# Rosnilimab, a Depleter and Agonist Antibody Targeting PD-1+ T Cells, in Clinical Development for Ulcerative Colitis, Reduces Pathogenic PD-1+ T Cells and Inflammatory Cytokine Secretion in Patient Blood and in a Mouse Model of Colitis

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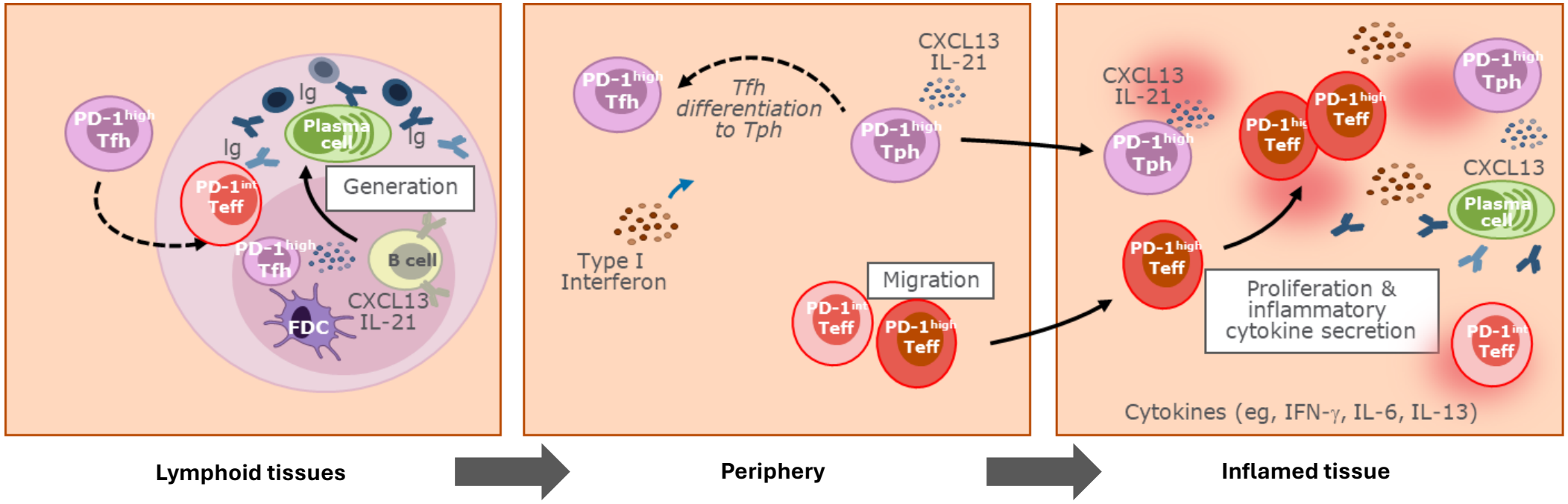
Disclosures: All authors are employees and stockholders of Anaptys

# Dysregulation of Programmed Cell Death Protein (PD-1) Signaling Impacts Critical T Cell Responses in Inflammatory Diseases such as UC

- **PD-1 is a coinhibitory receptor expressed on activated T cells**
  - Functions to downregulate activated T cells by inducing negative signaling when engaged with its ligand PD-L1
  - PD-1 pathway mutations increase human susceptibility to multiple autoimmune diseases; insufficient PD-1 signaling can lead to dysregulated T cell responses

**PD-1 expressed preferentially on activated Teff and Tfh/Tph cells mediating autoimmune pathology**

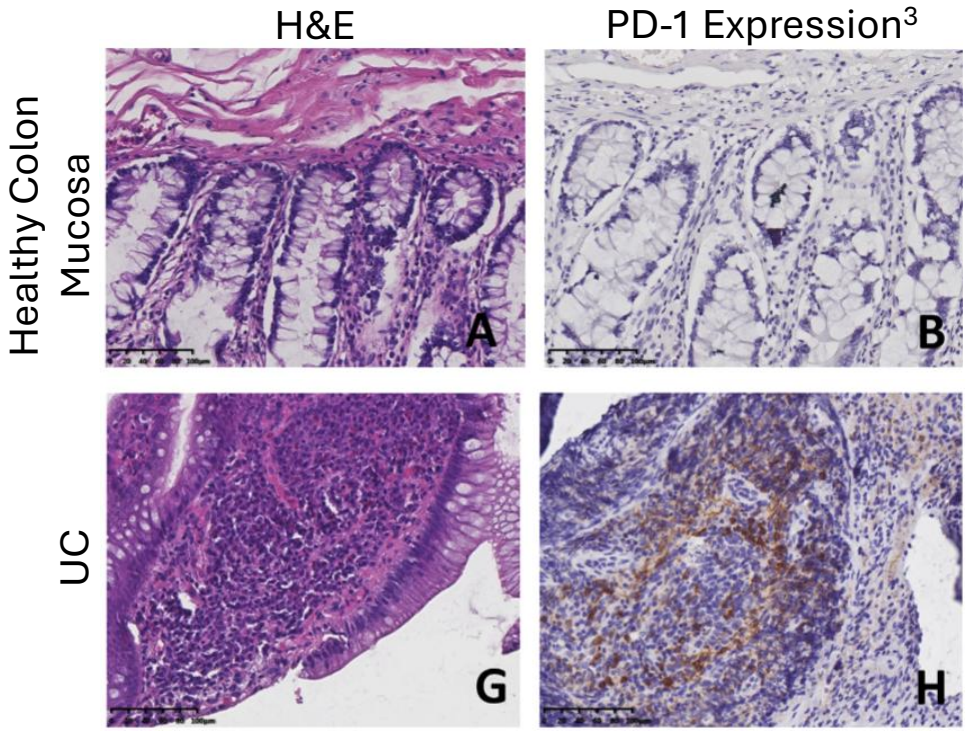



Adapted from Akiyama et al, Ann Rheum Dis, 2023.

