Chapter 6

# Hematopoietic Source and Immune Cells in Cell-Based Therapy

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## Abstract

Immune cell-based therapies represent a rapidly advancing domain in biomedical research. Cellular sources, with emphasis on bone marrow-derived immune cells are included in this chapter. To this end, key cell types such as T, B cells, and NK[1] cells are described in terms of immunological roles and therapeutic relevance. Particular attention is given to genetically engineered variants such as CAR-T[2] and CAR-NK cells, which have demonstrated potent antitumor activity in hematological and solid malignancies. Besides, biotechnological strategies used for enhancing immune cell specificity, persistence, and cytotoxicity, including receptor engineering, cytokine modulation, and resistance to immunosuppressive signals, were discussed. Clinical trials highlighting the efficacy of CAR-T and CAR-NK therapies in targeting tumor-associated antigens were also included. The therapeutic efficiency and the dynamic interplay between infused immune cells and the host immune system were also highlighted. These insights underscore the need for integrated approaches using engineered cells and microenvironmental modulation to optimize outcomes in immune cell-based therapy.

**Keywords**: Natural Killer Cells; Immune Cell Therapy; Regenerative Medicine; Human

## 1. Introduction

Cell-based therapies are a novel approach in regenerative medicine and immuno-oncology, suggesting targeted, durable, and personalized treatment options for a wide range of diseases [1]. Among these, hematopoietic and immune cell-based therapies have exhibited notable

[1]. Natural killer
[2]. Chimeric antigen receptor T-cells

clinical outcomes, particularly in patients with hematological malignancies and immune-mediated disorders [2]. The hematopoietic system serves as a critical source of stem cells and progenitor cells capable of reconstituting hematopoiesis and regenerating immune competence following transplantation or cytotoxic therapy [3]. The primary sources of HSPCs[1] include bone marrow, PB[2], and UCB[3]—each characterized by distinct cellular composition, immunogenicity, and clinical applicability [4]. Last decade advances in the production of engineered cells have expanded the therapeutic efficiency of immune effector cells derived from these hematopoietic sources. Autologous and allogeneic T lymphocytes, NK cells, Tregs[4], and genetically manipulated immune cells such as CAR–T and CAR–NK cells are now being developed as powerful tools to eliminate malignant or dysfunctional cells and to modulate immune responses [5]. While autologous products provide high specificity and reduced immunological risk, their manufacturing complexity and patient-dependent variability limit scalability [6]. Conversely, HSCs[5] and immune cells from allogeneic donors—including UCB and iPSC[6]–derived progenitors—offer an “off-the-shelf” alternative for broader clinical accessibility [7]. Understanding the biological characteristics, advantages, and limitations of different hematopoietic sources is therefore essential for optimizing cell-based therapies. Factors such as stem cell yield, immune compatibility, graft-versus-host potential, and ex vivo expandability critically influence clinical outcomes [8]. This review explores the current landscape of hematopoietic sources and immune cell types used in cell-based therapy,

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1. Hematopoietic stem and progenitor cells
2. Peripheral blood
3. Umbilical cord blood
4. Regulatory T cells
5. Hematopoietic stem cells
6. Induced pluripotent stem cell

highlighting recent advances, challenges in standardization and manufacturing, and emerging trends shaping the future of regenerative and immune therapeutics.

## 2. Application of T lymphocytes in cell therapy

### a. CAR-T and TCR[1]-T Cell Therapies: Overcoming Antigen Escape in Cancer Treatment

Application of CAR-T cells has increased tumoricidal effects in blood cancer patients. In this regard, CD19-directed therapies, including Kymriah, Tecartus, Breyanzi, and Yescarta, have resulted in prominent therapeutic outcomes in B-cell malignancies, while BCMA[2]-targeted Abecma is effective in the control of refractory MM[3] [9, 10]. Nearly 50% of tumor relapse is because of the loss of CD19 or BCMA on tumor cells, preventing recognition by CAR-T cells [11, 12]. To circumvent this issue, multi-antigen targeting strategies are at the center of attention. One early approach used the APRIL[4] protein to interact with TACI[5] on myeloma cells. Although APRIL-expressing AUTO2 CAR-T could recognize TACI on BCMA$^-$ myeloma cells [13, 14]. Other antigens associated with MM, such as CD19, CD38[6], CS1/SLAMF7[7], and GPRC5D,[8] are at the center of debate [15-17]. Bispecific CAR-T approaches are under investigation to prevent antigen escape. In patients who relapse or show CAR-T resistance, TCR-T[9] may provide a later-line option. For example, WT1-TCR-T cells transferred into high-risk acute myeloid leukemia patients achieved relapse-free survival in

