Potency-reduced IL15/IL15Rα heterodimeric Fc-fusions display enhanced in vivo activity through increased exposure

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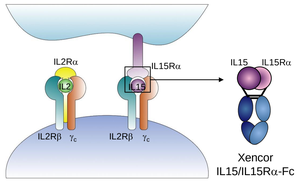
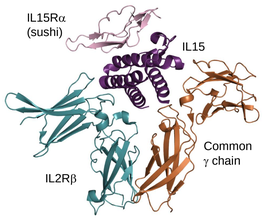
Introduction

- 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 (γ_c)
- The recombinant IL15/IL15Rα heterodimer is highly active and exclusively targets IL15 to IL2Rβ/γ_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
- We found that potency-reduced variants are more active in vivo due to enhanced exposure and engineered IL15 at the IL2Rβ/γ_c interface to optimize in vivo pharmacodynamics
- 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 γ_c receptor interactions; rationale for design of IL15/IL15Rα-Fc

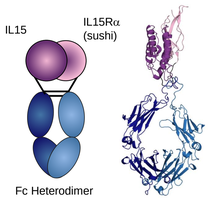


Structure of the IL15-receptor complex

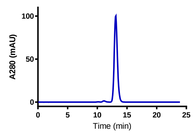


IL15/IL15Rα-Fc heterodimers are engineered for optimal activity with reduced in vitro potency and extended in vivo half-life

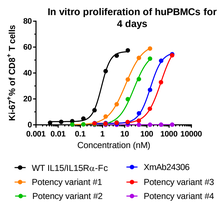
Structural model of IL15/IL15Rα-Fc heterodimer



Analytical SEC of purified IL15/IL15Rα-Fc heterodimer

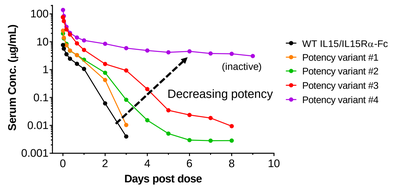


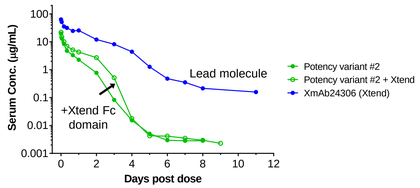
Potency-reduced for optimal PK and PD



- 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)
- IL15/IL15Rα-Fc are produced in high yields and purified by standard methods

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

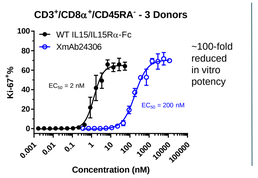




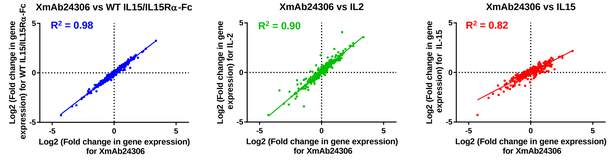
- We identified that IL15/IL15Rα-Fc variants engineered with substitutions to reduce potency demonstrated a dramatic inverse correlation of in vitro potency and in vivo half-life in monkeys
- The addition of Xencor's Xtend Fc domain (enhanced affinity to FcRn @ pH 6) further increases half-life
- XmAb24306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

