Combined Inhibition of TL1A and Integrin β7 is Superior to Either Monotherapy in Mouse Models of Colitis, and Coadministration of SPY001 and SPY002 Demonstrates No Drug-Drug Effects on Exposure in Non-Human Primates

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Background

- **Combined** use of **targeted biologic agents** has the potential to break through the IBD treatment efficacy ceiling while avoiding the risks associated with broad immunosuppression.
- **SPY001** and **SPY002** are investigational **half-life extended antibodies** against validated IBD targets (**α4β7 integrin** and **TL1A,** respectively) being evaluated as monotherapies and in combination to treat IBD.

Methods and Results

SPY120 (a combination of SPY001 and SPY002) targets α4β7 and TL1A – orthogonal drivers of IBD

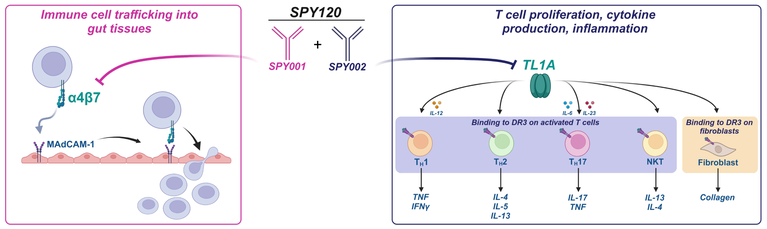

Figure 1: *Mechanistic rationale for SPY120. SPY001 is a recombinant humanized anti-β7 mAb[1]; SPY002 is a fully human anti-TL1A mAb[2].*

Anti-mouse surrogates for SPY120 and its monotherapy components were studied in two murine colitis models

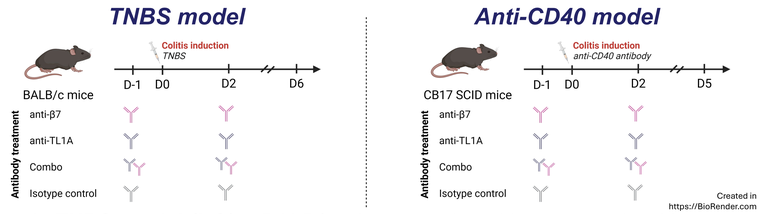

Figure 2: ***TNBS model (left)*** *– BALB/c mice were dosed intravenously with test article (25 mg/kg) on Day -1 and Day 2, with Day 0 representing TNBS administration per prior methods[3].* ***Anti-CD40 model (right)*** *– CB17 SCID mice were dosed intravenously with test article (25 mg/kg) on Day -1 and Day 2, with Day 0 representing anti-CD40 antibody administration per prior methods[4].*

Anti-β7 and anti-TL1A combination improved disease activity score in murine colitis models

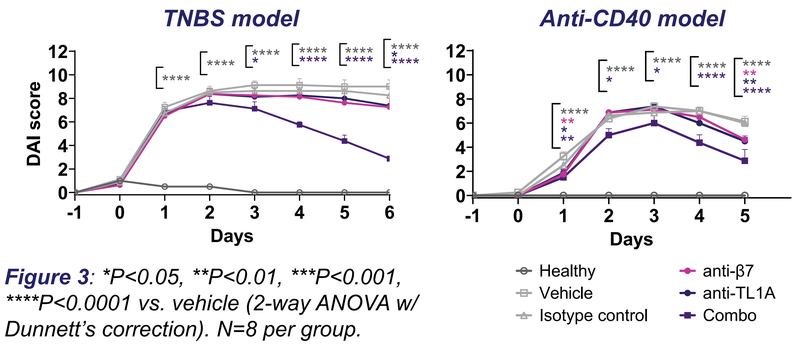

Figure 3*: *P<0.05, **P<0.01, ***P<0.001, ****P<0.0001 vs. vehicle (2-way ANOVA w/ Dunnett's correction). N=8 per group.*

Anti-β7 and anti-TL1A combination improved colon histopathology score and weight:length ratio in murine colitis models

