Bioactive Materials 42 (2024) 379–403

Contents lists available at ScienceDirect

Bioactive Materials

journal homepage: www.keaipublishing.com/en/journals/bioactive-materials

Review article

# Advancements in adoptive CAR immune cell immunotherapy synergistically combined with multimodal approaches for tumor treatment

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ARTICLE INFO

*Keywords:*
Adoptive cellular immunotherapy
Immune cell engineering
Multiple-model synergistic therapy
Tumor microenvironment

ABSTRACT

Adoptive immunotherapy, notably involving chimeric antigen receptor (CAR)-T cells, has obtained Food and Drug Administration (FDA) approval as a treatment for various hematological malignancies, demonstrating promising preclinical efficacy against cancers. However, the intricate and resource-intensive autologous cell processing, encompassing collection, expansion, engineering, isolation, and administration, hamper the efficacy of this therapeutic modality. Furthermore, conventional CAR T therapy is presently confined to addressing solid tumors due to impediments posed by physical barriers, the potential for cytokine release syndrome, and cellular exhaustion induced by the immunosuppressive and heterogeneous tumor microenvironment. Consequently, a strategic integration of adoptive immunotherapy with synergistic multimodal treatments, such as chemotherapy, radiotherapy, and vaccine therapy etc., emerges as a pivotal approach to surmount these inherent challenges. This collaborative strategy holds the key to addressing the limitations delineated above, thereby facilitating the realization of more precise personalized therapies characterized by heightened therapeutic efficacy. Such synergistic strategy not only serves to mitigate the constraints associated with adoptive immunotherapy but also fosters enhanced clinical applicability, thereby advancing the frontiers of therapeutic precision and effectiveness.

## 1. Introduction

Decades ago, adoptive cellular therapy targeting malignant cells was pioneered in a xenogeneic murine model, sparking interest in cancer immunotherapy [1,2]. Allogeneic T cells, administered during hematopoietic progenitor or stem cell transplantation, donor lymphocyte infusion, have shown efficacy in generating graft-versus-leukemia responses, particularly in cases of leukemia patients with human leukocyte antigen discordance [3–7]. However, unselected transduced donor T cells with the high potential of leading to graft-versus-host disease (GVHD), limiting their utility [8,9]. In contrast, the infusion of isolated autologous tumor-infiltrating lymphocytes (TILs) have demonstrated impressive clinical outcomes in melanoma patients, highlighting a potential of adoptive cellular therapy (ACT) without GVHD risk [10–13]. Nevertheless, the process of isolating and expanding TILs is technically challenging and time-consuming, necessitating faster methods to generate tumor-targeting effector immune cells [14,15]. The advancements in ex vivo growth and genetic engineering T cells have enabled the rapid production of effector immune cells specifically targeting tumor-associated antigens, thereby expanding the scope of cancer immunotherapy [16–18]. This genetic engineering typically involves transgenic expression of high-affinity chimeric antigen receptors (CARs) or T cell receptors (TCRs)for tumor antigen recognition [18,19].

While CAR T cells and other CAR immune cells have demonstrated significant potential, they also present several challenges [20–22]. These include inefficient immune responses, high off-target toxicity, limited persistence, difficulties in addressing tumor heterogeneity, and overcoming the suppressive tumor microenvironment [23–25]. In contrast, antibody-antigen interactions are highly specific and common in humans. Furthermore, various cancer or other diseases treatments such as chemotherapy, radiation therapy, vaccine therapy, and oncolytic virus therapy have been investigated for their ability to modify the

Peer review under responsibility of KeAi Communications Co., Ltd.
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https://doi.org/10.1016/j.bioactmat.2024.08.046
Received 24 June 2024; Received in revised form 26 August 2024; Accepted 31 August 2024

tumor or disease microenvironment [26–29]. This tumor or disease microenvironment modulation aims to enhance the effectiveness of immunotherapeutic interventions by creating a more conducive environment for immune cells to target and attack cancer cells [28–31]. For example, chemotherapy can alter tumor microenvironments by reducing immunosuppressive cells and enhancing tumor antigen presentations [32–35]. Radiation therapy can stimulate the cancer cells to release of tumor-associated antigens, making cancer cells more recognizable to the immune system [36,37]. Vaccine therapy offers benefits like specificity, adaptability to target specific tumor antigens, and potential long-term immune memory against tumor recurrence [38,39]. Similarly, oncolytic virus therapy presents advantages such as tumor specificity, systemic immune activation potential, and the ability to target tumor heterogeneity [3,40,41]. However, challenges such as pre-existing immunity, limited viral spread within solid tumors, and off-target effects on healthy tissues must be addressed for optimal immunotherapeutic efficacy and safety [42,43]. By comprehensively understanding and leveraging these interactions and interventions, researchers aim to overcome the limitations of CAR T and immune cell therapy and other immunotherapeutic approaches [44–46]. This effort ultimately leads to more effective treatments for not only cancer but also other diseases.

The following sections aim to offer a concise overview of recent research developments, focusing on key questions: (1) What are the sources of adoptive cells, and how are these immune cells engineered for immunotherapy? (2) How can CAR immune cells be synergized with other therapeutic models to achieve an optimal therapeutic effect within the tumor microenvironment? (3) What challenges are associated with combined therapeutic models involving CAR immune cells?