[1] T Cell Receptor
[2] B-Cell Maturation Antigen
[3]. Multiple myeloma
[4]. BCMA's natural ligand
[5]. Transmembrane Activator and CAML Interactor
[6]. Target of daratumumab and isatuximab
[7]. Target of elotuzumab
[8]. Target of the experimental bispecific antibody talquetamab
[9]. T cell receptor T cell therapy

all 12 treated patients, compared to 54 percent in a matched cohort, and persisted long-term while maintaining antigen-specific activity [18]. TCR-T therapy may also have advantages in solid tumors with low antigen density [19, 20]. High-avidity TCR-T cells efficiently detect and eliminate tumor cells expressing fewer target molecules, as observed in B cell malignancies with low CD20 [21]. Early clinical trials show promise, with NYESO1-targeted TCR-T cells producing response rates of 45–55 percent in metastatic melanoma, 50–61 percent in synovial sarcoma, and 80 percent in multiple myeloma, accompanied by minimal toxicity [22, 23]. Neoantigens derived from tumor mutations or viral proteins provide additional high-avidity targets that are beyond the reach of CAR-T cells [24]. Despite promising results [25, 26], TCR-T therapy is limited by poor persistence, relapse without T cell infiltration, and suppression by the tumor microenvironment (**Table 1**) [27].

## 2.2. Historical Development of TIL Adoptive Cell Therapy

### *2.2.1. IL-2*

Rosenberg's group found that lymphocytes cultured with IL-2 could destroy fresh tumors without harming normal cells [28, 29]. In models, anti-tumor activity was achieved by IL-2 alone, adoptive transfer of IL-2–expanded lymphocytes, or both together [29, 30]. In metastatic melanoma patients, combining IL-2–expanded lymphocytes with systemic IL-2 treatment produced durable regressions in some cases [31].

### *2.2.2. TILs*[1]

Early ACT studies used T cells from PB, but Rosenberg's team turned to TILs, reasoning they would be richer in tumor-reactive cells. TILs expanded with IL-2 showed significantly greater effectiveness than

[1]. Tumor-Infiltrating Lymphocytes

peripheral lymphocytes in mouse tumor models [32]. In humans, TILs derived from resected melanomas exhibited strong activity against autologous tumors and could be expanded nearly 100,000-fold without losing cytotoxic function [33]. Clinical trials in metastatic melanoma reported a 34% response rate, including some complete remissions, though most responses were transient [34].

#### *2.2.2.1. Adoptive TIL Therapy in Cervical Cancer: Workflow and Challenges*

Cervical tumor tissue TILs have cultured *ex vivo* using explant culture methods that preserve viability, and reinfused after lymphodepleting chemotherapy, with IL-2 supporting their survival and cytotoxic function [35-37]. The REP[1] generates large numbers of active T cells for therapy [38]. High-dose IL-2 increases TIL activity but is toxic, while low-dose IL-2 is safer yet less effective. Lymphodepletion enhances engraftment by raising IL-7 and IL-15 [39-41]. In metastatic cervical cancer, TIL therapy has achieved significant tumor regression, though prolonged *ex vivo* expansion and IL-2 management remain challenges [37, 41].

## 3. B-cell and plasma cell-based therapy

### *3.1. Therapeutic Targeting of Plasma and B Cells*

B cells and plasma cells have a crucial role in adaptive immunity and are major targets in blood cancers and autoimmune disorders, with outcomes affected by disease characteristics and age (**Table 2**). In multiple myeloma and Waldenström's macroglobulinemia, therapies directed at CD38, CD138, CD20, and CD19 help control malignant cells, while in autoimmune disorders, proteasome inhibitors and plasma

[1]. Rapid expansion protocol

exchange are used to reduce harmful antibodies [42-45]. Engineered plasma cells can provide long-term therapeutic protein production with minimal immune reaction. In cancer, plasma cells influence tumor progression and affect responses to immunotherapy, with signatures such as Plasma cell. Sig and S100A9 subtypes guiding treatment [46, 47].

