Development and Characterization of a Novel Extended Half-life Monoclonal Antibody Drug Candidate Targeting Integrin α4β7 for the Treatment of IBD

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SPYRE THERAPEUTICS

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Background

- **Antagonism of the interaction between the cellular adhesion integrin α4β7 and MAdCAM-1** has proven to be safe and effective in the treatment of Crohn's disease (CD) and ulcerative colitis (UC).
- **Additional benefit** may be gained from an α4β7 antagonist administered via the **subcutaneous (SC) route at extended intervals (e.g., every 8 to 12 weeks)** during maintenance therapy.

Methods and Results

α4β7 blockade is a validated therapeutic mechanism in IBD

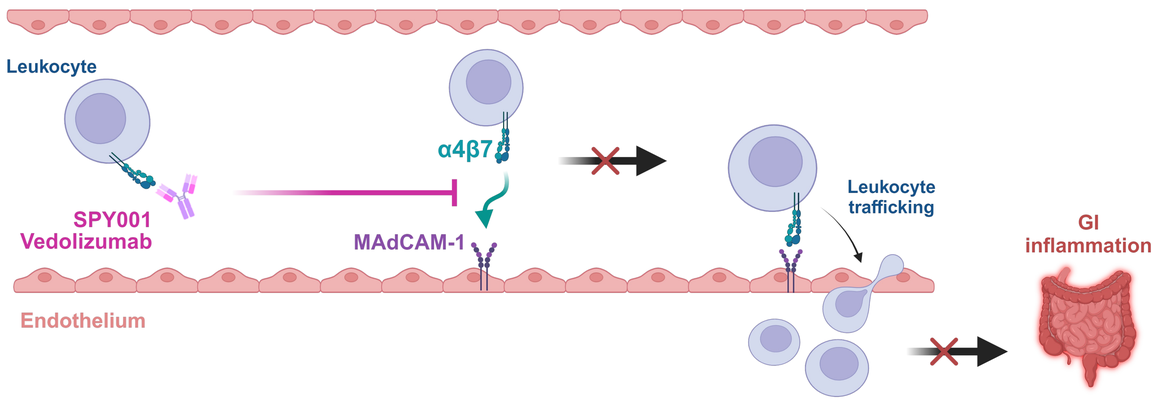

Figure 1: *Binding of SPY001 (or vedolizumab) to α4β7 prevents its association with MAdCAM-1 and is anticipated to inhibit leukocyte trafficking across the endothelium and reduce GI inflammation. Created with BioRender.com.*

SPY001 is a novel antibody that binds to the same epitope as vedolizumab

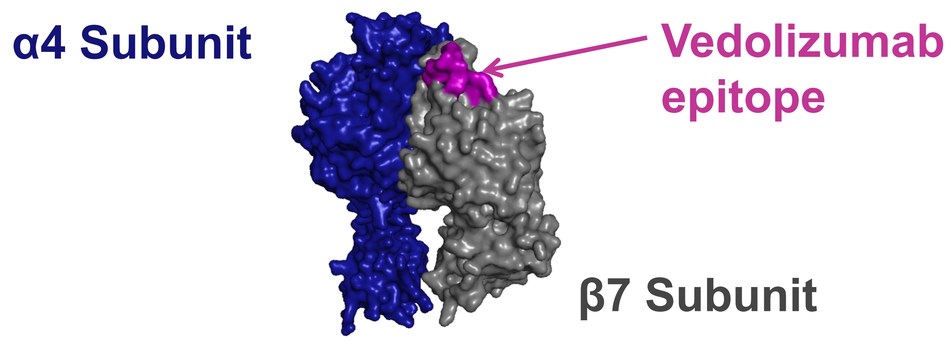

Figure 2*: Predicted binding site for SPY001 and vedolizumab on α4β7.*

SPY001 demonstrates potent and selective binding to α4β7 in vitro

Antibody	K_D		
	α4β7	α4β1	αEβ7
SPY001	<1 nM	NB[1]	NB[1]
Vedolizumab	<1 nM	NB[1]	NB[1]

Table 1*: SPY001 and vedolizumab dissociation constants (K_D) for α4β7 by KinExA and for related integrins by surface plasmon resonance. [1]NB = no binding.*

SPY001 is a potent & selective inhibitor of α4β7-mediated cellular adhesion

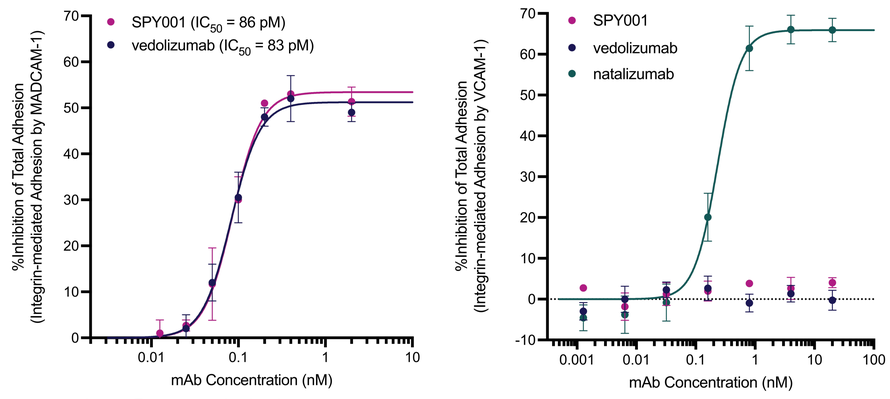

Figure 3*: SPY001 and vedolizumab both inhibit α4β7-mediated cellular adhesion to MAdCAM-1 (left); neither SPY001 nor vedolizumab inhibit α4β1-mediated cellular adhesion via VCAM-1 (right).*

