IL12 Fc-fusions engineered for reduced potency and extended half-life exhibit strong anti-tumor activity and improved therapeutic index compared to wild-type 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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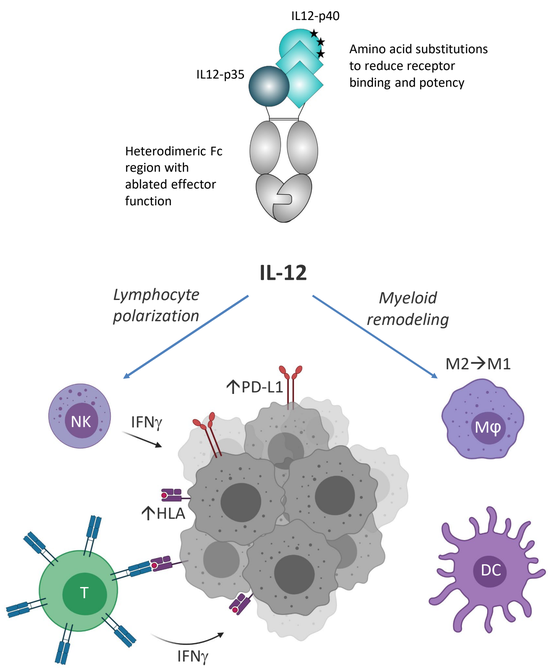
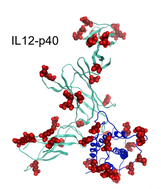
Introduction

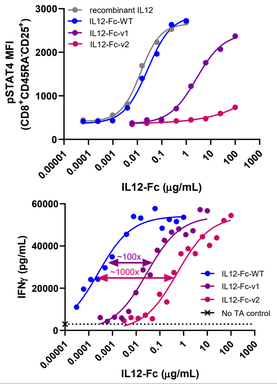
Interleukin-12 (IL12) is a heterodimeric proinflammatory cytokine that induces differentiation of Th1 cells, increased proliferation and cytotoxicity of T and NK cells, and may aid in myeloid remodeling. Stimulation with IL12 leads to production of IP10 and IFNγ. These immune-stimulating aspects of IL12 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



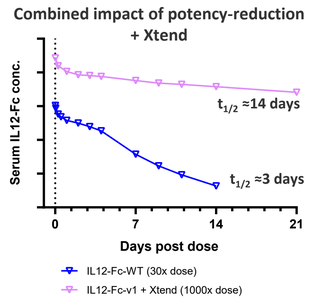
IL12-Fc were engineered for reduced in vitro potency



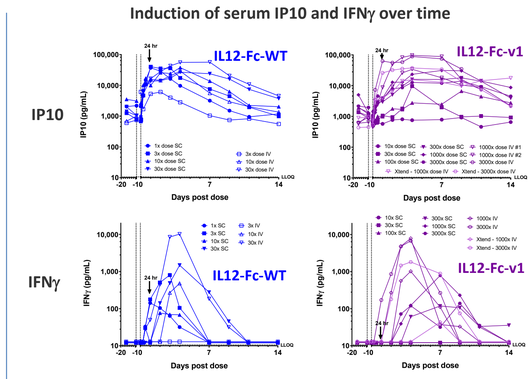


- A library of amino acid substitutions at putative IL12-receptor-interface positions (in red) was created and variants were screened for pSTAT4 signaling (15 min assay) or for IFNγ release in an MLR assay (5 day assay).
- Two lead variants were selected, IL12-Fc-v1 with ~100x-reduced potency and IL12-Fc-v2,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

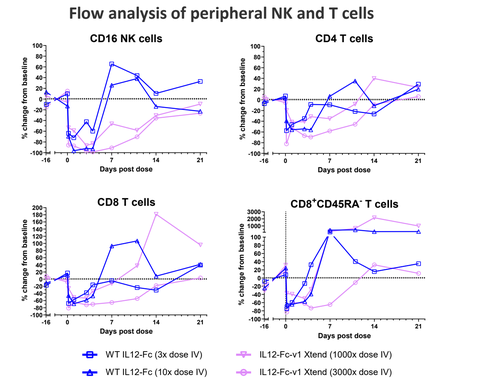
Potency-reduced IL12-Fc have substantially improved PK, PD, and therapeutic index in non-human primates



- Potency-reduced IL12-Fc have superior exposure due to slower receptor-mediated clearance
- Xtend (LS) Fc domain further improves exposure



