Discovery and Characterization of XmAb412: A Novel, High-Affinity, Anti-TL1A x Anti-IL23(p19) Native-Like Bispecific Antibody with Extended Half-life for the Treatment of Inflammatory Bowel Disease

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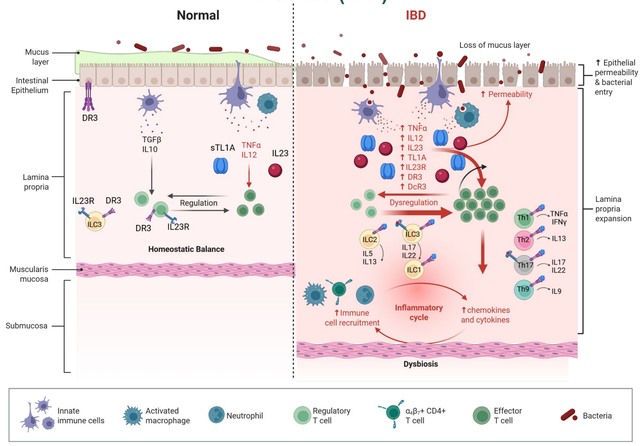
Poster #Tu1468

Background

- Interleukin (IL) 23 and tumor necrosis factor-like ligand 1A (TL1A) signaling is implicated in multiple autoimmune diseases, including ulcerative colitis (UC) and Crohn's disease (CD).
- IL23 is a central driver of chronic intestinal inflammation, promoting maturation and maintenance of pathogenic Th17 cells.
- TL1A interaction with death receptor 3 (DR3) amplifies effector T cell activation, cytokine secretion, and tissue remodeling.
- Clinical data demonstrate that therapeutic blockade of either IL23- or TL1A-mediated pathways can induce remission in UC and CD.
- Here we describe a novel, human native-like, effector-less bispecific antibody incorporating Xtend™ half-life extension technology that simultaneously blocks signaling stimulated by IL23 and TL1A.

IL23 Initiates and TL1A Amplifies Cytokine Signaling to Enhance Interstitial Damage in Inflammatory Bowel Disease (IBD)



INFγ, TNF, IL17, and IL22 are upregulated by IL23 and TL1A signaling.
Figure created in BioRender.

Methods

- Multiple anti-TL1A and anti-IL23(p19) variable domains and antibody formats were screened using biochemical and functional assays. Lead domains were affinity matured by phage display, targeted CDR engineering, and AI/ML-guided optimization.
- Affinity and selectivity for soluble TL1A and IL23 were assessed by SPR and KinExA.
- Mechanistic activity was assessed through inhibition of TL1A-DR3 binding, suppression of TL1A-DR3 signaling, and blockade of IL23-IL12Rβ1/IL23R signaling in reporter assays.
- The bispecific antibody was benchmarked against clinical-stage TL1A antagonists and approved IL23 antagonists.
- Pharmacokinetics and pharmacodynamics of the lead Xtend-engineered therapeutic candidate were assessed in non-human primates.

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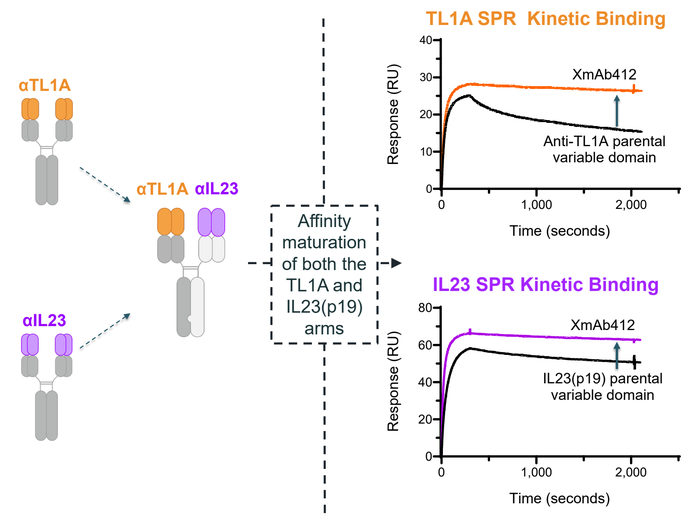
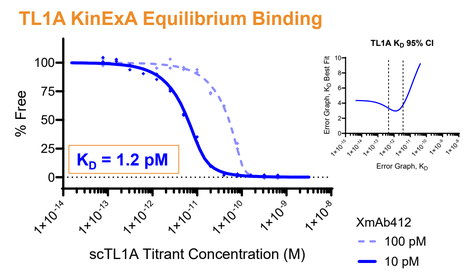
XmAb412 BindsTL1A and IL23 with Single-Digit Picomolar and Sub-picomolar Affinity



