

Combining IL-23 Blockade With Anti- $\alpha 4\beta 7$ or Anti-TL1A for the Treatment of IBD is Supported by In Vitro and Mouse IBD Model Experiments

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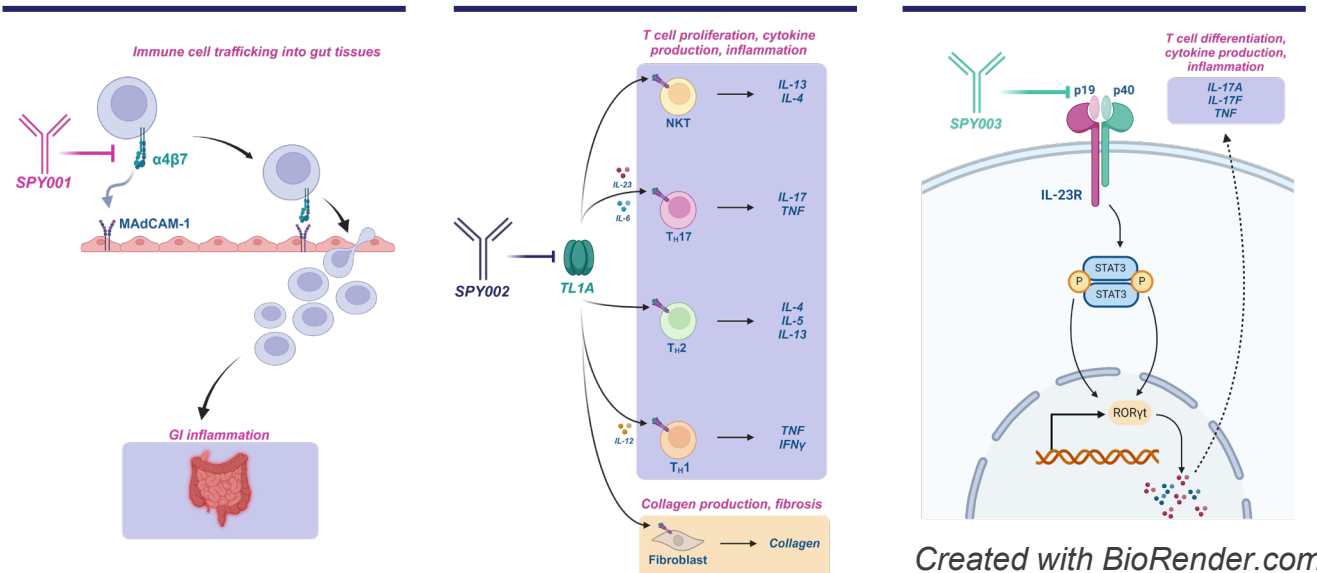
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Background

- IL-23 and $\alpha 4\beta 7$ inhibition (e.g., with risankizumab and vedolizumab, respectively) are both **well-tolerated and effective** treatments for **Crohn's disease (CD) and ulcerative colitis (UC)**.
- TL1A inhibition has been shown to **ameliorate disease activity** in patients with **CD and UC**.
- Combined** use of **targeted biologic agents** may improve efficacy by inhibiting multiple pathways while avoiding the risks associated with broad immunosuppression.

$\alpha 4\beta 7$, TL1A, and IL-23 blockade are each clinically validated therapeutic mechanisms in IBD

- Blockade of $\alpha 4\beta 7$ prevents circulating immune cells from entering gut tissues
- Neutralization of TL1A suppresses inflammation and reduces fibrosis by inhibiting fibroblast activation
- Neutralization of IL-23 inhibits cascade of various proinflammatory cytokines



