# An IL15/IL15Rα heterodimeric Fc-fusion engineered for reduced potency demonstrates an optimal balance of in vivo activity and exposure

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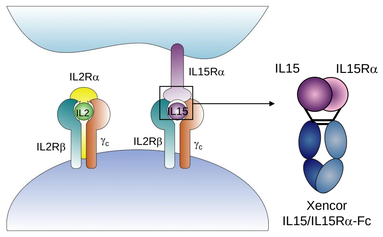
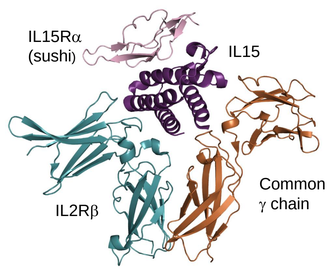
## Introduction

- IL15 is a highly active cytokine that stimulates NK and CD8$^+$ T cells
- Unlike IL2, IL15 avoids biased Treg activation
- The IL15/IL15Rα complex is presented in *trans* to NK and CD8$^+$ T cells expressing IL2Rβ and the common gamma chain ($\gamma_c$)
- The recombinant IL15/IL15Rα heterodimer is highly active and exclusively targets IL15 to IL2Rβ/$\gamma_c$ expressing cells
- To create a long-acting IL15 therapeutic, we engineered IL15/IL15Rα heterodimeric Fc-fusions using Xencor's well-validated suite of Fc domains
- Potency-reduced variants were created and found to promote superior exposure and more pronounced pharmacodynamics in vivo
- Addition of our extended half-life Fc domain (Xtend®) further enhanced in vivo half-life and provided even greater sustained exposure

**IL2 and IL15 share IL2Rβ and $\gamma_c$ receptor interactions; rationale for design of IL15/IL15Rα-Fc**

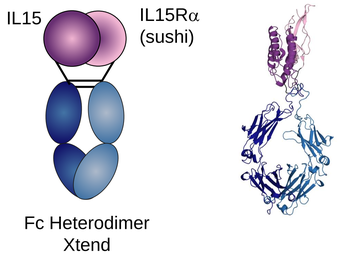



**Structure of the IL15-receptor complex**

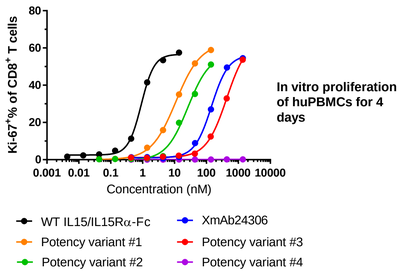



## XmAb24306 is engineered for optimal activity with reduced potency and extended in vivo half-life

**Structural model of IL15/IL15Rα-Fc heterodimer**

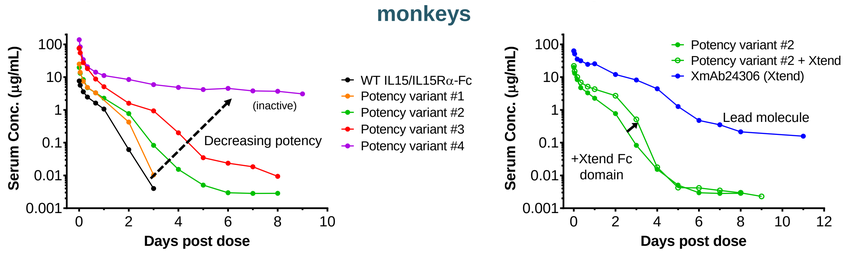



**Potency-reduced for optimal PK/PD**



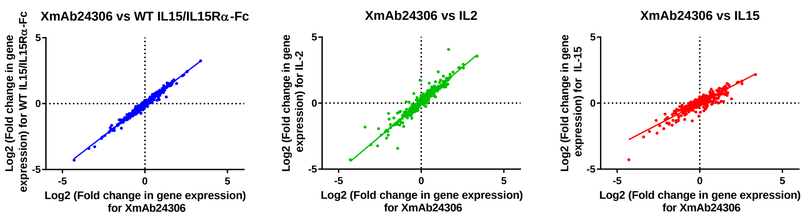

- Potency-reduced IL15/IL15Rα(sushi domain) is attached to Xencor's well-validated heterodimeric Fc domain
- The Fc domain is further modified to eliminate FcγR interactions and contains Xtend Fc technology to promote longer half-life and extended pharmacodynamics (PD)

### Potency reduction and Xtend technology combine to improve in vivo half-life in monkeys




- We identified that IL15/IL15Rα-Fc variants engineered with substitutions to reduce potency demonstrated a dramatic inverse correlation of in vitro potency and in vivo half-life in monkeys
- The addition of Xencor's Xtend Fc domain (enhanced affinity to FcRn @ pH 6) further increases half-life
- **XmAb24306 was selected as the lead due to optimal combination of potency and half-life**