# PD-1 and its Role in Ulcerative Colitis

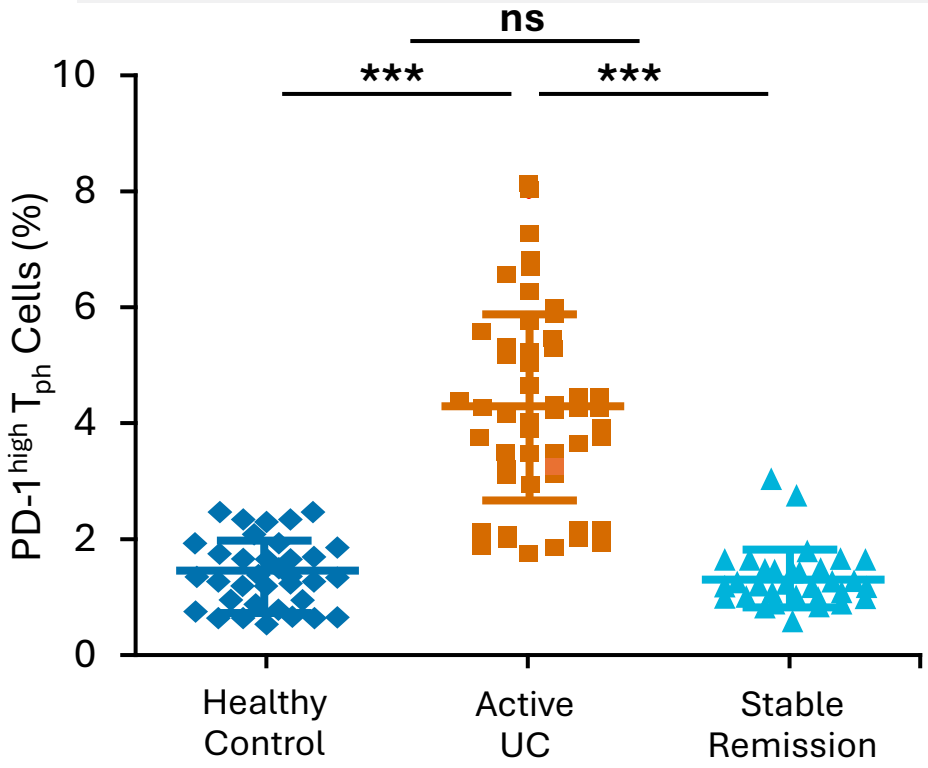
## Elevated levels of PD-1+ inflammatory cells is associated with active UC and lower remission rates

High expressing PD-1+ T cells (PD-1$^{high}$) represent highly inflammatory cells that are elevated and dysregulated in UC[1-3]




Adapted from Shi W, et al. The significance of PD-1/PD-L1 imbalance in ulcerative colitis. PeerJ 2023;11:e15481.

Reduction of elevated PD-1$^{high}$ $T_{ph}$ cells correlates with remission in UC[4]




Reprinted from Immunology Letters, 233; Long Y, Xia C, Sun Y, Ma Y, Xu L, Song Y, Increased circulating PD-1$^{hi}$CXCR5- peripheral helper T cells are associated with disease severity of active ulcerative colitis patients, 2-10, 2021, with permission from Elsevier.

Peripheral helper T cell ($T_{ph}$): support B cell differentiation and maturation

1. Roosenboom B, et al. Scand J Gastroenterol 2021: 56:671-79; 2. Uzzan M, et al. Nature Med 2022;28: 766-779; 3. Shi W, et al. PeerJ 2023:e15481; 4. Long Y, et al. Immunol Letters 2021: 2-10.

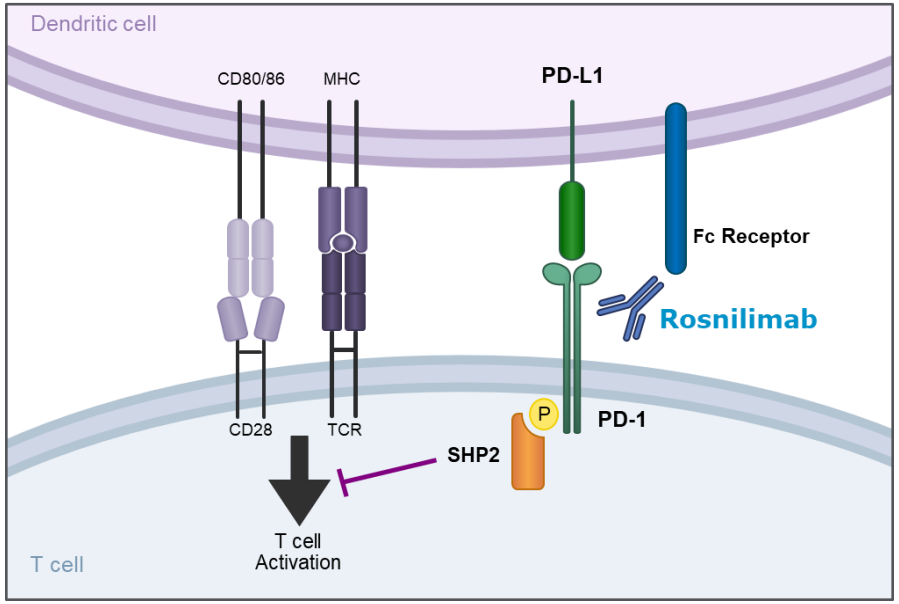
# Proposed Mechanism of Action for Rosnilimab

## Modulation through PD-1 may restore immune homeostasis in numerous autoimmune and inflammatory indications, including UC

### Rosnilimab aims to:

1. Rapidly engage homeostatic mechanisms to induce clinical response
2. Achieve durable remission through histologic normalization

| Immune Cells Impacted | Mechanism | Proposed Immunologic Outcome |
|---|---|---|
| PD-1$^{high}$ $T_{eff}$ | depletes[1] | ↓ T cell proliferation<br>T cell migration<br>Cytokine secretion |
| PD-1$^{high}$ $T_{fh}$/$T_{ph}$ | depletes | ↓ *downstream effect on B cells*<br>Plasma cell generation<br>Autoantibody levels |
| PD-1+ $T_{eff}$ | reduces[2] | ↓ T cell proliferation<br>T cell migration<br>Cytokine secretion |




Antibody attributes contributing to optimal depletion and agonistic function:

- Membrane proximal binding
- FcR engagement

Effector T cells ($T_{eff}$): activated T cells (cytotoxic, helper, Treg); Follicular/Peripheral Helper T cells ($T_{fh}$, $T_{ph}$): support B cell differentiation and maturation

