

# Characterization of Two Novel Extended Half-life Monoclonal Antibody Drug Candidates Targeting TL1A for the Treatment of IBD

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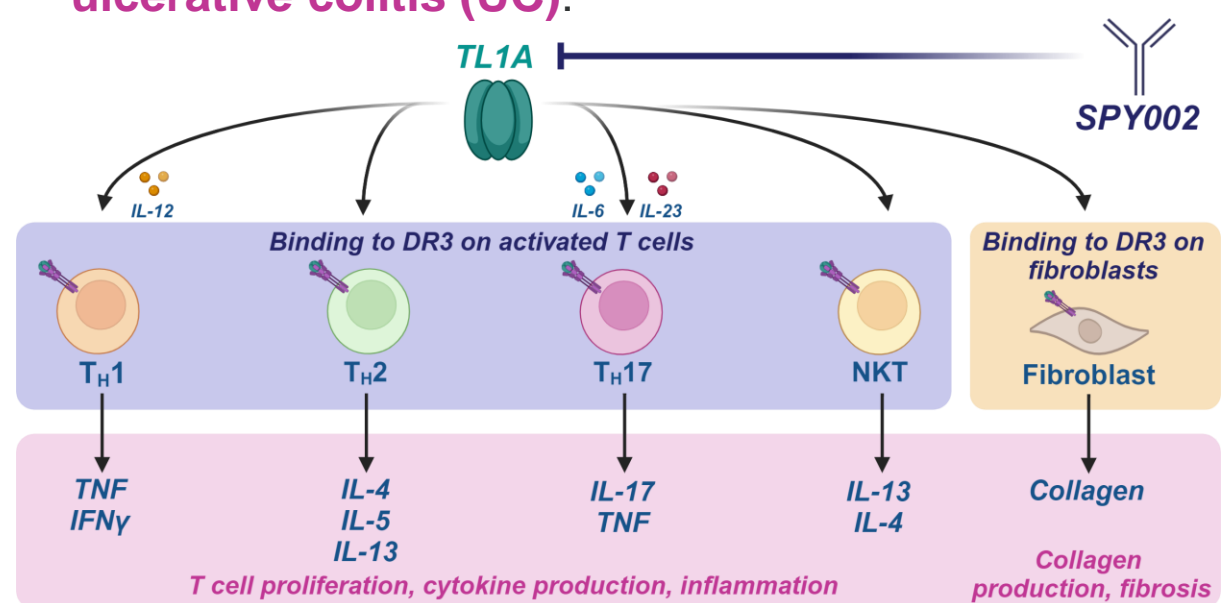


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## Background

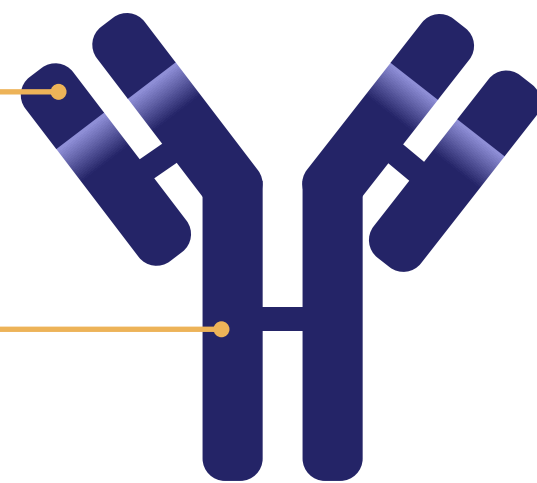
- Blocking the interaction of TL1A with its cognate receptor DR3 has been shown to ameliorate disease activity in patients with Crohn's disease (CD) and ulcerative colitis (UC).



