We hypothesized that we could selectively target tumor and NK cells. Serum IFN-γ-0.5 chain LAG3 x IL15 shows a promising profile of selective delivery to LAG3+ TIL while avoiding peripheral lymphocytes. NeoTCR vs. all other T cells neoantigen specific T cells compared to PD1. 56 CD8+ T Cells counts due to reduced potency IL15/IL15Rα heterodimeric Fc domain targets IL15/IL15R with minimal peripheral activity and may help to preferentially expand LAG3+ TILs in patients with cancer, while potentially shrinking systemic toxicity due to off-target activation and expansion of peripheral lymphocytes.

LAG3 x IL15 promotes T cell proliferation and IFNγ production in huPBMC-engrafted NSG mice (GVHD model)

**Introduction**

- IL2 and IL15 are potent cytokines that cause activation and proliferation of T and NK cells.
- Having evolved for local activity at very low concentrations, they suffer from low tolerability and very fast clearance that limits therapeutic window when given systemically as therapeutics.
- Tumor-infiltrating lymphocytes (TIL) are known to express multiple immune checkpoints (CP) such as PD1 and LAG3, and these have limited peripheral expression in normal human PBMCs.
- We hypothesized that we could selectively target tumor-reactive TIL by combining a reduced potency IL15/IL15Rα heterocomplex with a Fab-based LAG3-targeting arm to bias binding and activation to LAG3-positive TILs, potentially improving therapeutic index.
- LAG3 was chosen as the CP targeting arm due to its frequent co-expression with PD1, bias to CD8+ T Cells, ability to easily combine with anti-PD1 agents, and recent promising results with anti-LAG3 agents in the clinic.

LAG3 x IL15 bispecific Fc fusions are engineered for optimal activity to LAG3+ TIL with minimal peripheral activity

**Rationale and design of LAG3 x IL15**

IL2 and IL15 share IL2R and γc receptor interactions

LAG3 x IL15 is designed to selectively deliver IL15 to LAG3+ TIL while avoiding peripheral lymphocytes

- Potency-reduced IL15/IL15Rα(sushi domain) and a Fab arm targeting LAG3 are attached to Xencor’s heterodimeric Fc domain.
- The Fc domain is further modified to eliminate Fcγ-R interactions and contains Xtend™ Fc technology to promote longer half-life and extended pharmacodynamics (PD).
- Fab domain targets IL15/IL15Rα to LAG3+ TIL; minimal peripheral activity on LAG3 cells due to reduced potency IL15 arm and low or lack of LAG3 expression on normal cells.

LAG3 x IL15 has superior in vivo PK and shows selective targeting of LAG3+ peripheral T cells in NHP

**Summary**

- LAG3 x IL15 bispecific Fc fusions were constructed and show high selectivity for LAG3+ cell populations in multiple in vitro and in vivo models.
- LAG3 x IL15 shows a promising profile of selective delivery to LAG3+ cells with minimal peripheral activity and may help to preferentially expand LAG3+ TILs in patients with cancer, while potentially suppressing systemic toxicity due to off-target activation and expansion of peripheral lymphocytes.