Optimally engineered IL18 Fc-fusion protein balance potency and pharmacokinetics to promote strong anti-tumor activity

Alex Nisthal, Sung-Hyung Lee, Matthew A. Dragovich, Christine Bonzon, Ruschelle Love, Kendra N. Avery, Rumana Rashid, Panida Lertkiatmongkol, Nicole Rodriguez, Irene Leung, Michael Sheard, Sher Karki, Norm Barlow, Seung Y. Chu, Rena Bahjat, Gregory L. Moore, and John R. Desjarlais

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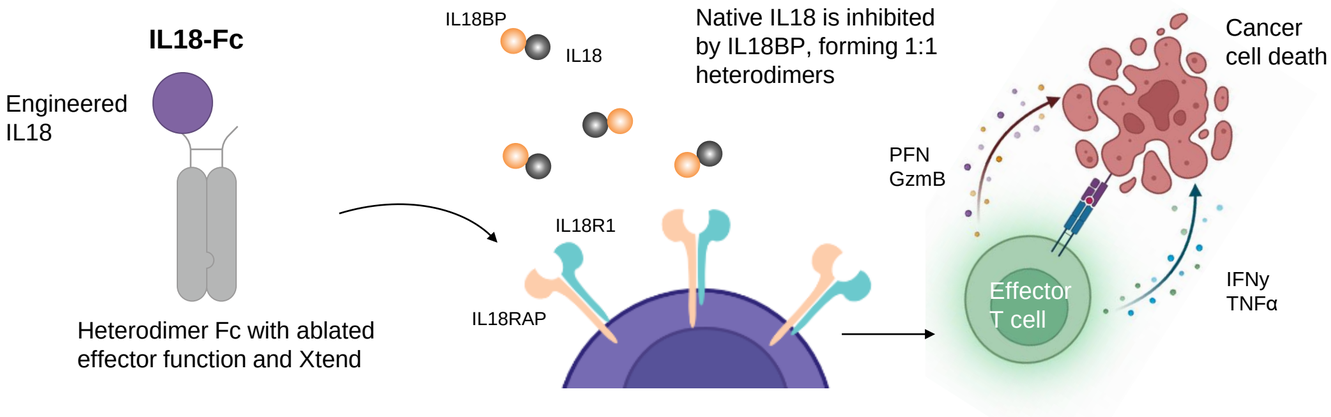
Introduction

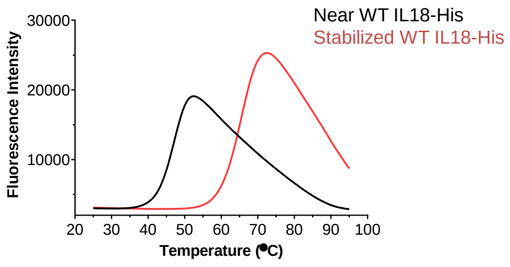
- Interleukin-18 (IL18) is a proinflammatory cytokine that modulates both the innate and adaptive immune responses. Although anti-tumor activity is observed in preclinical studies, clinical trials testing recombinant IL18 were lackluster, presumably due to upregulation of pM affinity IL18BP and subsequent IL18 inhibition.
- To combat the IL18BP negative feedback loop and improve on IL18's poor drug-like properties, we created a series of stabilized, IL18BP insensitive, potency-modulated IL18 cytokines and fused them to one arm of our XmAb® heterodimeric Fc platform. We also created surrogate mouse IL18 cytokines with equivalent properties for testing in immune competent syngeneic mouse models. Finally, we extended our IL18 platform by creating bispecific molecules that more selectively target IL18 to T cells.
- Our IL18-Fc fusion proteins, enhanced by our Xtend™ Fc technology for longer serum half-life, features dramatically improved thermal stability, insensitivity to IL18BP inhibition, and dose-dependent pharmacologic activity in vivo.