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## About SPY002-DC1 and SPY002-DC2

- Fully human mAbs with novel epitopes targeting TL1A monomers and trimers
- Half-life extension through validated Fc modification to enable Q8W-Q12W SC dosing
- IND-enabling tox studies completed with NOAEL at the highest dose tested (300 mg/kg)



Phase 1 expected to start in Q4 2024

## Methods and Results

SPY002-DC1 and SPY002-DC2 bind to novel epitopes, both on a single TL1A subunit

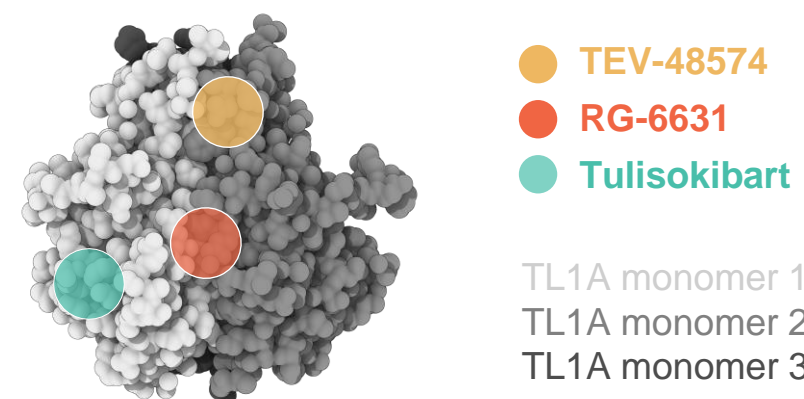


Figure 1: Epitopes for TL1A antibodies were resolved by CryoEM; illustrative locations are overlaid with the crystal structure of trimeric TL1A (PDB: 2O00).

SPY002 DCs include a YTE modification in the Fc region for extended half-life

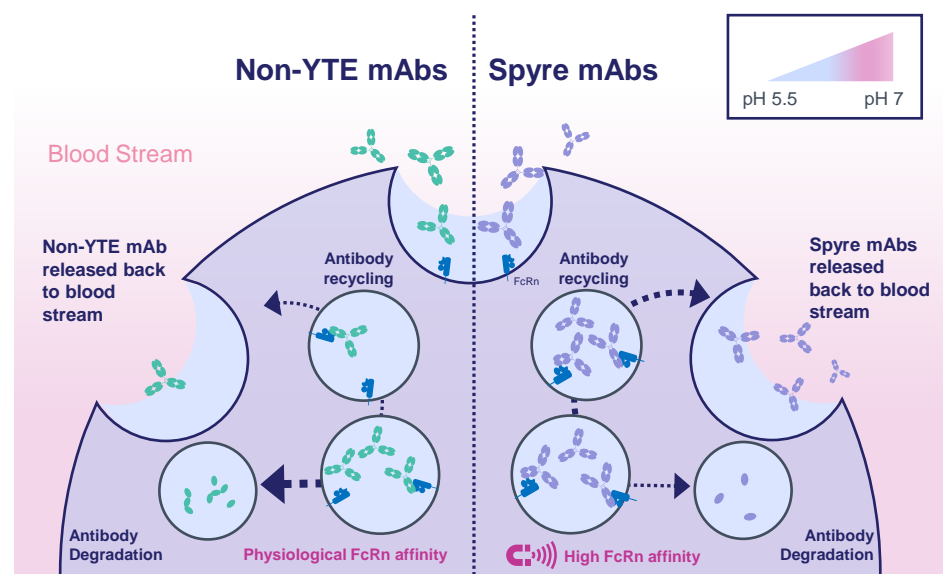


Figure 3: YTE modification extends half-life by increasing IgG binding affinity to FcRn at low pH, increasing antibody recycling and reducing lysosomal degradation.

SPY002 drug candidates have superior or comparable in vitro potency as first-generation TL1A inhibitors

