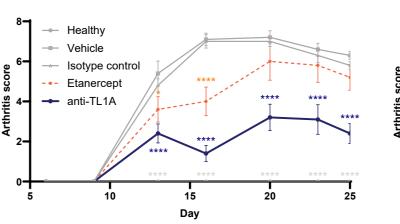


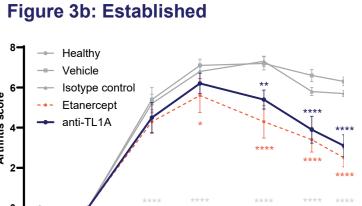
Spyre analysis of Li et al.; whole blood microarray; N=52 axSpA, 20 HC; \*\*\* P ≤0.001; unpaired t-test.

### Results

### Anti-TL1A antibody meets or exceeds the efficacy of etanercept when assessing <u>disease activity scores</u> in rat CIA models



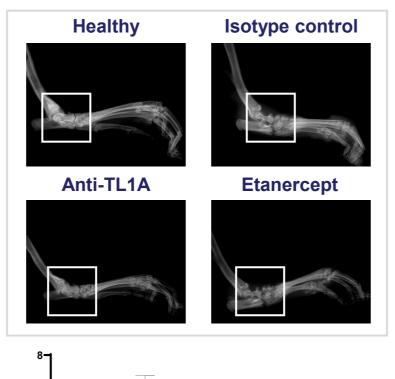


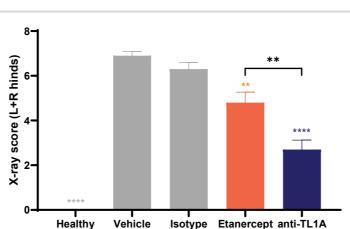


N=10 per group; \* P<0.05, \*\* P<0.01, \*\*\* P< 0.001, \*\*\*\* P< 0.0001 vs. vehicle control; 2-way ANOVA using Dunnett's correction for multiple comparisons.

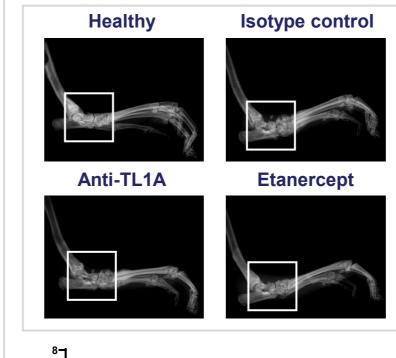
### Anti-TL1A antibody meets or exceeds the efficacy of etanercept when assessing <u>x-ray scores</u> in rat CIA models

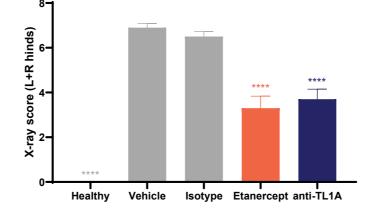
Figure 4a: Semi-established





#### Figure 4b: Established





N=10 per group; \*\* P< 0.01, \*\*\* P<0.001, \*\*\*\* P<0.0001 vs. vehicle control (for p-values shown above colored bars); 1-way ANOVA with Dunnett's correction for multiple comparisons. Higher score = more severe disease.

# Anti-TL1A antibody exceeds the efficacy of etanercept when assessing <u>histology</u> in the semi-established rat CIA model

Figure 5a: H&E score

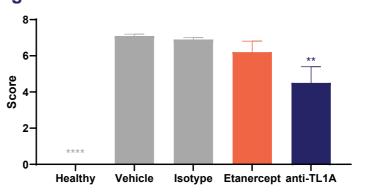
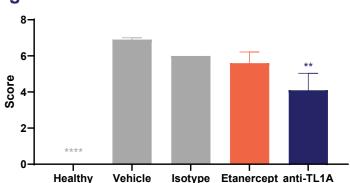


Figure 5b: Safranin O score



N=10 per group; \*\* P< 0.01, \*\*\* P<0.001, \*\*\*\* P<0.0001 vs. vehicle control; 1-way ANOVA with Dunnett's correction for multiple comparisons. H&E score - infiltration of cells and pannus severity grade. Safranin O score – cartilage lesion severity grade and bone resorption severity grade. All scores are on a scale of 0-4 and scores were combined. Higher score = more severe disease

#### Conclusions

- TL1A gene expression is increased in the blood of RA and axSpA patients and in skin lesions of PsA patients compared to healthy controls, based on analysis of gene expression data from published studies<sup>5-7</sup>.
- Anti-TL1A antibody treatment reduced disease symptoms and pathology scores in the rat CIA model, with superior efficacy relative to etanercept when initiated prior to full symptom onset.
- 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).

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