

Igniting CAR-NKT cells with IL-18

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Adoptive cell therapies based on chimeric antigen receptor (CAR)-engineered T (CAR-T) cells have transformed the treatment of hematologic malignancies, yet their application in solid tumors is hindered by poor tumor infiltration, limited persistence, and exhaustion in the immunosuppressive tumor microenvironment (TME). Cytokine armoring has been widely employed to enhance the efficacy of adoptive cell therapies, including CAR-T cells and CAR-engineered invariant natural killer T (NKT) cells. However, uncontrolled cytokine activity can introduce dose-limiting toxicities, underscoring the need to precisely balance immune potentiation with safety. In this issue of *Molecular Therapy*, Barragán Bravo et al. describe engineered interleukin-18 (IL-18) expressing CAR-NKT cells and present evidence that IL-18 armoring enhances anti-tumor efficacy by augmenting NKT effector function and reshaping the tumor immune microenvironment without compromising the intrinsic safety features of the NKT platform (Figure 1).¹ This work represents a mechanistically informed application of IL-18 armoring to innate-like T cells, leveraging NKT biology to couple immune activation with controlled cytokine output.

NKT cells are a distinct subset of innate-like T lymphocytes that express a semi-invariant T cell receptor recognizing glycolipid antigens presented by the monomorphic molecule CD1d. This mode of antigen recognition, together with their thymic acquisition of an effector-ready state, distinguishes NKT cells from conventional $\alpha\beta$ T cells.² Functionally, NKT cells respond rapidly to antigenic and inflammatory cues, secrete large amounts of immunomodulatory cytokines, and exhibit cytotoxic activity while maintaining low alloreactivity.³ In cancer, NKT cells can directly eliminate CD1d-expressing tumor cells and tumor-supportive myeloid populations, while simultaneously activating NK cells, dendritic cells, and

endogenous T cell responses—properties largely absent from polyclonal T cell products.⁴

These biological attributes make NKT cells an attractive platform for cancer immunotherapy. In contrast to conventional CAR-T cells, CAR-NKT cells exhibit intrinsic tumor-homing capacity, resistance to exhaustion, and a markedly reduced risk of graft-versus-host disease, owing to their CD1d-restricted, non-polymorphic antigen recognition. Clinically, this has translated into favorable safety profiles, with minimal cytokine release syndrome (CRS) and neurotoxicity observed in early trials. Multiple strategies have been developed to generate therapeutic NKT cell products. Early efforts focused on *ex vivo* expansion of NKT cells from peripheral blood mononuclear cells (PBMCs), enabling autologous CAR-engineered NKT therapies that demonstrated safety and preliminary efficacy, most notably in neuroblastoma. However, donor-to-donor variability, limited scalability, and inconsistent product purity have constrained broader application.⁵ To overcome these limitations, hematopoietic stem and progenitor cell (HSPC)-based differentiation platforms have emerged as a complementary strategy. By engineering HSPCs with invariant NKT cell receptors and CARs, large numbers of clonal, uniformly engineered NKT cells can be generated in a feeder-free, clinically compatible manner.⁶ This approach enables off-the-shelf allogeneic CAR-NKT products with defined composition, robust antitumor activity, and favorable immunogenicity profiles across both hematologic and solid tumor models.^{7–9} These advances establish NKT cells as a versatile and scalable cellular substrate for next-generation cancer immunotherapies.

The team has years of experience of engineering PBMC-derived CAR-NKT cells.^{5,10}

Prior work from this group and others has demonstrated that rational cytokine armoring can further enhance the persistence of CAR-NKT cells. Expression of IL-15 has been shown to promote CAR-NKT cell survival, metabolic fitness, and *in vivo* persistence while preserving safety.^{6,10} In their first-in-human trial of GD2-targeting CAR-NKT cells in patients with relapsed or refractory neuroblastoma, GD2-targeting CAR-NKT therapy induced one complete response and two partial responses among 12 patients. Meanwhile, other cytokine armoring strategies such as IL-12-engineered CAR-NKT cells have highlighted the potential of cytokine engineering to reshape the TME and amplify endogenous antitumor immunity.¹¹

In the Barragán Bravo et al. study, the authors introduce IL-18 as a distinct and mechanistically complementary cytokine payload for CAR-NKT cells. IL-18 signaling enhances interferon- γ production, promotes cytotoxic function, and engages surrounding immune cells without requiring direct antigen recognition. By engineering IL-18 expression into CAR-NKT cells, this work expands the cytokine-armoring paradigm beyond persistence and survival and

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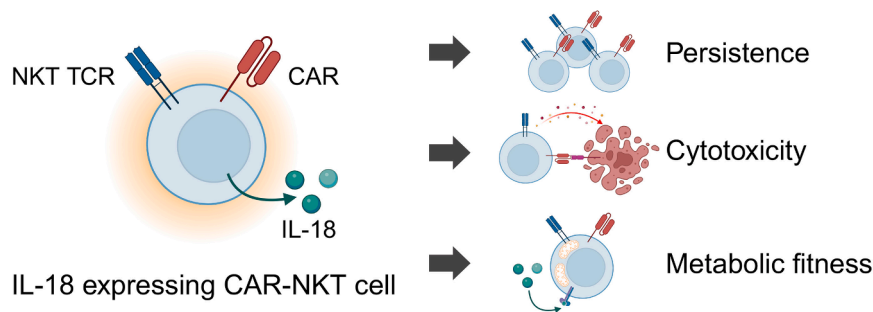


Figure 1. Engineering IL-18-boosted CAR-NKT cell therapy

Peripheral blood-derived NKT cells are genetically engineered to co-express tumor-specific CAR and IL-18, followed by *ex vivo* expansion to generate IL-18-armed CAR-NKT cells for adoptive cancer immunotherapy. Expression of IL-18 augmented the persistence and cytotoxicity of CAR-NKT cells while improving their metabolic fitness through IL-18-driven cytokine amplification.

toward deliberate modulation of the TME. The study demonstrates that IL-18-armed CAR-NKT cells achieve augmented antitumor activity while retaining the favorable safety and trafficking properties intrinsic to the NKT lineage. Collectively, these findings establish IL-18 engineering as a conceptually new strategy for enhancing CAR-NKT therapies and further underscore the flexibility of NKT cells as programmable immune effectors.

In the clinical setting, IL-18 engineering has been applied to adoptive CAR-T cell therapy, where IL-18-expressing CAR-T cells demonstrated robust antitumor activity, including high objective response rates in heavily pretreated patients, while maintaining a manageable safety profile characterized predominantly by low-grade CRS and minimal neurotoxicity.¹² These findings support the concept that IL-18 can enhance CAR-mediated efficacy, potentially by promoting immune activation within the TME. However, intrinsic biological differences between conventional T cells and NKT cells, including antigen recognition, cytokine responsiveness, tissue residency, and interactions with myeloid cells, raise important questions regarding the generalizability of

IL-18 armoring across immune cell platforms. Whether IL-18 engineering can safely and effectively enhance CAR-NKT cell therapy therefore requires further validation, particularly in clinical settings. In parallel, alternative cytokine engineering (e.g., IL-10, IL-12, IL-21) have been applied to CAR-T cells, enhancing therapeutic efficacy by promoting T cell fitness, sustaining cytotoxic function, and reshaping the TME. Collectively, these cytokine engineering strategies may be adaptable to CAR-NKT cells; however, their safety, functional impact, and translational benefit within the distinct biological context of NKT cells require rigorous preclinical and clinical evaluation.

DECLARATION OF INTERESTS

The authors declare no competing interests.

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