Discovery and Characterization of a Novel High-Affinity Anti-TL1A Monoclonal Antibody With Extended Half-Life for the Treatment of Inflammatory Bowel Disease

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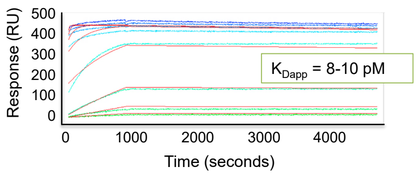
Introduction

- Tumor necrosis factor (TNF)-like ligand 1A (TL1A) mediates a broad spectrum of pro-inflammatory and fibrotic effects and is genetically linked to multiple immunologic disorders.
- In clinical trials, antagonist antibodies that interfere with the interaction between TL1A and death receptor 3 (DR3) reduce disease activity in ulcerative colitis (UC) and Crohn's disease (CD).
- Here, we provide data on XmAb®942, a novel human IgG1 effector-less anti-TL1A monoclonal antibody (mAb) that incorporates the Xtend™ half-life extension technology.
- This antibody binds soluble and cell surface-expressed TL1A with high affinity and selectivity, and potently inhibits TL1A-mediated signaling, including apoptosis, NFκB induction, and IFNγ release.

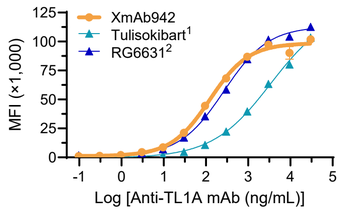
XmAb942 Binds Soluble and Membrane-Bound Trimeric TL1A

Binding to Soluble TL1A



Binding of an XmAb942 analog to increasing concentrations of recombinant human TL1A trimer (up to 100 nM) was assessed at 37°C via surface plasmon resonance.

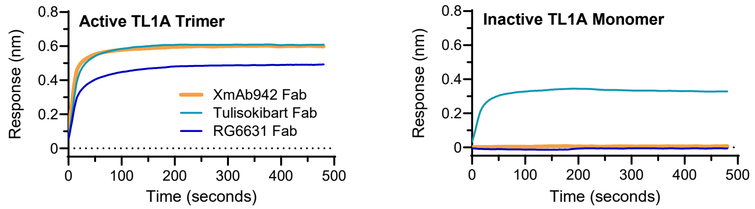
Binding to Membrane-Bound TL1A



CHO cells transiently transfected with TL1A were incubated with anti-TL1A mAbs for 1 hour at 4°C and analyzed by flow cytometry. Data are means ± SD (n = 3).

	XmAb942	Tulisokibart[1]	RG6631[2]
Soluble TL1A K_{Dapp} (pM)	10	57	14
Membrane-Bound TL1A EC_{50} (nM)	1.1	12.8	1.8

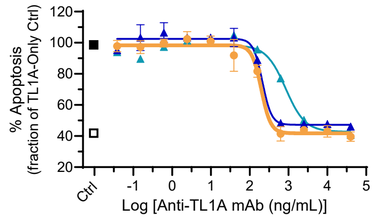
Binding to Trimeric TL1A



Binding of anti-TL1A Fabs (200 nM) to immobilized TL1A monomer or trimer was measured at 25°C via biolayer interferometry.

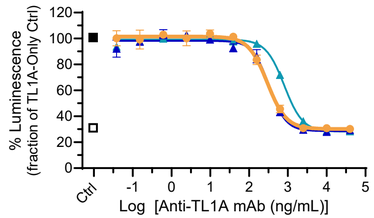
XmAb942 Inhibits TL1A-Mediated Signaling With Comparable or Superior Potency to First-Generation Anti-TL1As

Inhibition of TL1A-Induced Apoptosis



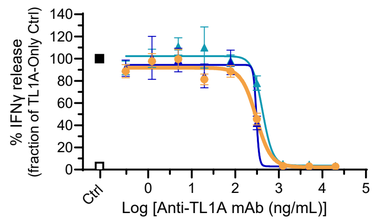
Cycloheximide-treated TF-1 cells were incubated with anti-TL1A mAbs and 0.2 µg/mL of TL1A, then caspase 3/7 activity was assessed after 6 hours. Data are means ± SEM (n = 2, except n = 1 for tulisokibart).

Inhibition of TL1A-Induced NFκB Signaling



A Jurkat reporter cell line was incubated with anti-TL1A mAbs and 0.4 µg/mL of TL1A, then luciferase activity (reflecting the induction of NFκB) was measured after 5 hours. Data are means ± SEM (n = 2, except n = 1 for tulisokibart).