**Table 1.** Overview of recent advances in preclinical and clinical CAR-T cell therapy research

| *Cell type* | *Study type/ clinical phase* | *Therapy approach* | *Cell source* | *Target disease (s)* | *Result* | *Advantages/Challenges* | *Ref* |
|---|---|---|---|---|---|---|---|
| *T Cell* | Preclinical (2025) | Dual-signaling CAR-T | Autologous | MM | Stronger anti-tumor responses than single-target CAR-T | Reduced recurrence due to antigen loss | [48] |
| *T Cell* | Preclinical (2024) | DCAR-T | Autologous | | Enhanced anti-tumor activity; no toxicity | Potential alternative to anti-BCMA CAR-T | [49] |
| *T Cell* | Preclinical (2024) | h2CAR-T | Autologous | | Suppressed tumor growth >90 days; prolonged survival | No systemic or organ-related toxicities | [50] |
| *T Cell* | Preclinical (2024) | UCARTCS1 | Allogeneic | | Potent anti-MM activity in cell lines and xenograft models | Off-the-shelf therapy potential | [51] |
| *T Cell* | Preclinical (2024) | BCMA CAR-T | Autologous | | Low toxicity; good anticancer activity | Supports future clinical studies | [52] |
| *T Cell* | Preclinical (2022) | CS1-CAR-T & Bispecific CS1-BCMA CAR-T | Autologous/Allogeneic T cells | | Effective in vitro and in vivo killing; tumor growth inhibition in mice | Dual targeting reduces antigen escape; translation to humans pending | [53] |
| *T Cell* | Preclinical (2022) | Optimized anti-BCMA CAR design | Autologous T cells | | Enhanced CAR stability and tumor killing in MM models | Overcomes BCMA antigen loss; needs clinical validation | [54] |
| *T Cell* | Clinical-Phase I, II (2025) | BCMA CAR-T | Autologous | | Safe and efficacious in refractory cases; durable responses with improved survival | Limited by BCMA antigen loss; risk of antigen escape | [55] |

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|---|---|---|---|---|---|---|---|
| *T Cell* | Clinical- Phase I (2023) | PHE885 (BCMA-CAR-T, T-Charge platform) | Autologous T cells | Relapsed or Refractory MM | High response rates; manageable CRS/ICANS | Faster manufacturing; durability under evaluation | [56] |
| *T Cell* | Clinical- Phase I (2023) | Allogeneic BCMA-CAR-T (UNIVERSAL trial) | Allogeneic donor T cells | | Demonstrated safety, tolerability, and early efficacy | Off-the-shelf" use; GVHD and rejection possible | [57] |
| *T Cell* | Clinical- Phase I (2021) | Idecabtagene vicleucel (ide-cel, bb2121, anti-BCMA CAR-T) | Autologous | | Overall response rate (ORR) ~73%; median PFS ~8.8 months; durable responses in some patients | First FDA-approved CAR-T for MM; CRS/ICANS remain challenges | [58] |
| *T Cell* | Clinical- Phase I (2019) | bb2121 (early study) | Autologous | | High initial ORR; manageable CRS; laid groundwork for ide-cel | Proof-of-concept for BCMA CAR-T in MM | [59] |

**Abbreviations:** CRS: Cytokine Release Syndrome; ICANS: Immune effector cell–associated neurotoxicity syndrome; GVHD: Graft-versus-Host Disease; Antigen loss: Loss of targeted antigen reducing CAR-T effectiveness; Dual targeting: CAR-T cells recognizing two antigens simultaneously; Off-the-shelf: Allogeneic CAR-T ready without patient-specific manufacturing; MM: Multiple Myeloma