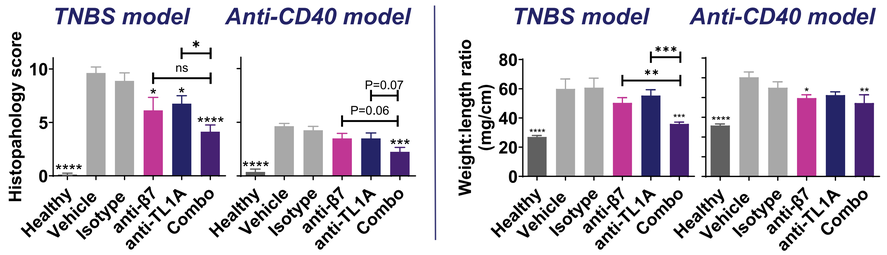

Figure 4: *Histopathology scoring (left) of distal colon and weight:length ratio (right) of full colon harvested on D6 (TNBS) or D5 (anti-CD40). *P<0.05, **P<0.01, ***P<0.001, ****P<0.0001 vs. vehicle (1-way ANOVA w/ Dunnett's correction and t-test for individual comps.). N=8 per group.*

All treatments led to a decrease in TNF and IL-6 levels in colons of murine colitis models

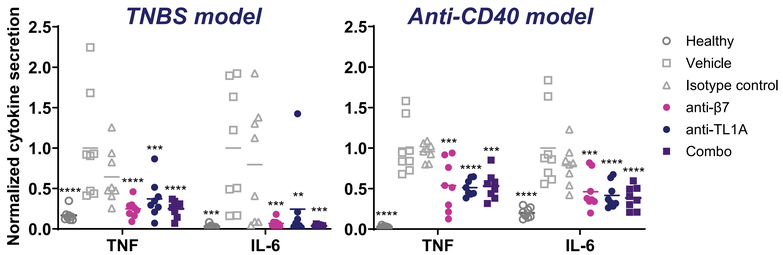

Figure 5*: TNF and IL-6 levels in mid-colon harvested on D6 (TNBS) or D5 (anti-CD40). *P<0.05, **P<0.01, ***P<0.001, ****P<0.0001 vs. vehicle (1-way ANOVA with Dunnett's correction). N=8 per group.*

Serum concentrations of monotherapies and combination therapy were similar in NHPs

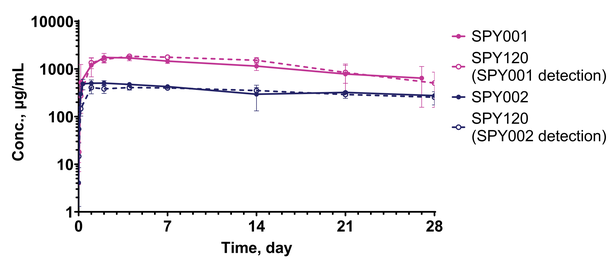

Figure 6*: Mean serum concentrations in cynomolgus NHPs following a single SC dose of SPY001 (anti-α4β7, 150 mg/kg), SPY002 (anti-TL1A, 50 mg/kg), or SPY120 (160 mg/kg SPY001 + 50 mg/kg SPY002). N=3 per group.*

Conclusions

- Combined **anti-β7 integrin** and **anti-TL1A** therapy showed **additive or greater than additive** *in vivo* activity relative to either monotherapy in the **TNBS and anti-CD40 mouse colitis models.**
- **PK profiles** of SPY001 and SPY002 were similar in NHPs whether dosed as monotherapy or in combination, indicating potential for **Q3-6M dosing** for SPY001, SPY002, and SPY120 based on human PK simulations.
- These preclinical results support the **advancement** of the **combination** of SPY001 and SPY002 into **clinical trials** and **inclusion** in a **Phase 2 UC platform** study planned to start in **mid-2025.**

References

1. Zhu, E. *et al.* A Novel Monoclonal Antibody Drug Candidate SPY001 Targeting Integrin α4β7 for the Treatment of IBD: In Vitro Properties and Non-Human Primate Pharmacokinetics and Safety. *UEGW*, PP1103 (2024).
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4. Uhlig, H. *et al.* Differential Activity of IL-12 and IL-23 in Mucosal and Systemic Innate Immune Pathology. *Immunity* 25(2), P309-318 (2006).

Disclosures

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