

# Engineered IL18 heterodimeric Fc-fusions featuring improved stability, reduced potency, and insensitivity to IL18BP



Alex Nisthal, Sung-Hyung Lee, Christine Bonzon, Ruschelle Love, Kendra N. Avery, Rumana Rashid, Panida Lertkiatmongkol, Nicole Rodriguez, Michael Hackett, Michael Sheard, Hanh Nguyen, Araz Eivazi, Sher Karki, Norm Barlow, Seung Y. Chu, Rena Bahjat, Gregory L. Moore, and John R. Desjarlais

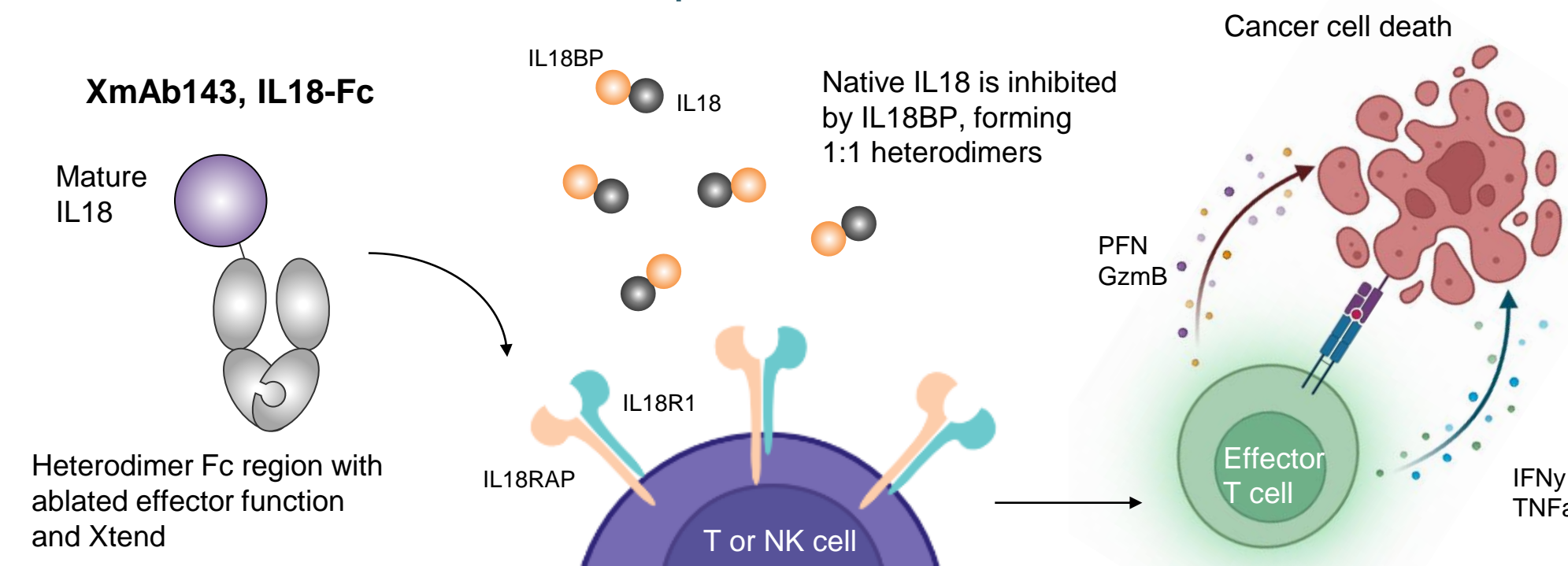
\*Contact: jrd@xencor.com

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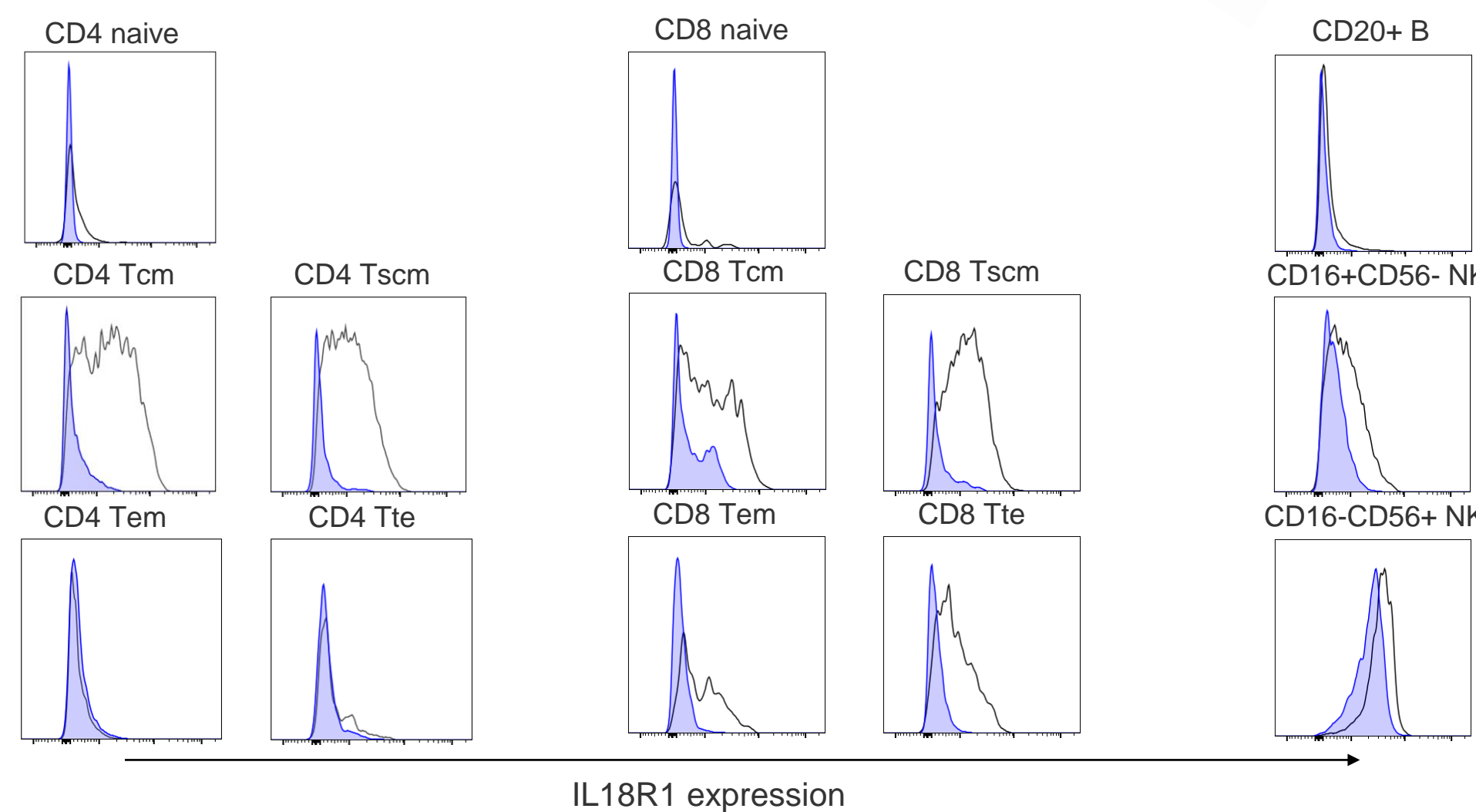
## Introduction

