LAG3-targeted IL15/IL15Rα-Fc (LAG3 x IL15) fusion proteins for preferential TIL expansion via cis delivery of IL15 to LAG3+ cells

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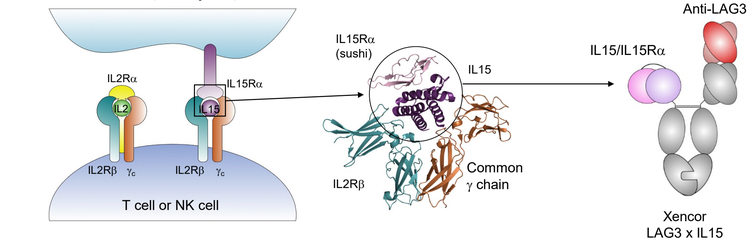
Introduction

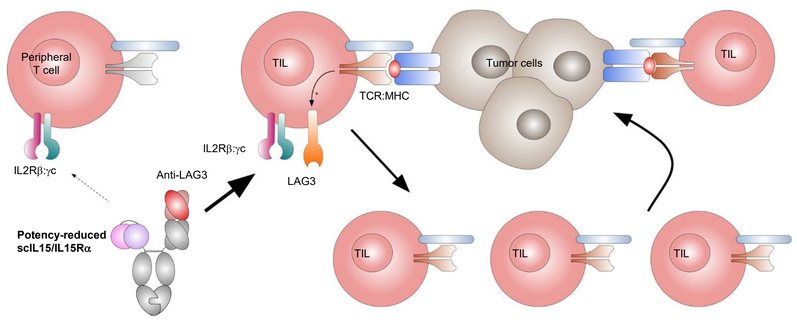
- IL2 and IL15 are potent cytokines that cause activation and proliferation of T and NK cells. Having evolved for local activity at very low concentrations, they suffer from low tolerability and very fast clearance that limits therapeutic window when given systemically as therapeutics.
- Tumor-infiltrating 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



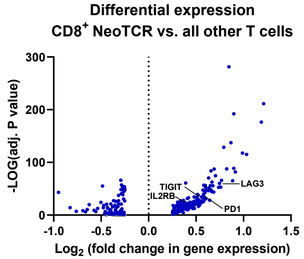
LAG3 x IL15 are designed to selectively deliver IL15 to LAG3+ TIL while avoiding peripheral lymphocytes



- **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 FcγR 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

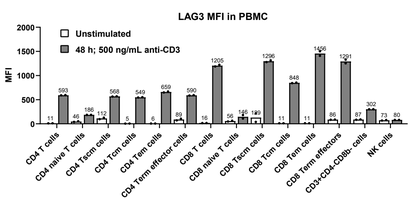
LAG3 is CD8-biased and LAG3 x IL15 demonstrates potent activity and high selectivity for LAG3+ T cells in vitro

LAG3 is CD8-biased and more highly expressed on CD8+ neoantigen specific T cells compared to PD1

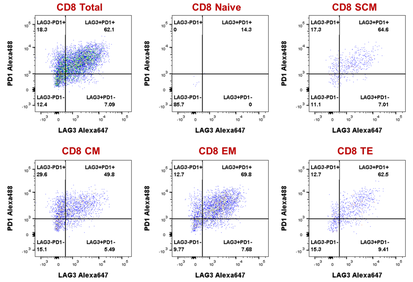


Data from F. J. Lowery et al., Science 10.1126/science.abl5447 (2022). Data from scRNA-seq and TCR-seq on CD8+ and CD4+ T cells within metastatic cancers from 10 patients across multiple solid tumor types.