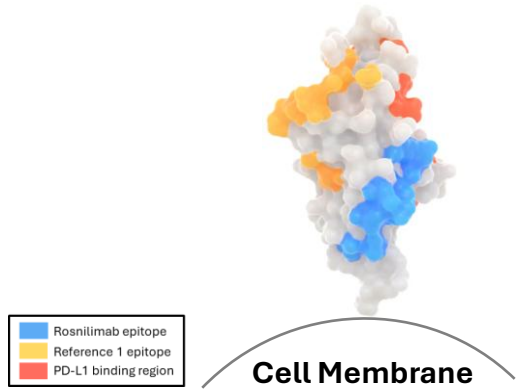
1. Luu K, et al. J Crohn's Colitis;2024:18(suppl 1):i226; 2. Dahl ME, et al. Presented at FOCIS 2022, San Diego, CA, June 21-24, 2022

# Membrane Proximal Binding Rosnilimab Results in Greater Reduction of PD-1+ T Cells, T Cell Proliferation and IFN-γ Secretion In Vitro

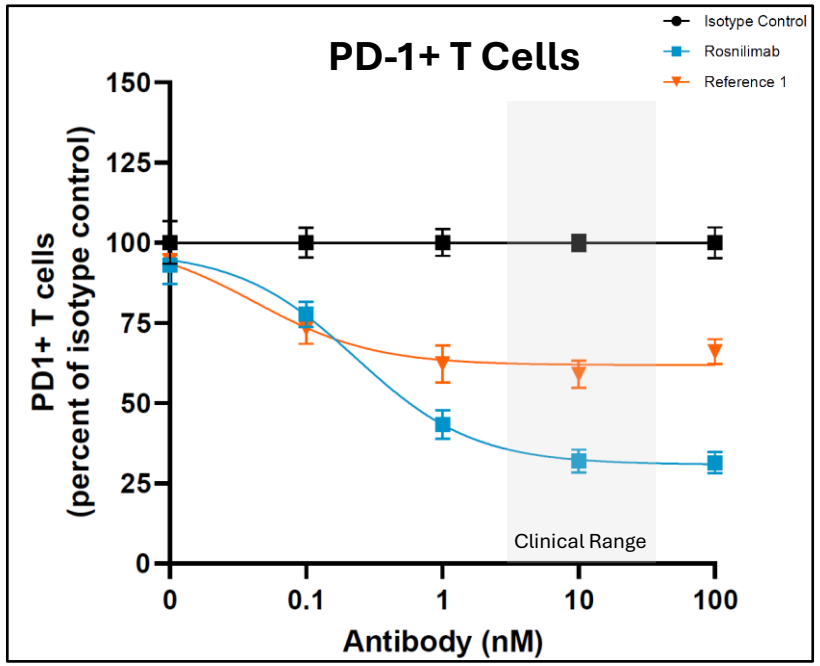
## Rosnilimab Reduced T Cell Proliferation and PD-1+ T Cells

| Test Article | PD-1 Membrane Binding Epitope | T Cell Proliferation* | No. of PD-1+ T Cells* |
|---|---|---|---|
| Reference 1 | Distal | ~20% ↓ | ~40% ↓ |
| Rosnilimab | Proximal | **~75%** ↓ | **~70%** ↓ |