Proinflammatory activity by engineered IL18-Fc is not inhibited by IL18BP

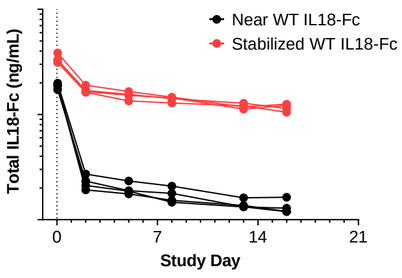


Human IL18-Fc fusions are stabilized, insensitive to IL18BP inhibition, and occupy a wide potency ladder

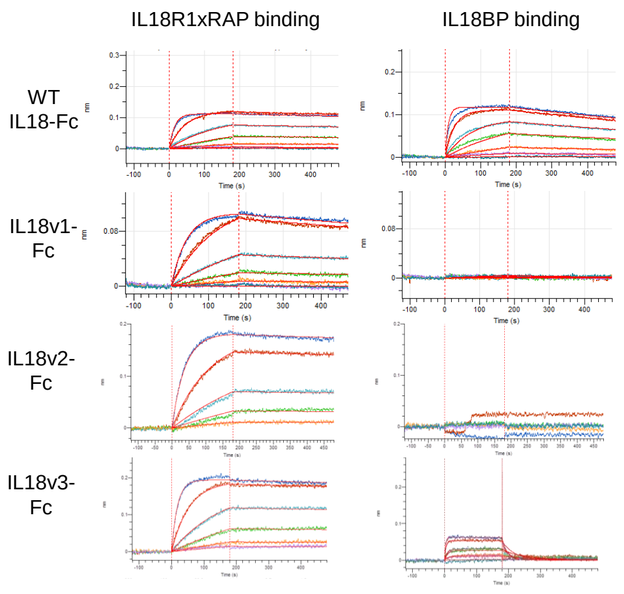
Engineered disulfide stabilizes IL18 by 20°C



