Combining IL-23 Blockade With Anti-α4β7 or Anti-TL1A for the Treatment of IBD is Supported by In Vitro and Mouse IBD Model Experiments

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Background

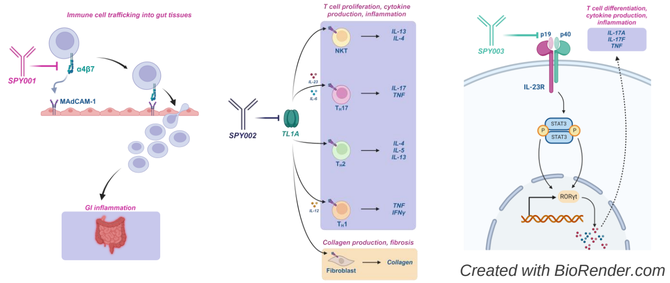
- **IL-23** and **α4β7 inhibition** (e.g., with risankizumab and vedolizumab, respectively) are both **well-tolerated and effective** treatments for **Crohn's disease (CD) and ulcerative colitis (UC).**
- **TL1A inhibition** has been shown to **ameliorate disease activity** in patients with **CD** and **UC**.
- **Combined** use of **targeted biologic agents** may improve efficacy by inhibiting multiple pathways while avoiding the risks associated with broad immunosuppression.

α4β7, TL1A, and IL-23 blockade are each clinically validated therapeutic mechanisms in IBD

Blockade of **α4β7** 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



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Methods

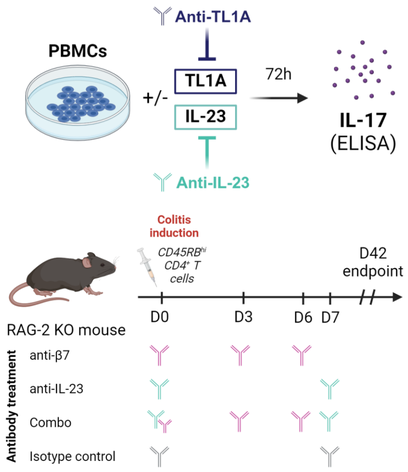


Figure 1: *IL-17 was measured by ELISA after human peripheral blood mononuclear cells (PBMCs) were incubated with IL-23 and/or TL1A with or without anti-IL-23 and/or anti-TL1A (500 nM or 83 nM) for 72 hours (top). CD45RB^{hi}CD4^{+} T cells were transferred into RAG-2 KO mice to induce colitis. Mice were treated with isotype control Ab, murine anti-β7 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

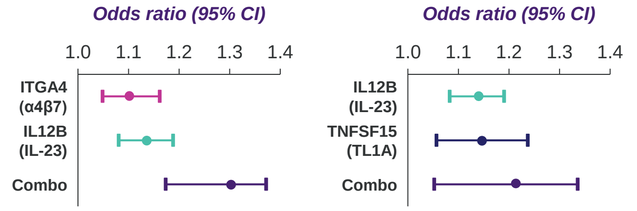


Figure 2: *The contribution of lead variants in each of the three (α4β7, TL1A, and IL-23) target gene pathways to the risk of IBD, alone and in combination of two at a time, was explored by genetic association using the UK Biobank.*

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

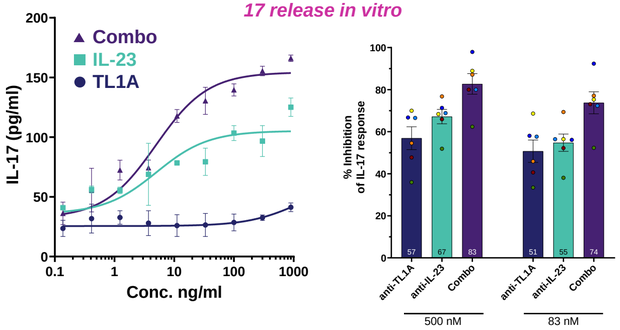
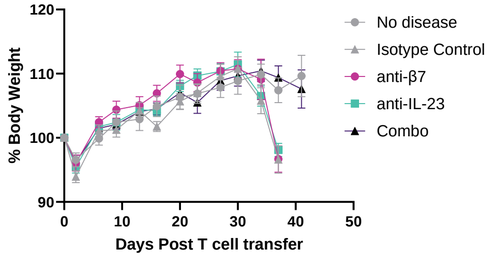


Figure 3: *TL1A enhances IL-23-dependent IL-17 secretion by human PBMCs (left) and a combination of anti-IL-23 and anti-TL1A mAb leads to greater inhibition of IL-17 secretion by human PBMCs (right).*

Combination of anti-β7 and anti-IL-23 increases efficacy and PD in T-cell transfer colitis



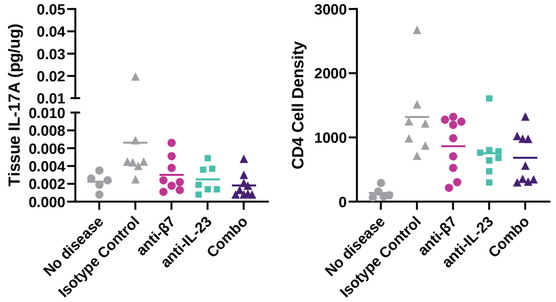


Figure 4: *Anti-β7 and anti-IL-23 mAb in combination led to lower weight loss than either one alone (top), to lower IL-17 levels by ELISA of colonic lysates (bottom left) and to lower CD4^{+} T cell infiltration in the colon by immunohistochemistry (bottom right).*

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.
- β7 and IL-23 blockade have additive effects in the murine T-cell transfer colitis model.
- Spyre is developing extended half-life mAbs against α4β7 (**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.