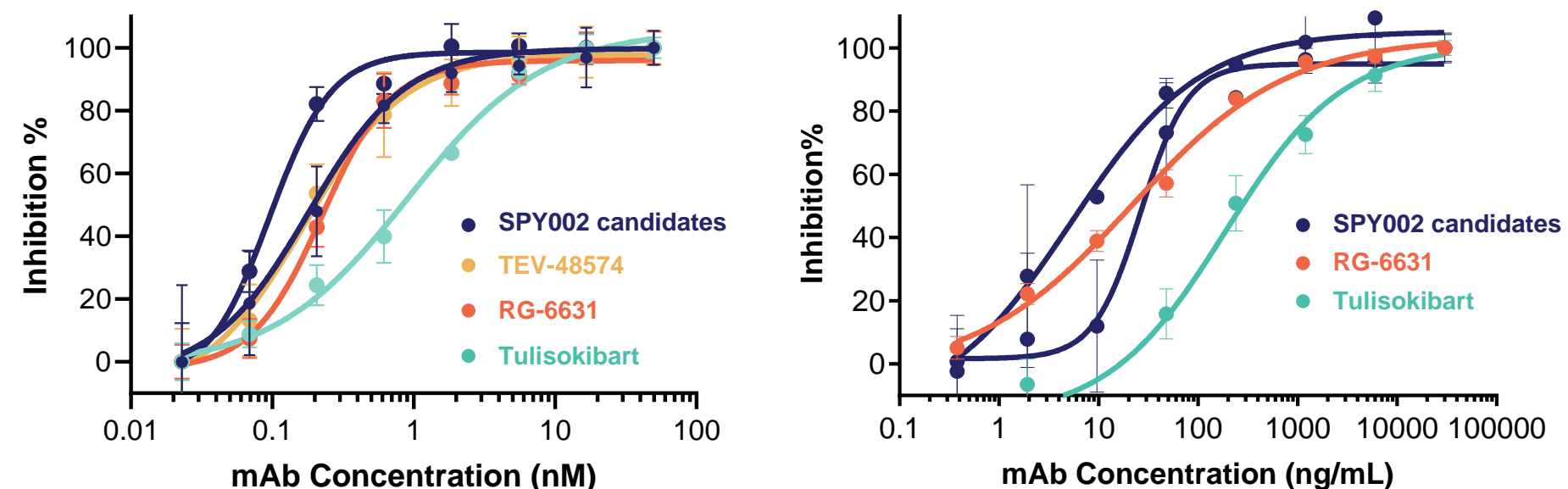


Figure 2: SPY002-DC1 and -DC2 potentially inhibit the induction of apoptosis in human TF-1 cells treated with TL1A and cycloheximide (left). SPY002-DC1 and -DC2 potentially inhibit IFNγ secretion in human whole blood treated with TL1A, IL-12, and IL-18 (right).

SPY002 drug candidates both exhibit increased half-life in non-human primates compared to first-generation anti-TL1As