SPY001 binds to α4β7-expressing peripheral blood mononuclear cells

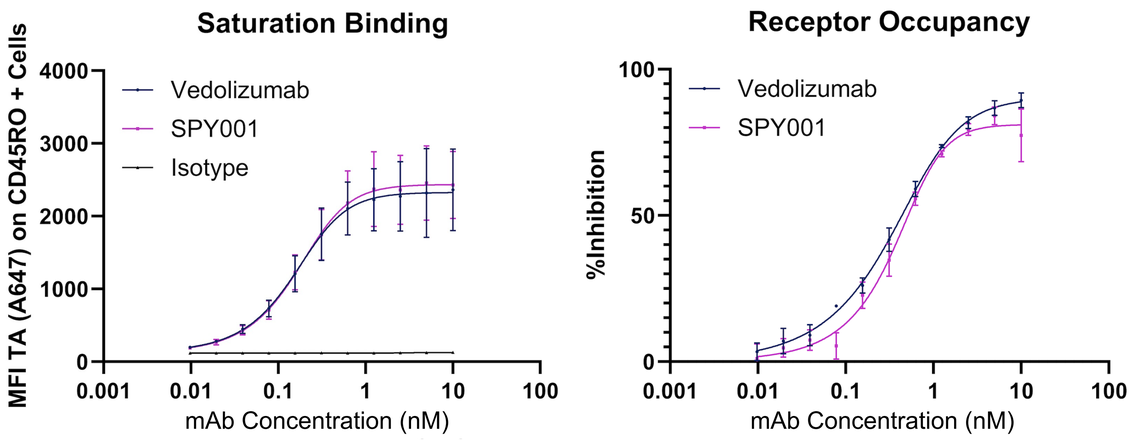

Figure 4*: Labeled (AlexaFluor-647) SPY001 binds to α4β7-expressing cells isolated from PBMCs (left); competing off AF647-SPY001 with unlabeled SPY001 demonstrates receptor occupancy (right). N=3 donors.*

SPY001 is engineered to include a YTE modification in the Fc region for extended half-life ***(See P765)***

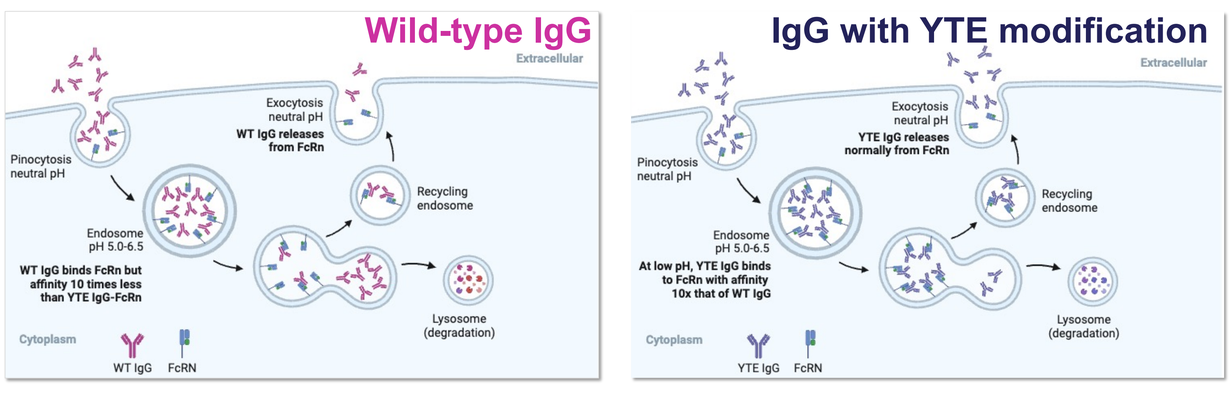

Figure 5*: YTE modification extends half-life by increasing IgG binding affinity to FcRn at low pH, increasing antibody recycling and reducing lysosomal degradation (1). Adapted from "extracellular vesicles" by BioRender.com (2023).*

Conclusions

- SPY001 is a novel humanized monoclonal IgG1 demonstrating **high affinity for α4β7 and potent, selective inhibition of the α4β7/MAdCAM-1 interaction**.
- SPY001 **offers the potential for effective and safe treatment of CD and UC** as a monotherapy or **combination backbone**, with the advantage of **infrequent SC dosing**. First-in-human studies are planned for 2024.

Citations

1. Dall'Acqua, W. F., Kiener, P. A. & Wu, H. Properties of Human IgG1s Engineered for Enhanced Binding to the Neonatal Fc Receptor (FcRn). J. Biol. Chem. 281, 23514–23524 (2006).

Disclosures

EZ, DR, RV, HS, and JO are employees of Paragon Therapeutics. JF, DN, and AS are employees of Spyre Therapeutics. All authors own equity in Paragon Therapeutics and/or Spyre Therapeutics.