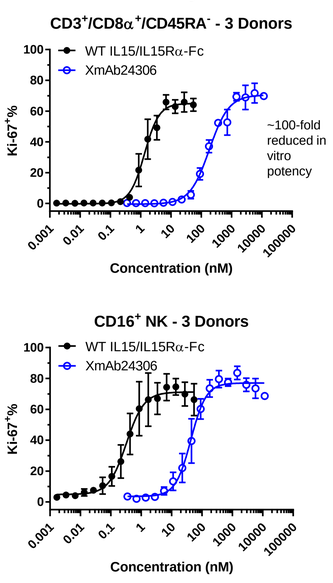
### Potency reduction does not impact gene expression pattern when adjusted for dose



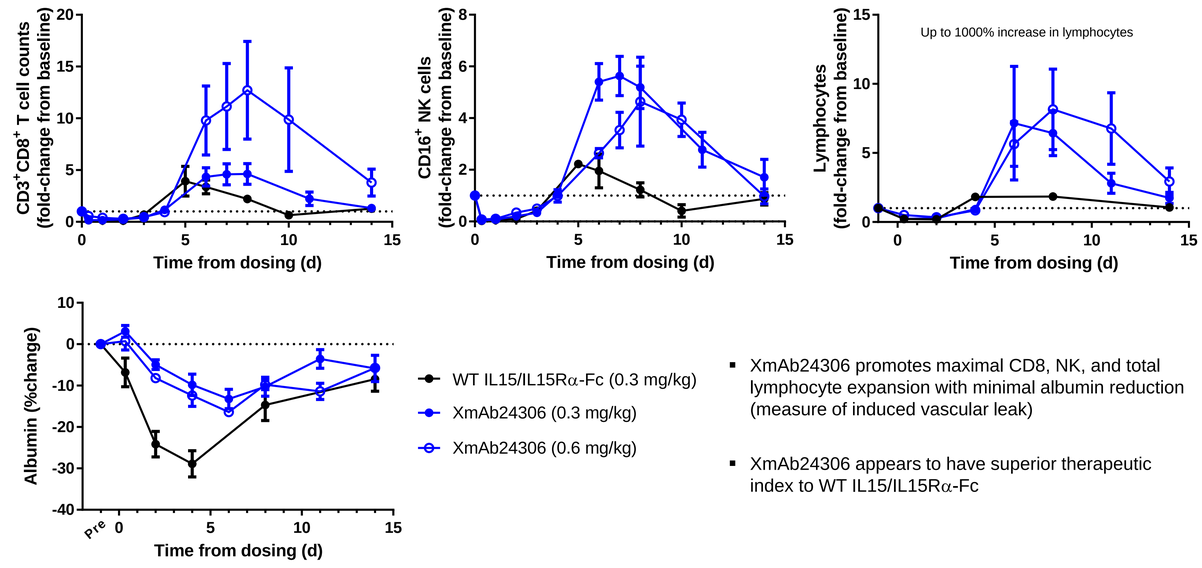

- NanoString gene expression analysis of huPBMCs + XmAb24306, WT IL15/IL15Rα-Fc, IL2, or IL15 dosed at proliferation EC50 for 48 hr.
- XmAb24306 promotes similar gene expression compared to WT IL15/IL15Rα-Fc, IL2, and IL15

## Potency-reduced candidate XmAb24306 promotes enhanced and sustained lymphocyte expansion and has improved tolerability in monkeys compared to WT IL15/IL15Rα-Fc

**In vitro proliferation of huPBMCs for 4 days**



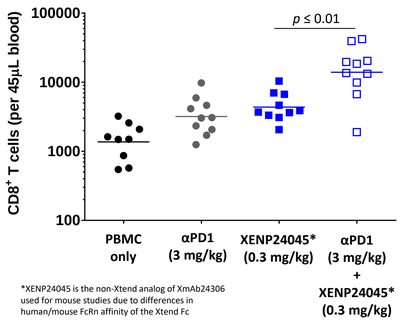

**Pharmacodynamics (PD) of single-dose WT IL15/IL15Rα-Fc or XmAb24306 in cynomolgus monkeys**




- XmAb24306 promotes maximal CD8, NK, and total lymphocyte expansion with minimal albumin reduction (measure of induced vascular leak)
- XmAb24306 appears to have superior therapeutic index to WT IL15/IL15Rα-Fc

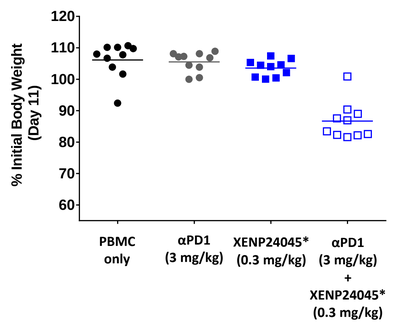
## Potency-reduced IL15/IL15Rα-Fc combines productively with anti-PD1 in GVHD and anti-tumor models