**Table 2.** TPE[1] & Plasma Cell Neoplasms

| *Cell type* | *Study type/ clinical phase* | *Therapy approach* | *Cell source* | *Target disease(s)* | *Result* | *Advantages / Challenges* | *Ref* |
|---|---|---|---|---|---|---|---|
| *Plasma B Cells* | Preclinical (2024) | Leukemia (animal model( | Human plasma B cells | Leukemia (animal model) | Successful treatment in an animal model | Potential for targeted therapy; challenges in translation to humans | [60] |
| *Plasma B Cells* | Preclinical (2018) | Bispecific antibody targeting CD19 and CD47 | Human plasma B cells | B-cell lymphoma and leukemia | Demonstrated safety and efficacy in preclinical models | Potential for targeted therapy; challenges in translating to human models | [61] |
| *B cells/Plasma B cells* | Preclinical (2018) | Bispecific mAb that binds CD20 (on B cells) and CD3 (on T cells) — modeling depletion & activation dynamics | Not therapy in patients, in vitro / animal models | B-cell populations in immunological settings (non-MM) | Rapid depletion of peripheral B cells, T cell expansion; model captures elimination of B-cells & drug PK behavior | Useful for understanding B-cell depletion dynamics, helps design therapy, but not MM/plasma-cell neoplasm–specific | [62] |

[1]. Therapeutic Plasma Exchange

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | | | | | | disease model | |
| *B-Cell* | Clinical (Phase 1, 2025) | Relapsed/Refractory Multiple Myeloma | Autologous T cells | Relapsed/Refractory Multiple Myeloma | 65 patients, 39% high-risk cytogenetics, 43% extramedullary disease | Optimized manufacturing process; challenges in efficacy and toxicity | [63] |
| *Plasma B Cells* | Clinical (Retrospective, 2021) | Anti-BCMA CAR T-cell therapy | Autologous T cells | Multiple Myeloma | Higher incidence of viral infections/reactivations during long-term follow-up | Highlights the need for vigilant monitoring and management of viral infections in CAR T-cell therapy patients | [64] |
| *Plasma B Cells* | Clinical (Retrospective, 2020) | Anti-BCMA CAR-T cell therapy | Autologous T cells | Multiple Myeloma | Feasible in patients with chronic or resolved HBV infection; antiviral prophylaxis recommended | Demonstrated safety and efficacy; need for antiviral management | [65] |

**Abbreviations:** BCMA: B-cell maturation antigen; CAR: Chimeric antigen receptor; HBV: Hepatitis B virus; MM: Multiple myeloma; PK: Pharmacokinetics; RRMM: Relapsed/Refractory Multiple Myeloma; mAb: Monoclonal antibody; CD: Cluster of differentiation

## 4. NK Cells in Therapy

### *4.1. NK cells application in immunotherapy*

Immunotherapy involving T cells may trigger GVHD[1], leading to significant tissue injury. In contrast, NK cells inhibit unwanted responses by releasing IL-10 and direct destruction of the host's APCs[2], thereby attacking leukemic cells [66]. NK cells are the frontline cells to initiate the tumoricidal properties in leukemia patients undergoing allogeneic stem cell transplantation. However, the TME[3] remains a major barrier that can impair NK cell function. Numerous studies have been carried out to address and overcome these key challenges [67]. To use NK cells in hematologic malignancies and solid tumors, both allogeneic and autologous sources can be isolated from PB, bone marrow, or UCB, then expanded in the lab using cytokines such as IL-2, IL-15, and IL-21, before being administered back to the patient. Approaches focusing on isolating NK cells through donor apheresis, stimulating them with IL-2, and promptly administering them to patients provide complete remission in numerous cases of AML[4] [68]. In recent methods, NK cells are initially differentiated and/or grown outside the body, then frozen and thawed right before being given to the patient. NK cells expanded in vitro exhibit distinct metabolic characteristics compared to natural NK cells. Unlike endogenous NK and T cells, NK cell products do not exhibit mitochondrial damage or buildup of reactive oxygen species [69]. NK cells can be genetically modified using various methods, such as viral and non-viral gene transfer or CRISPR[5]/Cas9-mediated gene deletion, to create NK cell products that

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[1]. Graft-Versus-Host Disease
[2]. Antigen-presenting cells
[3]. Tumor microenvironment
[4]. Acute myeloid leukemia
[5] clustered regularly interspaced short palindromic repeats

are more targeted, effective, and durable [70]. Additionally, the application of various strategies to produce allogeneic NK cells for immediate bedside use should be described in detail. Preclinical studies indicate this goal is achievable. For instance, NK cells engineered to target and eliminate MDSCs[1] help CAR-T cells better infiltrate the TME, thereby improving survival in mice. Additionally, in mouse models, NK cells have been shown to attract dendritic cells to the TME, boosting immune regulation [71]. Several attempts have been undertaken to enhance the effectiveness of NK cell therapy, which we will review below.

