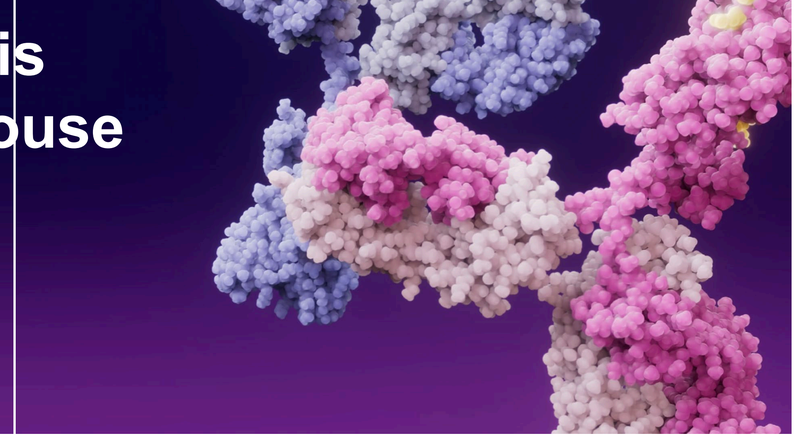
Anti-TL1A and Anti-IL-23 Combination Therapy is Superior to its Constituent Monotherapies in Mouse Anti-CD40 Colitis



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SPYRE THERAPEUTICS

P0023

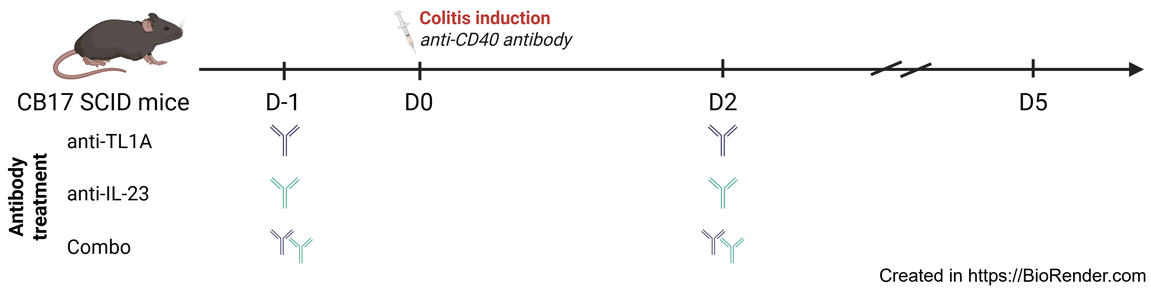
Background

Advanced combination therapy (ACT), particularly with **co-formulated targeted biological agents**, has the potential to break through the IBD treatment efficacy ceiling while avoiding the risks associated with broad immunosuppression.[1]

SPY002 and **SPY003** are investigational **half-life extended antibodies** against the validated IBD targets **TL1A** and **IL-23**, respectively.[2,3] Both are being evaluated as **monotherapies and in combination** to treat IBD in the SKYLINE-UC Phase 2 platform study in ulcerative colitis (UC; NCT07012395).[4]

Methods

Figure 1: Anti-mouse surrogates of SPY002 and SPY003 were studied as monotherapies and in combination in the anti-CD40 murine colitis model



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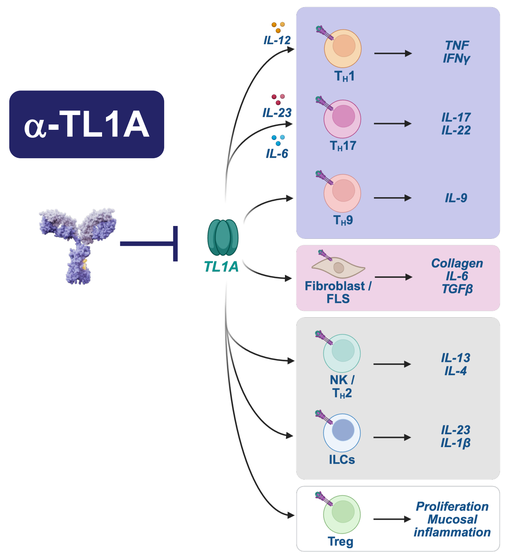
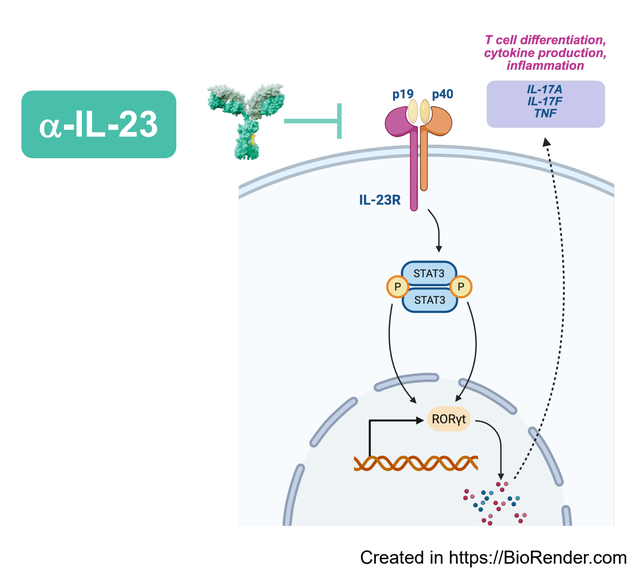
- CB17-SCID mice were dosed with test article (IV, 5 or 25 mg/kg) on Day -1 and Day 2.
- Anti-CD40 agonist antibody was dosed (IV, 5 mg/kg) on Day 0.
- Histopathology was conducted only in the 25 mg/kg dose group.