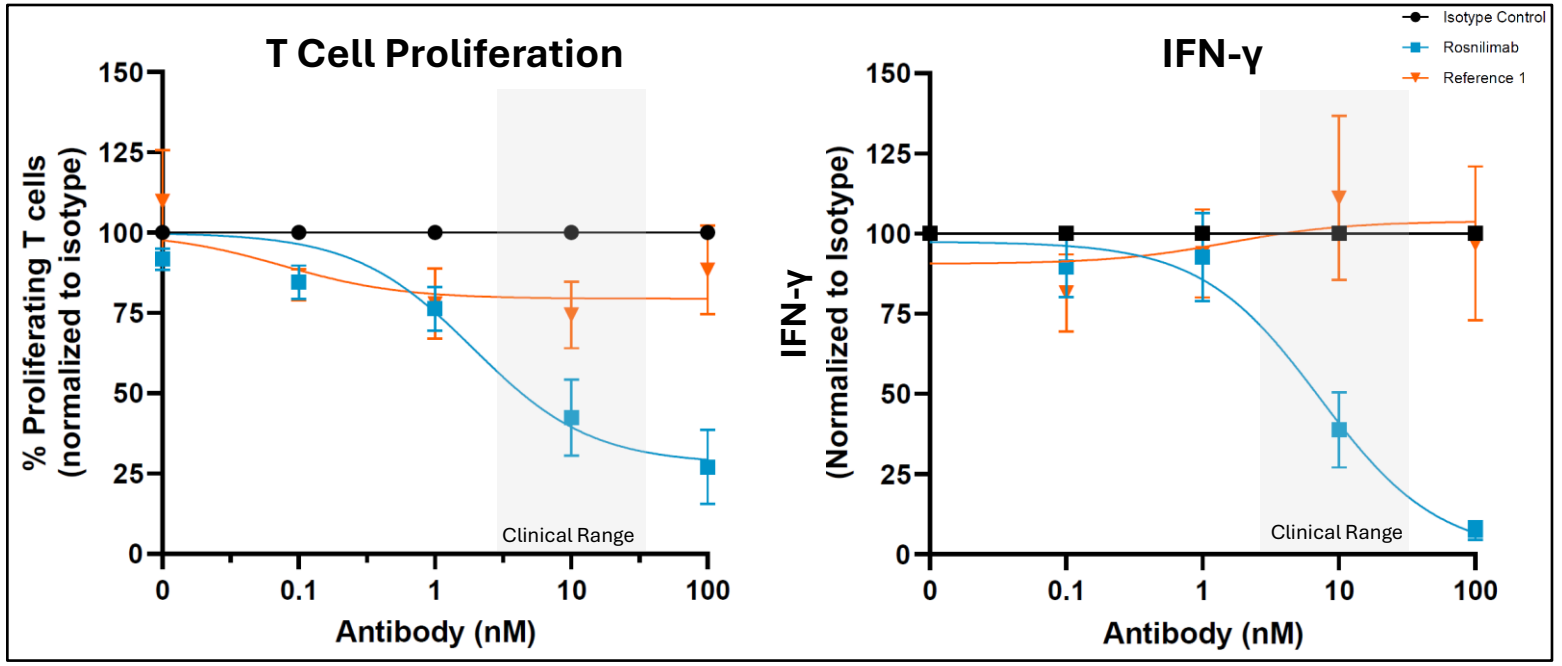
*Compared to isotype control




## Depletion




## Agonism




Parmley, et al. Presented at the ECCO meeting, Stockholm, Feb 21-24, 2024

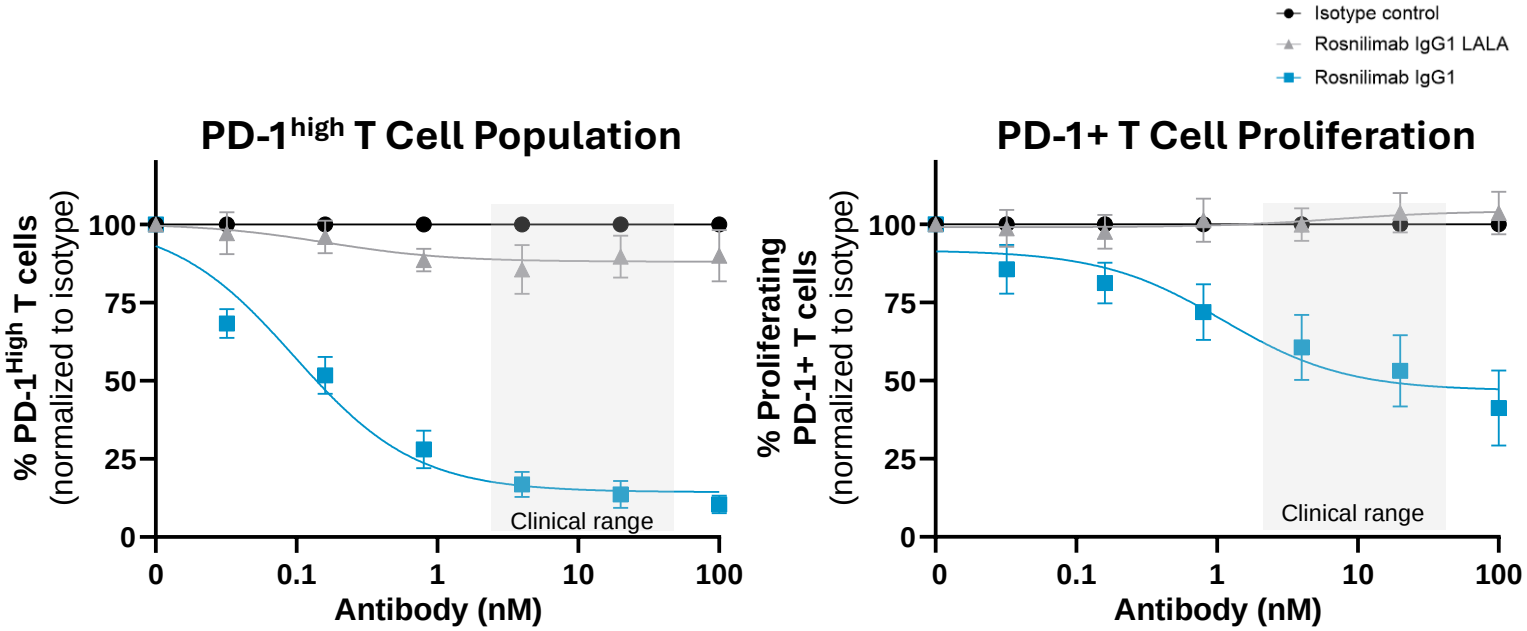
Statistical analysis performed using ordinary two-way ANOVA followed by Dunnett's multiple comparisons test with four comparisons per gene and thresholds for significance relied on multiplicity adjusted P values.

# FcR Engagement via IgG1 Domain of Rosnilimab Results in Reduced PD-1$^{high}$ T cells and Inflammatory Cytokine Secretion in UC Patient-Derived PBMCs

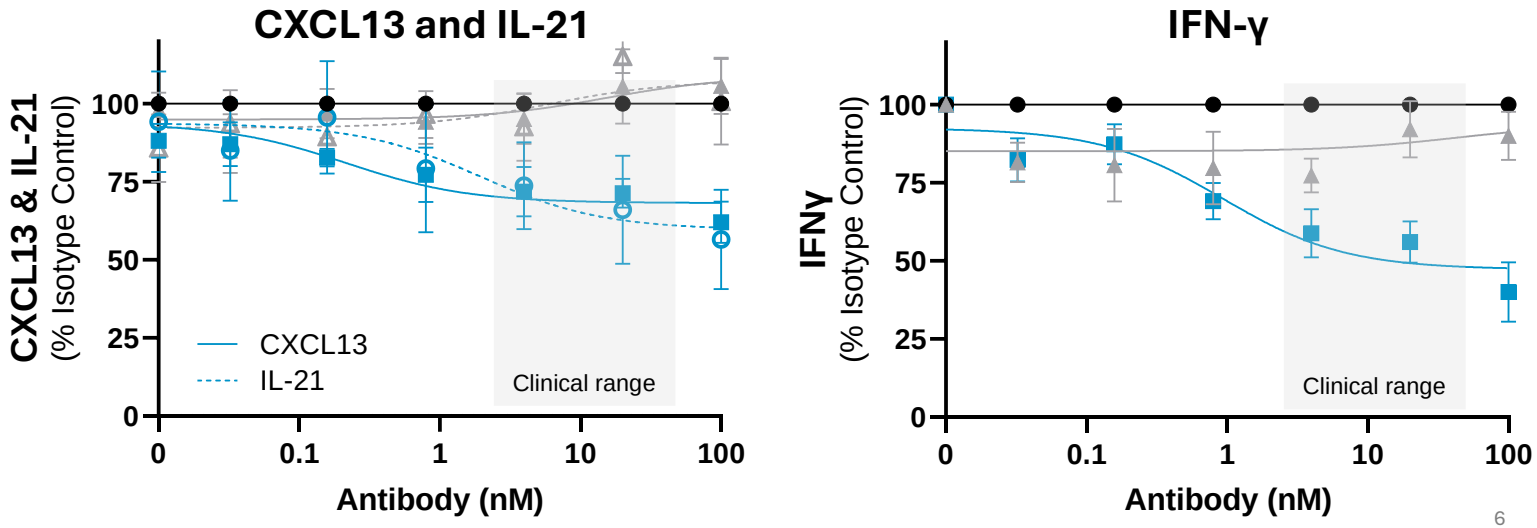
## Rosnilimab IgG1 reduced PD-1$^{high}$ T cells and proliferating PD-1+ T cells

| Test Article | FcR Engagement | No. of PD-1$^{high}$ T Cells* |
|---|---|---|
| Rosnilimab IgG1-LALA | X | ↓ 14% |
| Rosnilimab IgG1 | ✓ | ↓ **90%** |