## 2. Adoptive immune cell sources and engineering

### *2.1. 2-1. The brief history of adoptive cellular therapy (ACT)*

Since the 1960s, inspired by the pivotal role of lymphocytes in allograft rejection among experimental animals, T cells have been explored to treat transplanted murine tumors (Fig. 1) [47–50]. In 1976, a major breakthrough occurred with the discovery of T cell growth factor (interleukin-2 (IL-2)), enabling the ex vivo expansion of T lymphocytes without compromising their effector functions [51,52]. By 1986, in vitro studies demonstrated that human tumor-infiltrating lymphocytes, first-generation derived from resected melanomas possessed a capability to specifically recognize autologous tumors [53]. This laid the foundation for the first successful demonstration of adoptive cell therapy (ACT) using autologous TILs to achieve objective regression the melanoma tumor metastasis in the melanoma patients and setting a milestone in 1988 [54]. The evolution of chimeric antigen receptor (CAR) T cell therapy began in 1987, when Yoshihisa Kuwana described the first CAR structure that contains the extracellular variable region of an antibody and the constant intracellular region of a T cell receptor [55,56]. In 1989, Gross et al. described that the $V_HC\alpha$ or $V_HC\beta$ chimeric chains can pair with the endogenous β or α chains of the recipient T cell to form a functional αβ heterodimeric receptor. This receptor endows the T cell with a chimeric receptor possessing antibody-like specificity, enabling targeted T cell activation [57]. Further advancements in 1991 by Arthur et al. led to a construction of the first-generation CAR incorporating the intracellular signaling domain of CD3ζ and the single-chain fraction variable (scFv) domain of an immunoglobulin [58,59]. However, initial clinical trials employed these first generation CAR T cells yielded discouraging results. Recognition of the importance of co-stimulatory signals in 1998 [60], particularly CD28 [61,62], by Helen M. Finney, marked the inception of second-generation CARs [63]. These improved CARs enhanced T cell proliferation, cytokine secretion, survival, and tumor-killing ability. Subsequent enhancements with the inclusion of a 4-1BB co-stimulatory domain in 2004 further bolstered T cell persistence in vivo [64]. The progression to third-generation CARs around 2010 [65], incorporating multiple intracellular co-stimulatory domains, such as CD28, CD27, OX40, and 4-1BB, signified a leap in CAR T cell therapeutical potential. The advent of fourth-generation CARs post-2012 recognized an integration of immunomodulatory factors such as cytokines, chemokines, growth factors, interferon, and tumor necrosis factor, along with safety mechanisms like logic-gate combinations and ON/OFF switches [66,67].

Notable milestones during the clinical application of CAR T therapy included Dr. Carl June's team at the University of Pennsylvania, pioneering CAR T therapy for HIV patients in 1997 [68], followed by

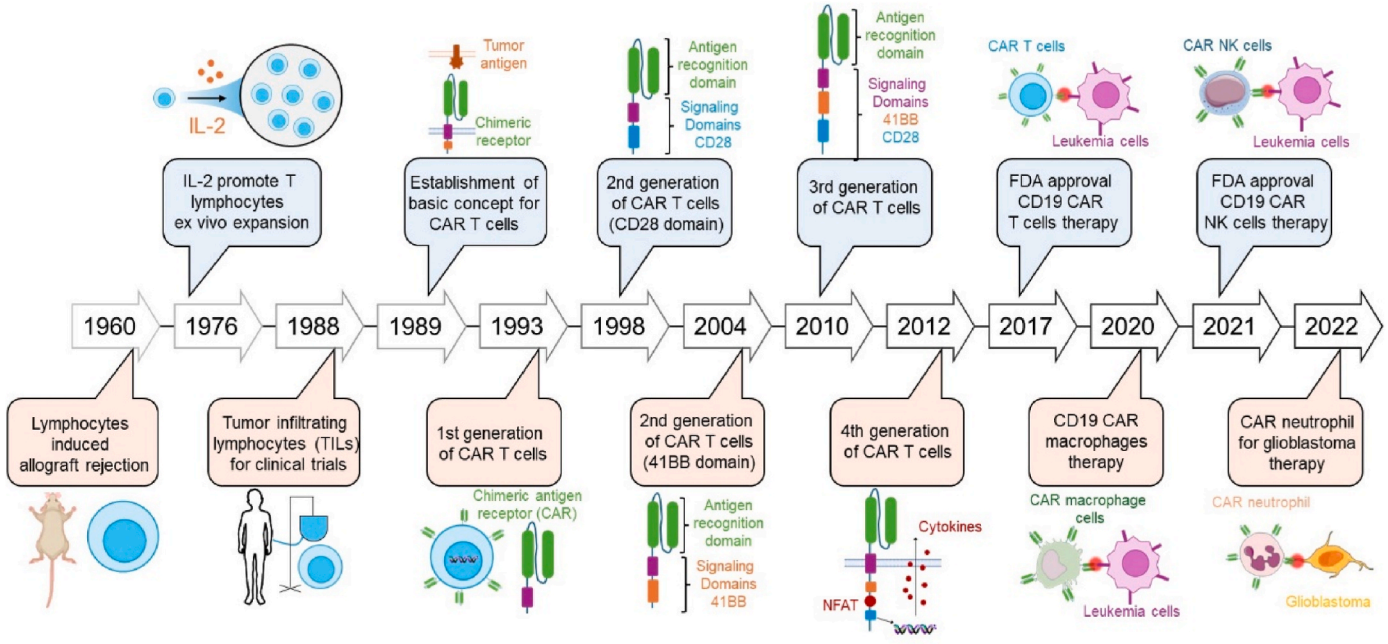


**Fig. 1. A brief history of adoptive cellular therapy**. Highlighted key milestones in the evolution of adoptive cellular therapy, the progressive development of techniques and innovations that have contributed to the therapeutic application of cellular therapies in treating cancer.

