Pharmacokinetic and pharmacodynamic study of NKTR-255, a polymer-conjugated IL-15, in cynomolgus monkey
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Introduction
Interleukin-15 (IL-15) is a common cytokine that activates and provides survival benefit to memory T and NK cells. IL-15 is predominantly produced by myeloid cells and its receptor is a heterotrimer consisting of the IL-15Rα subunit and IL-2/IL-15Rβγ subunit. Exploiting the therapeutic value of native IL-15 has been challenging due to its unfavorable pharmacokinetic properties and undesirable tolerability profile. NKTR-255 is a polymer-conjugated human IL-15 that retains binding affinity to the subunit of the IL-15 receptor and exhibits reduced clearance to provide a sustained pharmacodynamics response. Here we investigate the biological effects of NKTR-255 in naïve cynomolgus monkey.

IL-15-mediated signaling through cis- and trans-presentation
IL-15 binds the unique IL-15Rα chain and presents to the IL-2/IL-15Rβγ complex on the same (cis) or adjacent cell (trans). Engagement of the IL-2/IL-15Rβγ complex can induce JAK-STAT signaling, increasing survival and proliferation. This process is crucial for the proper support of IL-15 biology.

Methods

In vitro assay:
Cynomolgus monkey whole blood was stimulated with the indicated concentration of NKTR-255 or IL-15 for 20 minutes and the percentage of pSTAT5 positive populations in each of NK, CD4 T and CD8 T cells was determined by flow cytometry.

In vivo PK:
Male cynomolgus monkeys received single IV doses of 0.001, 0.01 or 0.1 mg/kg of NKTR-255. Blood samples were collected to measure STAT5 phosphorylation, Ki-67 expression, Granzyme B expression and frequency of cell populations.

Results

NKTR-255 induced dose-dependent phosphorylation of STAT5 in monkey whole blood (BDCA values NK: 6.9 mg/mL, CD4 T cells: 59 mg/mL, CD8 T cells: 53 mg/mL). The half-life and clearance of NKTR-255 were 28k and 38k lower, respectively, than of IL-15. NKTR-255 engaged the IL-15 signaling pathway in vivo, demonstrating a more robust and sustained STAT5 phosphorylation in lymphocytes. NKTR-255 dose the proliferation of total CD8 T cells and NK cells in a dose-dependent manner, with dramatic and durable increased observed in NK cells. CD8 T cells and absolute numbers of NK cells, 61 and fold increase (CD8 T cells: 3.8 fold from baseline on day 5 at 0.1 mg/kg). These effects were strongly biased towards CD8 T cells and NK cells, with substantially less induction of CD4 T cells. The Ki67 response of the T cell subpopulation revealed a higher response of memory populations than naïve T cells. Among memory T cells, effector memory T cells showed the highest response over stem cell memory T cells and central memory T cells. NKTR-255 also increased the expression of Granzyme B in both NK and CD8 T cells, consistent with an enhancement in target cell lysis. Finally, repeated administration of NKTR-255 sustained the Ki67 response of NK and CD8 T cells at levels similar to those observed at the single dose.

Conclusions
• NKTR-255 engages the JAK/STAT5 pathway with 10-fold less potency compared with IL-15
• A single dose of NKTR-255 exhibited reduced clearance and longer half-life than IL-15
• A single dose of NKTR-255 substantially enhanced in vivo proliferation and activation of NK and CD8 T cells
• A single dose of NKTR-255 resulted in a higher response of memory populations than naïve T cells
• A single dose of NKTR-255 increased levels of a cytotoxic enzyme in NK and CD8 T cells
• Repeat dosing of NKTR-255 does not reduce the magnitude of Ki67 responses in NK and T cells

References
1. Matsui et al. Regulation of mouse NK cell development and function by cytokines. Front Immunol. 10 Dec 2013