### *4.1.1. Allogeneic NK cell immunotherapy*

Infusing autologous NK cells is generally simpler than using allogeneic NK cells because of the potential mismatch between donor KIR receptors and recipient HLA[2] ligands [72]. This mismatch can trigger GVL[3] effects by boosting NK cell activity against tumors. However, early clinical trials have proven that autologous NK cell administration tends to be less effective against metastatic cancers compared to allogeneic NK cells [73]. Therefore, clinical trials increasingly use allogeneic NK cell sources. Additionally, autologous NK cells are often collected from individuals subjected to chemotherapy, which can affect their quality, unlike allogeneic NK cells [74]. These factors limit the broader use of autologous NK cells. Furthermore, lympho-depleting chemotherapy increases IL-15 levels, a key factor for the expansion and persistence of donor NK cells [75]

[1]. Myeloid-Derived Suppressor Cells
[2]. Human Leukocyte Antigen
[3]. Graft-versus-leukemia

### *4.2. Use of NK cells in AML*

In recent years, NK cell-based immunotherapy has demonstrated significant promise in treating AML. Early studies demonstrated that IL-2 can stimulate NK cell number while increasing remission in patients with refractory AML. One reason would be that IL-2 activates regulatory T cells; IL-15 is now preferred as an alternative to promote NK cell activity selectively [76]. In another study, allogeneic NK cell therapy in AML patients was found not only to trigger ADCC [1]but also to enhance NK cell natural cytotoxicity [77]. Research has shown several promising outcomes in AML treatment, including improved patient survival when NK cell infusion is combined with chemotherapy. Additionally, pairing NK cells with targeted therapies such as IL-15 alongside PD-1 inhibitors has been linked to enhanced NK cell function against leukemic cells. Other strategies, like inhibiting TGF-β1 or activating NKp46, have also been explored to modulate NK cell activity in AML patients [78].

A clinical trial (NCT02782546) explored the simultaneous application of NK cells HSCT[2] in cases with relapsed/refractory AML. The results showed favorable patient responses, including improvements in high-risk mutations such as TP53 variants. These outcomes indicated that integrating NK cell therapy with HSCT lowers the probability of GVHD and enhances treatment effectiveness. Moreover, ML[3] NK cells have the potential to target high-risk mutations and sustain long-term activity, which underscores their potential as a critical component in advanced AML treatment approaches [79]. Despite promising progress, several significant challenges remain. One major hurdle is producing sufficient numbers of

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[1]. Antibody-Dependent Cellular Cytotoxicity
[2]. Hematopoietic stem cell transplantation
[3]. Memory-like

highly activated NK cells, as well as addressing issues related to donor compatibility and long-term function in allogeneic NK cell therapies [80]. The advances in NK cell-based vaccines to strengthen antitumor immunity also hold promise for future advances. Another critical issue is overcoming NK cell aging, exhaustion, and functional suppression, key mechanisms by which AML evades immune responses [81]. Addressing these challenges is crucial for developing more effective and durable NK cell therapies for AML. A deeper understanding of these factors will be vital to fully realizing the therapeutic potential of NK cells in AML treatment.

### *4.3. NK cells and solid tumors*

In solid tumor patients, NK cell-based immunotherapy has demonstrated favorable ORRs[1], defined as partial response or better, and DCRs[2], defined as stable disease or better. These effects have been particularly notable in cases of HCC [3][82]. Compared with T cells, NK cells have higher infiltration in both low-grade brain gliomas and glioblastoma. Numerous preclinical and clinical studies have explored the use of NK cells in the treatment of gliomas [83].

