

Anti-α4β7 integrin, anti-TL1A, and anti-IL-23 are efficacious in TNBS-induced colitis using humanized mice, and combinations further improve efficacy

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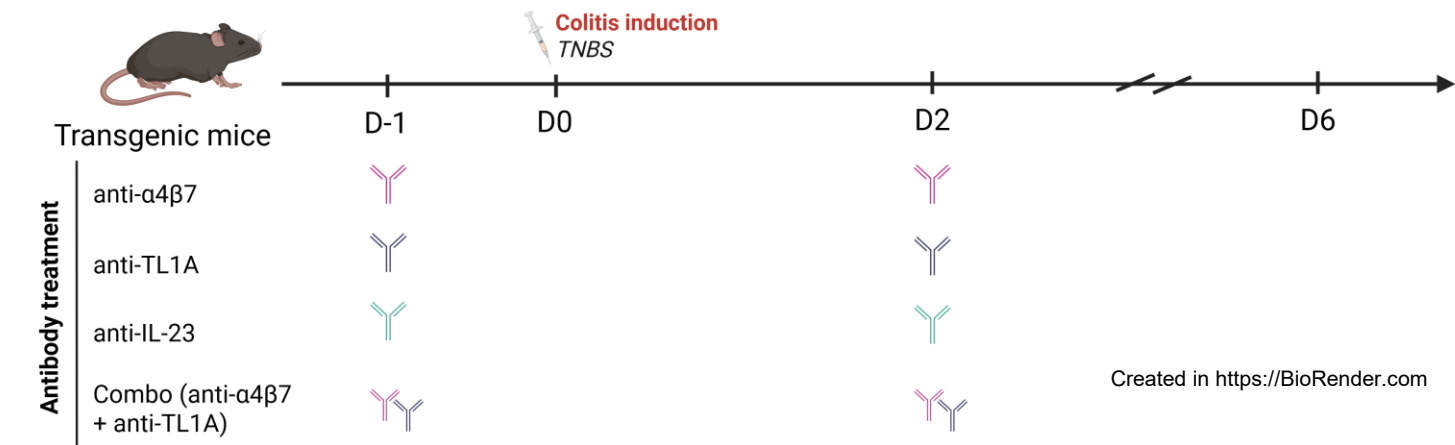
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Background

- SPY001**, **SPY002**, and **SPY003** are investigational **half-life extended antibodies** against validated IBD targets (**α4β7 integrin**, **TL1A**, and **IL-23**, respectively)^{1,2,3} being evaluated as **monotherapies** and in **pairwise combinations** to treat IBD in the SKYLINE Phase 2 platform study in ulcerative colitis (UC; NCT07012395).
- Prior work showed **combinations of anti-β7, anti-TL1A, and anti-IL-23 provided greater efficacy than either monotherapy** in mouse TNBS-induced colitis.⁴
- Here, we extend those findings using **transgenic mice expressing human α4β7, TL1A, and IL-23**, allowing for the evaluation of each antibody against their human targets in the TNBS-induced colitis model.

