Development and Characterization of SPY002, a Novel Extended Half-life Monoclonal Antibody Drug Candidate Targeting TL1A for the Treatment of IBD

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SPYRE THERAPEUTICS

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Background

- Blockade of the interaction of TL1A with its cognate receptor DR3 has been shown to **ameliorate disease activity in patients with CD and UC**.
- SPY002-091 is a novel, **extended half-life**, fully human IgG1 mAb that binds TL1A with **high affinity and specificity** and potently inhibits TL1A-mediated signaling.

Methods and Results

TL1A blockade is a clinically validated therapeutic mechanism in IBD

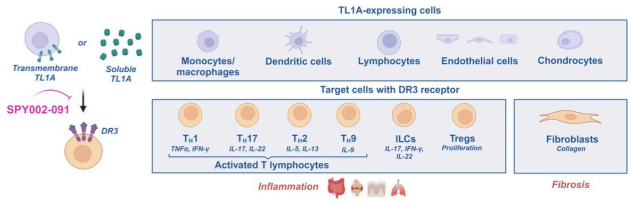
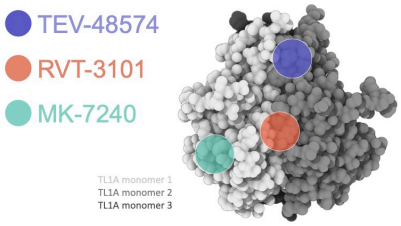


Figure 1: *Binding of SPY002-091 to TL1A prevents its association with DR3, thereby reducing production of inflammatory cytokines and chemokines by DR3-expressing cells. Created with BioRender.com.*

SPY002-091 binds a novel epitope on a single TL1A subunit, with some RVT-3101 & TEV-48574 overlap



SPY002-091

- Potency of 150 pM
- Binds single TL1A subunit
- Epitope overlaps the **DR3 binding interface**, resulting in potent functional blockade of signaling

Figure 2*: Epitopes for TL1A antibodies were resolved by CryoEM; illustrative locations are overlayed with the crystal structure of trimeric TL1A (PDB: 2O0O).*

SPY002-091 demonstrates potent and selective binding to human TL1A in vitro

Antibody	TL1A	FasL	TRAIL	LIGHT
SPY002-091	0.15 nM	NB[2]	NB[2]	NB[2]
MK-7240[1]	0.71 nM	NB[2]	NB[2]	NB[2]
RVT-3101	0.57 nM	NB[2]	NB[2]	NB[2]
TEV-48574	0.44 nM	NB[2]	NB[2]	NB[2]

Table 1: *SPY002-091 and other clinical anti-TL1A mAb dissociation constants (K_D) for TL1A and related superfamily proteins as determined by surface plasmon resonance. [1]Formerly PRA023; [2]NB = no binding.*

SPY002-091 binds to membrane TL1A

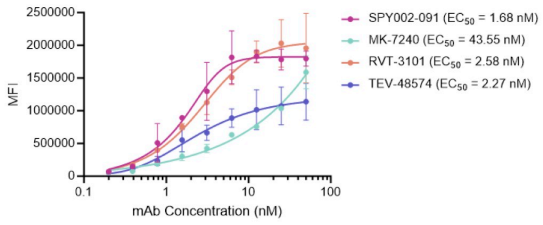


Figure 3*: Antibody binding to CHO cells expressing membrane TL1A as determined by FACS. No binding was observed to WT CHO cells (data not shown). MFI, mean fluorescence intensity.*

SPY002-091 inhibits TL1A-induced apoptosis and IFNγ secretion with comparable or lower IC_{50} values vs. other clinical stage anti-TL1A mAbs

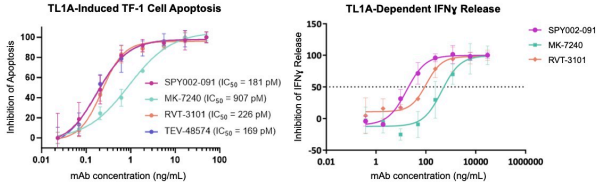


Figure 4*: Inhibition of TL1A-induced TF-1 cell apoptosis (left) and IFNγ secretion in primary human whole blood. One of 4 donors shown (right).*

SPY002-091 has an extended half-life in both NHPs and mice compared to clinical stage anti-TL1A mAbs

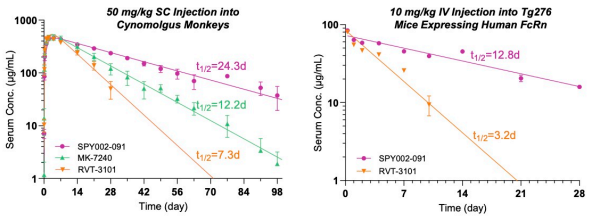


Figure 5*: Serum concentration of SPY002-091 after one SC dose in cynomolgus monkeys (left) or an IV bolus dose in Tg276 transgenic mice expressing human FcRn (right).*

Conclusions

- SPY002-091 exhibits **high selectivity and affinity for TL1A**, demonstrates **effective blockade** of the TL1A interaction with DR3, and potently **inhibits downstream cellular signaling**.
- With an **extended half-life in NHPs**, SPY002-091 demonstrates the potential for effective and safe treatment of CD and UC as a monotherapy or **combination backbone**, with the advantage of **infrequent SC dosing (Q8-12W)**. First-in-human studies are planned for 2024.

Disclosures

EZ, DR, RV, HS, JM, JM, 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.