leukemia trials in 2010 [69]. In 2010, Rosenberg and Kochenderfer's group demonstrated regression of advanced B cell lymphoma using CD19 CAR T cells, setting the stage for further advancements [70,71]. The landmark FDA approvals in 2017 of Tisagenlecleucel and Kymriah targeting CD19 for relapsed or refractory B-cell precursor marked a significant turning point [72].

Since then, the FDA has approved several more CAR T cell therapies targeting various antigens for hematologic malignancies and solid tumors. Additionally, research has expanded to myeloid immune cells, such as macrophages [73] and neutrophils [74], and natural killer (NK) cells [75], each with unique cytotoxic mechanisms and potentials in tumor immunotherapy. Macrophages, through phagocytosis and immunomodulation, show promise in CAR targeting, while neutrophils' cytotoxic functions and CAR NK cells' diverse mechanisms offer exciting avenues for further exploration and therapeutic development in fighting cancer.

### 2.2. Autologous immune cell engineering

Autologous peripheral blood T lymphocytes are widely used cellular sources. They are collected and genetically modified to create tumor-specific targeting T cells in various academic centers [76]. This approach's potential is exemplified by the success clinicl trials of CD19 CAR T cells. The manufacturing process involves T cell activation, transduction, and expansion (Fig. 2). Specifically, autologous T cells are engineered with CARs from Ficoll-Hypaque purified PBMCs, activated using anti-CD3 monoclonal antibody (mAb) or irradiated feeder or stromal cells, then engineered with a CAR-encoding vector [77]. These processes start by selecting and activating autologous T cells from patient peripheral blood with anti-CD3 and anti-CD28 mAbs, enriching $CD3^{+}CD28^{+}$ double positive T cells, culturing, retrovirally engineering in RetroNectin-coated bags, expanding in a bioreactor, and formulating cells for infusion or freezing [78]. This production usually takes 10–14 days, adaptable for various vectors and T cell expansions, supporting clinical trials. Several factors influence the functional potentials of in vivo transferred T cell, including but not limited to initial TCR/CAR designs, manufacturing platforms, chosen T cell subsets, and the T cell's differentiation stages [79]. Peripheral blood T cells comprise naïve T cells (NTs), stem cell memory T cells (SCMTc), central memory T cells (CMTs), effector memory T cells (EMTs), and terminal effector T cells (ETs), with investigations ongoing on optimal subsets for adoptive therapy. T cell transfer studies in primates and murine models show rapid maturation of CAR-redirected and virus-specific $CD8^{+}$ T cells to ETs, while a subset acquires memory features and persists longer. Polyclonal $CD8^{+}$ CMTs isolated from leukapheresis products, without feeder cells activation [80], and expanded in IL-2/IL-15, generates autologous CAR-redirected $CD8^{+}$ T cells for adoptive transfer post-transplantation in $CD19^{+}$ high risk non-Hodgkin lymphomas [81]. Correlating attributes of in vivo persistent tumor antigen-specific T cells with tumor inhibition efficacy are under study, requiring careful phenotypic and biological characterizations for optimal T cell products in adoptive cell therapy, considering manufacturing and economic practicalities [82].

### 2.3. Allogeneic immune cell engineering as a substrate for immunotherapy

The potential of engineering T cell therapy would have been immense, promising significant clinical advancements with the readily accessible histocompatibility T cells [83]. While autologous methods have proven effective, challenges arise in personalized manufacture, particularly in patients treated with chemotherapy or HIV-induced immune deficiencies, or for small infants [84]. Donor-derived T cells, though easily obtained, are hindered by their high alloreactive potential, leading to complications, such as graft rejection and graft-versus-host disease (GVHD) (Fig. 2) [85]. To mitigate these risks, strategies involve suppressing endogenous T cell receptor (TCR) activity, leaving engineered TCRs or chimeric antigen receptors (CARs) as primary drivers of T cell functions [86]. This can be achieved by genetical disruption technologies like zinc-finger nucleases (ZFNs) or CRISPR/-Cas9, which exhibited efficacy in targeting specific genes like the HIV co-receptor CCR5 or disrupting TCRA and TCRB genes to eliminate endogenous TCR expressions [87]. However, challenges remain in optimizing gene disruption techniques to ensure precise targeting without off-target effects. Ensuring that virtually all T cells have disrupted TCR genes is crucial for preventing GVHD, necessitating robust cell selection processes [88].

