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 immunotoxicity is mediated by hyperproliferation and activation of NK cells (Guo Y, J Immunol 2015). In this study, we investigated safety and efficacy of T cells loaded with Deep IL-15 (Deep IL-15 Primed T cells), in a syngeneic mouse model. Deep IL-15 is a multimer of chemically crosslinked IL-15/IL-15 Fc heterodimers (IL15-Fc) 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 cells without causing the immunotoxicological 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 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 cells without causing the immunotoxicological effects normally associated with IL-15.

Results
Deep IL-15 results in lower exposure to IL15-Fc and lower IFN-γ release compared to soluble IL15-Fc

In contrast to IL15-Fc, Deep IL-15 does not affect leukocyte counts

PMEL model: surrogate for human Deep IL-15 Primed multi-targeted T cells

Deep IL-15 does not expand endogenous CD8+, CD4+ and NK cells

Deep IL-15 primed PMEL cells show in vitro expansion comparable to multi-targeted T cells

PMEL cells show in vitro expansion comparable to multi-targeted T cells

Model enables evaluation of antigen-specific T cell activity in a fully immunocompetent mouse

Donor CD8+ PMEL T cells express a transgenic T cell receptor (TCR) directed against PMEL-17, and are loaded with Deep IL-15 (Deep IL-15 Primed T cells), in a syngeneic mouse model. Deep IL-15 is a multimer of chemically crosslinked IL-15/IL-15 Fc heterodimers (IL15-Fc) 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 cells without causing the immunotoxicological 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 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 cells without causing the immunotoxicological effects normally associated with IL-15.

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

Deep IL-15 loading results in minimal/mild histopathology findings

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

Deep IL-15 Primed PMEL cells: [CD90.1+] in blood, spleen, left and right lymph nodes (LN) were enumerated by flow cytometry. ([CD90.1+] = 10 x 106). Deep IL-15 Primed PMEL cells: [CD90.1+] in blood, spleen, left and right lymph nodes (LN) were enumerated by flow cytometry. ([CD90.1+] = 10 x 106). Deep IL-15 Primed PMEL cells: [CD90.1+] in blood, spleen, left and right lymph nodes (LN) were enumerated by flow cytometry. ([CD90.1+] = 10 x 106). Deep IL-15 Primed PMEL cells: [CD90.1+] in blood, spleen, left and right lymph nodes (LN) were enumerated by flow cytometry. ([CD90.1+] = 10 x 106).

Summary
• Deep IL-15 Primed PMEL cells: Preferentially expand CD8+ T cells in circulation and intratumorally
• Do not increase bystander circulating neutrophils or lymphocytes, including NK cells, which are associated with the immunotoxicity for systemic IL-15
• Result in dramatically lower systemic exposure to IL-15-Fc
• Do not induce significant systemic cytokine release
• Do not result in significant body weight loss
• Result in histopathology findings of lower severity compared to IL15-Fc across multiple organs
• 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 show improved in vivo expansion and anti-tumor activity compared to PMEL
• Clinical trials with Deep IL-15 Primed multi-target T cells (TRQ15-01) are expected to start in 2018.

References