- Interleukin-18 (IL18) is a proinflammatory cytokine that modulates both the innate and adaptive immune responses. IL18 receptor 1 (IL18R1), the primary co-receptor for IL18, is overexpressed on memory T cell subsets, which have recently been found to be critical for anti-tumor responses. Preclinical studies have demonstrated anti-tumor activity in animal models, including impressive synergy with immune checkpoint inhibitors and CAR-T therapies.
- In contrast with potent cytokines such as IL2 or IL12, IL18 was very well tolerated in clinical trials, and was discontinued due to lack of efficacy despite heavy dosing. As IL18 participates in a negative feedback loop with a very high affinity natural inhibitor, IL18 binding protein (IL18BP), it is hypothesized that its lackluster clinical benefit was due to overexpression of IL18BP.
- To combat inhibition by IL18BP, and improve on IL18's poor drug-like properties, we fused a stabilized, potency-modulated IL18 cytokine to one arm of our XmAb<sup>®</sup> heterodimeric Fc platform.
- Our monovalent IL18-Fc, enhanced by our Xtend<sup>™</sup> Fc technology for longer serum half-life, features dramatically improved serum stability, insensitivity to IL18BP inhibition, and dose-dependent inflammatory activity in vivo.

### Lead IL18-Fc's proinflammatory activity is not inhibited by IFN $\gamma$ -induced IL18BP



### IL18R1 expression is biased toward NKs and memory T cell subsets

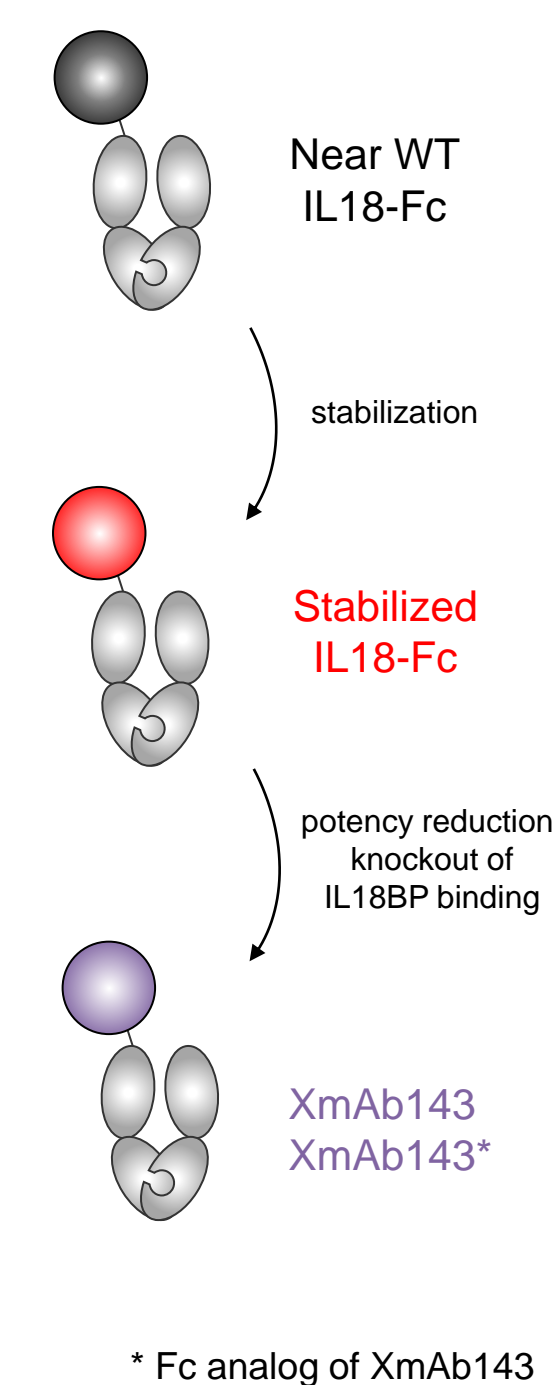


Unstimulated PBMCs  
cCD3 stimulated PBMCs

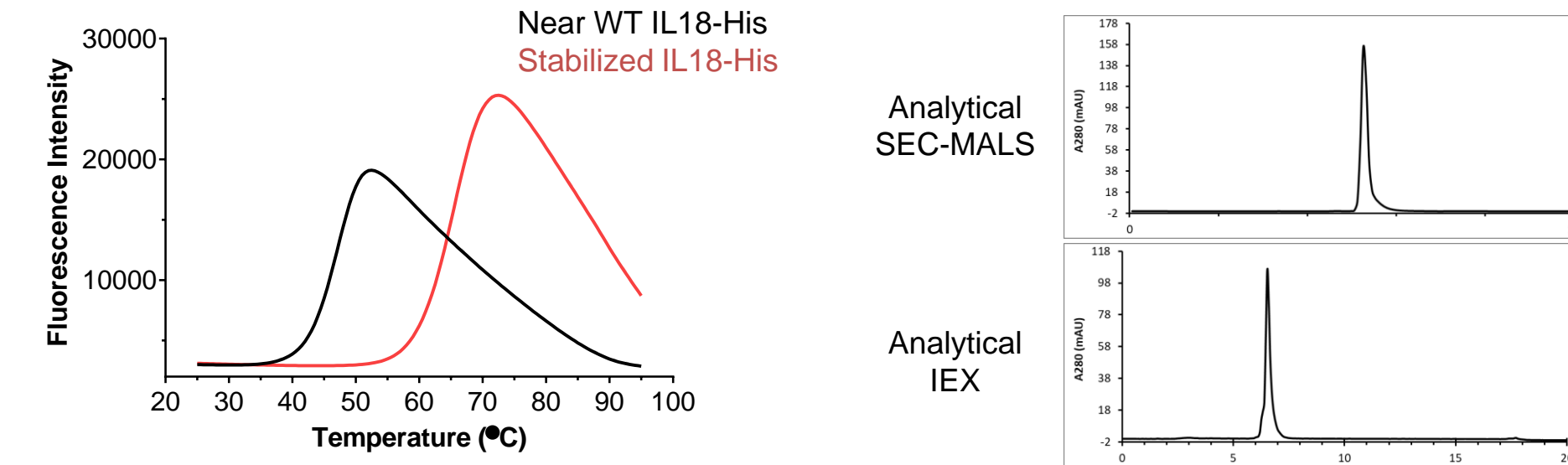
Human PBMC were stimulated with 500 ng/mL plate-bound anti-CD3 (OKT3) for 48 h and then analyzed by flow cytometry. Gates for B and NK cells are as shown, and T cell subsets are defined as naive (CD28+CD95-CCR7+), memory (CD28+CD95+CCR7+), and effectors (CD28-CD95midCCR7-). Central Memory (Tcm) and effector memory (Tem) T cells were further gated by CD45RA-, and stem-cell like memory (Tscm) and terminal effectors (Tte) T cells were further gated by CD45RA+.