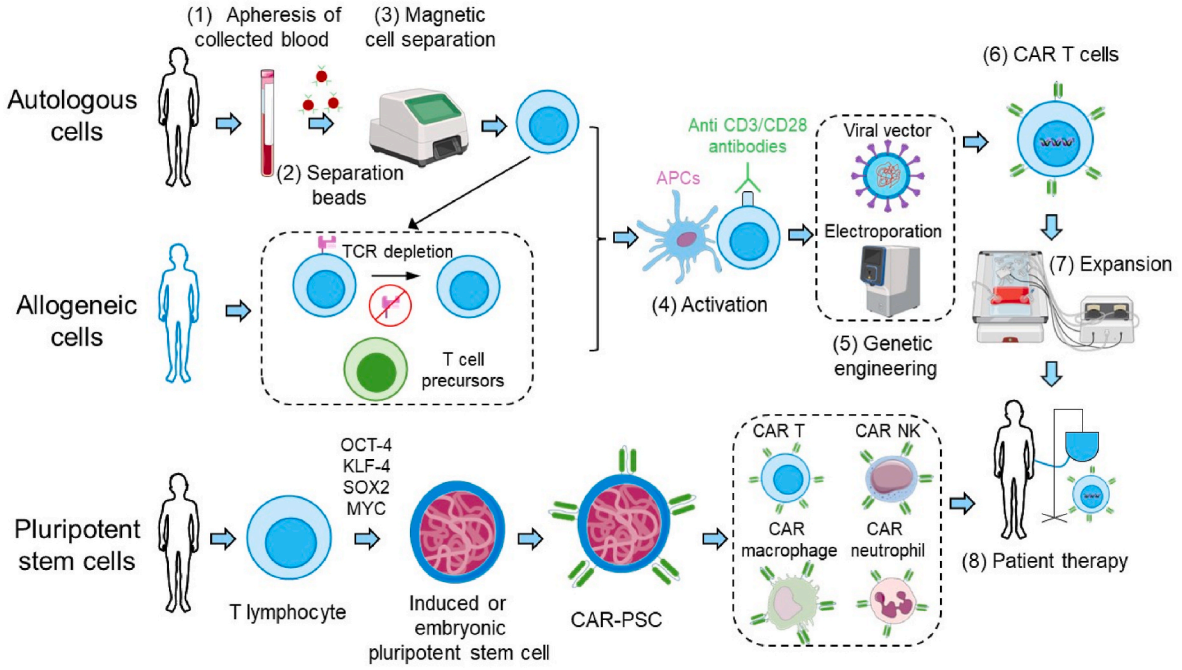


**Fig. 2. General schematic illustration of various immune cell source manufacturing**. Autologous and allogeneic cells were collected, separated, activated, genetically engineered, and expand for patient therapy. Pluripotent stem cell-derived immune cells were induced by a stage-specific manner.

Another approach involves using T cell precursors, which do not provoke GVHD since they are not mature, and these T precursors are selected in the recipient's thymus and become tolerant to host cells [89]. Expanding these precursors in culture and transducing them with CARs allow for tumor-targeted T cell production without having GVHD risks. This strategy offers the advantage of not requiring strict histocompatibility, potentially enabling "off-the-shelf" therapies with scaled-up manufacturing of T progenitor cells. Considering allogeneic T cells may pose GVHD risks, observations suggest that certain circumstances, such as CD19 CAR-engineered allogeneic donor T cells, exhibit decreased GVHD potential, although the mechanisms behind this are not fully understood [90]. In conclusion, advancing gene disruption technologies and leveraging T cell precursor immunotherapy hold promise in enhancing the therapeutic efficacy and safety of engineered T cell therapies, paving a way for transformative clinical outcomes in treating various diseases.

Unconventional T cells, such as lipid-restricted invariant natural killer T (iNKT) cells [91,92], MR1-restrict mucosal associated invariant T (MAIT) cells [93], and gamma delta T (γδT) cells [94], possess unique characteristics that make them promising candidates as universal donor cells for cancer and disease immunotherapy [95–97]. iNKT cells represent a distinct T cell subpopulation characterized by semi-invariant T cell receptors (TCRs) that recognize lipid antigens in the context of the monomorphic antigen-presenting molecule CD1d [98,99]. Upon TCR engagement, iNKT cells can upregulate killing receptors (e.g., FasL, TRAIL) and rapidly secrete cytotoxic molecules (perforin and granzymes), along with high levels of cytokines (e.g., IFN-γ, TNF-α, IL-2, IL-4, and IL-17) [100,101]. This leads to the activation of both innate and adaptive immune cells, enabling them to swiftly attack tumor cells through multiple mechanisms and strongly modulate the tumor microenvironment [102]. Mucosal-associated invariant T (MAIT) cells represent a distinct subset of innate T lymphocytes characterized by their semi-invariant T cell receptor (TCR). This TCR is composed of a unique invariant TCRVα chain that pairs with a limited repertoire of TCRVβ chains [103]. MAIT TCRs are specialized to recognize microbial riboflavin metabolite-based antigens and folate derivatives, which are presented by the highly conserved and monomorphic MR1 protein. These cells make up roughly 5 % of the total T cell population in humans and are distributed in a tissue-specific manner. Upon TCR engagement, MAIT cells rapidly secrete perforin, granzyme B, and a spectrum of TH1 and TH17 cytokines, contributing to their role in immune defense [104]. Another promising candidate for the development of off-the-shelf cell therapy is butyrophilin (BTN)-restricted Vγ9Vδ2 T cells, commonly known as γδ T cells [105]. These γδ T cells comprise approximately 0.5 %–5 % of the total T cell population. They are unique in that they express an invariant T-cell receptor (TCR) that specifically responds to phosphoantigens (pAgs) or phosphorylated isoprenoid metabolites, which are commonly found on transformed or infected cells with dysregulated metabolism [106]. Upon activation, γδ T cells exhibit effector functions like conventional T cells, including the secretion of perforins and granzymes, which directly kill tumor cells. Additionally, they produce pro-inflammatory cytokines that modulate the immune response. Moreover, γδ T cells can act as antigen-presenting cells (APCs) by phagocytosing cells and cross-presenting antigens, which subsequently leads to the activation of conventional T cells. This dual functionality highlights their potential in enhancing immune responses against tumors [107].

