T cell priming with Deep™ IL-15 improves preclinical safety compared to systemic IL-15, and increases in vivo persistence and activity

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Introduction
Interleukin-15 (IL-15), provides strong activation of both CD8+ T cells and NK cells, without regulatory T cell activation, making it an attractive immune modulator in cancer therapy. Systemic delivery of IL-15 to patients has revealed dose-limiting toxicities resulting primarily from expansion of NK cells. Preclinical data suggest that IL-15 immunomodulation is mediated by hyperproliferation and activation of NK cells (Guo Y. ImmunoMed 2015). In this study, we investigated safety and efficacy of T cells loaded with Deep IL-15 (Deep IL-15 Primed T cells), a synergistic mouse model. Deep IL-15 is a multimer of chemically crosslinked IL-15/IL-15 Ra/Fc heterodimers (IL-15Fc) that is designed to be surface-anchored to T cells prior to adoptive cell transfer with the aim of improving the therapeutic window by autocrine signaling to the primed cell without causing the immunomodulatory effects normally associated with IL-15. Deep IL-15 is loaded on the T cells and, upon crosslinker cleavage, releases IL15-Fc to stimulate the primed cell. This novel T cell-based therapeutic approach enables autocrine T cell activation and expansion, and limits systemic exposure to IL15-Fc, thus reducing associated toxicities.

Deep IL-15 Provides Autocrine Cytokine Stimulation

Deep IL-15 Primed PMEL cells show improved in vivo persistence across multiple tissues compared to PMEL cells or PMEL + IL15-Fc treated mice for the individual tissues at the end of the study (Day 16).

Results

Deep IL-15 improves persistence of transferred PMEL cells across multiple tissues

Figure 3. Deep IL-15 loading improves expansion and anti-tumor activity compared to PMEL

• Deep IL-15 Primed PMEL cells do show different biodistribution in naïve vs tumor – bearing mice:
  • Reduced accumulation in spleen of tumor – bearing mice
  • Enhanced accumulation in tumor-draining LN compared to contralateral LN

• Loading of PMEL cells with Deep IL-15 results in increased persistence of PMEL cells in circulation as well as in the periphery and at the tumor site.

• Deep IL-15 primed PMEL cells showed improved in vivo expansion and anti-tumor activity compared to PMEL.

• Clinical trials with Deep IL-15 Primed multi-target T cells (TRQ5015) are expected to start in 2018.

Summary

References