What is IL-12?

Cytokines are small proteins that carry messages between cells and serve as master regulators of the immune system. Interleukins are groups of cytokines expressed and secreted by immune cells that regulate their activity. Interleukin-12 (or IL-12) has emerged as one of the most potent cytokine mediators of antitumor activity because of its multiple effects on different immune cells in the tumor microenvironment. IL-12 is able to activate and bridge both innate (natural killer or NK cell) and adaptive (cytotoxic CD8+ T and CD4+ T cells) immunity to promote tumor cell killing while further coordinating additional anti-cancer defenses such as regulatory T-cell suppression and anti-angiogenic effects.

IL-12: The ‘Holy Grail’ of Immuno-Oncology

Not all tumors are created equal. Some are immunologically “cold” and lack immune cell infiltrates such as NK or T cells or may contain immune suppressive cells (e.g., ovarian, prostate, pancreatic, MSS colorectal). Others are “hot,” abundant with NK and CD8+ T cells and a pro-inflammatory microenvironment that is more conducive for an immunotherapy agent to kill tumor cells (e.g., melanoma, head & neck, non-small cell lung, triple-negative breast, MSI high colorectal, endometrial).

Traditional immuno-oncology (I-O) therapies have been most effective at targeting hot tumors. IL-12, however, ‘remodels’ the tumor microenvironment, potentially shifting cold tumors to warm or hot. Furthermore, IL-12 can synergize with other cytokines like IL-2 to potently stimulate anti-tumor immunity. There are presently no approved IL-12 therapies due to severe systemic toxicity with unmodified IL-12. An I-O candidate that can harnesses the potential of IL-12 and direct its potency selectively toward the tumor could deliver a transformative range of therapeutic opportunity.

Cancer Immunotherapy

Xilio Therapeutics is pioneering an innovative platform to progress a pipeline of novel, tumor-activated immunotherapies that have the potential to significantly improve outcomes for patients living with cancer. Xilio is focused on developing tumor-activated cytokine immunotherapies with exemplary clinical activity and tolerability.

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**XTX301: Xilio’s Tumor-Activated IL-12 Candidate**

Xilio engineered XTX301 as a highly potent, extended half-life, tumor-activated IL-12 that has the potential to deliver a therapeutic dose with low systemic toxicity for a broad therapeutic index.

When XTX301 enters the body, the protein-engineered masking domain prevents it from binding to IL-12 receptors on cells and activates them in the blood stream. Once XTX301 reaches the tumor microenvironment, enzymes present in the tumor called matrix metalloproteinases (MMPs) activate a switch in XTX301 and release the active IL-12 cytokine. Once activated, XTX301 can unleash its potent immune stimulatory effects selectively in the tumor with the goal of promoting an anti-tumor response. In addition to single-agent application, XTX301 has significant potential as a combination agent with other I-O agents, including IL-2 (XTX202) and checkpoint inhibitors including anti-CTLA-4 (XTX101) and anti-PD-1.

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**XTX301 In Pre-Clinical Studies**

A murine version of XTX301 (mXTX301) potently inhibited tumor growth in MC38 (hot) and B16F10 (cold) syngeneic tumor mouse models without toxicity. Furthermore, XTX301 was well-tolerated in non-human primates with repeated dosing. XTX301 demonstrated robust activation in human tumor samples but was minimally activated *in vitro* in human patient plasma, suggesting tumor-selective activation.

XTX301 is designed to achieve potent anti-tumor activity while widening the potential therapeutic index of IL-12 treatment.

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**XTX301 In the Clinic**

The U.S. Food and Drug Administration cleared an investigational new drug (IND) application for XTX301 in November 2022. Xilio anticipates initiating a Phase 1 dose-escalation trial to characterize the safety and tolerability profile of XTX301 in patients with advanced solid tumors in the first quarter of 2023.

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Visit [xiliotx.com](http://xiliotx.com) to learn more about XTX301 and other Xilio clinical programs.