Cell therapy with surface-tethered IL-12 provides immune system priming and strong anti-tumor activity

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Abstract

Efficacy in the absence of lymphodepletion enables further improved tumor control using multiple cell doses. In a second experiment mice were treated with two cell doses spaced two weeks apart (B). Lymphodepletion with cyclophosphamide was used one day prior to the first cell dose; the second cell dose was given in the absence of additional lymphodepletion. Multiple doses of tumor-specific T cells carrying a Deep IL-12 approach to augment the efficacy of cell therapy for cancer, including for solid tumors. This multi-targeted T cells for paracrine-like, time-limited release in the tumor microenvironment.

Deep IL-12 Key Findings

- Enables strong loading and persistence of IL-12 on the T cell surface
- Improves tumor-specific T cell therapy through >100-fold greater activity of systemically administered IL-12
- Effect in the absence of lymphodepletion enables further improved tumor control through multiple cell doses

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Deep IL-12 enables tumor-specific cell therapy better than >100x systemic IL-12

Efficacy in the absence of lymphodepletion can enable further improved tumor control using multiple cell doses.

Conclusions

- Antibody-mediated cytokine tethering enables high loading and strong surface persistence of IL-12 on the T cell surface.
- Multi-targeted T cells for paracrine-like, time-limited release in the tumor microenvironment.
- Deep IL-12-loaded T cells carry high IL-12 loading and persistence on the T cell surface, which enables strong immune priming and activation in the tumor microenvironment.

Figure 1. Antibody-mediated tethering of IL-12 to an abundant cell surface receptor supports strong cell loading and signaling. (A) Schematic for fusion protein between scFv-12 and a high-affinity anti-CD45 antibody. (B) Presence of anti-CD45 receptor expression was confirmed on PMEL and PMEL-IL12 + Ford ACT T cells.

Figure 2. Deep IL-12 augments tumor-specific T cell therapy in solid tumor models. (A) We first constructed a mouse surrogate model in order to evaluate Deep IL-12 in an immune competent mouse model. The mouse was injected with luciferase-expressing tumor cells and tumors were monitored over time. (B) Tumor growth in mice injected with tumor cells alone or with PMEL-IL12 + Ford ACT T cells was monitored over time. Deep IL-12 + Ford ACT enabled T cell activation and persistence for several days after the removal of unbound IL-12. Combined pulse IL-12 lead candidate supported high IL-12 loading and persistence on the T cell surface, persistent activation of surface tethered IL-12 (top) and cell expansion (bottom).

Figure 3. Deep IL-12 enables further improved tumor control with multiple cell doses. We evaluated the ability of Deep IL-12 to augment the efficacy of tumor-specific cell therapy in the absence of lymphodepletion using the T2B mouse model. Pmel/B16 model (A). The improved anti-tumor activity in the absence of lymphodepletion enabled the potential for further improved tumor control using multiple cell doses. In a second experiment mice were treated with two cell doses spaced two weeks apart (B). Lymphodepletion with cyclophosphamide was used one day prior to the first cell dose; the second cell dose was given in the absence of additional lymphodepletion. Multiple doses of tumor-specific T cells carrying a Deep IL-12 approach to augment the efficacy of tumor-specific T cells alone - further augmented enhanced efficacy and survival.

Figure 4. Deep IL-12 induces proliferation of antigen-experienced CD8 T cells. Flow cytometry analysis of antigen-experienced CD8 T cell phenotype distribution in mice treated with Deep IL-12 alone or in combination with Pmel/3.5IL12 + Ford ACT T cells. The effect was followed by proliferation analysis (top) and cytokine production analysis (bottom). Deep IL-12 activated antigen-experienced CD8 T cells and promoted tumor-specific T cell expansion in vivo.

Figure 5. Lack of overt toxicity from tumor-specific T cells carrying Deep IL-12. To monitor inflammation, cytokine secretion, and body weight loss, mice were treated with Pmel cells alone or in combination with Pmel / Deep IL-12. Mice treated with Pmel / Deep IL-12 showed no overt toxicity in terms of body weight loss or sustained systemic cytokine release. The results indicate that the Deep IL-12 technology platform can enable safe and effective tumor-specific T cell therapy by reducing systemic immune responses and potentiating tumor-specific T cell activation.