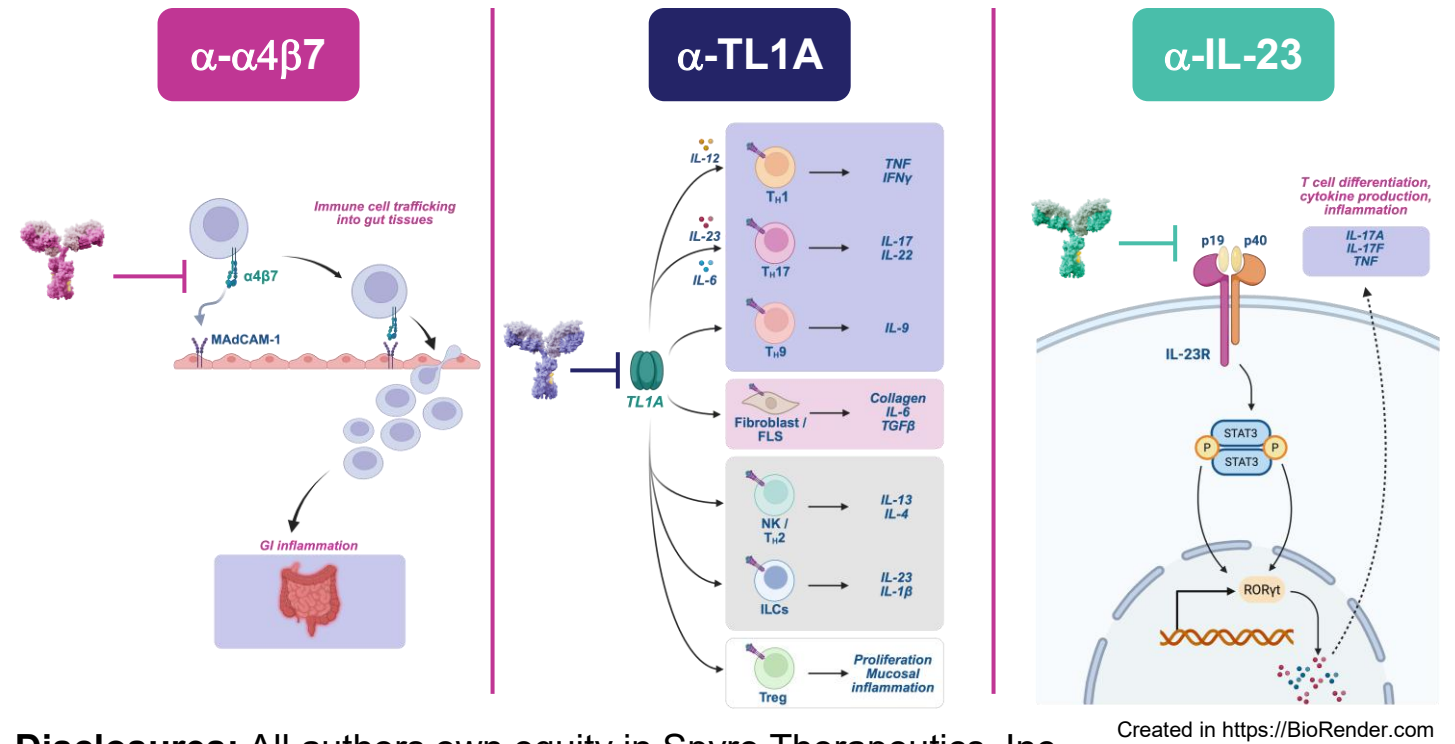
Methods

Figure 1: Antibodies targeting human α4β7 integrin, human TL1A, and human IL-23 (p19) were studied as monotherapies and as combinations (α4β7 and TL1A) in the TNBS murine colitis model



- Female transgenic mice expressing human α4β7, human TL1A, and human IL-23 were dosed intravenously with test article (5 or 25 mg/kg) on Day -1 and Day 2, with Day 0 representing 2% TNBS administration.

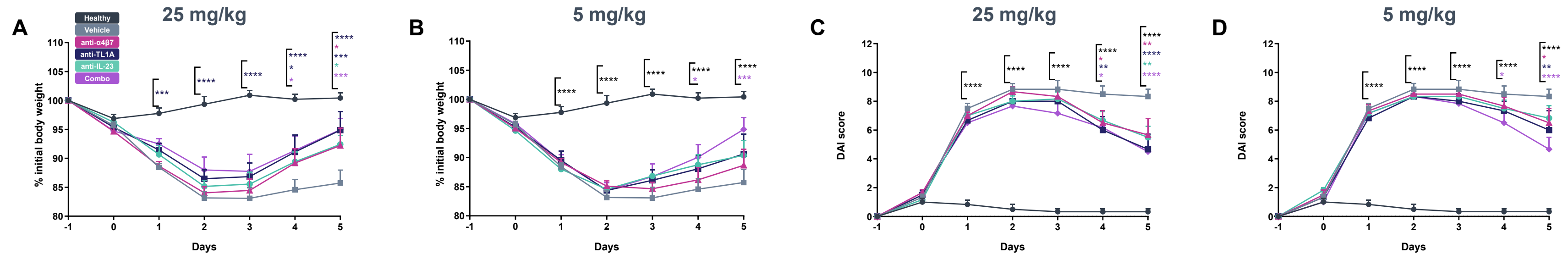
Figure 2: Mechanistic rationale for SPY001¹, SPY002², and SPY003³



