XmAb143, an engineered IL18 heterodimeric Fc-fusion, features 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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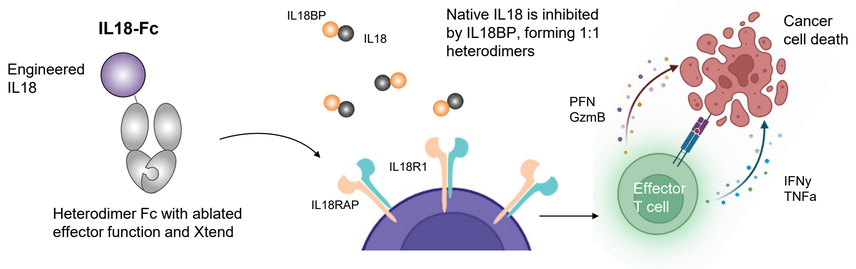
Introduction

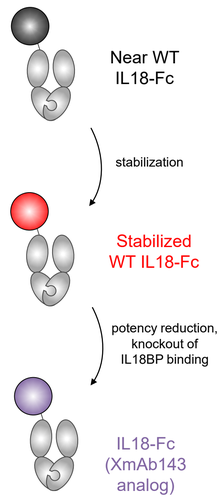
- Interleukin-18 (IL18) is a proinflammatory cytokine that modulates both the innate and adaptive immune responses. Preclinical studies have demonstrated anti-tumor activity in animal models, including impressive synergy with immune checkpoint inhibitors and CAR-T therapies.
- IL18 participates in a negative feedback loop with a natural high affinity inhibitor, IL18 binding protein (IL18BP), and it is hypothesized that lackluster clinical trials with recombinant IL18 were due to upregulation of IL18BP and subsequent IL18 inhibition.
- To combat IL18BP inhibition and improve on IL18's poor drug-like properties, we fused a stabilized, potency-modulated IL18 cytokine to one arm of our XmAb® heterodimeric Fc platform.
- Our monovalent IL18-Fc, enhanced by our Xtend™ Fc technology for longer serum half-life, features dramatically improved thermal stability, insensitivity to IL18BP inhibition, and dose-dependent inflammatory activity in vivo.

XmAb143's proinflammatory activity is not inhibited by IL18BP

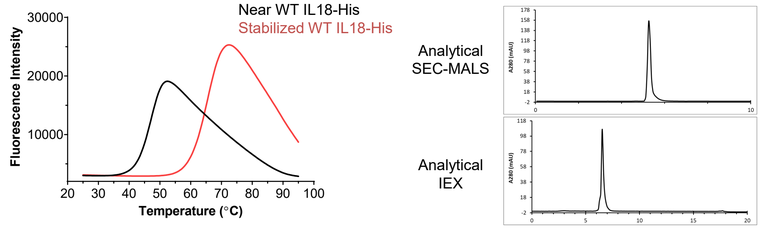


IL18-Fc is stabilized, potency reduced, and insensitive to IL18BP based inhibition

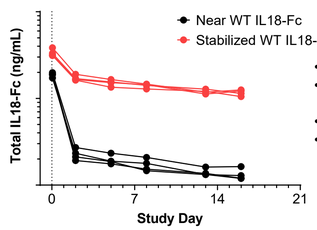
Cytokine engineering workflow



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

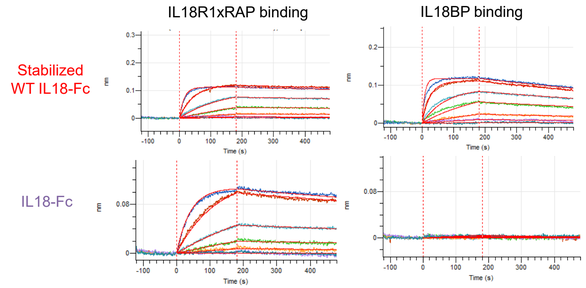


Stabilized IL18-Fc has greatly improved PK in mice

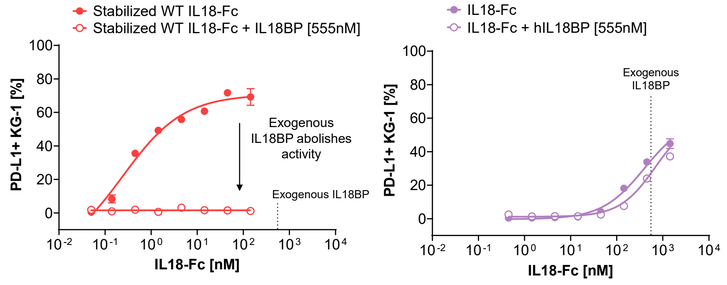


- IV injection of each TA
- Total IL18-Fc was detected using a generic PK assay
- N = 4 C57BL6/J mice
- Stabilized IL18-Fc has antibody-like PK, with an estimated half-life of 3 weeks