### 2.4. 2-4. Pluripotent stem cells or hematopoietic stem and progenitor cells derived immune cells and engineering

Pluripotent stem cells offer a solution by potentially providing an endless supply of therapeutic immune cells, making human pluripotent stem cells (hPSCs) an attractive source for immunotherapy. The development of cellular source therapeutics, reliant on validated [108], banked, broadly histocompatibility cell types, could profoundly impact the accessibility and affordability of adoptive immune cell therapies. This shift highlights the challenge of creating functional immune cells artificially instead of modifying occurring ones naturally [109,110]. Researchers have successfully differentiated hPSCs into hematopoietic stem and progenitor cells (HSPCs) using various techniques such as key transcription factor overexpression and exposure to differentiation stage-specific cytokine cocktails (Fig. 2) [111]. These blood progenitors can be further induced differentiation into diverse immune cells like T cells, natural killer (NK) cells, macrophages, neutrophils, B cells, and dendritic cells (DCs) [112]. While CAR hPSC-derived CAR T cells show promise in cancer and various disease immunotherapy, generating cytotoxic T cells from CAR engineered hPSCs remains complex due to various factors combined functions together like epigenetic memory, TCR signaling, and CAR expression. Recent studies have reported successful generation of CD19 CAR T cells from induced pluripotent stem cells (iPSCs), derived from peripheral blood lymphocytes, using lentiviral transduction to introduce the CAR construct [113,114]. These resulting pluripotent stem cell-derived CAR T cells exhibited potent antitumor ability against $CD19^{+}$ lymphoma cells. Additionally, there are ongoing efforts to engineer CAR NK cells from hPSCs for cancer immunotherapy [115]. These CAR NK cells, designed with typical T cell-specific CAR constructs, demonstrated potent cytotoxicity against target cancer cells in vitro, leading to multiple ongoing clinical trials investigating their potential. Moreover, macrophages and neutrophils derived from hPSCs are also being explored for their immunotherapeutic potential [116]. hPSC-derived macrophages showed innate phagocytic ability against targeted cancer cells, and when engineered with CAR constructs, they displayed enhanced antitumor specificity and increased proinflammatory cytokine expression [114]. Similarly, hPSC-derived neutrophils engineered with CAR constructs showed enhanced cytotoxic activity against glioblastoma cells, indicating their potential as an available allogeneic cell source for cancer and disease immunotherapy [74].

Hematopoietic stem and progenitor cells (HSPCs) are typically sourced from umbilical cord blood, donor bone marrow, or granulocyte colony-stimulating factor-mobilized peripheral blood [92,117,118]. Similar to the differentiation protocol for pluripotent stem cells, these HSPCs can be further differentiated into a wide array of immune cells [92]. This process is crucial in generating specific immune cell types for therapeutic applications, including immunotherapy. By guiding the differentiation of HSPCs, researchers can produce immune cells that are tailored for combating cancer [94].

### 2.5. 2-5. Immune cell non-genetic surface membrane engineering

To overcome the challenges associated with genetic modifications, efforts have been directed toward developing non-genetic strategies for engineering cell surfaces with targeting elements that can facilitate specific cell-cell interactions [119–121]. These methods are generally more transient or reversible and are particularly applicable to immune cells. Several diverse non-genetic approaches to cell membrane engineering have been explored [120]. Typically, they fall into one of five categories: (1) The insertion of hydrophobic moieties into the lipid bilayer. The hydrophobic effect governs the incorporation and orientation of integrated proteins, securing them on the cell surface and preventing internalization by the cell membrane. This principle has been harnessed in cellular engineering, where a desired ligand or chemical moiety is conjugated to a hydrophobic anchor and subsequently incubated with the target cell population for labeling. Zhong et al. developed a biologically site-selected, in situ controlled radical polymerization platform for live cell surface engineering [122]. This method employs metabolic labeling techniques to restrict polymer growth sites and incorporates a cytocompatibility Fenton-RAFT polymerization technique. (2) The direct chemical modification of cell surface constituents. A straightforward membrane-engineering strategy involves the direct chemical conjugation of small molecules and tethered cargo to

