Regulatory T cell selective IL-2-Fc fusion proteins for the treatment of autoimmune diseases

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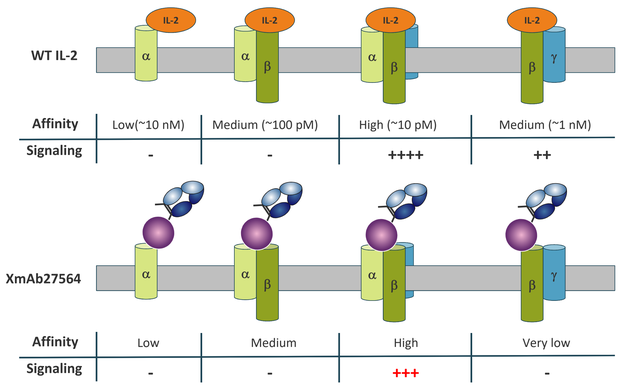
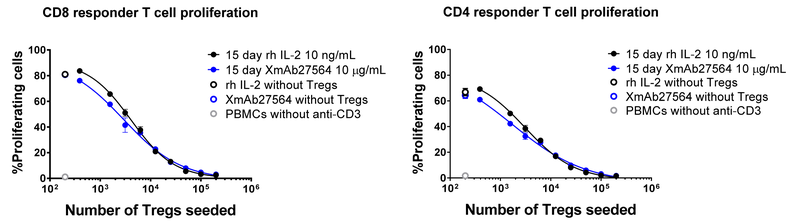
Introduction

- Regulatory T cells (Tregs) are CD4+FoxP3+ cells expressing CD25 (IL-2Rα) that maintain immune tolerance in tissues by suppressing the function of both CD4 and CD8 effector T cells.
- Tregs are dysfunctional in most autoimmune diseases, and a promising therapeutic approach has been to restore their numbers and function. One such approach has been a low-dose IL-2 regimen since Treg homeostasis depends on IL-2. However, IL-2 as a drug suffers from fast in vivo clearance and a narrow therapeutic index.
- To solve this problem we generated a long-lasting IL-2-Fc fusion protein with greater selectivity for Tregs:
  - To increase selectivity for Tregs, we weakened the interaction of IL-2-Fc with CD122 (IL-2Rβ) and/or strengthened the interaction with CD25.
  - We improved half-life by engineering IL-2-Fc so that it has reduced potency on Tregs.
  - Further half-life extension was achieved by using Xencor's Xtend® Fc domain to increase FcRn binding to identify our lead molecule XmAb®27564.



XmAb27564 preserves suppression of rapamycin-expanded human Tregs

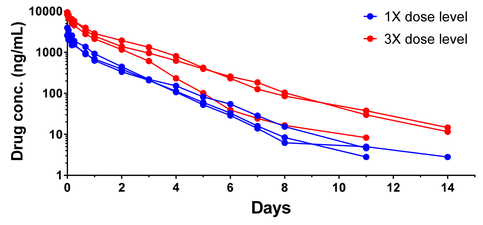
Suppression assay seeded with 1 x 10^5 CFSE labeled human PBMCs and indicated numbers of Tag-it Violet labeled Tregs on plate-bound anti-CD3 (OKT3; 100 ng/mL).



Tregs were cultured in RPMI media containing 10% FBS, 0.5 μg/mL anti-CD28, 100 ng/mL rapamycin and either 10 μg/mL XmAb27564 or 10 ng/mL recombinant human IL-2 for 15 days prior to seeding suppression assay.

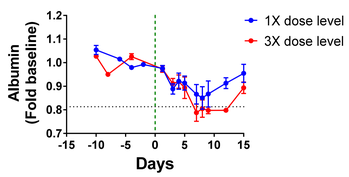
XmAb27564 exhibits enhanced pharmacokinetics in cynomolgus monkeys

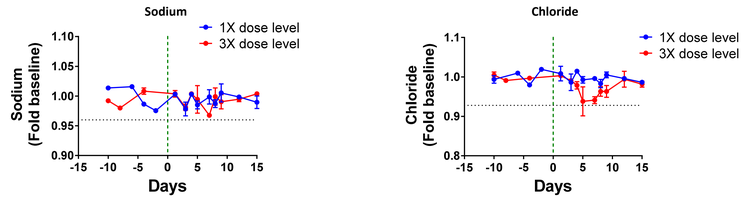
Sustained pharmacokinetics up to several days in cynomolgus monkeys

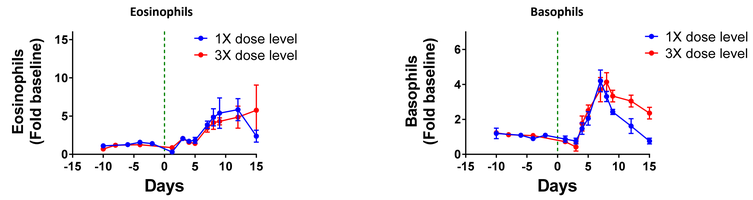


XmAb27564 is well-tolerated in cynomolgus monkeys

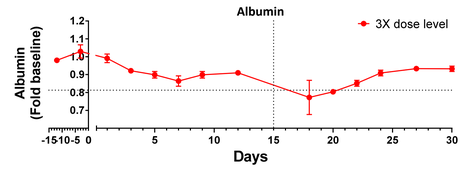
Serum albumin as a measure of vascular leakage

