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

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 remodelling. 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 IL12/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 Xencor’s IL12 heterodimeric Fc-fusions (IL12-Fc) with reduced potency in order to improve tolerability, slow receptor-mediated clearance, and prolong half-life compared to therapies using native (wild-type) IL12.

IL12-Fc were engineered for reduced in vitro potency

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

IL12 mechanism and design of Xencor IL12-Fc

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

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

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.