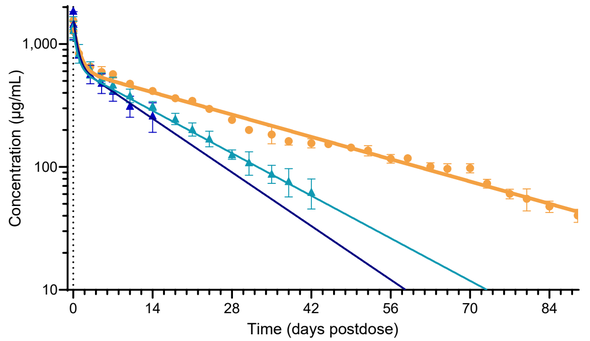
Inhibition of TL1A-Induced IFNγ Release



IL12- and IL18-stimulated CD4+ T cells from 8 PBMC donors were treated with anti-TL1A mAbs and 0.2 µg/mL of TL1A, then IFNγ release was measured after 24 hours. Data are means ± SEM.

XmAb942 Tulisokibart RG6631
TL1A-Only Ctrl No mAb, No TL1A Ctrl

XmAb942 Demonstrates Increased Half-Life in Monkeys Compared With First-Generation Anti-TL1As



- XmAb942 was well-tolerated at all doses in a GLP study in cynomolgus monkeys.

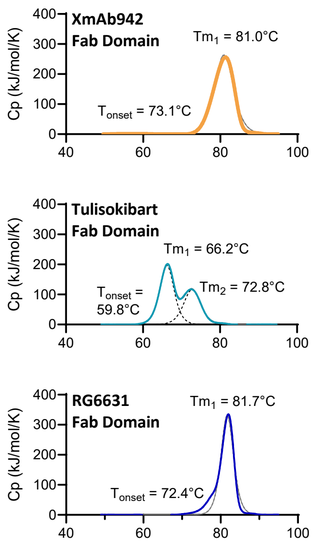
	$t_{1/2}$ (days)	
	NCA	2CA
XmAb942	23.0	23.2
Tulisokibart	12.3	12.2
RG6631	10.5	9.6

2CA, two-compartment analysis; NCA, noncompartmental analysis; $t_{1/2}$, half-life.

Allometric scaling adjusted for half-life engineered antibodies predicts that XmAb942 will have $t_{1/2} \geq 70$ days in humans,[3] potentially enabling dosing intervals every 8 weeks or longer.

Cynomolgus monkeys received a single intravenous (IV) injection of the indicated anti-TL1A mAbs. Concentration vs time data were analyzed by NCA and 2CA. Data are means ± SEM; n = 3 monkeys/group. The vertical dashed line denotes the day of dosing.

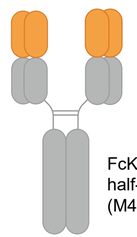
XmAb942 Is Highly Thermostable



Anti-TL1A mAbs (1 mg/mL) were evaluated using differential scanning calorimetry from 25°C to 95°C at a ramp rate of 1°C/minute.

Summary

XmAb942 is a promising anti-TL1A mAb clinical candidate that incorporates the clinically validated Xtend half-life extending mutations. Thus, XmAb942 has the potential to reduce UC/CD disease activity with more convenient dosing.



- ✓ Proprietary half-life extension provides a predicted **$t_{1/2}$ of ≥ 70 days in humans**[3]
- ✓ Modeling supports convenient, less frequent (**Q8-12W**) dosing
- ✓ High concentration formulation with low viscosity (< 10 cP) for subcutaneous administration
- ✓ Predicted **low immunogenicity**

- XmAb942 binds trimeric TL1A with high affinity and specificity, but not the related TNF ligand superfamily members LIGHT, TRAIL and FasL.
  - Binds soluble TL1A with apparent K_D < 20 pM at 37°C
  - Binds TL1A over-expressed on the cell membrane with EC_{50} of 1.1 nM
- XmAb942 in vitro potency suggests comparable or superior clinical efficacy to first-generation anti-TL1A antibodies.
- XmAb942 demonstrates superior pharmacokinetics to first-generation anti-TL1A antibodies, potentially improving patient convenience and compliance.
- The first subject will be dosed with XmAb942 in a Phase 1 healthy volunteer trial (NCT06619990) in Q4 2024.

References: **1.** US patent 11,999,789 B2. **2.** WIPO patent WO 2021/260577. **3.** Haraya K, Tachibana T. *BioDrugs*. 2023;37(1):99-108.
Author disclosures: All authors were employees of Xencor, Inc. with equity interests when the reported work was conducted.

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