## XmAb143 is stabilized, potency reduced, and insensitive to IL18BP based inhibition

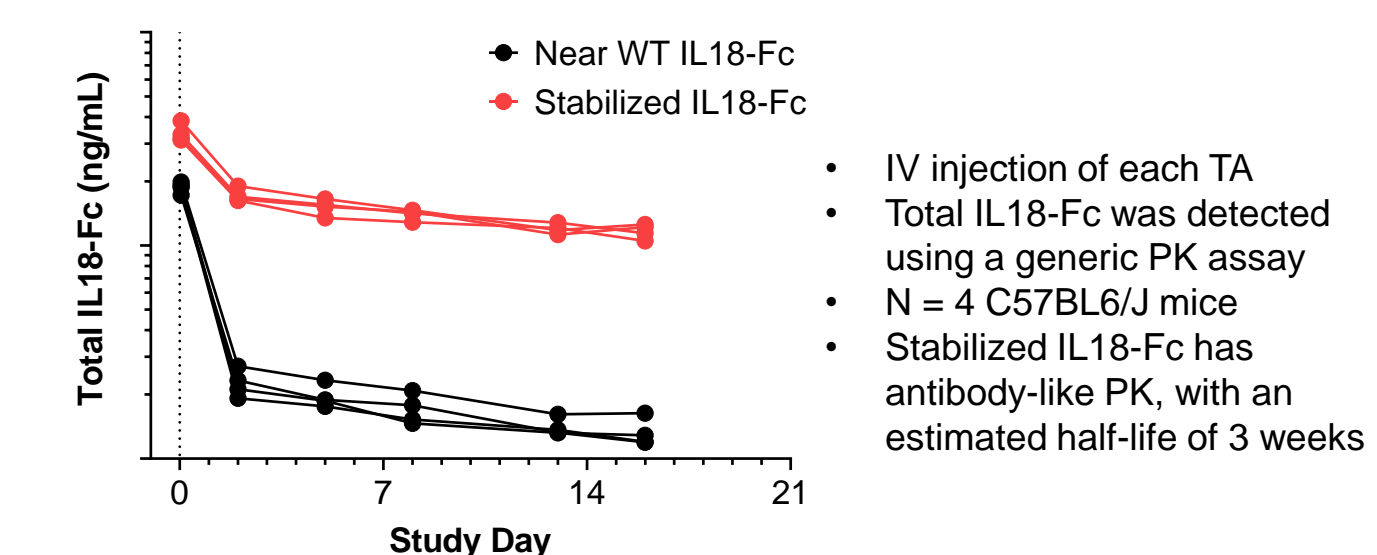
### Cytokine engineering workflow



### IL18 was stabilized by 20°C, enabling improved solution behavior and facile purification

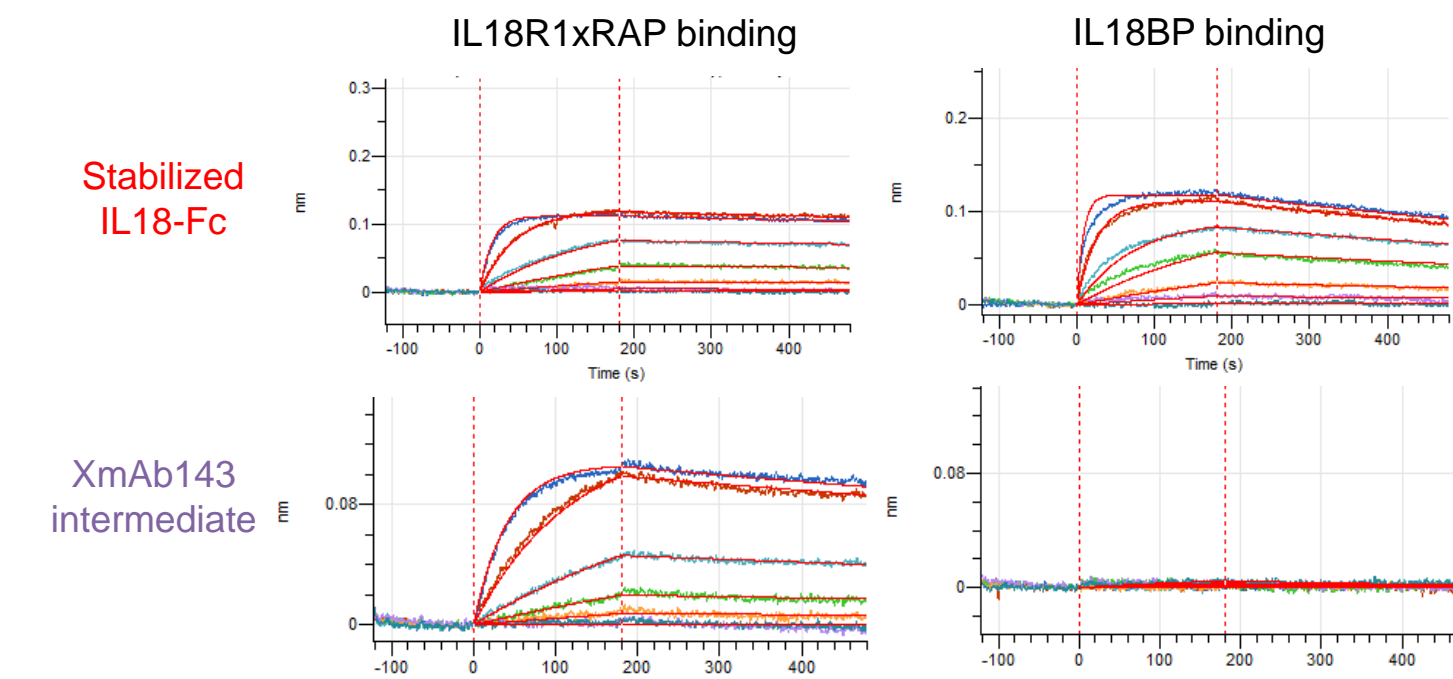