### *4.4. Use of NK cells in HSC transplantation*

NK cells play a crucial role in the early recovery of the immune system following HSCT. Increased NK cell counts during HSCT, NK cell-based immunotherapy post-transplant, and preventive NK cell infusions have all been associated with improved outcomes, including survival, lower relapse rates, reduced GVHD, and fewer infections after HSCT. The NK cell doses used in both therapeutic and preventive settings have varied widely, from

[1]. Objective response rates
[2]. Disease control rates
[3]. hepatocellular carcinoma

$1 \times 10^5$ to $1 \times 10^8$ cells per kilogram. However, it remains unclear whether higher NK cell doses improve effectiveness [84]. Although NK cell therapies are currently being tested in numerous clinical trials, the field remains in its early stages and faces numerous challenges (**Figure 1**). Various approaches are being explored to advance the next generation of NK cell treatments, including blocking inhibitory pathways, improving antigen recognition, boosting efficacy and stability, and evading host immune responses. The most actively researched areas include allogeneic NK cell therapy, CAR-NK cell therapy, and ML-NK[1] cell therapy. Leading countries in this research include China, the United States, Germany, Italy, and France. Despite significant progress, obstacles such as expanding and activating NK cells and overcoming resistance mechanisms remain difficult to overcome. Looking forward, sophisticated NK cell engineering and combination therapies involving NK cells are anticipated to be major focuses of future investigations.

[1]. Memory-Like NK

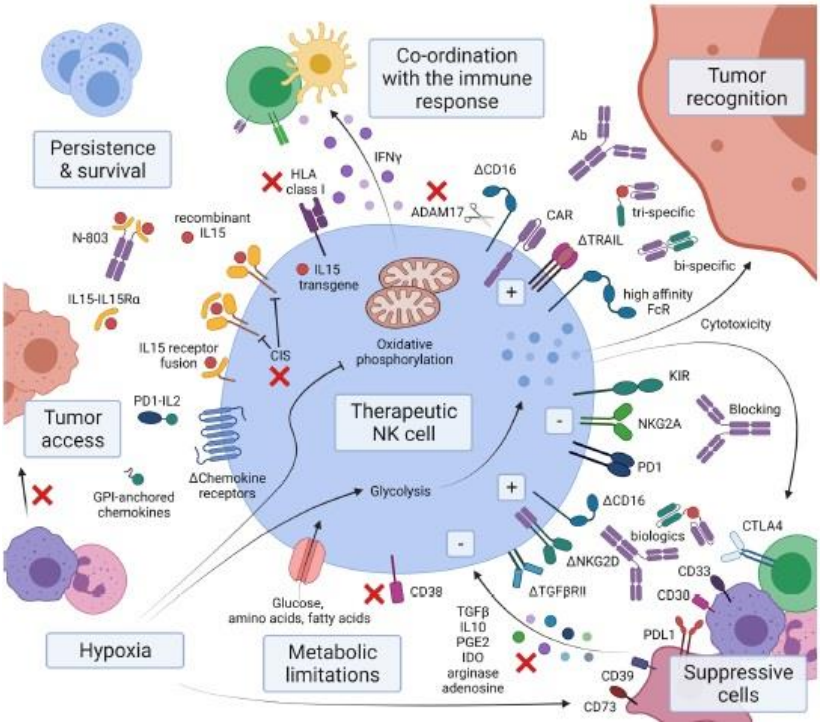


**Figure 1.** Strategies can be used to address the challenges of NK cell therapy. Reproduced with permission. [85]. Stem Cell Research and Therapy. 2022.

### *4.5. CAR-NK therapy*

CAR-T cell immunotherapy has indicated highly promising outcomes, but it's also linked with several complications, including GVHD caused by the use of autologous cells, CRS[1], neurotoxicity, and off-target effects due to the identification of TAAs on normal cells due to antigenic similarities. Other barriers involve tumor cells evading the immune system, T-cell exhaustion, limited availability of T cells, MHC restrictions, and, most critically, disease relapse due to the loss or escape of the targeted tumor antigen on cancer cells [86, 87]. Thus, predicting a novel, readily available cell source for CAR engineering could significantly advance

[1]. Cytokine release syndrome

immunotherapy development. As mentioned, the distinctive features of NK cells have recently attracted growing attention, resulting in CAR-NK therapy appearing as an alteration to CAR-T cell therapies [88]. After isolating NK cells, they are grown in specialized culture media, typically NK92, along with cytokines, for example, IL-15 and IL-2, to promote the expansion of these cells. In addition, the appropriate CAR construct is introduced into cells via transfection, producing CAR-NK cells. Both viral and non-viral protocols are applied for this transfection [89]. Until now, four generations of CAR-NK cells have been expanded, and clinical trials are currently in progress within this area as follows.