**Human CD8$^+$ T cell counts**

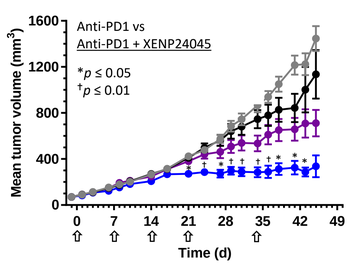



*XENP24045 is the non-Xtend analog of XmAb24306 used for mouse studies due to differences in human/mouse FcRn affinity of the Xtend Fc

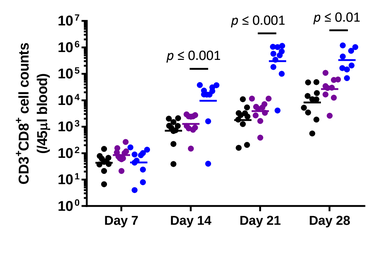
**GVHD is exacerbated**




**Anti-tumor activity**

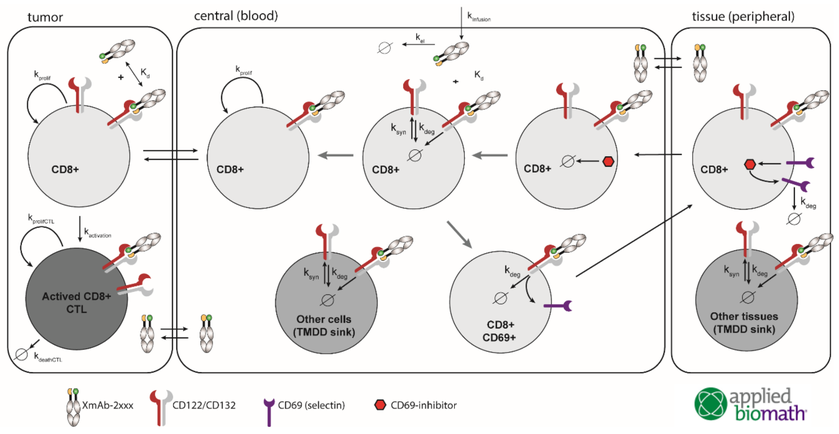


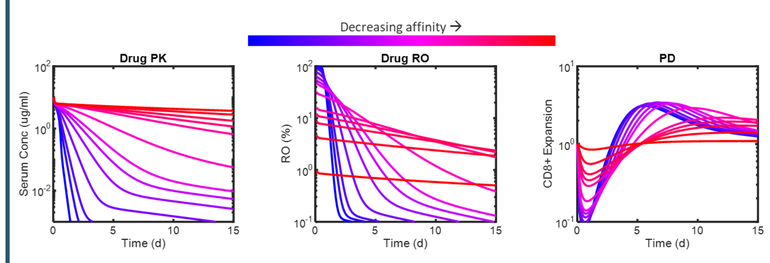

**Peripheral T cell expansion**



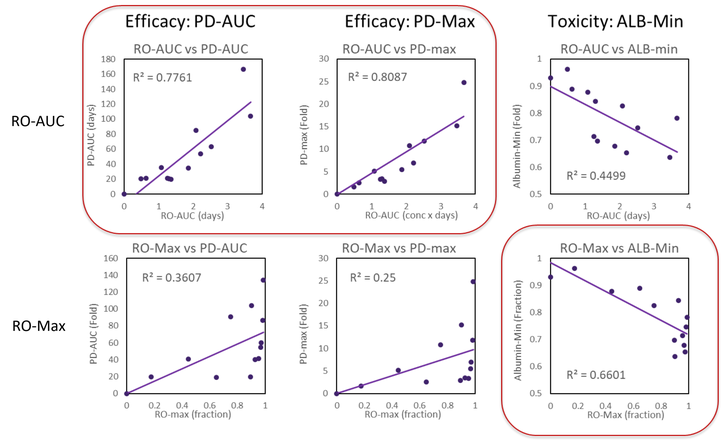

PBS only (no huPBMCs) · huPBMC + anti-PD1 (3 mg/kg) · huPBMC + PBS · huPBMC + XENP24045* (0.5 mg/kg) + anti-PD1 (3 mg/kg)

## Mechanism-based PK/PD model predicts optimal affinity to promote maximal PD




- Model demonstrates that reduced potency prolongs exposure
- Model demonstrates that an optimal $K_d$ exists for maximal PD (T cell expansion)




- Simulated RO-AUC predicts experimental PD
- Albumin decrease is best predicted by RO-Max

## Summary

- XmAb24306 consists of a reduced potency IL15/IL15Rα combined with an extended half-life heterodimeric Fc domain
- XmAb24306 demonstrates more sustained in vivo lymphocyte proliferation and improved tolerability in monkeys compared to WT IL15/IL15Rα-Fc

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