functional groups already present on the cell surface. Zhao et al. developed a versatile strategy for assembling biologically active nanocomplexes—including proteins, DNA, mRNA, and even viral carriers—on cellular surfaces to create a cell-based hybrid system [123]. This innovative system can be used to engineer a wide range of immune cells. Additionally, the same research group reported a tumor-targeting cellular drug delivery system (MAGN) by surface engineering tumor-homing macrophages with biologically responsive nanosponges [124]. (3) The membranous fusion of functionalized liposomes. Lipid membrane fusion is a vital process in normal cell biology and has been extensively studied. Functional group-containing liposomes can spontaneously fuse with cell membranes when incubated with cells, thereby presenting the respective functional groups on the cell surface. Shi et al. developed T-cell-targeting fusogenic liposomes designed to regulate and quantify T cell activity by targeting their surface redox status. These fusogenic liposomes, equipped with 2,2,6,6-tetramethylpiperidine (TEMP) groups, neutralize reactive oxygen species, thereby protecting T cells from oxidation-induced loss of activity [125]. (4) The use of functionalized sugar analogs to metabolically label surface glycoproteins. The technique of metabolically introducing novel functional groups to the plasma membrane was first pioneered in 1992 [120]. This method leveraged the promiscuity of natural carbohydrate biosynthesis pathways to metabolically incorporate non-physiological amino sugar analogs into membrane glycoconjugates [126]. Building on this approach, Jurkat cells were metabolically labeled with the azide-functionalized mannose derivative, N-azideacetylmannosamine, enabling the incorporation of azido sialic acid residues on the cell surface. Kim et al. later demonstrated that these azide-CAR T cells could be further modified with biodegradable fluorescent nanoparticles via azide-alkyne cycloaddition conjugation [127]. (5) The enzymatic remodeling of membrane proteins. Shi et al. reported a synthetic method for functionalizing the surface of natural killer (NK) cells with a supramolecular aptamer-based polyvalent antibody mimic (PAM). PAM is synthesized directly on the cell surface through nucleic acid assembly and hybridization. The data demonstrate that PAM outperforms its monovalent counterpart in enhancing NK cell binding to cancer cells and that PAM-engineered NK cells exhibit a greater ability to effectively kill cancer cells [128].

## 3. Chemotherapy in combination with adoptive immune cells immunotherapy

Chemotherapy remains a cornerstone for effective treatment for various types of tumors, which usually involved the use of chemical drugs to kill or slow the growth of cancer cells in the patient. However, there are still several obstacles for chemotherapy, for examples, some tumor exhibited intrinsic resistance to chemotherapy drugs due to their genetic mutations or variations; long-term treated tumors can develop resistance over time through mechanisms like drug efflux pumps, DNA repair enhancements, and changes in drug targets; repeated chemotherapy cycles may hold the potential causing cumulative organ damage. Hopefully, combining chemotherapy with CAR immune cells together showed great promising to address these significant obstacles posed by chemotherapy alone, meanwhile, chemotherapy can also overcome the limitations for CAR immune cells under the tumor microenvironment. Table 1 summarized the clinical trials involving CAR T and CAR NK cells in combination with chemotherapy. This combination leverages the strengths of both modalities to enhance therapeutic efficacy, reduce side effects, and achieve better pre-clinical and clinical outcomes, making it an urgent and promising strategy in cancer treatment.

### 3.1. 3-1. T cells in combination with chemotherapy

Chemotherapy can significantly enhance the efficacy of CAR T cell therapy, as research indicated that monotherapy is less effective compared to their combination. Alone, neither treatment can fully eradicate tumors or inhibit metastasis (Fig. 3) [129,130]. Chemotherapy boosts immune function and reduces tumor load, promoting mature and active DC and T cells migration into the tumor microenvironment [131]. Chemotherapeutic agents induce damage-associated molecular patterns (DAMPs), such as high mobility group box 1 (HMGB1), which are recognized by Toll-like receptor 4 (TLR4), thereby promoting the maturation and activation of dendritic cells (DCs) [132]. Furthermore, chemotherapy can reduce immunosuppressive elements such as regulatory T cells (Tregs),myeloid-derived suppressor cells (MDSCs), and cytokines like IL-10 and TGF-β. Chemical agents impact immunosuppressive elements (Tregs and MDSCs) more than normal T cells, intensifying T cell immunogenicity and their presence in the tumor microenvironment [133]. Primary chemotherapy, particularly with cyclophosphamide, significantly increases CAR T cell persistence and response. Moreover, chemotherapy sensitizes tumor cells to immunotherapy, enhancing CAR T cells penetration and tumor cell sensitivity to granzyme B [134]. It increases antigen delivery and facilitates CAR T

**Table 1**
Summary of CAR T and CAR NK cell combination with chemotherapy clinical trials for cancer treatment (ClinicalTrials.gov).