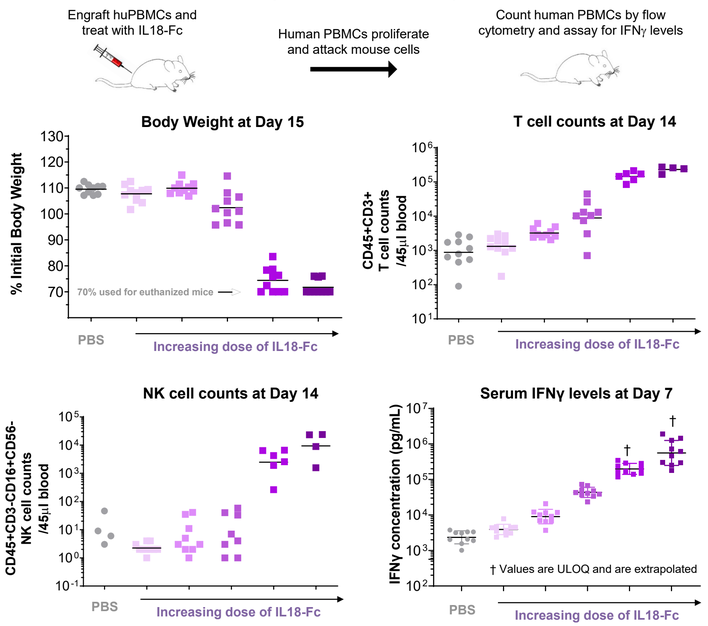
IL18 receptor binding is maintained as IL18BP binding is knocked out



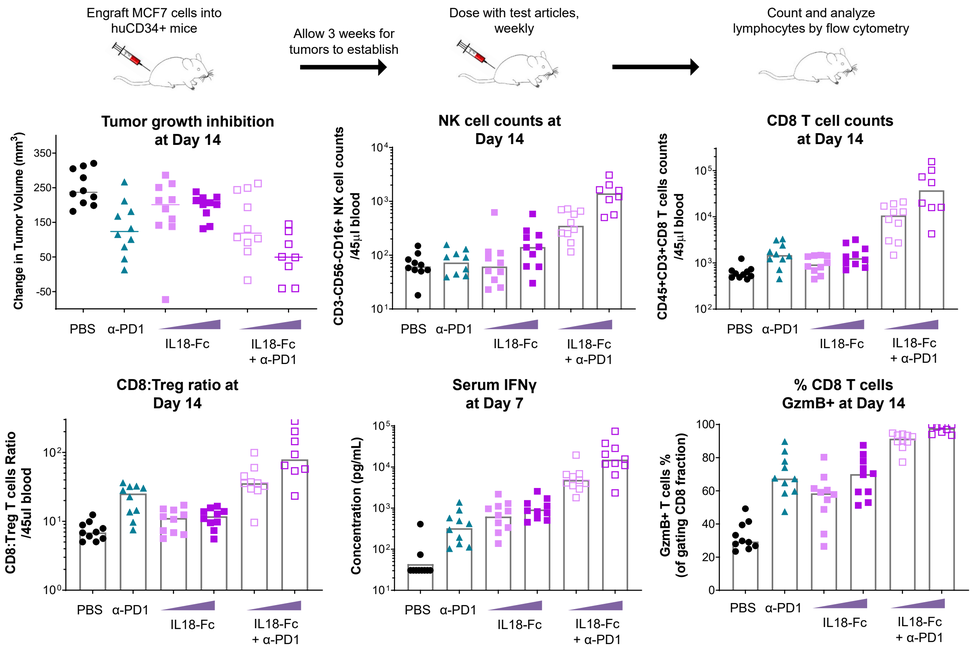
Engineered IL18-Fc is potency reduced and insensitive to IL18BP



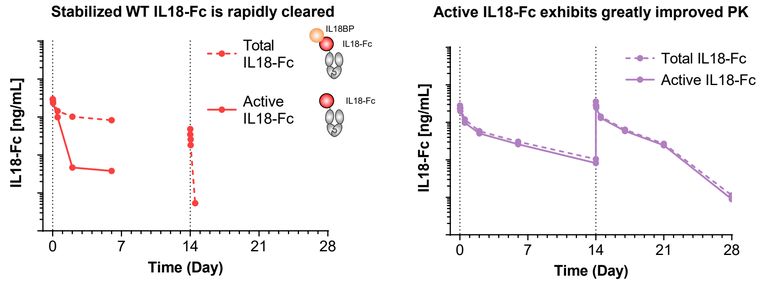
IL18-Fc promotes NK, T cell proliferation and IFNγ production in huPBMC-engrafted NSG mice (GvHD model)



IL18-Fc demonstrates tumor growth inhibition, T cell proliferation and activation in CD34+ humanized mice



In NHP, IL18-Fc 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
- IL18-Fc exacerbates body weight loss in an in vivo model of GvHD, consistent with significant expansion of CD4 and CD8 T cells, CD16+CD56- NK cells, and IFNγ induction
- MCF7 tumors are inhibited in a CD34+ mouse model by IL18-Fc and anti-PD1, correlating with T and NK cell expansion, granzyme B and IFNγ induction, and Treg reduction
- Potency reduced and stabilized IL18-Fc shows increased exposure in NHP with slow receptor-mediated clearance and improved serum half-life
- IL18-Fc's robust in vivo activity in mice and clean safety profile in NHP support further development as a novel cytokine therapy for cancer patients