In vitro proliferation of huPBMCs for 4 days

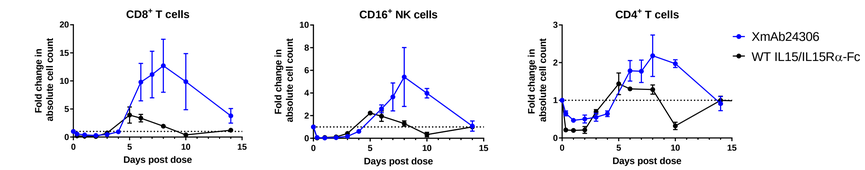


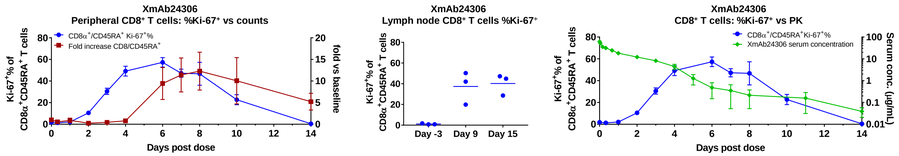
NanoString gene expression analysis of huPBMCs + XmAb24306, WT-IL15/IL15Rα-Fc, IL2, or IL15 dosed at proliferation EC50 for 48 hr.



- XmAb24306 promotes similar gene expression compared to WT IL15/IL15Rα-Fc
- XmAb24306 promotes similar gene expression compared to IL2 and IL15

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

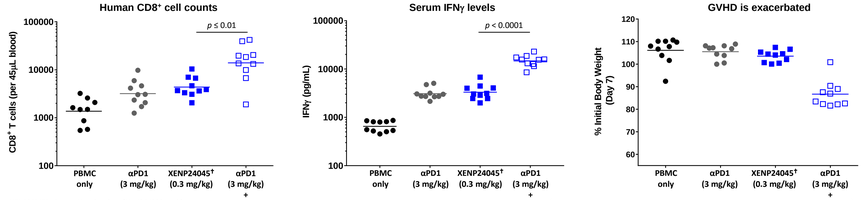




- Peripheral Ki-67 positivity observed through Day 10
- Lymph node Ki-67 positivity observed out to Day 15 (end of study)

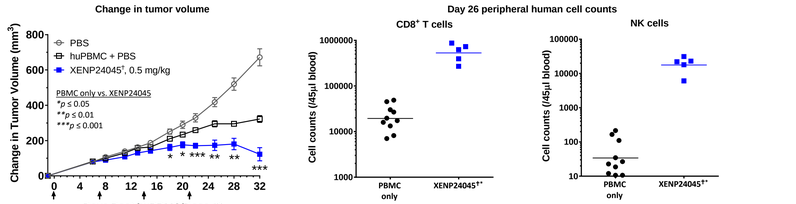
→ Prolonged PD effects may support convenient dosing schedule

Potency-reduced IL15/IL15Rα-Fc combines with anti-PD1 and promotes T cell proliferation and IFNγ production in huPBMC-engrafted NSG mice (GVHD model)



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

Potency-reduced IL15/IL15Rα-Fc promotes expansion of CD8$^+$ T cells and NK cells, and significantly reduces tumor size in a huPMBC-pp65-MCF7 xenograft model



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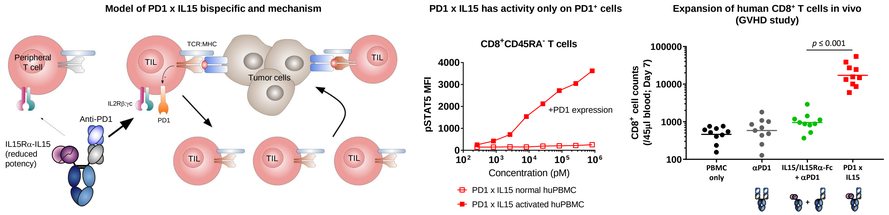
*5 mice died in the XENP24045 group due to GVHD

Reduced potency platform expansion: TIL-selective targeting of IL15



Conclusion

- Potency-reduced IL15/IL15Rα-Fc heterodimers have been produced using Xencor's heterodimer and Xtend Fc domains
- An inverse correlation of in vitro potency and in vivo clearance was observed, with reduced potency variants allowing higher in vivo doses and enhanced lymphocyte proliferation due to more sustained exposure
- XmAb24306 consists of a reduced potency IL15/IL15Rα combined with an extended half-life Fc domain. The combination results in sustained in vivo lymphocyte proliferation and may allow a less frequent dosing schedule.

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