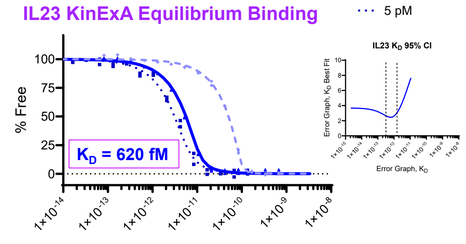
TL1A SPR Kinetic Binding

IL23 SPR Kinetic Binding

TL1A KinExA Equilibrium Binding



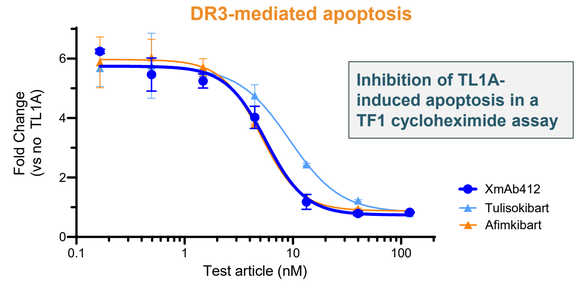
IL23 KinExA Equilibrium Binding



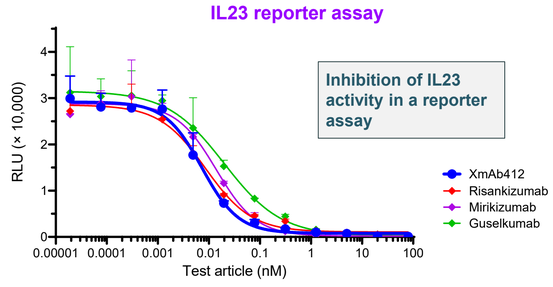
SPR binding performed with monovalent variable domains as analyte. KinExA binding performed with XmAb412 as constant binding partner and TL1A or IL23 as titrant.

XmAb412 Robustly Suppresses Inflammatory Pathways

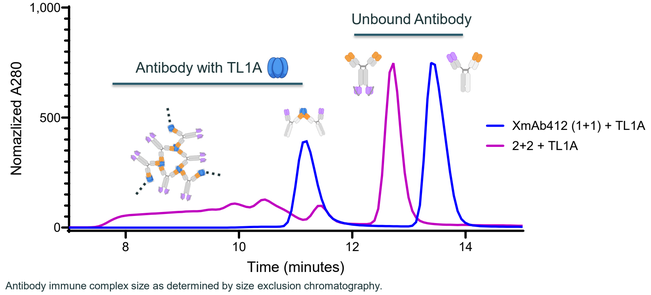
DR3-mediated apoptosis



IL23 reporter assay

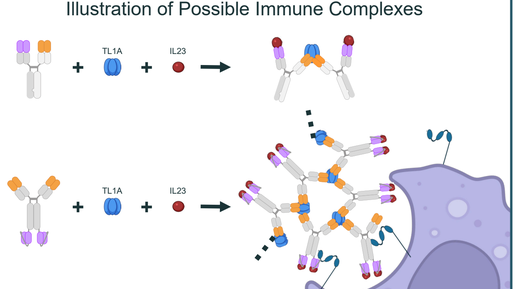


XmAb412 1+1 Format Avoids Large Immune Complex Formation of 2+2 Formats



Antibody immune complex size as determined by size exclusion chromatography.

Illustration of Possible Immune Complexes

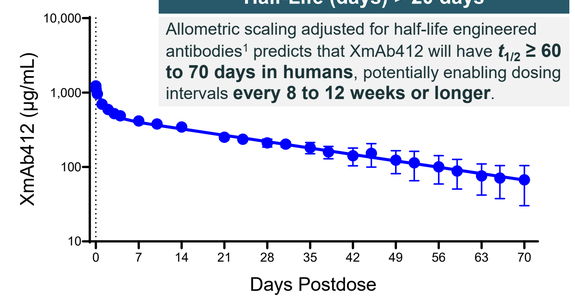


XmAb412 in Non-Human Primates

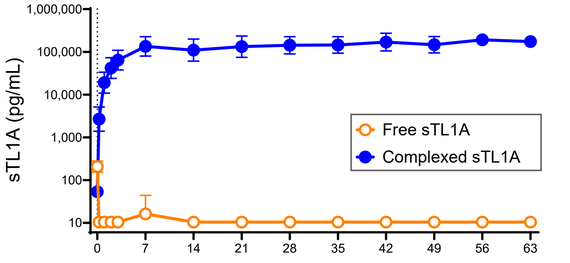
Extended Half-Life

Half-Life (days) > 20 days

Allometric scaling adjusted for half-life engineered antibodies[1] predicts that XmAb412 will have $t_{1/2}$ **≥ 60 to 70 days in humans**, potentially enabling dosing intervals **every 8 to 12 weeks or longer**.



Durable TL1A Engagement



Cynomolgus monkeys received a single intravenous injection of XmAb412. Concentration vs time data (upper plot) were analyzed by 2-compartment analysis. Data are means ± SEM. Free or XmAb412-complexed soluble (s) TL1A was measured (lower plot). Data are geometric means ± geometric SD. The vertical lines indicate the day of dosing. [1]Haraya K, Tachibana T. *BioDrugs*. 2023;37(1):99-108.

Conclusions

- **XmAb412 binds TL1A and IL23(p19) with single-digit picomolar affinity for TL1A and sub-picomolar affinity for IL23.**
- **XmAb412 robustly suppresses both inflammatory pathways.**
  - In cellular assays, XmAb412 demonstrated IC_{50} values comparable or superior to clinical-stage TL1A antagonists and approved IL23 antagonists.
- Allometric scaling predicts that XmAb412 will have a **half-life ≥ 60 to 70 days in humans**.
  - In non-human primates, XmAb412 achieved a half-life exceeding 20 days, with similar target engagement to monospecific antibodies.
- XmAb412 supports high-concentration, low viscosity, citrate-free formulation suitable for subcutaneous dosing.
- Evaluation of XmAb412 in healthy volunteers is expected to begin in the second half of 2026.

Author disclosures: All authors are employees of Xencor, Inc.