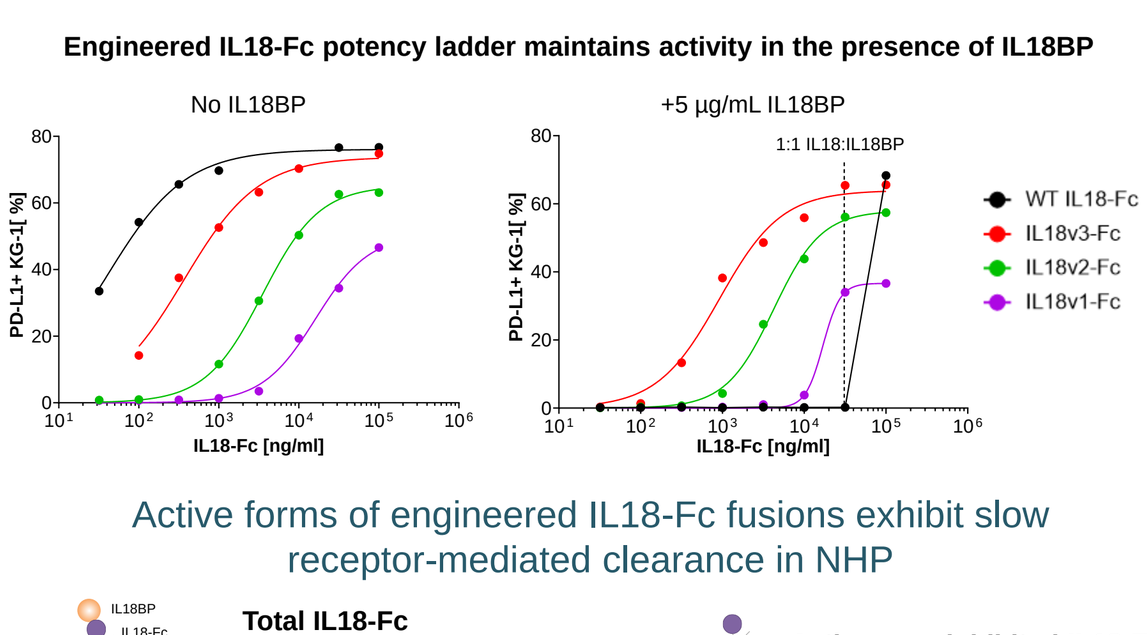
Mouse PK improved by stabilization



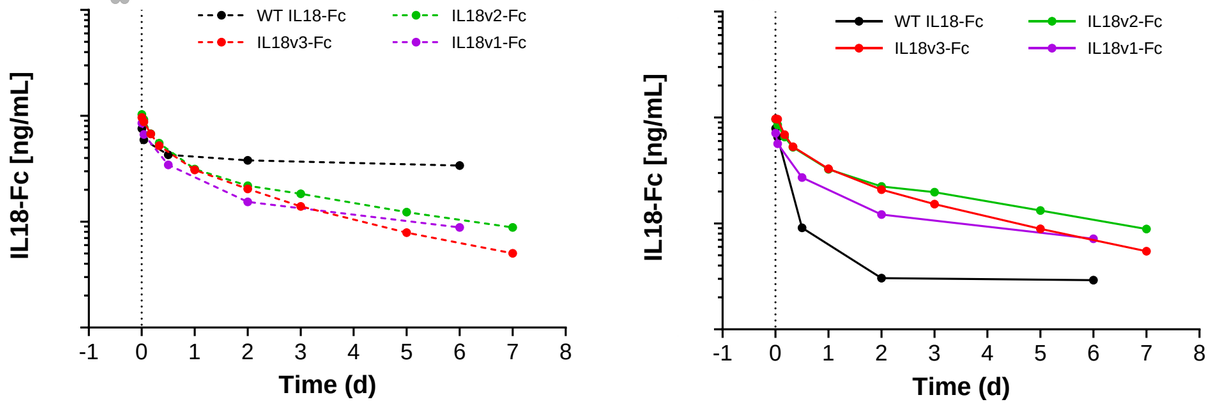
IL18 receptor binding is maintained as IL18BP binding is abrogated



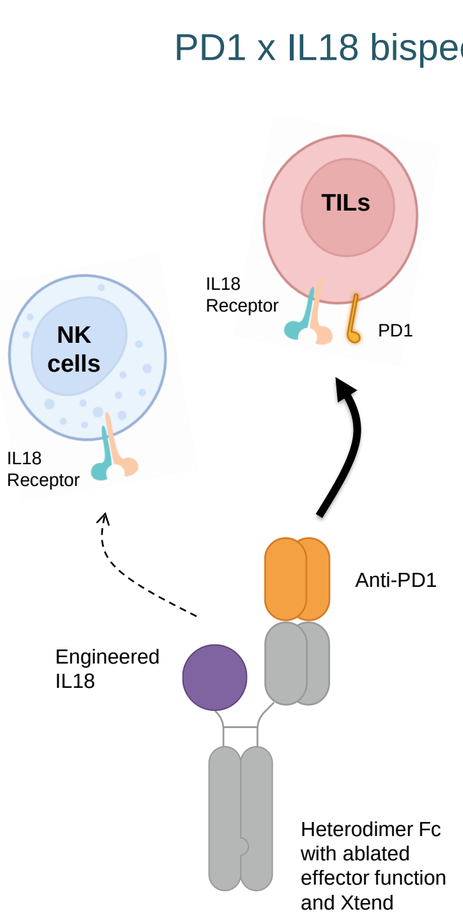
Engineered IL18-Fc potency ladder maintains activity in the presence of IL18BP



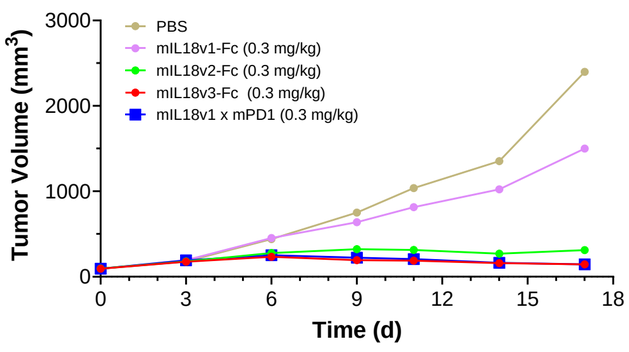
Active forms of engineered IL18-Fc fusions exhibit slow receptor-mediated clearance in NHP



