IL15/IL15Rα heterodimeric Fc-fusions with extended half-lives

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Abstract #1595

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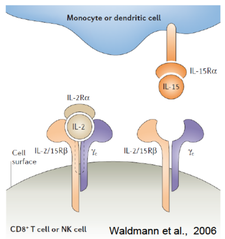
Introduction

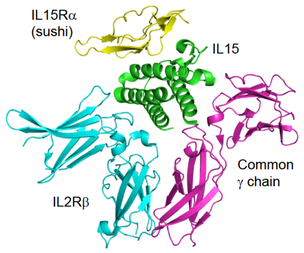
- IL15 is a highly active cytokine that stimulates the proliferation and differentiation of T and NK cells, yet has an in vivo half-life of <1 hr which limits its utility as a therapeutic.
- IL15 is produced by monocytes and dendritic cells and functions as a stabilized heterodimeric complex with membrane-bound IL15Rα present on the same cells.
- On APCs, the IL15/IL15Rα complex is presented in *trans* to NK cells and CD8⁺ T cells expressing IL2Rβ and the common gamma chain. It has been shown that recombinant IL15/IL15Rα heterodimer is highly active.
- To create a more druggable IL15 therapeutic, we engineered IL15/IL15Rα heterodimeric Fc-fusions that can be produced by standard industry methods, have high activity, and extended serum half-life.

IL15 is presented in *trans* to NK and T cells as an IL15/IL15Rα complex on APCs:



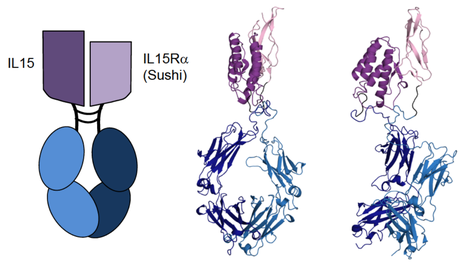
Waldmann et al., 2006

Structure of the IL15-receptor complex:

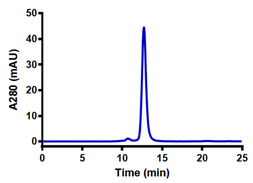


A IL15/IL15Rα-Fc heterodimers are engineered for optimal activity and extended serum half-life

Schematic and 3D structural model of IL15/IL15Rα-Fc heterodimer



Analytical SEC of purified IL15/IL15Rα-Fc heterodimer

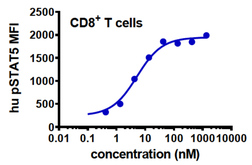


- Monovalent IL15/IL15Rα(sushi domain) is attached to Xencor's well-validated heterodimeric Fc domain
- Fc domain is modified to eliminate FcγR interactions
- Fc domain may also be modified with Xtend® Fc technology to promote longer half-life
- Produced in high yields and purified by standard methods

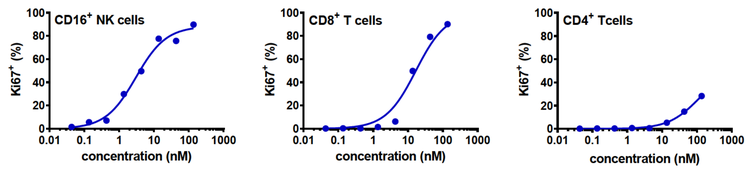
B IL15/IL15Rα-Fc heterodimers promote signaling and cell proliferation in vitro

- STAT5 phosphorylation assay
  - huPBMCs are treated with IL15/IL15Rα-Fc for 15 minutes, followed by analysis by flow cytometry
  - IL15/IL15Rα-Fc induces potent signaling of CD8⁺ T cells
- Cell proliferation assay
  - huPBMCs are treated with IL15/IL15Rα-Fc for 3 days, followed by analysis by flow cytometry
  - IL15/IL15Rα-Fc induces potent *in vitro* proliferation of NK cells, CD8⁺ T cells, and to a lesser extent CD4⁺ T cells

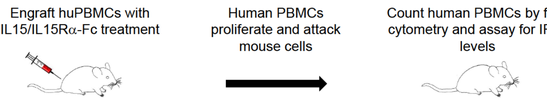
In vitro signaling activity of IL15/IL15Rα-Fc