| Immune cells | Chemotherapy Drug | CAR Target | Phase | Reference |
|---|---|---|---|---|
| CAR T | (1) Cyclophosphamide, fludarabine | CD7 | I | NCT04572308 |
| | | CD19 | I | NCT04653493 |
| | | | II, III | NCT04404660 |
| | | | II, III | NCT03937544 |
| | | CD20 | I | NCT03881761 |
| | | CD22 | I | NCT04134325 |
| | | | I, II | NCT04715217 |
| | | CD30 | I | NCT02917083 |
| | | | II | NCT04083495 |
| | | CD33 | I | NCT03126864 |
| | | CD34 | I | NCT04214886 |
| | | CD44v6 | I, II | NCT04097301 |
| | | CD138 | I | NCT03672318 |
| | | APRIL | I, II | NCT03287804 |
| | | BCMA | I | NCT04637269 |
| | | | I, II | NCT03322735 |
| | | B7-H3 | I | NCT04897321 |
| | | | I, II | NCT05323201 |
| | | CS1 | I | NCT03710421 |
| | | EGFRvIII | I | NCT02844062 |
| | | | I, II | NCT01454596 |
| | | GD2 | I | NCT04099797 |
| | | GFRα4 | I | NCT04877613 |
| | | GPC3 | I | NCT05003895 |
| | | IM9 | I, II | NCT05155215 |
| | | IM73 | I | NCT04766840 |
| | | IL13Rα2 | I | NCT04510051 |
| | | LCAR-C18S | I | NCT04467853 |
| | | LCAR-M23 | I | NCT04562298 |
| | | MESO | I, II | NCT03916679 |
| | | MUC1 | I | NCT04025216 |
| | | PSCA | I | NCT03873805 |
| | | TAG72 | I | NCT05225363 |
| | | TriPRIL | I | NCT05020444 |
| | (2) Fludarabine, Cytoxan, Melphalan | CD5 | I | NCT03081910 |
| | | CD7 | I | NCT04264078 |
| | | CD19 | I | NCT04264039 |
| | (3) Gemcitabine, Capecitabine | CEA | II, III | NCT04037241 |
| | (4) Cytoxan, Fludara, Keytruda | GD2 | I | NCT01822652 |
| | (5) FOLFOX, FOLFIRI | NKG2D | I | NCT03692429 |
| | (6) Temozolomide | B7-H3 | I, II | NCT04077866 |
| NK or CAR NK | Melphalan | CD19 | I, II | NCT03579927 |
| | Nelarabine, Etoposide | No target | I | NCT05563545 |
| | Rituximab, Fludarabine | No target | I | NCT02280525 |
| | Carmustine, Cytarabine | No target | I | NCT03019640 |

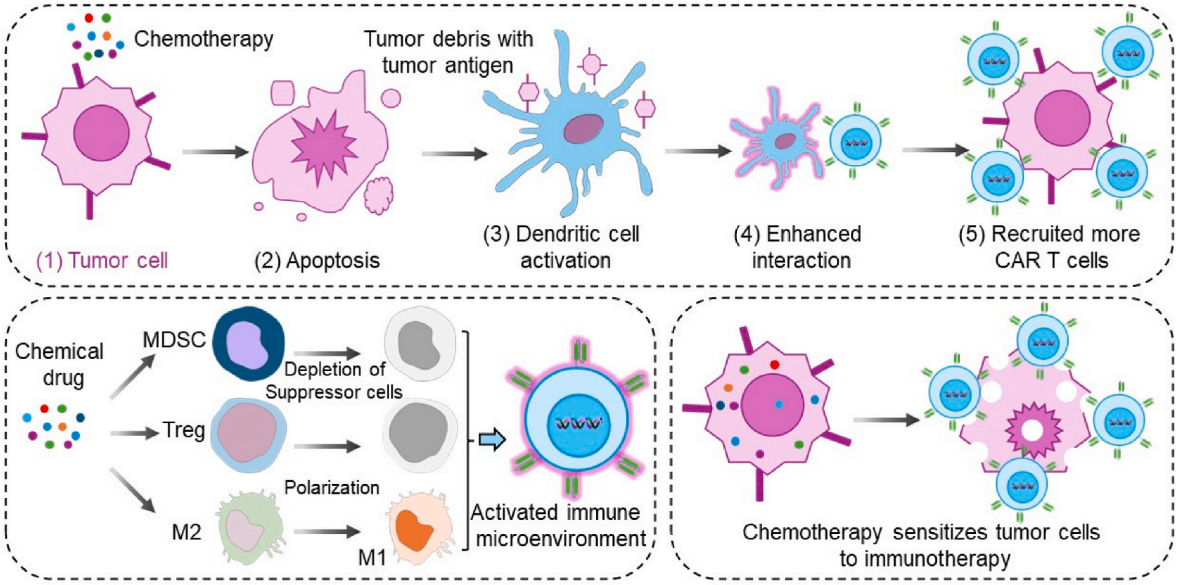


**Fig. 3.** The schematic illustration of T cells in combination with chemotherapy. Chemical drugs triggered tumor cell lysis, activated dendritic cell, and promoted CAR T cell therapeutic efficiency. Chemical drugs converted the "cold" immunosuppressive cell into "hot" state for activated immune microenvironment. Chemical drugs sensitized tumor cell to adoptive immune cells.

cell recognition [135]. Lymphodepleting chemotherapy prior CD19 CAR T cell treatment for acute lymphoblastic leukemia extends event-free survival by enhancing CD19 CAR T cell proliferation and stability [136,137].

### 3.2. 3-2. NK cells in combination with chemotherapy

Here, we'll explore evidence indicating that chemotherapy treatment can enhance the function of innate NK cell, laying the groundwork for combining these treatments with NK cell-based therapies.