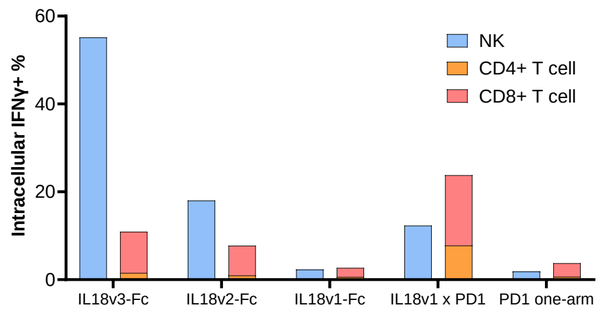
PD1 x IL18 bispecifics can selectively target TILs



mPD1 x mIL18v1 shows marked activity in CT26 tumor model

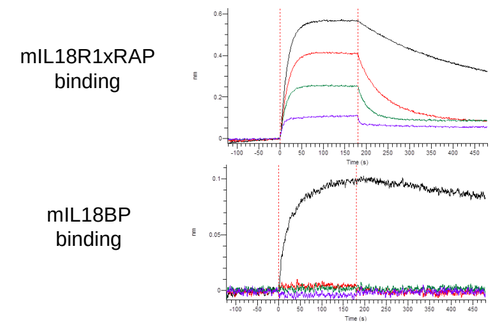


5-day MLR demonstrates T cell directed activity of IL18v1 x PD1

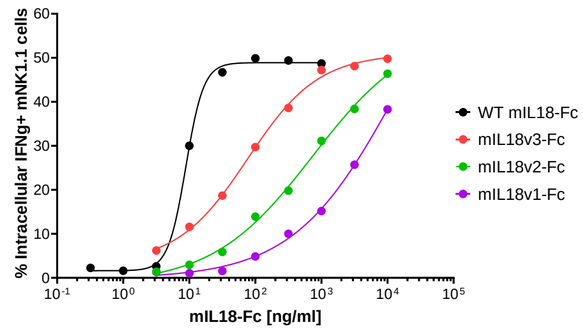


Surrogate mouse IL18-Fc fusions mirror the drug-like properties of the human IL18-Fc fusion proteins

mIL18 receptor binding is maintained as IL18BP binding is knocked out

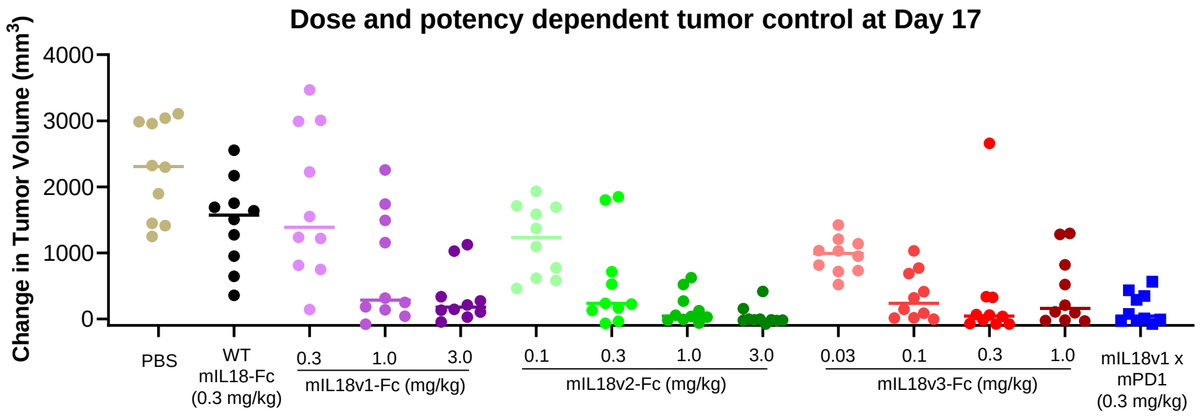


mIL18-Fc fusions exhibit potencies 10-300 fold reduced from WT

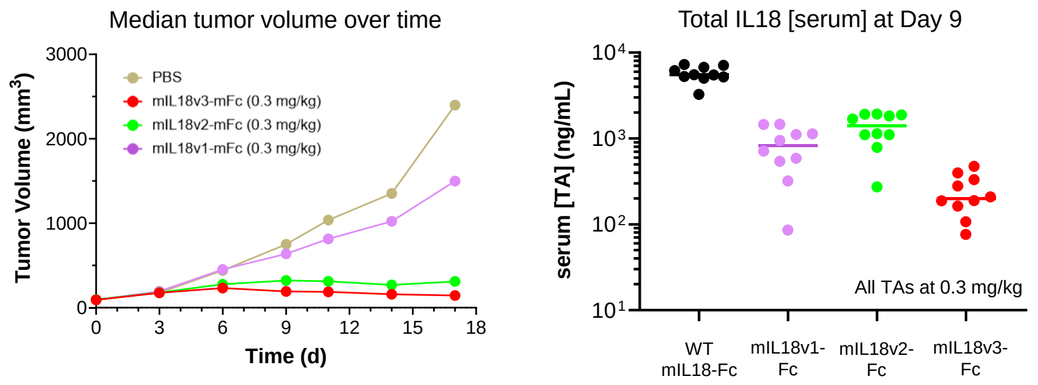


Engineered mIL18-Fc fusions demonstrate anti-tumor activity in a syngeneic CT26 tumor model

