IL12 heterodimeric Fc-fusions engineered for reduced potency exhibit strong anti-tumor activity and improved therapeutic index compared to native IL12 agents

Matthew J. Bernett*, Ke Liu, Christine Bonzon, Rumana Rashid, Nicole Rodriguez, Nargess Hassanzadeh-Kiabi, Connie Ardila, Katrina Bykova, Michael Hackett, Norman J. Barlow, Irene Leung, Hanh Nguyen, Araz Eivazi, Seung Y. Chu, Kendra N. Avery, Rajat Varma, Umesh S. Muchhal, John R. Desjarlais

*Contact: mbernett@xencor.com

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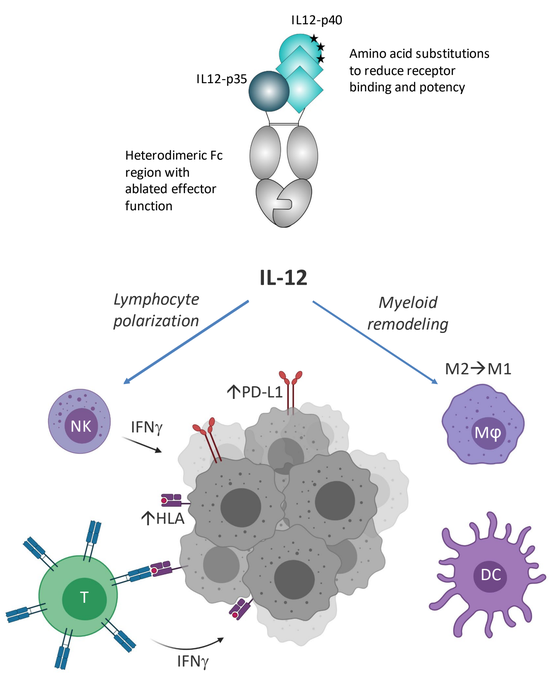
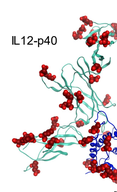
Introduction

Interleukin-12 (IL12) is a heterodimeric proinflammatory cytokine that induces differentiation of Th1 cells, increased proliferation and cytotoxicity of T and NK cells, and may aid in myeloid remodeling. Stimulation with IL12 leads to production of IP10 and IFNγ. These immune-stimulating aspects of IL12 are promising for cancer treatment and may help to convert immunologically suppressed "cold" tumors into inflamed "hot" tumors. Preclinical studies in mice revealed that IL12 can have a dramatic effect on shrinking syngeneic tumors; however, clinical studies in humans have resulted in severe toxicity and a small therapeutic window, limiting response rates. Prior work at Xencor demonstrated that reduced-potency IL15/IL15Rα-Fc fusion proteins exhibited superior pharmacokinetics, pharmacodynamics, and safety in non-human primates through reduction of receptor-mediated clearance. Applying similar principles to IL12, we created XmAb® IL12 heterodimeric Fc-fusions (IL12-Fc) with reduced potency in order to improve tolerability, slow receptor-mediated clearance, and prolong half-life compared to therapeutics using native (wild-type) IL12.

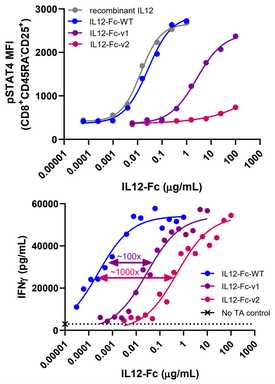
IL12 mechanism and design of Xencor IL12-Fc



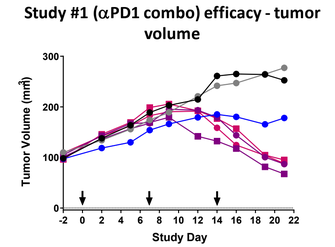
IL12-Fc were engineered for reduced in vitro potency