*Compared to isotype control

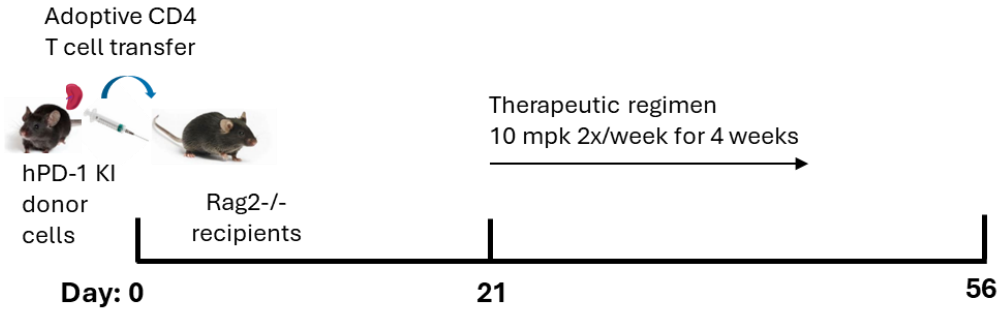



## Rosnilimab IgG1 reduced secretion of inflammatory cytokines



# Therapeutic Dosing of Rosnilimab mIgG2a Demonstrated Efficacy in a Murine Model of Colitis

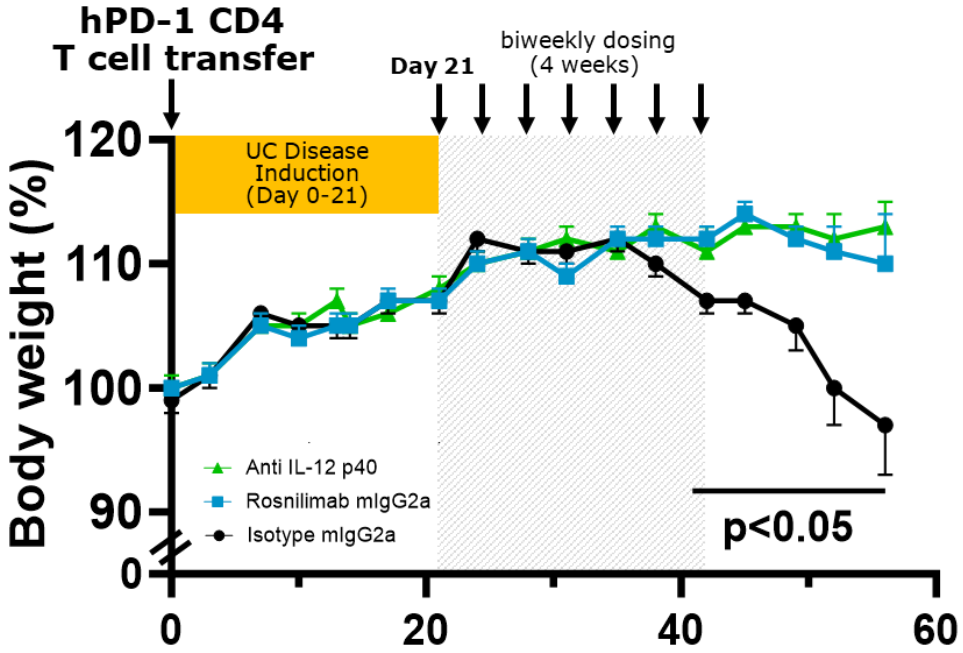
**Study Design for hPD1 CD4+ Transfer Murine Model of Colitis**




Groups
1. Naïve (untransferred)
2. Isotype mIgG2a
3. Rosnilimab mIgG2a
4. Anti IL-12 p40

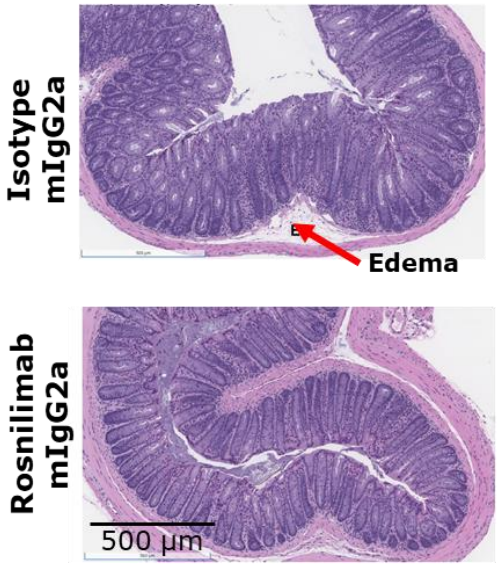
## Rosnilimab mIgG2a maintained body weight

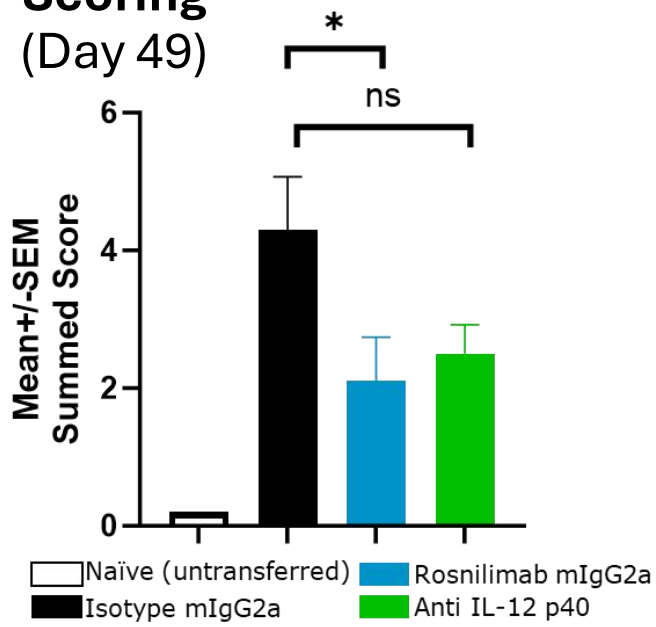
### Colitis Induction and Mouse Body Weight Measurements