### Stabilized IL18-Fc has greatly improved PK in mice

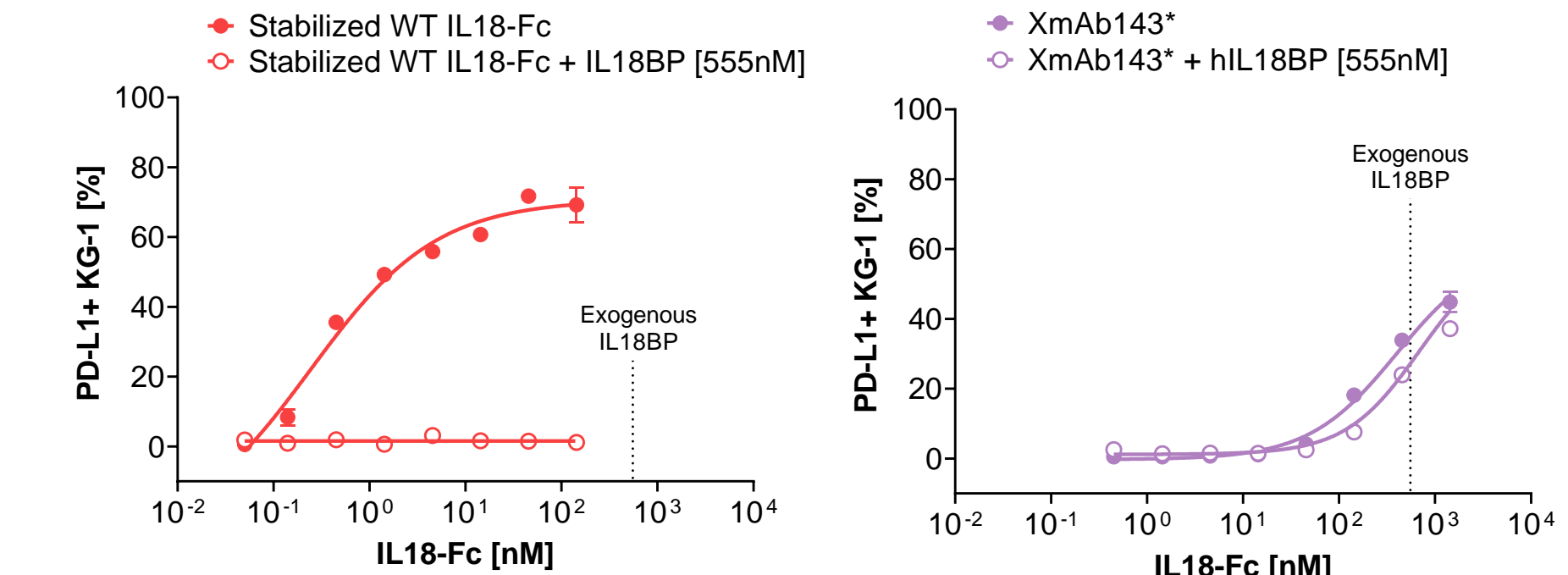


- IV injection of each TA
- Total IL18-Fc was detected using a generic PK assay
- N = 4 C57BL6/J mice
- Stabilized IL18-Fc has antibody-like PK, with an estimated half-life of 3 weeks

