Title: NT-I7, a long-acting recombinant human interleukin-7, enhances T cell reconstitution following total body irradiation

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Abstract:

Total body irradiation (TBI) causes profound T cell depletion, increasing chances of infection. Therapeutic options for improving T cell recovery following TBI are not available. Exogenous administration of IL-7 has been shown to increase peripheral blood (PB) T cell levels in mice and humans, albeit offset by its short half-life in circulation. NT-I7 (efineptakin alfa) is a long-acting recombinant human IL-7 fused with a hybrid Fc fragment that has been shown to significantly and persistently increase T cell counts in the clinical setting.

In mice exposed to TBI (5 Gy), total T cell count in the NT-I7 treated group recovered back to normal much quicker than that in the vehicle control group (Figure 1A). NT-I7 also enhanced naïve, central memory, as well as effector memory T cell recovery. To determine whether NT-I7 also stimulates systemic T cell recovery, we established a T cell-specific luciferase reporter strain, CD4-Cre x $Luc^{flox/flox}$ (T-Luc), to monitor T cell recovery in vivo. Robust T cell recovery was observed in NT-I7-treated animals following TBI (Figures 1B). Notably, the effect on T cell recovery persisted after the last injection and was readily detected in the thymus, lymph nodes, spleen, and the gastrointestinal tract. These findings were subsequently validated by significantly increased absolute T cell counts after TBI (NT-I7 vs. vehicle, $P < 0.05$, CD8 PB and BM T cells; $P < 0.001$, PB CD4 T cells and spleen CD8 T cells). Imaging analyses showed that both irradiated BM cells and remaining peripheral T cells contributed to T cell recovery by NT-I7 through thymic-dependent and -independent mechanisms. Interestingly, thymocyte development showed that NT-I7 preferentially enhanced CD8 fate commitment, which may be critical for mounting cytotoxic response against pathogen challenges. Functional assays suggested that expression of Granzyme B, IFN-**γ** and TNF-α, were preserved in NT-I7 group, in addition to preservation of proliferation capacity in response to TCR stimuli. Altogether, we have demonstrated that NT-I7 enhances rapid induction of systemic T cell regeneration and preserves effector T cell functions, indicating that NT-I7 is a promising therapeutic for significantly accelerating T cell recovery after radiation exposure.