- First-generation: it is composed of an extracellular region that binds to the target antigen, a transmembrane region, and a CD3ζ signaling domain.
- Second-generation: Includes the antigen-binding extracellular domain, transmembrane domain (CD16, NKp44, NKp46, and NKG2D), a signaling region (CD3ζ), plus a co-stimulatory domain including DAP12, 2B4, etc., either alone or in combination with CD3ζ.
- Third-generation: it contains the extracellular antigen-binding region, transmembrane area, signaling region (CD3ζ), and two co-stimulatory domains, typically CD28, along with 4-1BB or 2B4.
- Fourth-generation or Novel CAR-NK: this comprises the extracellular antigen-binding region, transmembrane area, and incorporates an inducible or constitutive gene cassette to enable expression of a transgenic protein. An IL-15-encoding transgene was inserted under the control of an NFAT-responsive element, along with a CAR construct targeting CD44. After the CAR recognized the target antigen, a signaling cascade was initiated, leading to NFAT activation and IL-15 secretion,

thereby improving NK cell cytotoxicity in a triple-negative breast tumor spheroid model [88].

Novel generation CAR designs are inclined to sophisticated and customized models that can synergistically address additional obstacles restraining CAR-NK functionally, which include:

- Incorporating autocrine cytokine or cytokine receptor cargo into the CAR plasmid to facilitate CAR-NK persistence, proliferation, or activation.
- Co-expression of autocrine chemokines or chemokine receptors with CAR molecules to augment trafficking and infiltration of CAR-NK.
- Equipped with a safety switch such as iCasp9 to avoid excessive cytotoxicity and healthy tissue impairment.
- KIR-based inhibitory CARs
- Multiple antigens targeting [90].

### *4.6. The effect of CAR-NK in hematological neoplasms*

Previous research has shown that common antigens used in hematological malignancies, including CD19, BCMA, CD22, and CD33, are often targeted by CAR-NK therapies. Initial research primarily focused on treating blood cancers, specifically those originating from B cells. One of the earliest studies evaluated the impact of CD19-CAR-CIK (cytokine-induced killer) cells on a pre-B ALL[1] cancer cell line; these engineered cells successfully overcame the cancer's resistance to T and NK cells, leading to complete remission and sustained molecular remission in treated mice [91]. CD19 is a frequently targeted antigen in CAR-NK therapies, and is highly effective in eliminating B-cell leukemia and lymphoma in affected patients. Additionally, CD20 and FLT3 present as other targets for immunotherapy in cancers originating from B cells. Recent research has

[1]. Acute lymphoblastic leukemia

suggested that CAR-NK cells set to target both CD19 and CD20 shown increased cytotoxic activity versus ALL cells [92]. In general, in vitro studies demonstrate that both CD20-CAR-NK and CD19-CAR-NK cells are capable of targeting resistant lymphoblasts, with the cytotoxic impact of these engineered NK cells on lymphoblasts being well documented [93]. A notable finding of the research is that CD19-CAR NK cells can effectively target CD19-positive malignant lymphoid cells that are resistant to the body's natural NK cells [94]. Additionally, CD19-CAR NK cells also exhibit cytotoxic activity against B-cell leukemia and lymphoma [95]. Results of a Phase I and II clinical trial evaluating CD19-CAR NK therapy in patients with refractory or relapsed CD19-positive non-Hodgkin lymphoma showed positive clinical and safety outcomes, with an overall response rate of about 73%. Besides, 64% of patients achieved complete remission within 30 days of treatment [96]. A preclinical study investigated the use of UC-derived NK cells and fourth-generation CAR-NK therapy, along with IL-15, to boost CAR functionality and treat Raji lymphoma, highlighting the antitumor activity of CD19-CAR-NK cells against cancer cells. A key benefit of this research was the use of UCB as the source of NK cells [97]. Following that, an allogeneic CAR-NK cell line derived from UCB that targeted CD19 in patients with CD19-positive lymphoid cancers was used, and a large proportion of complete remission was achieved [98]. The first clinical trial involving CAR-NK therapy in patients with prior relapse and treatment-resistant AML targeted CD33 and achieved measurable MRD[1] without showing significant adverse effects [99]. Other CAR-NK therapies designed for AML, such as CD123-CAR-NK in pediatric cases, NPM1 CIML CAR-NK, and CD38-CAR-NK, have also shown positive impacts on malignant cells. Among these, CD123 is the most extensively researched