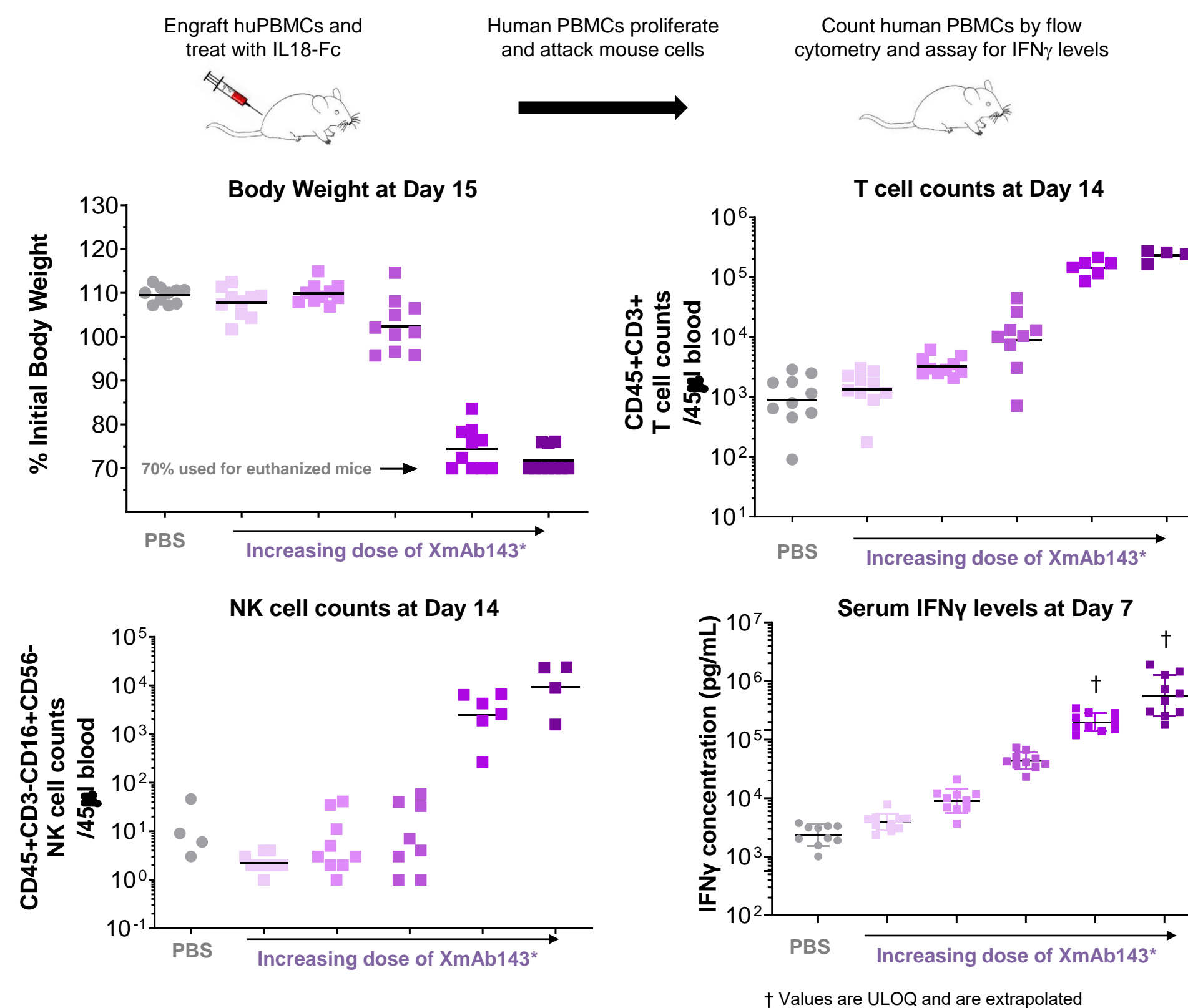
### IL18 receptor binding is maintained as IL18BP binding is knocked out