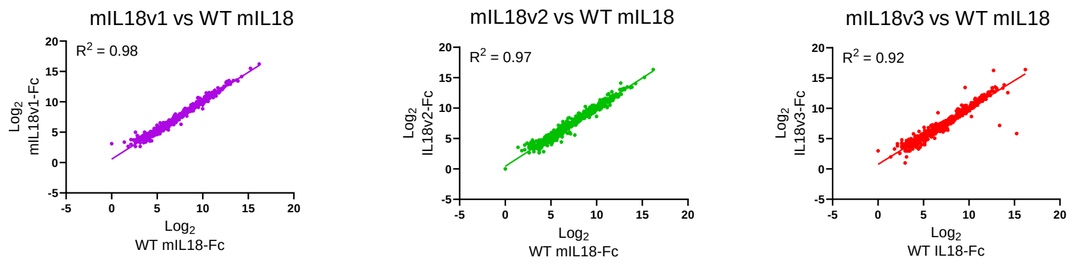
Dose and potency dependent tumor control at Day 17



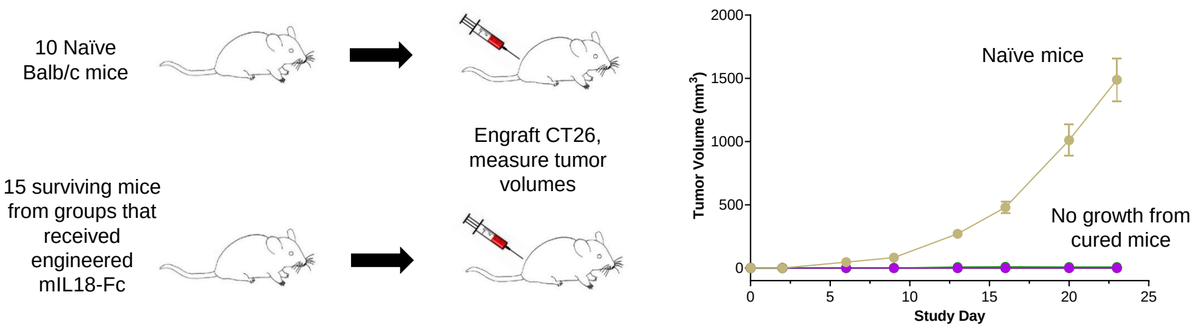
mIL18v2-Fc demonstrates an optimal balance of in vivo potency and pharmacokinetics



Potency reduction does not impact gene expression pattern of Day 9 tumor infiltrates



Tumor-free mice from engineered mIL18-Fc fusions prevent tumor growth upon rechallenge



Summary

- Stabilized WT IL18 served as a platform to further engineer a series of potency reduced IL18 cytokines with near absent affinity toward IL18BP. Engineered IL18-Fc fusion proteins maintain in vitro activity on KG-1 cells with and without IL18BP, and exhibit increased exposure in NHP with improved serum half-life.
- WT mIL18 was similarly engineered to create a series of surrogate cytokine Fc fusions. In a CT26 syngeneic tumor model mIL18-Fc fusions led to impressive tumor control in a dose- and potency-dependent manner. mIL18v2-Fc, 100-fold potency reduced from WT, exhibited an optimal balance of in vivo potency and PK. Surviving mice from the study, majority from groups receiving mIL18v2-Fc, were resistant to rechallenge.
- Bispecific targeting of mIL18v1 to mPD1 demonstrated remarkable tumor growth inhibition that matched higher potency untargeted mIL18-Fc fusions, and activity directed towards T cells was confirmed in vitro.
- Mono and bispecific IL18-Fc fusions exhibit robust anti-tumor activity in a surrogate mouse model and feature improved PK in NHP compared to WT IL18.

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