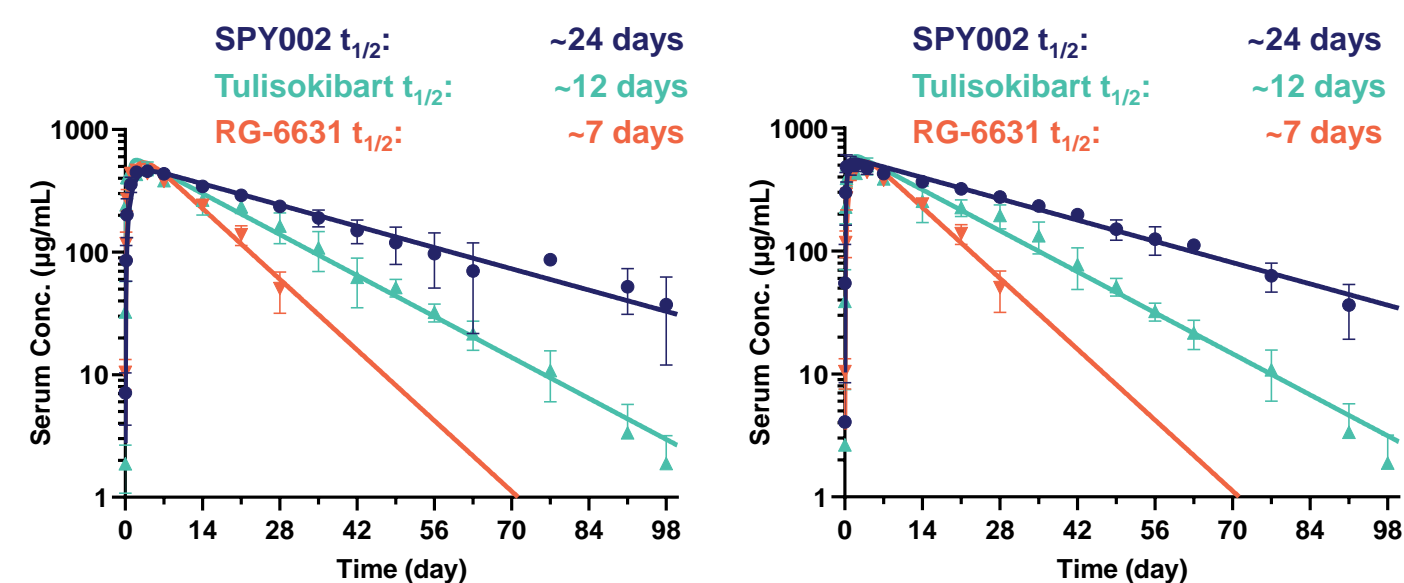


Figure 4: Measurement of SPY002-DC1 (left), -DC2 (right), tulisokibart, or RG-6631 half-life in cynomolgus monkeys following a single 50 mg/kg dose. N = 5 for SPY002-DC1, -DC2 at final timepoints; no RG-6631 was detectable after day 28.

The projected SPY002 human half-life supports Q8 to Q12W SC maintenance dosing

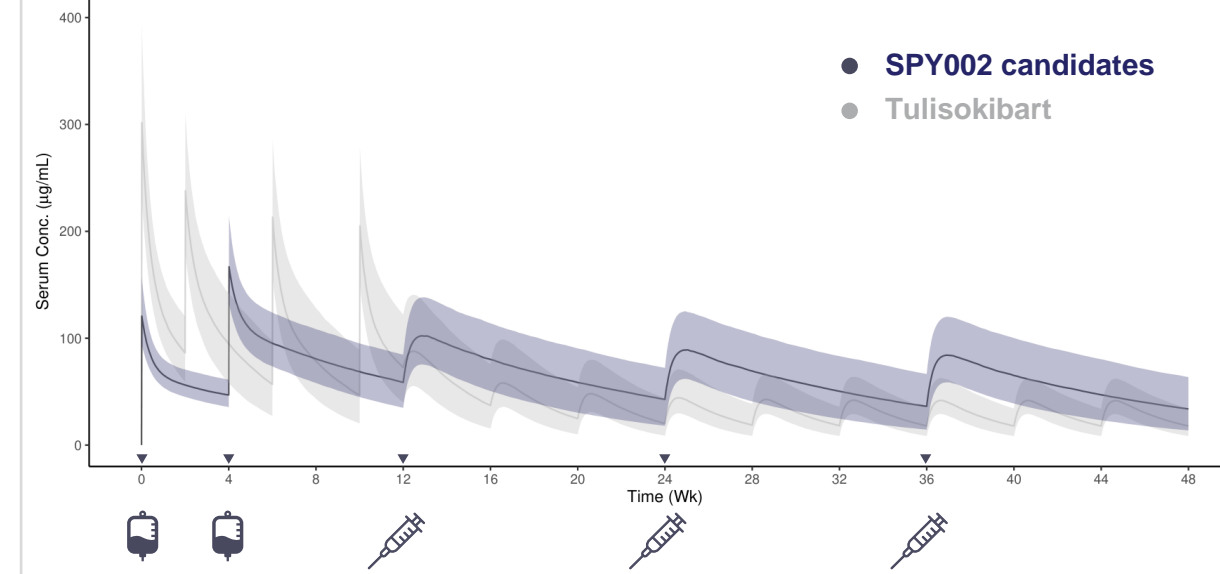


Figure 5: Simulated PK profiles of SPY002 (IV at W0, W4; SC dose at W12 and Q12W) and tulisokibart (IV 1000 mg W0, 500 mg W2, 6, 10; SC 250 mg Q4W). Based on average  $t_{1/2}$  extension of ~3x with YTE and published tulisokibart  $t_{1/2}$  of 19 days. Solid line: simulated median; Shaded area: IQR; Stochastic simulations: n=2,000 virtual subjects.

## Conclusions

- SPY002-DC1 and SPY002-DC2 exhibit high selectivity and affinity for TL1A and potentially inhibit downstream cellular signaling.
- SPY002 offers the potential for effective and safe treatment of CD and UC as a monotherapy or combination backbone, with the advantage of infrequent SC maintenance dosing.

## References

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## Disclosures

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

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