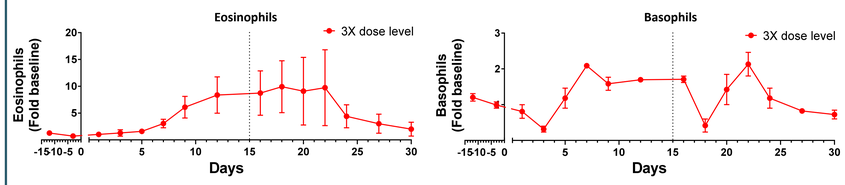




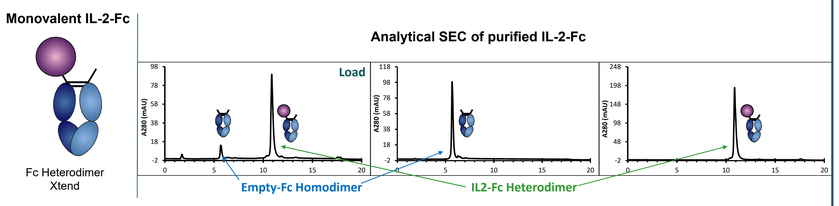


Repeat dosing of XmAb27564 is well tolerated in cynomolgus monkeys

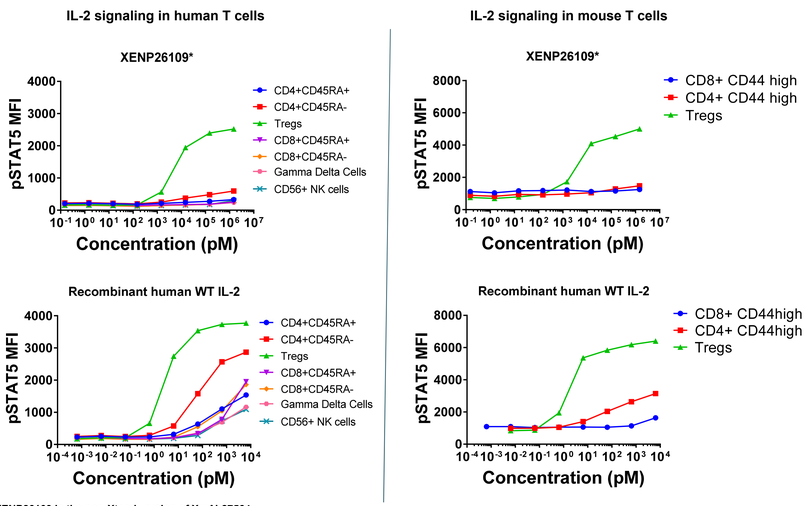




Treg selective IL-2-Fc are engineered using Xencor's Fc domains

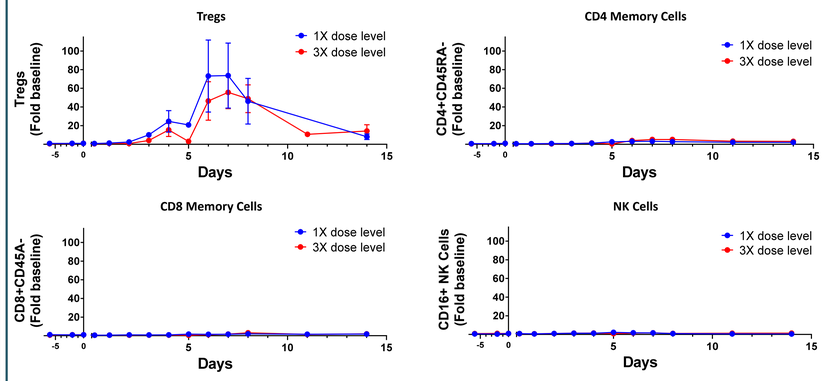


Engineered IL-2-Fc selectively promotes Treg signaling in humans and mice

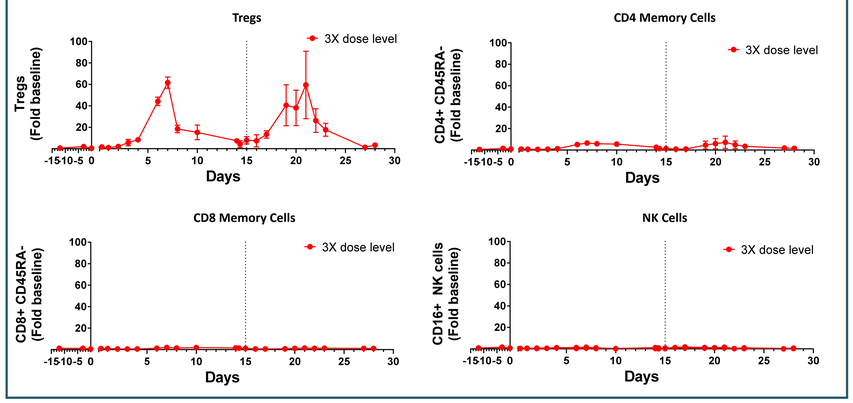


*** XENP26109 is the non-Xtend version of XmAb27564**

XmAb27564 promotes the selective and sustained expansion of Tregs in cynomolgus monkeys



Treg expansion in response to repeat dosing of XmAb27564 on day 0 and day 15 in cynomolgus monkeys



Conclusion

- XmAb27564 is a Treg selective IL-2-Fc protein that has been produced using Xencor's heterodimer and Xtend Fc domains.
- XmAb27564:
  - selectively leads to STAT5 phosphorylation in human and mouse Tregs in vitro
  - has an extended in vivo half-life due to its low potency on Tregs and Xtend Fc domain
  - is well tolerated in single and multiple doses administered to cynomolgus monkeys
  - selectively promotes a profound and sustained proliferation of Tregs in monkeys
- XmAb27564 is equally selective and potent for Tregs in mice making it suitable for preclinical mouse models of autoimmune diseases.
- XmAb27564 is likely to improve the therapeutic index for autoimmune indications, where low dose IL-2 therapy has demonstrated promising results and therefore its clinical development is warranted.

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