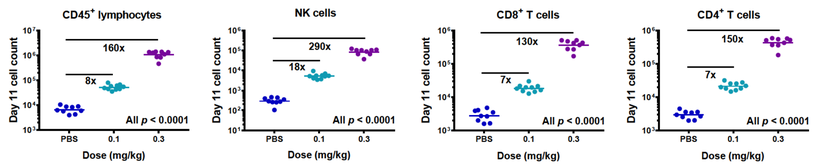
In vitro cell proliferation of human PBMCs by IL15/IL15Rα-Fc



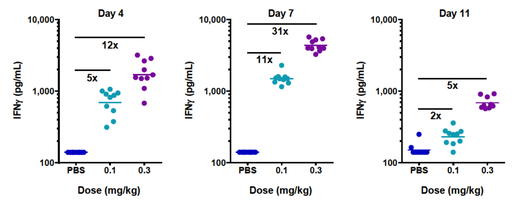
C IL15/IL15Rα-Fc heterodimers promote T cell proliferation and IFNγ production in huPBMC-engrafted NSG mice



- Human lymphocyte, NK cell, CD8⁺ T cell, and CD4⁺ T cell counts are significantly increased by IL15/IL15Rα-Fc heterodimers in a dose dependent manner:

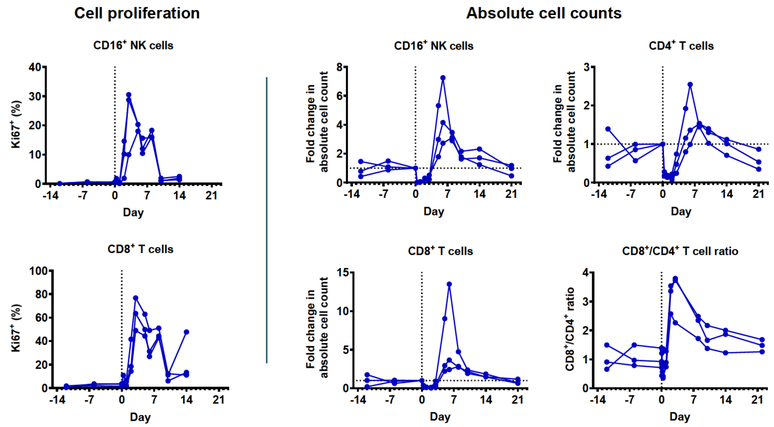


- Human IFNγ production is significantly increased by IL15/IL15Rα-Fc heterodimers:

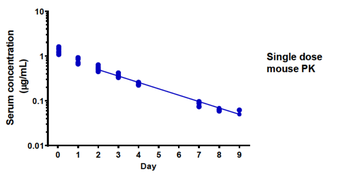


D IL15/IL15Rα-Fc heterodimers are active in cynomolgus monkeys

- Cynomolgus monkeys (n = 3 per group) were given a single IV dose of IL15/IL15Rα-Fc, and lymphocyte proliferation and counts were assessed over time for 21 days
- IL15/IL15Rα-Fc causes significant increases in lymphocyte subsets, peaking at Day 6; increased CD8⁺/CD4⁺ T cell ratio is also observed



E IL15/IL15Rα-Fc heterodimers have antibody-like PK in mice



- IL15/IL15Rα-Fc heterodimers have a much longer half life vs. <1 hr for recombinant IL15
- Longer half-life should allow for greater exposure and a more favorable dosing regimen

Summary

- Engineered IL15/IL15Rα-Fc heterodimers with extended serum half-life have been produced using Xencor's heterodimeric Fc domain.
- IL15/IL15Rα-Fc heterodimers stimulate potent in vitro and in vivo proliferation and activation of human lymphocytes.
- IL15/IL15Rα-Fc heterodimers are active in cynomolgus monkeys and show expansion of multiple lymphocyte subsets.
- IL15/IL15Rα-Fc heterodimers have extended half-life in mice.
- These results support clinical testing of an IL15/IL15Rα-Fc heterodimer as a novel cytokine therapy in cancer patients.

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