[1]. Minimal residual disease

antigen in AML and is targeted by multiple CAR-NK types, including NK92 cells, and peripheral and cord blood-derived NK cells. CAR-NK cells targeting CD38 and CD138 have been associated with enhanced cell-killing and tumor shrinkage in the treatment of MM[1]. Additionally, CAR-NK therapies have shown effectiveness against various T-cell TAA, including CD3, CD4, CD5, and CD7, with CD5 identified as a significant therapeutic target in T-cell cancers. An emerging approach in CAR-NK development involves creating CAR-NKs with multiple targeting capabilities, incorporating inhibitory CARs, using genome-editing techniques in CAR design, and combining CAR therapy with monoclonal antibodies [100-102].

## 5. DCs[2] immunotherapy

DCs are highly effective APCs that can elicit specific immune responses and enhance innate immunity. This represents a favorable choice for promoting anti-tumor immune activity and preventing the tumor's immunosuppressive environment. These are considered an excellent choice for cancer immunotherapy due to their distinct immune properties and minimal toxicity. Compared with other points, they are less invasive and can generate long-lasting antitumor immune memory. Advances in understanding immune mechanisms, particularly the role of immune checkpoint inhibitors in activating the immune response, have highlighted these cells as key APCs capable of stimulating antigen-specific T cells, underscoring their therapeutic potential in cancer treatment [103]. DCs–based immunotherapy offers several benefits, including a personalized approach, enhanced immune activation, induction of long-term

[1]. Multiple myeloma
[2] Dendritic Cells

immunological memory, reduced likelihood of resistance, reduction of systemic side effects, and the potential to target “cold” tumors. However, there are notable limitations, including the complexity of tumoral cell culture in vitro, significant time and financial costs, the risks of T-cell anergy during induction, and the potential to promote the differentiation of regulatory T cells [104]. The early methods for dendritic cell activation in laboratory settings are typically achieved by incubating them with microbe-derived molecules, such as LPS and its analogs, notably polyinosinic: polycytidylic acid (poly I: C), which simulate viral infections and act as TLR[1]3 ligands. In addition, bacterial ODNs[2], the potent TLR9 agonists, are commonly used to stimulate DC activation in vitro. To establish a favorable environment for activation, proinflammatory cytokines were also used, including TNF and IL-6, though the specific components depend on the cellular origin and therapeutic purpose. Moreover, TLR ligands have a key role in promoting dendritic cell maturation, facilitating the polarization of helper T cells, and enhancing $CD8^+$ T-cell immune responses. In designing DC-based vaccines, it is critical to ensure that the cells effectively migrate to lymph nodes after administration. To optimize this process, various delivery methods, such as intravenous, subcutaneous, intraperitoneal, intratympanic, and intratumoral injections, have been tested to evaluate their impact on overall immunological outcomes. Intravenous and intradermal injection of DCs is ineffective mainly due to the fact that they do not efficiently migrate to lymph nodes; in addition, the efficacy of intratympanic, intravenous, and intradermal injections is low. In contrast, the intranodal injection has emerged as an innovative approach that increases immunogenicity by exposing DCs to T cells without requiring

[1]. Toll-like receptor
[2]. Oligodeoxynucleotides

migration [104]. In 2010, Provenge was the first FDA-approved DC vaccine for the treatment of prostate cancer. This personalized immunotherapy involves incubating patient-derived APCs with a recombinant fusion protein that combines PAP[1], a prostate tumor-specific antigen, with GM-CSF to evoke an immune response [105].

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