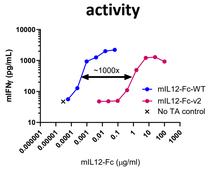
- Potency-reduced IL12-Fc have a more gradual dose response and induce more sustained levels of IP10 and IFNγ production compared to IL12-Fc-WT



- Potency-reduced IL12-Fc cause extended margination of NK and T cells, with some higher rebound especially in the CD8 memory population

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

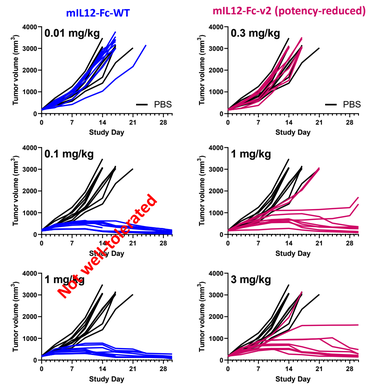


Human IL12 is inactive in mice, so a mouse surrogate IL12-Fc with reduced-potency was engineered to mimic IL12-Fc-v2

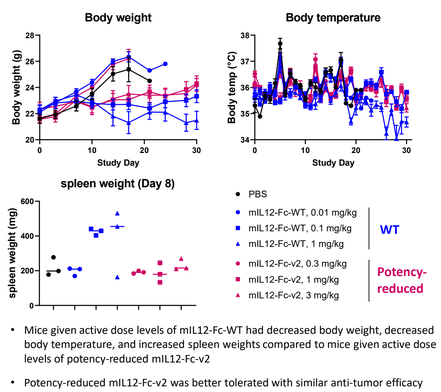
Study design

- WT BALB/c mice
- WT CT26 tumors
- 180-200 mm^3 starting MTV
- Q1W dosing (Day 0, 7, 14, 21)
- **Follow-up study with anti-PD1 combo planned**

Efficacy - tumor volume

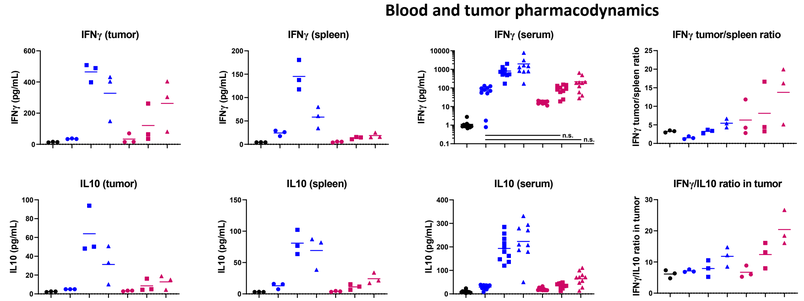


Tolerability



- 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

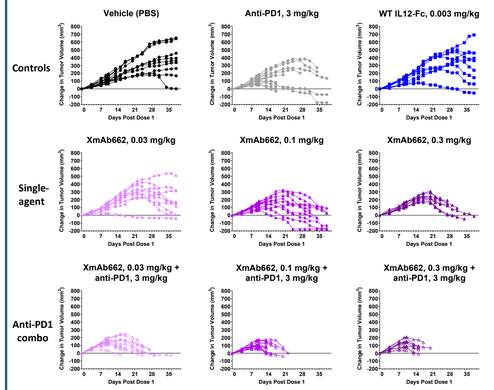
Blood and tumor pharmacodynamics



- 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

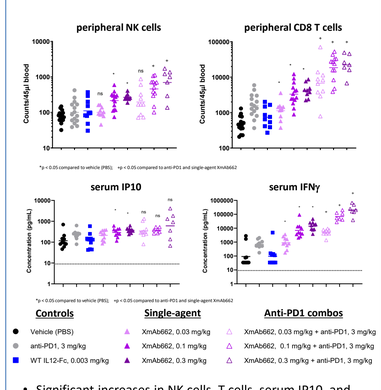
Lead candidate XmAb662 is efficacious as a single-agent and in combination with anti-PD1 in a huCD34 MCF7 tumor model

Anti-tumor efficacy



- HuCD34+ mice; established MCF7 tumors (~100 mm^3); Q1W IP dosing
- Significant anti-tumor activity with single-agent and in combination with anti-PD1

Peripheral PD activity



- Significant increases in NK cells, T cells, serum IP10, and serum IFNγ were observed in single-agent groups; further increases when combined with anti-PD1

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 and tumor-selective IFNγ production.
- Potency-reduced IL12-Fc have improved therapeutic index, improved PK, and more sustained PD compared to IL12-Fc-WT in non-human primates
- These results support clinical testing of lead candidate XmAb662 as a potential novel and better-tolerated IL12 cytokine therapy in cancer patients.