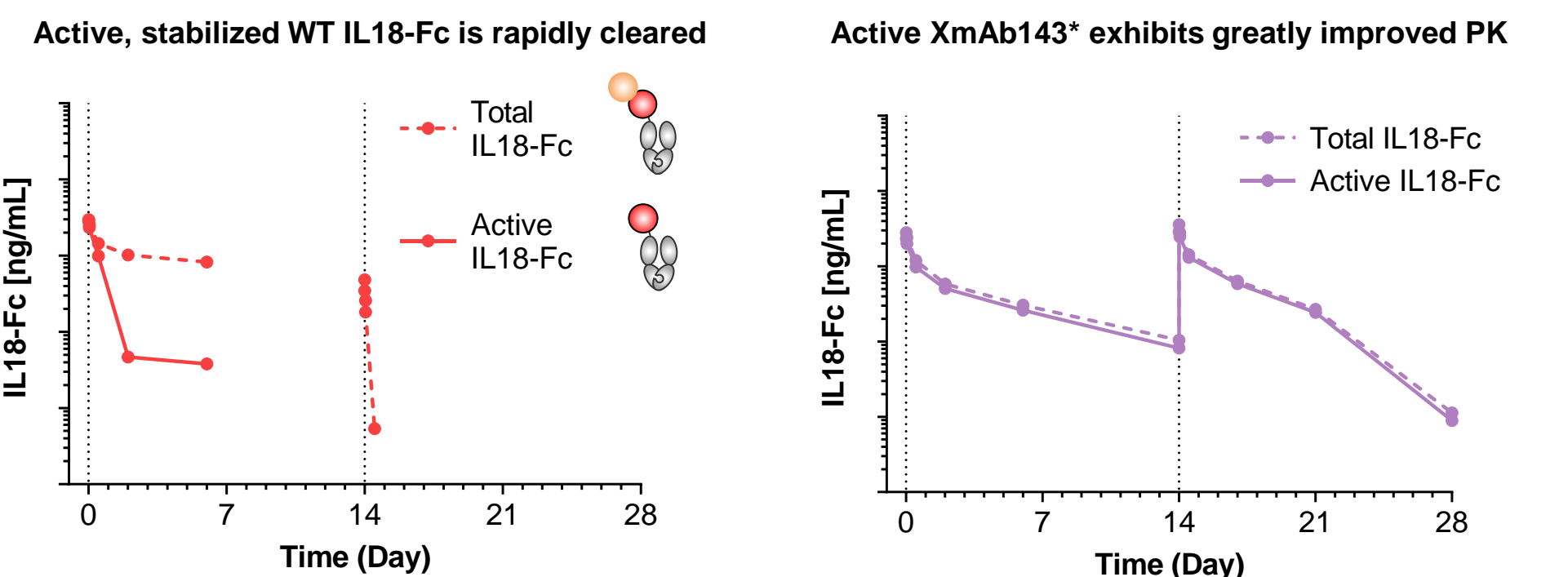
### XmAb143\* is potency reduced and insensitive to IL18BP



## XmAb143\* promotes NK, T cell proliferation and IFN $\gamma$ production in huPBMC-engrafted NSG mice (GVHD model)



## In NHP, XmAb143\* exhibited no clinical observations and slow receptor-mediated clearance



## Summary

- WT IL18 was stabilized, improving its expression, solution behavior, and in vivo mouse PK
- Stabilized IL18-Fc was further engineered to 1) not bind the natural pM inhibitor IL18BP, and 2) reduce potency and maintain efficacy on IL18 receptor expressing cells
- XmAb143\* exacerbates body weight loss in an in vivo model of GvHD, consistent with significant expansion of CD3+ T cells (CD4 and CD8), CD16+CD56- NK cells, and induction of IFN $\gamma$
- Potency reduced and stabilized XmAb143\* shows increased exposure in NHP with slow receptor-mediated clearance and improved serum half-life
- XmAb143's robust activity in a mouse GvHD model and clean safety profile in NHP support further development as a potential novel IL18 cytokine therapy for cancer patients