LAG3 expression is low on normal huPBMC but can be upregulated on T cells activated with anti-CD3

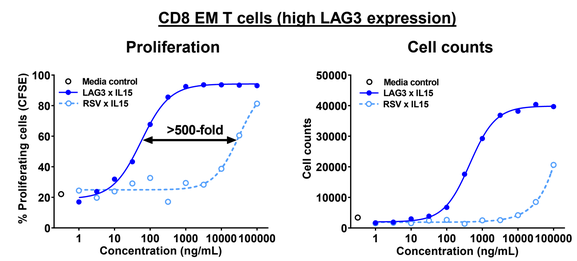


On activated huPBMC, LAG3 expression is highest on CD8 effector memory T cells and LAG3 is largely coexpressed with PD1



Human PBMC were activated with 500 ng/mL plate-bound anti-CD3 (OKT3) for 48 h and then analyzed by flow cytometry for LAG3 and PD1 expression.

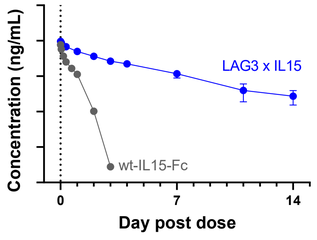
LAG3 x IL15 induces proliferation and increases LAG3+ cell counts; has pronounced selectivity (>500-fold) for LAG3+ cells in vitro



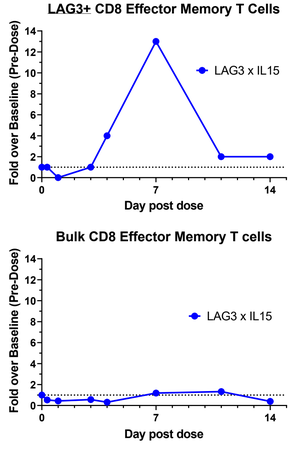
LAG3 x IL15 was constructed along with RSV x IL15 (anti-RSV Fab-arm) as a control for untargeted activity. Human PBMC were activated with 500 ng/mL plate-bound anti-CD3 (OKT3) for 48 h, labeled with CFSE, treated with targeted-IL15 molecules for 4 days at 37 °C, and then analyzed by flow cytometry.

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

LAG3 x IL15 has superior PK compared to wt-IL15-Fc in NHP

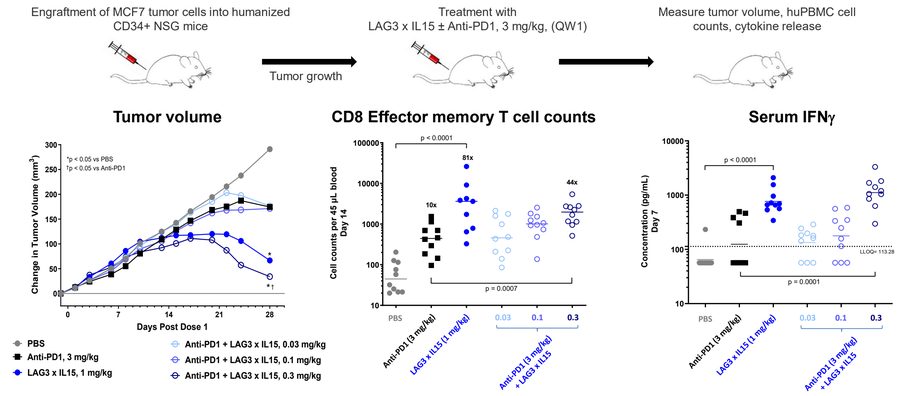


LAG3 x IL15 has selectivity for LAG3+ cells in NHP



A single dose of LAG3 x IL15 or IL15/IL15Rα-Fc (wild-type IL15) was administered to cynomolgus monkeys (NHP). Drug concentrations (PK, top) and lymphocyte counts (PD, right) were monitored over time.

LAG3 x IL15 is efficacious as a single-agent and in combination with anti-PD1 in a huCD34 MCF7 tumor model



Summary

- LAG3 x IL15 shows a promising profile of selective delivery to LAG3+ cells with minimal peripheral activity and may help to preferentially expand LAG3+ TIL in patients with cancer, while potentially avoiding systemic toxicity due to off-target activation and expansion of peripheral lymphocytes.