## Rosnilimab mIgG2a reduced colonic inflammation

### Distal Colon Histology and Scoring (Day 49)

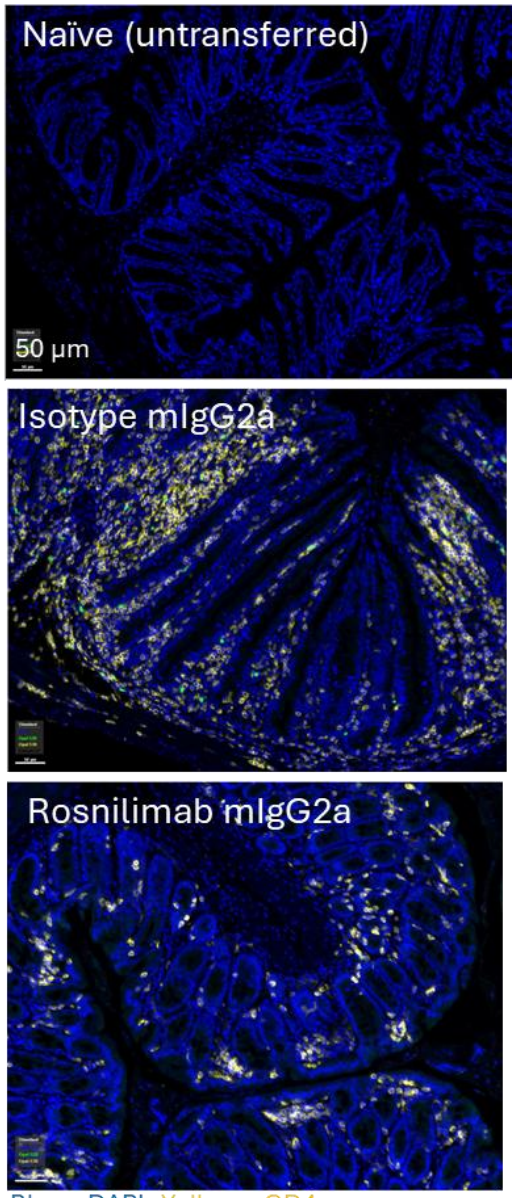


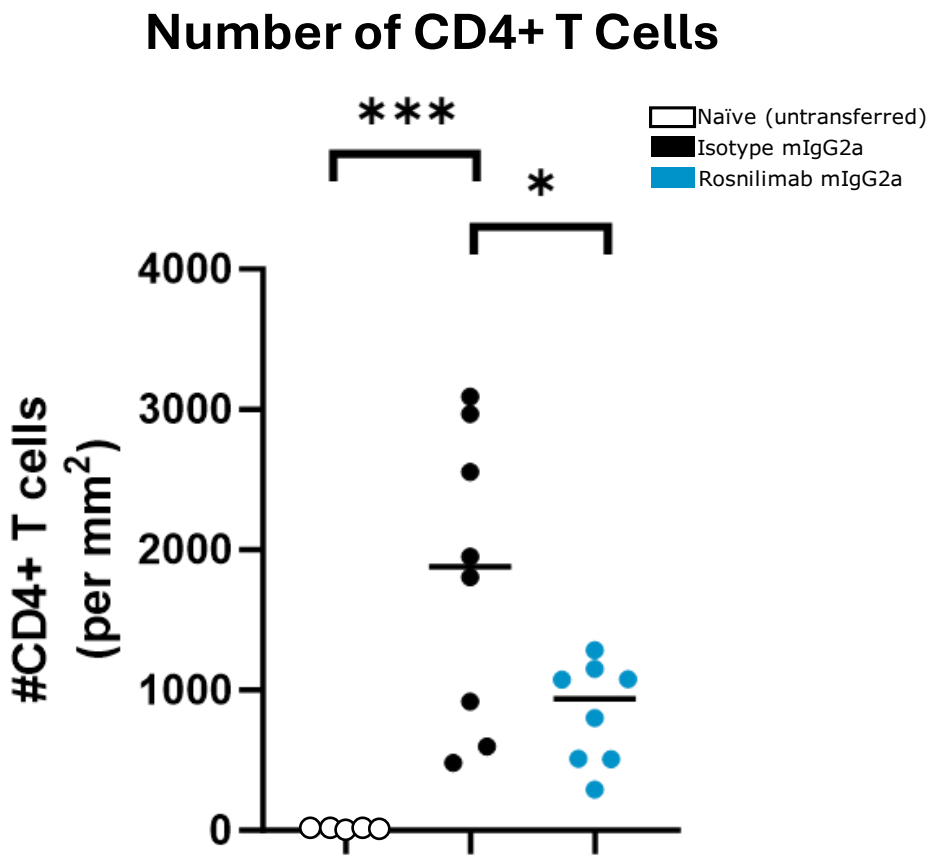



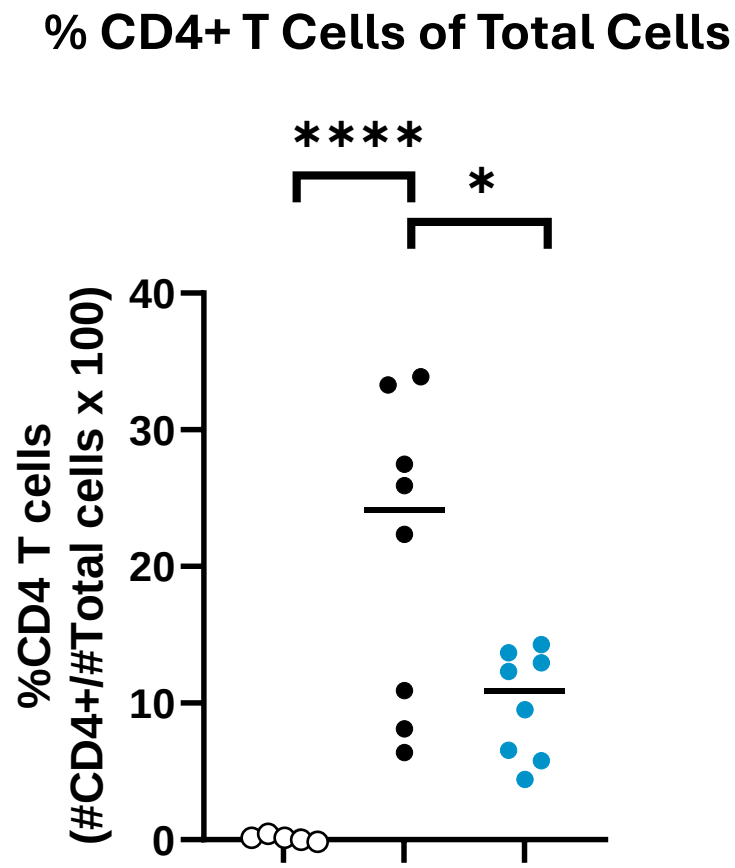

Parmley, et al. Presented at the UEGW meeting, Vienna, Oct 12-15, 2024

*p<0.05 rosnilimab compared to isotype mIgG2a

# Rosnilimab mIgG2a Significantly Reduced CD4+ T Cell Infiltration into the Colon of Mice with Colitis



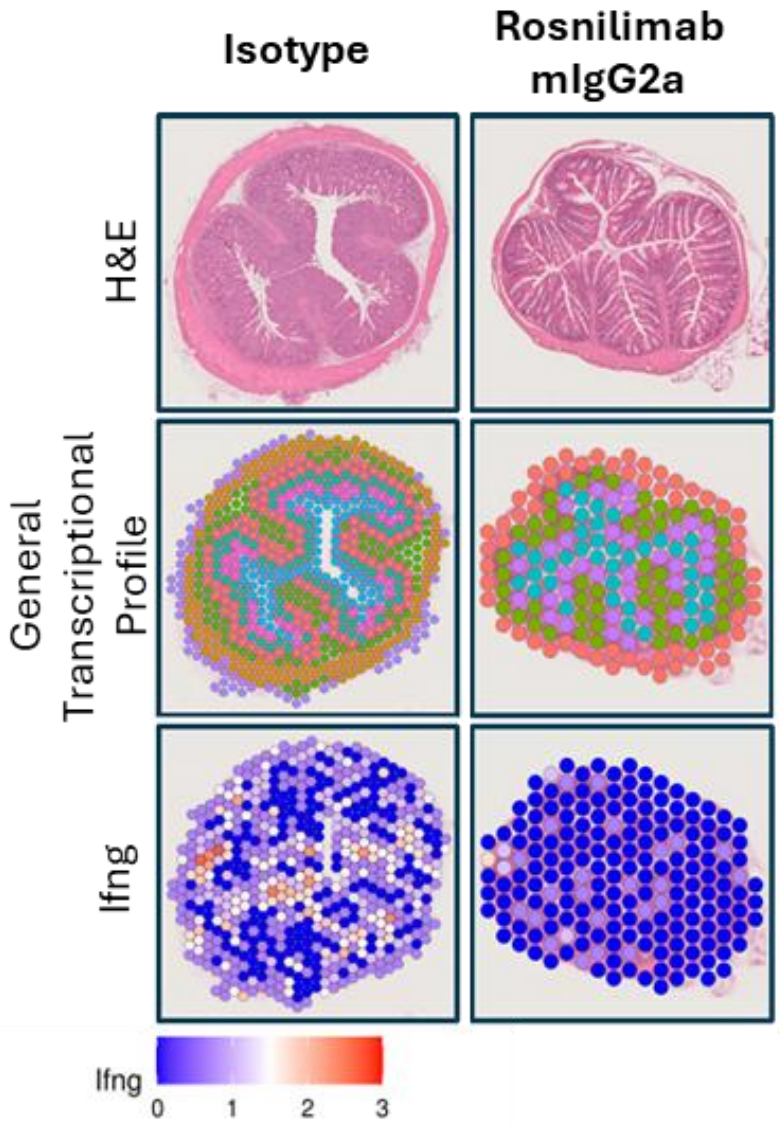



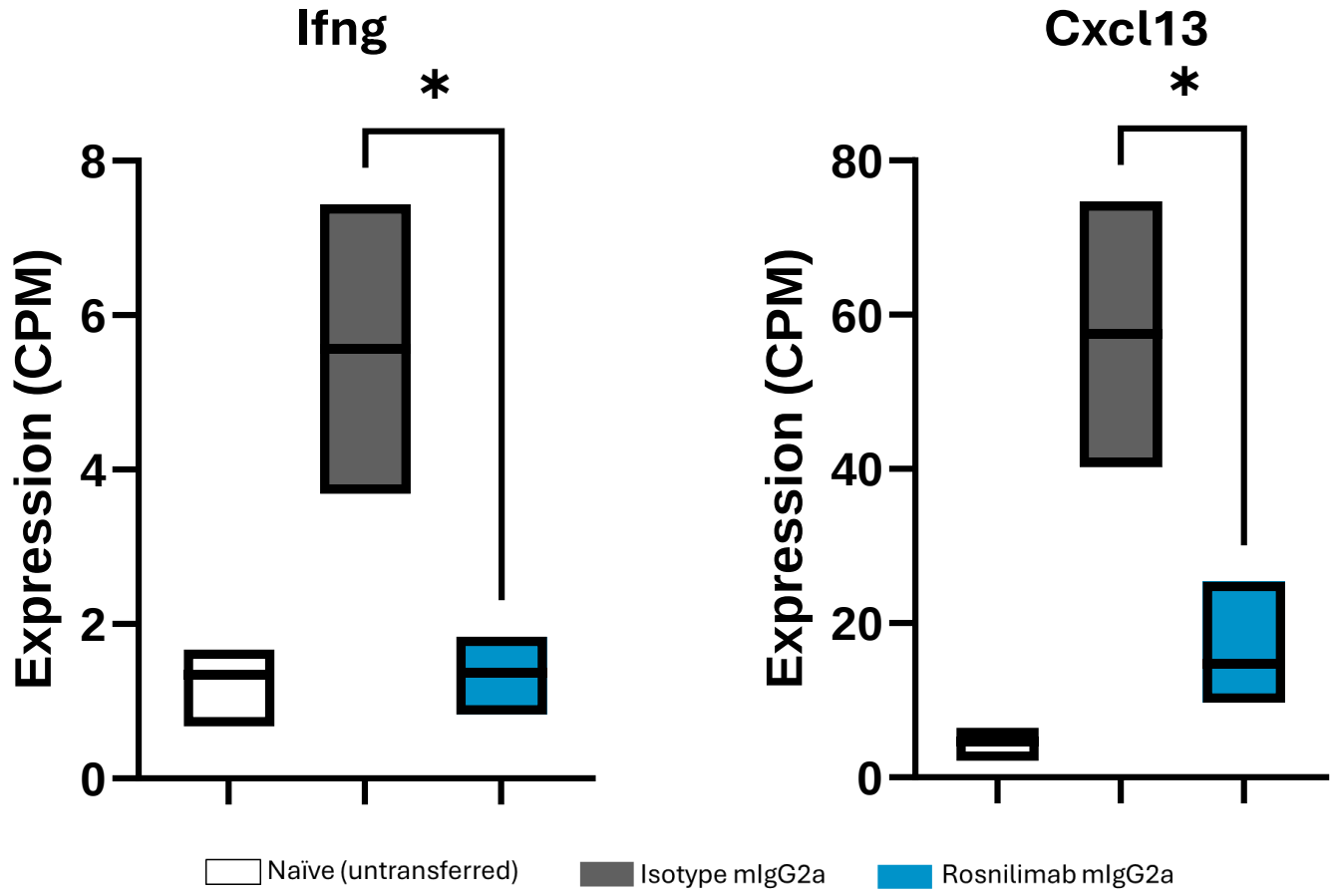




Parmley, et al. Presented at the UEGW meeting, Vienna, Oct 12-15, 2024

*p<0.05 , *** p < 0.001, **** p <0.0001 rosnilimab compared to isotype mIgG2a

# Rosnilimab mIgG2a Significantly Reduced Gene Expression of Inflammatory Cytokines in the Colon of Mice with Colitis



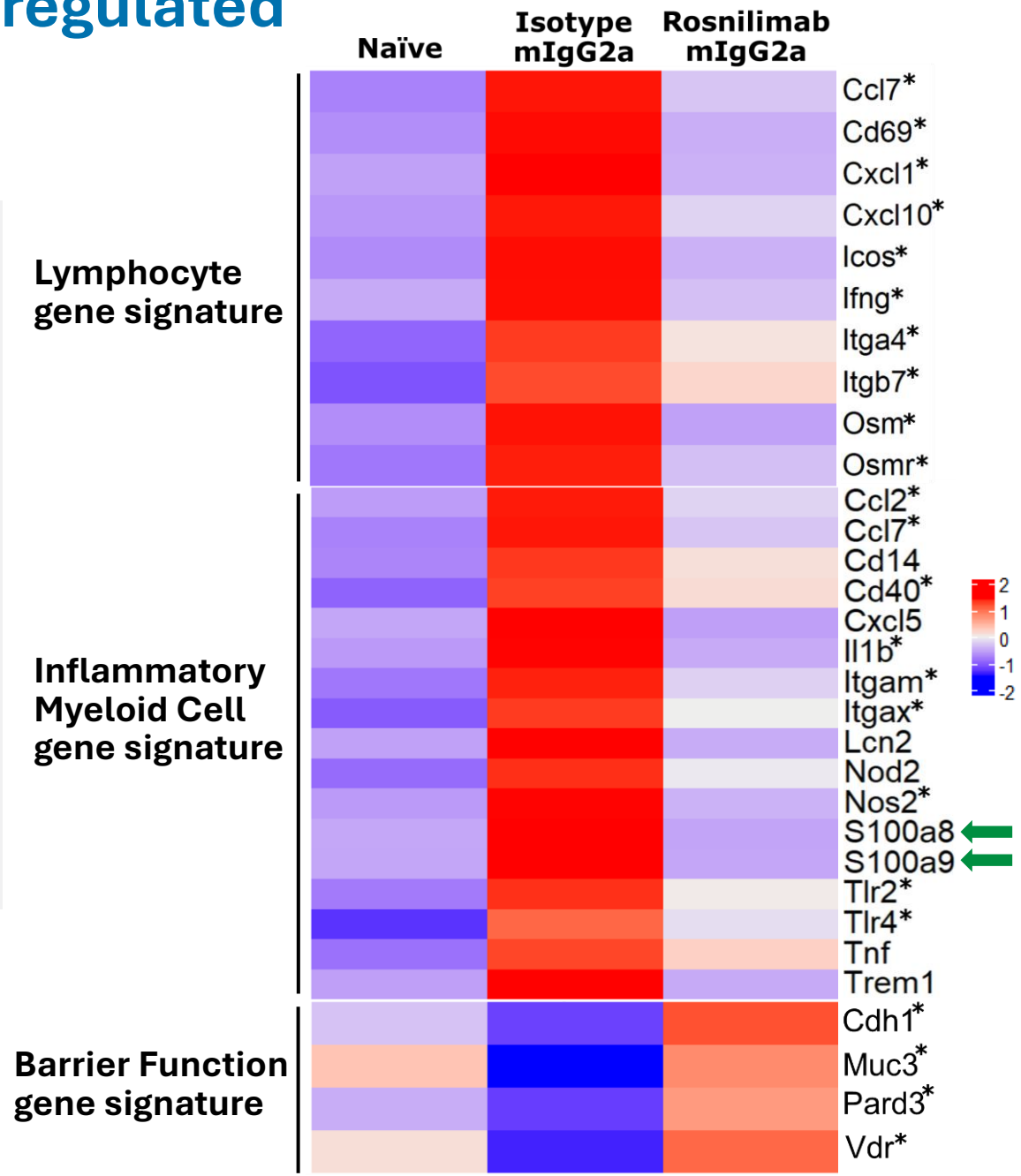