Methods

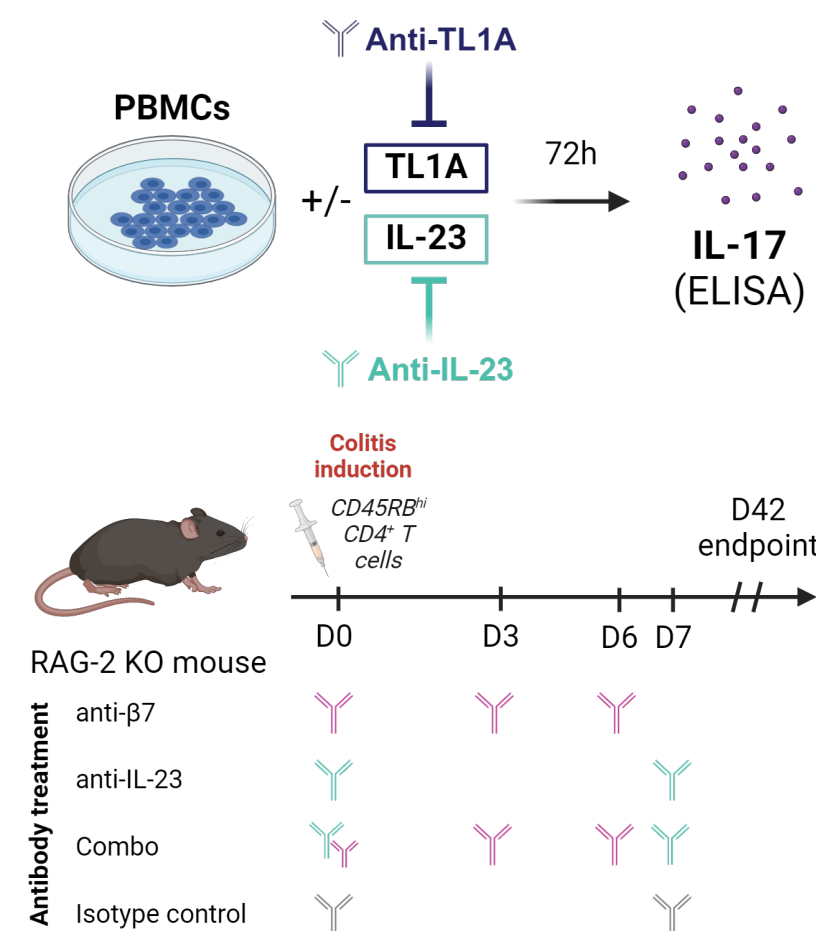


Figure 1: IL-17 was measured by ELISA after human peripheral blood mononuclear cells (PBMCs) were incubated with IL-23 and/or TL1A with or without anti-IL-23 and/or anti-TL1A (500 nM or 83 nM) for 72 hours (top). CD45RB^{hi}CD4⁺ T cells were transferred into RAG-2 KO mice to induce colitis. Mice were treated with isotype control Ab, murine anti- $\beta 7$ mAb (30 mg/kg), murine anti-IL-23 mAb (1 mg), or both. Body weight was measured weekly; colons were harvested at Day 42 for histologic, immunohistochemical, and colonic IL-17 quantitative analysis. Created with BioRender.com.

Results

Carriage of variants in any two of the pathways is associated with greater risk of IBD than any single variant

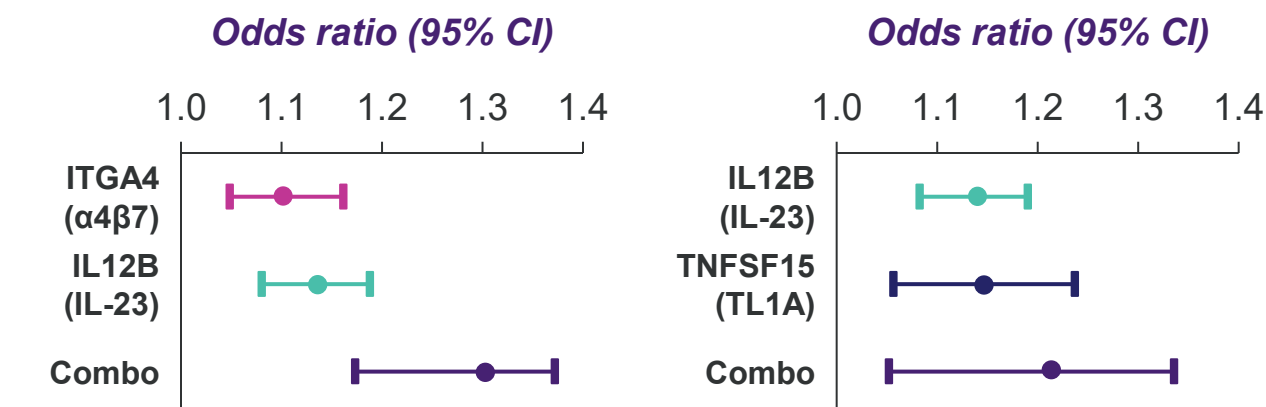


Figure 2: The contribution of lead variants in each of the three ($\alpha 4\beta 7$, TL1A, and IL-23) target gene pathways to the risk of IBD, alone and in combination of two at a time, was explored by genetic association using the UK Biobank.