Figure 2: SPY002 and SPY003 mechanisms of action[5,6]





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Results

Combining anti-TL1A + anti-IL-23 resulted in superior efficacy compared to either monotherapy alone:

Anti-TL1A (25 mg/kg) + Anti-IL-23 (25 mg/kg)

Figure 3A: Change in weight

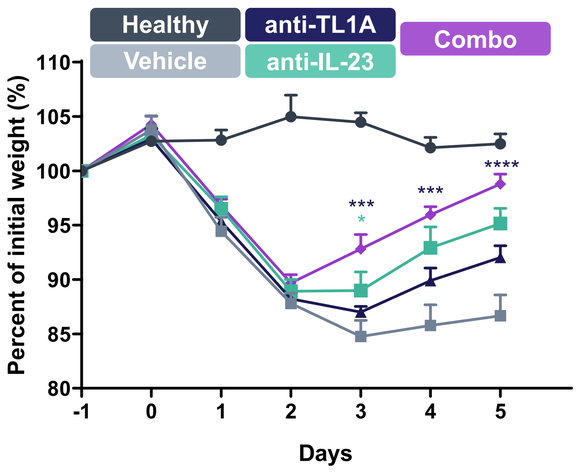


Figure 3B: Disease activity score

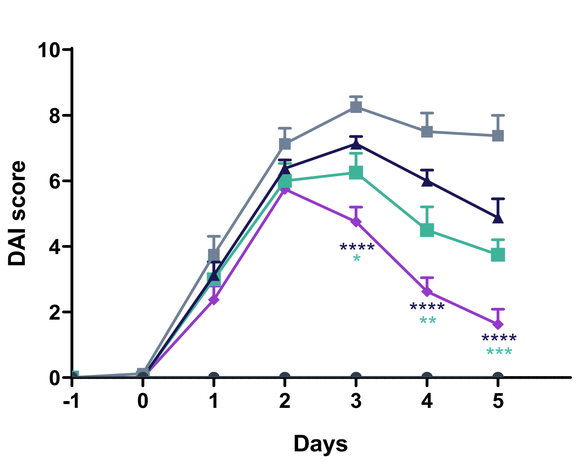


Figure 3C: Colon weight:length

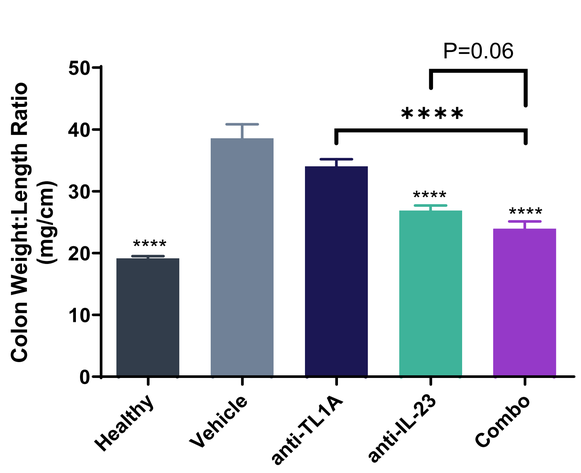
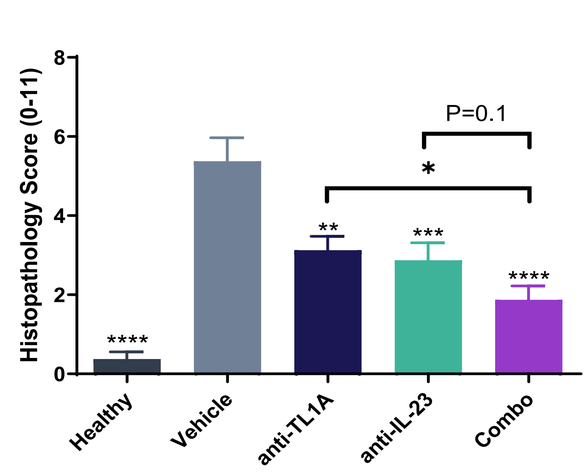