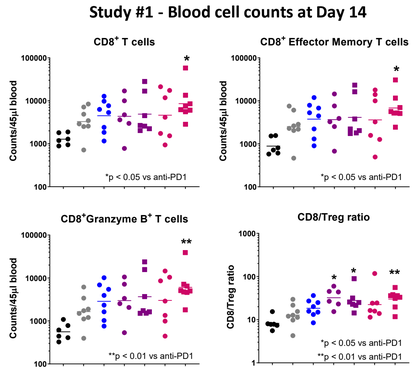


- A library of amino acid substitutions at putative IL12-receptor-interface positions (in red) was created and variants were screened for pSTAT4 signaling (15 min assay) or for IFNγ release in an MLR assay (5 day assay).
- Two lead variants were selected, IL12-Fc-v1 with ~100x-reduced potency and IL12-Fc-v2, with ~1000x-reduced potency.

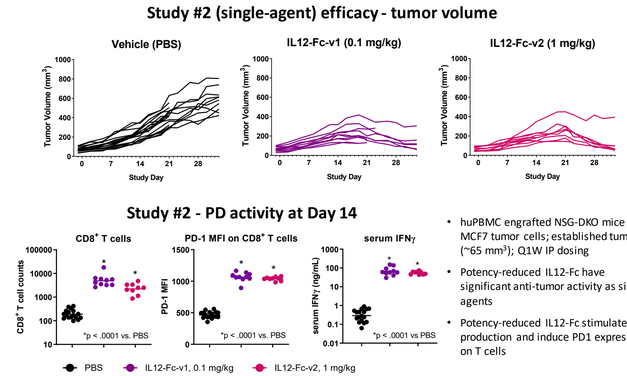


Potency-reduced IL12-Fc are highly efficacious as single-agents and in combination with anti-PD1 in multiple humanized mouse xenograft models





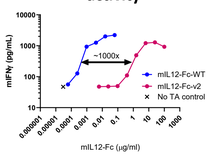
- huCD34+ humanized mice engrafted with MCF7 tumor cells
- Established tumors (~100 mm³); Q1W IP dosing
- Higher dose levels of potency-reduced IL12-Fc have significant anti-tumor activity and PD when combined with anti-PD1



- huPBMC engrafted NSG-DKO mice with MCF7 tumor cells; established tumors (~65 mm³); Q1W IP dosing
- Potency-reduced IL12-Fc have significant anti-tumor activity as single-agents
- Potency-reduced IL12-Fc stimulate IFNγ production and induce PD1 expression on T cells

Potency-reduced surrogate mIL12-Fc are highly efficacious, have superior intratumor PD, and are better tolerated than WT-mIL12-Fc in a CT26 tumor model

Mouse surrogate in vitro activity

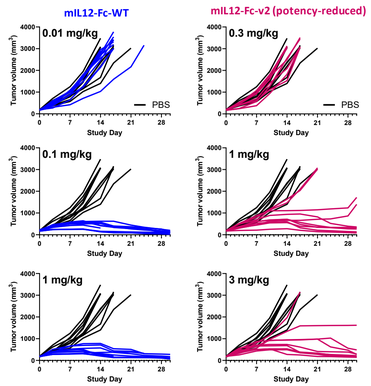


Human IL12 is inactive in mice, so a mouse surrogate IL12-Fc with reduced-potency was engineered to mimic IL12-Fc-v2

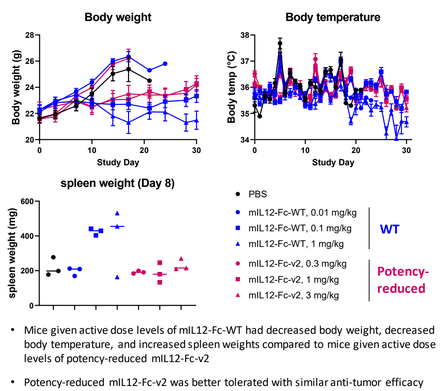
Study design

- WT BALB/c mice
- WT CT26 tumors
- 180-200 mm³ starting MTV
- Q1W dosing (Day 0, 7, 14, 21)
- **Follow-up study with anti-PD1 combo planned**