Combination of anti-TL1A and anti-IL-23 offers superior inhibition of IL-17 release in vitro

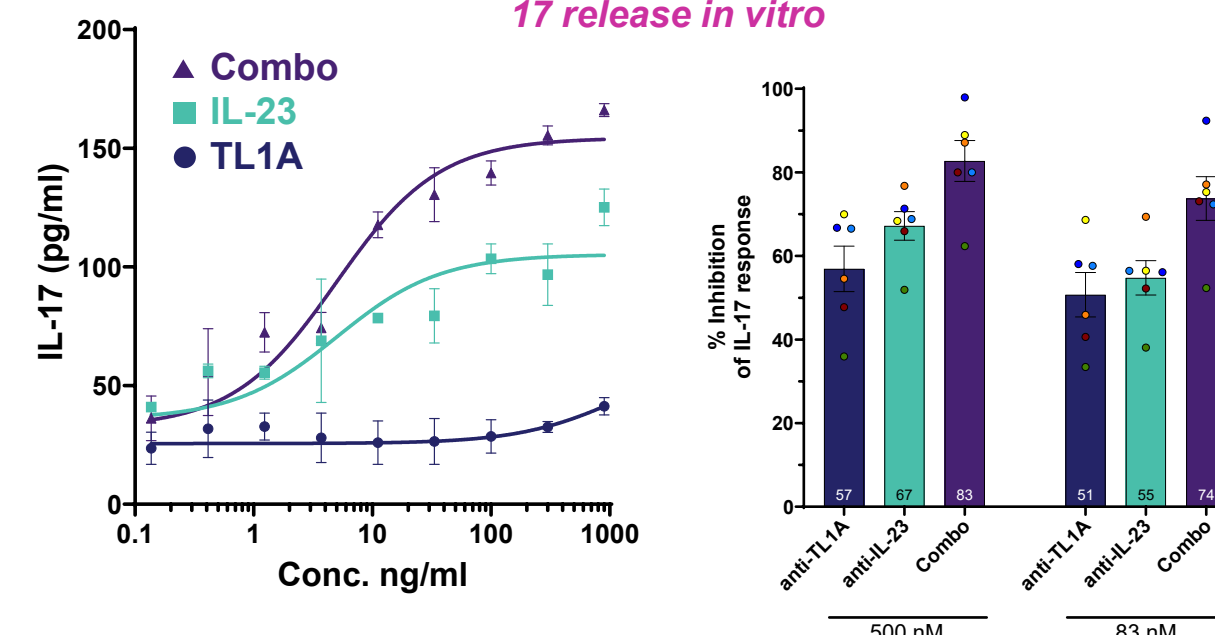


Figure 3: TL1A enhances IL-23-dependent IL-17 secretion by human PBMCs (left) and a combination of anti-IL-23 and anti-TL1A mAb leads to greater inhibition of IL-17 secretion by human PBMCs (right).

Combination of anti- $\beta 7$ and anti-IL-23 increases efficacy and PD in T-cell transfer colitis