Parmley, et al. Presented at the UEGW meeting, Vienna, Oct 12-15, 2024

*p<0.05 compared to isotype mIgG2a

# Rosnilimab Treatment Normalized Dysregulated Gene Signatures in Mice with Colitis

In the murine model of colitis, treatment with rosnilimab mIgG2a modulated pathway genes relevant in human UC:

- Reduced lymphocyte gene signature
- Reduced inflammatory myeloid cell gene signature, including genes encoding for S100a8 and S100a9 proteins
    - **Calprotectin:**
        - Comprised of both S100a8 and S100a9 protein
        - Established fecal biomarker of inflammation and therapeutic efficacy in IBD
- Improved barrier function gene signature




*p<0.05 rosnilimab compared to isotype mIgG2a

# Conclusion

- Rosnilimab reduced PD-1$^{high}$ T cells and inflammatory cytokine secretion in UC patient-derived PBMCs in vitro
- In a murine model of colitis, at Day 49, rosnilimab mIgG2a:
  - Demonstrated efficacy with a therapeutic dosing regimen
  - Significantly reduced colonic inflammation measured by histology
  - Reduced CD4+ T cell infiltration, IFN-γ, and CXCL13 expression
  - Reduced lymphocyte and inflammatory myeloid cell gene signatures, and improved barrier function gene signature, all pathways that are relevant in human UC
- Positive topline data from a Ph 2b study of rosnilimab in rheumatoid arthritis (NCT06041269) indicate therapeutic potential for rosnilimab in other inflammatory or autoimmune diseases
- These data, combined with results from existing data in humans, support the rationale for evaluating rosnilimab in moderate-to-severe UC in an ongoing Phase 2 study (NCT06127043)

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