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

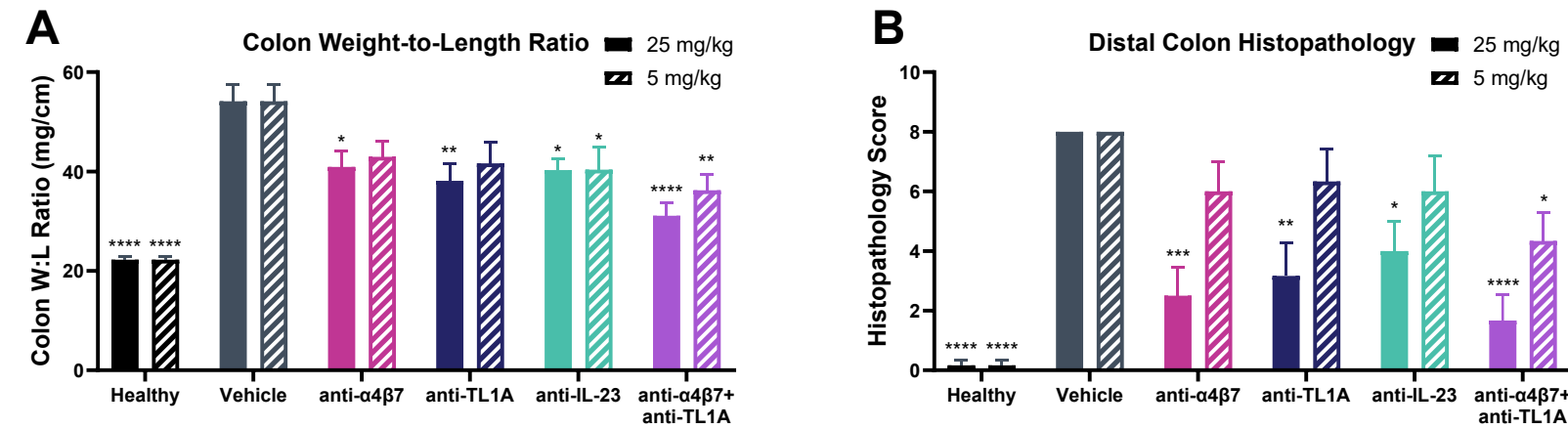
Results

Figure 3: Anti-α4β7, anti-TL1A, and anti-IL-23 showed significant improvement of similar magnitude in body weight and disease activity index at 25 mg/kg with a dose-response at 5 mg/kg; combination of anti-α4β7 and anti-TL1A improved these measures at the 5 mg/kg dose



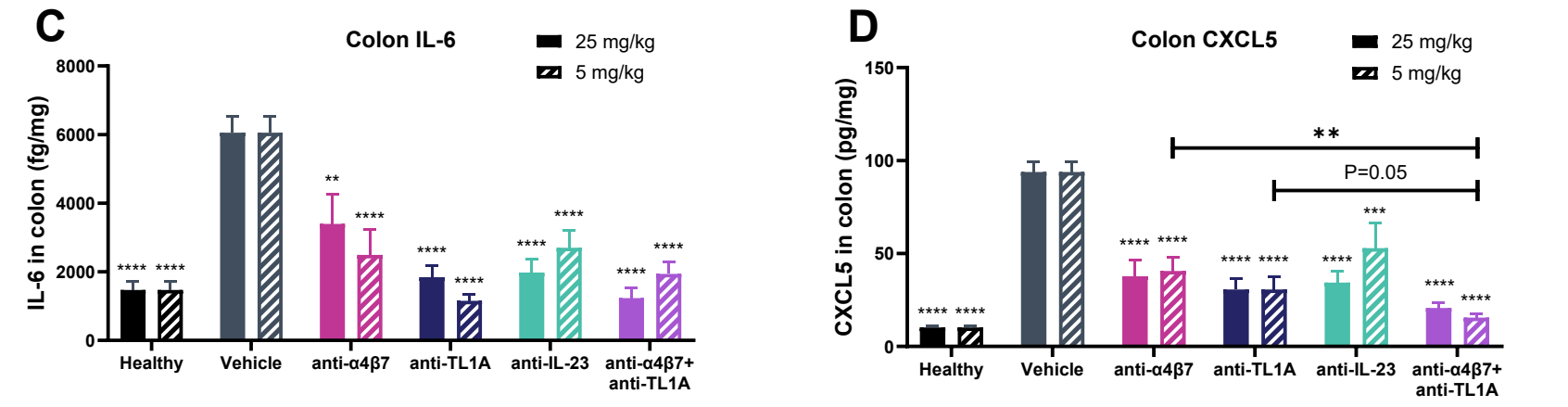
Statistical significance vs vehicle control calculated using two-way ANOVA with Dunnett's correction for multiple comparisons. * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$, **** $P < 0.0001$

Figure 4: All treatments showed significant improvement in colon weight-to-length ratio and histopathology score at 25 mg/kg with a dose-response at 5 mg/kg



Statistical significance vs vehicle control calculated using one-way ANOVA with Dunnett's correction for multiple comparisons. * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$, **** $P < 0.0001$

Figure 5: All treatments led to a decrease in IL-6 and CXCL5 levels in colons of the TNBS murine colitis model



Statistical significance vs vehicle control calculated using one-way ANOVA with Dunnett's correction for multiple comparisons. Statistical significance for combination therapy vs monotherapy calculated using unpaired t-test. * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$, **** $P < 0.0001$

Conclusions

- Anti-α4β7, anti-TL1A, and anti-IL-23 showed comparable efficacy** in a mouse model of colitis using **transgenic mice** expressing the human orthologs of each targeted protein.
- Combination of anti-α4β7 and anti-TL1A** resulted in greater improvements than the monotherapies (5 mg/kg), suggesting that therapies targeting multiple disease-relevant pathways may improve efficacy in IBD.
- These preclinical results support and provide biologic rationale for the ongoing **Phase 2 SKYLINE clinical trial** (NCT07012395) of **SPY001**, **SPY002**, **SPY003**, and their combinations.



Phase 2 *platform* trial initiated to evaluate SPY001, SPY002, SPY003 and pairwise combinations in ulcerative colitis.

UC	Monos	SPY001
		SPY002
		SPY003
	Combos	SPY120 (SPY001 + SPY002)
		SPY130 (SPY001 + SPY003)
		SPY230 (SPY002 + SPY003)
		Placebo

References

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