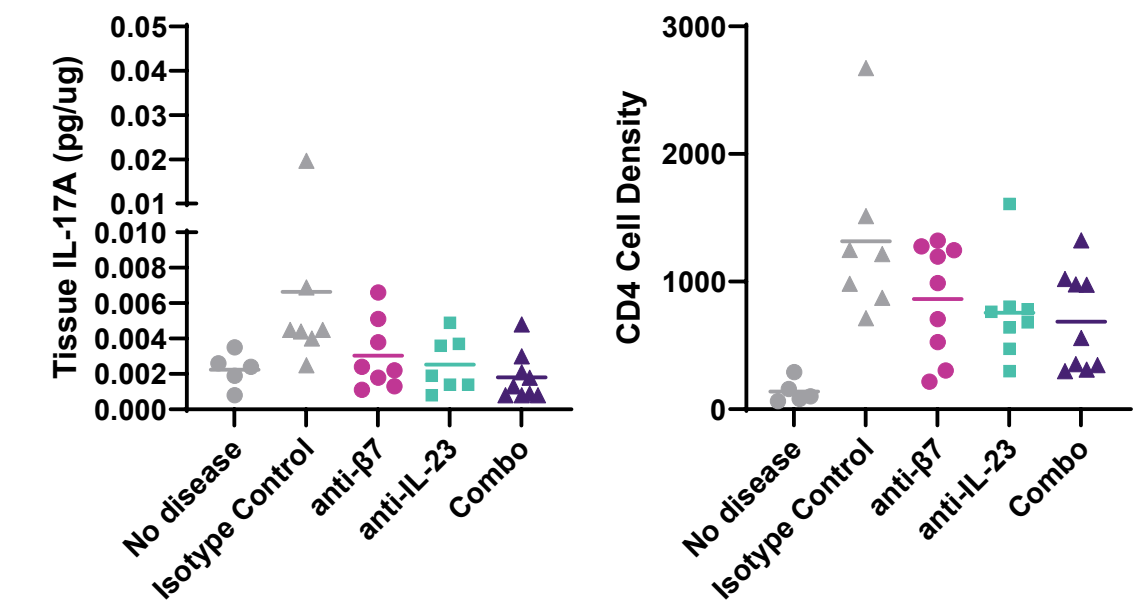
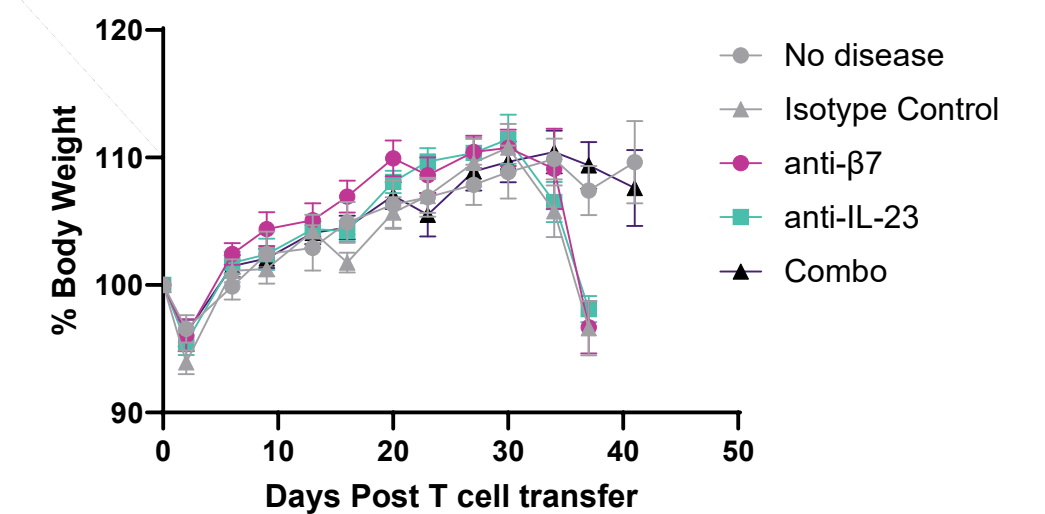


Figure 4: Anti- $\beta 7$ and anti-IL-23 mAb in combination led to lower weight loss than either one alone (top), to lower IL-17 levels by ELISA of colonic lysates (bottom left) and to lower CD4⁺ T cell infiltration in the colon by immunohistochemistry (bottom right).

Conclusions

- Dual blockade of TL1A and IL-23 results in additive inhibition of IL-17 production in PBMCs.
- Genetic association data are suggestive of a potential additive effect of **SPY001 and SPY003 combination** and **SPY002 and SPY003 combination** in the treatment of IBD.
- $\beta 7$ and IL-23 blockade have additive effects in the murine T-cell transfer colitis model.
- Spyre is developing extended half-life mAbs against $\alpha 4\beta 7$ (**SPY001**), TL1A (**SPY002**), and IL-23 (**SPY003**) for clinical development as combination therapies for IBD. (See posters PP1103, MP450, and MP118).

References

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Disclosures

DR, MA, JM, JV, JO, and HS are employees of Paragon Therapeutics. JF and AS are employees of Spyre Therapeutics. All authors own equity in Paragon Therapeutics and/or Spyre Therapeutics.