Efficacy - tumor volume

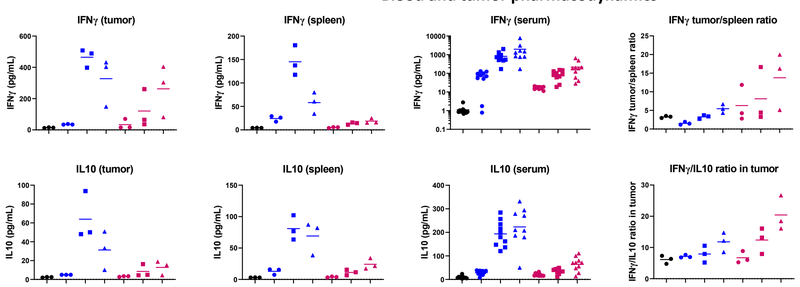


Tolerability



- Mice given active dose levels of mIL12-Fc-WT had decreased body weight, decreased body temperature, and increased spleen weights compared to mice given active dose levels of potency-reduced mIL12-Fc-v2
- Potency-reduced mIL12-Fc-v2 was better tolerated with similar anti-tumor efficacy

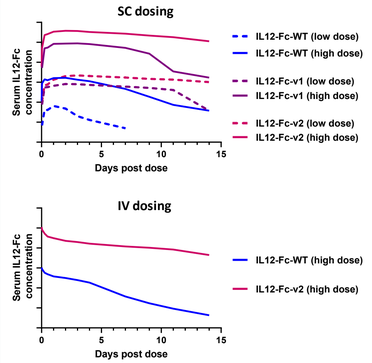
Blood and tumor pharmacodynamics



- At Day 8 (24 hr after second dose), serum cytokines were assayed for all mice, and tumor and spleen cytokines were assayed in a parallel cohort of 3 mice per group
- Mice given potency-reduced mIL12-Fc-v2 had more IFNγ production in tumor compared to spleen, and less IL10 production compared to mice given mIL12-Fc-WT

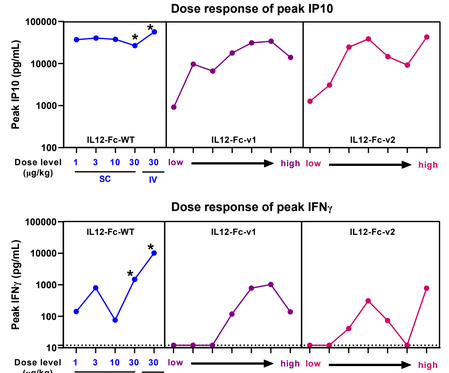
Potency-reduced IL12-Fc have improved PK and therapeutic index in non-human primates

Pharmacokinetics (PK)



Potency-reduced IL12-Fc dosed either SC or IV have superior exposure due to slower receptor-mediated clearance

Blood pharmacodynamics (PD) – serum cytokines



Potency-reduced IL12-Fc have a wider therapeutic window with a more gradual dose response and were well-tolerated at all dose levels tested, with similar levels of IP10 and IFNγ production compared to IL12-Fc-WT

*monkeys given 30 μg/kg IL12-Fc-WT showed signs of toxicity

Summary

- IL12 heterodimeric Fc-fusions (IL12-Fc) were engineered with a reduced potency IL12 in order to improve therapeutic index compared to therapeutics using native (wild-type) IL12.
- Potency-reduced IL12-Fc demonstrate significant anti-tumor activity in mice concurrent with activation and proliferation of CD8+ T cells, increased PD1 expression, and tumor-selective IFNγ production.
- Potency-reduced IL12-Fc have improved therapeutic index compared to IL12-Fc-WT in mice and non-human primates, supporting further testing of potency-reduced IL12-Fc as a potential novel and better-tolerated IL12 cytokine therapy in cancer patients.