Introduction

- Interleukin-12 (IL12) is a heterodimeric proinflammatory cytokine produced by activated antigen-presenting cells that induces differentiation of Th1 cells and increased proliferation and cytokotoxicity of T and NK cells.
- Stimulation of these cells by IL12 leads to production of high levels of IFNγ. These immune-stimulating aspects of IL12 are promising for cancer treatment and may help to correct 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 IL12/IL12-Fc fusion proteins exhibited superior pharmacokinetics, pharmacodynamics, and safety in non-human primates compared to native IL12 agents.

Mechanism and anti-tumor effects of IL12

- IL12 is a heterodimer consisting of p40 and p35 subunits that signals through the STAT4 pathway. IL12 may help to turn non-inflamed, cold tumors into inflamed, hot tumors that are amenable to checkpoint inhibitor therapy by inducing proliferation of NK and T cells and by production of IFNγ.

Design and analytical characterization of IL12-Fc heterodimers

- IL12 heterodimeric Fc-fusions exhibit strong anti-tumor activity with potentially improved therapeutic index compared to native IL12 agents.

Potency-reduced IL12-Fc are engineered for optimal activity and extended serum half-life

- Potency-reduced IL12-Fc-v2 demonstrated significant anti-tumor activity concurrent with activation and proliferation of CD8+ T cells, increased serum IFNγ, and ablated effector function.

IL12-Fc with reduced in vitro potency were engineered in order to improve therapeutic index

- These immune-stimulating aspects of IL12 are promising for cancer treatment and may help to correct immunologically suppressed "cold" tumors into inflamed "hot" tumors.

Potency-reduced IL12-Fc show strong anti-tumor activity and PD response as single-agent and in combination with anti-PD1

Summary

- IL12 heterodimeric Fc-fusions were engineered with a potency-reduced IL12 in order to improve tolerability, slow receptor-mediated clearance, and prolong half-life in vivo compared to therapeutics using native IL12.
- Potency-reduced IL12-Fc demonstrate significant anti-tumor activity concurrent with activation and proliferation of CD8+ T cells, increased PD1 expression, and increased serum IFNγ.
- These results support further testing of potency-reduced IL12-Fc as a potential novel cytokine therapy in cancer patients.