Figure 3D: Histopathology score



Anti-TL1A (25 mg/kg) + Anti-IL-23 (5 mg/kg)

Figure 4A: Change in weight

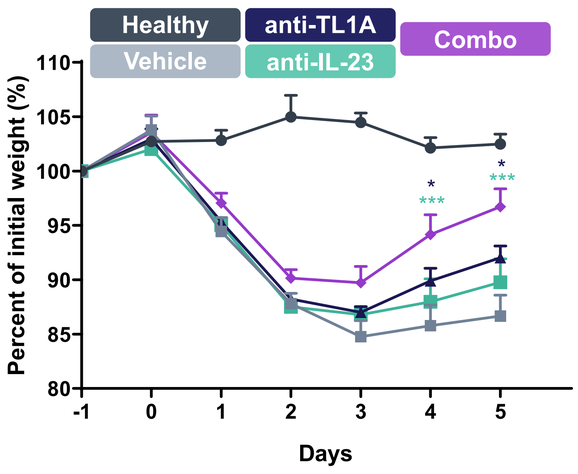


Figure 4B: Disease activity score

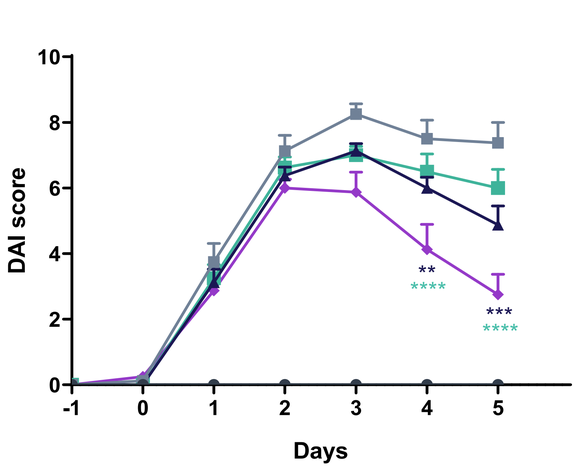
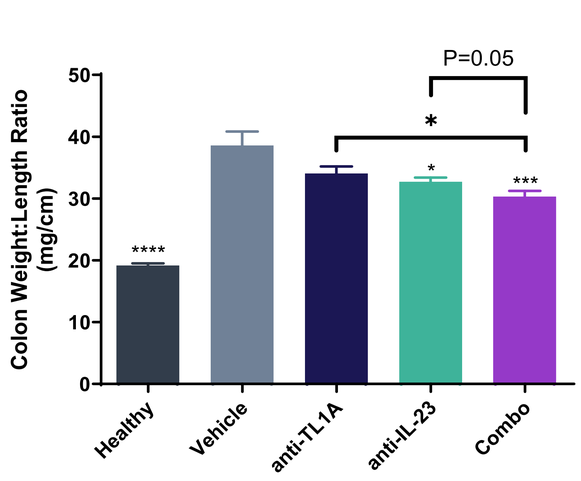


Figure 4C: Colon weight:length



Histology not conducted in lower dose study

*N=8 per group, dose was 25 mg/kg of anti-TL1A and 25 mg/kg or 5 mg/kg of anti-IL-23; * P<0.05, ** P<0.01, *** P< 0.001, **** P< 0.0001; two-way ANOVA for combo vs. mono using Dunnett's correction for % weight and DAI, one-way ANOVA vs. vehicle control using Dunnett's correction for colon W:L ratio; t-test for combo vs. mono.*

Conclusions

- The **combination** of **anti-TL1A** and **anti-IL-23** was more efficacious in mouse anti-CD40 colitis than anti-TL1A or anti-IL-23 monotherapies at a range of anti-IL-23 doses.
- These preclinical results support advancement of the **combination of SPY002 and SPY003** in the **SKYLINE-UC Phase 2 platform study** in UC which started in mid-2025 [see Spyre poster P0978 for further details[4]].

References

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2. Zhu, E. *et al.* Characterization of Two Novel Extended Half-life Monoclonal Antibody Drug Candidates Targeting TL1A for the Treatment of IBD. *UEGW*, MP450 (2024).
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Disclosures

All authors are employees of Spyre Therapeutics, Inc. and own equity in Spyre Therapeutics, Inc.