Previous preclinical studies reveal chemotherapy's impact on NK cells' numbers and functionality. For instance, maintenance chemotherapy in acute lymphoblastic leukemia patient can significantly suppress peripheral blood NK cell levels [138]. It has been reported that cytostatic drugs, as evaluated by the researchers show varied effects on NK cell-mediated cytotoxicity, with some drugs not affecting it while others interfere [139]. Furthermore, certain chemotherapy agents, such as doxorubicin and camptothecin, can enhance the NK cell therapy efficiency through two ways. First, they increase NK cell cytotoxicity by regulating the expression of NKG2D ligand on NK cell membrane surface. Second, they regulate NK cell receptor ligands on tumor cells, making tumor cells more vulnerable to NK cell attack [140]. However, in prostate cancer, docetaxel treatment can reduce NK cell-mediated cytotoxicity due to increased LLT1 production, an NK cell inhibitory ligand [141]. Clinical data from cancer patients undergoing chemotherapy suggests that while B cells decrease, T cells and NK cells remain relatively unchanged, indicating chemotherapy may not negatively impact NK cells [142]. Moreover, chemotherapy can counteract the immunosuppressive tumor microenvironment, potentially enhancing NK cell therapy's efficacy. Studies in patients who have cervical cancer or oral squamous cell carcinoma (OSCC) and are undergoing neoadjuvant chemotherapy, showed increased NK cell levels and improved progression-free survival, hinting at a synergy interaction between chemical drug treatment and NK cell-based immunotherapy [143]. For the ideal treatment model, combining low or intermittent does of chemical drug with NK cell therapy can maintain drug cytotoxic effects of the drugs while enhancing function of NK cells. Epirubicin, for instance, enhances NK cell cytotoxicity via various mechanisms like NKG2D ligand upregulation, increased cytokine secretion, and activation of the granzyme B/perforin pathway [144]. Studies also demonstrate enhanced growth inhibition and cytotoxic effects when combining chemotherapy with NK cell therapy in breast cancer cell lines.

### 3.3. 3-3. Myeloid cells in combination with chemotherapy

Macrophages, integral components of the myeloid mononuclear phagocytic system, display a range of functional phenotypes influenced by signals from the tumor microenvironment [145]. Traditionally, in addition to the M0-type macrophages, the remaining activated macrophages were categorized into two polarized phenotypes: the classically activated M1-type macrophages and the alternatively activated M2-type macrophages. Within the tumor microenvironment, various signals trigger extensive intracellular transcriptional crosstalk in macrophages, leading to a spectrum of functions from proinflammatory responses to anti-inflammatory phenotype [146]. Tumor-associated macrophages (TAMs) play a crucial role in the tumor microenvironment by influencing several biological processes, such as promoted angiogenesis in the tumor site, extracellular matrix remodeling, cancer cell proliferation modulation, cancer cell metastasis, immunosuppression microenvironment, and resistance to the therapeutic treatments (chemotherapy and checkpoint blockade immunotherapy), this macrophage role usually termed as M2 phenotype. Conversely, under appropriate activation, macrophages can convert into M1 phenotype, and they can phagocytose cancer cells, execute cytotoxic tumor killing function, and engage in effective bidirectional interactions with innate and adaptive immune components, which functioned as the immune activation process [147]. Consequently, macrophages have become promising targets to enhance the tumor therapeutic efficiency in cancer therapy. Several macrophage-targeting strategies were developed to combine with chemotherapy, such as inhibitors of cytokines and chemokines that involved in recruiting and polarizing tumor-promoting myeloid cells, along with activation of their tumor-killing and immunostimulant functions [148,149]. Several preclinical and clinical trials supported the notion that targeting negative regulators (checkpoints) of myeloid cell function holds antitumor potential with the combination of chemotherapy [150]. Given the continuous recruitment of myelomonocytic cells into tumor tissues and advancements in chimeric antigen receptor (CAR) technology, adoptive macrophage combined immunotherapy emerges as a focus. Co-administering pharmacological

immunotherapies or chemotherapy could further enhance the efficacy of CAR-M treatment.

Due to their short half-life and resistance to genetic alteration, it is hard for neutrophils to be manipulated with chimeric antigen receptors (CARs) expression like other immune cells to enhance their tumor targeting and immunotherapeutic potential. Recently, our research group has achieved a breakthrough by successfully modifying human pluripotent stem cells with CARs expression through CRISPR-Cas9 technology. These CAR engineered pluripotent stem cells were then differentiated into efficient neutrophils using a chemically distinct platform employed with stage-specific cytokines and chemokines. The engineered CAR neutrophils exhibit significantly enhanced and targeted cytotoxicity against tumor cells, both in vitro and in vivo. This advancement suggests that the large-scale production of CAR neutrophils could herald a new approach to cancer treatment. In a recent development, then we further utilized these genetically engineered CAR neutrophils to deliver hypoxia-responsive pro-drug tirapazamine (TPZ)-loaded silica nanoparticles (SiO2 NPs) (Fig. 4) [151]. The systemically administered CAR-neutrophil@R-SiO2-TPZ NPs first target external normoxic tumor cells, establishing immunological synapses and initiating phagocytosis to eliminate these cells. Following tumor cell apoptosis, CAR neutrophils released R-SiO2-TPZ NPs, which are then absorbed by the remaining tumor cells. This process specifically targets the hypoxic tumor microenvironment (TME), effectively eliminating the remaining cancer cells. This innovative chemo-immunotherapy approach demonstrates enhanced and targeted anti-cancer efficacy, particularly in a glioblastoma (GBM) mouse model. Overall, this biomimetic CAR-neutrophil drug delivery system represents a secure, robust, and adaptable platform for cancer therapy.

## 4. Radiotherapy in combination with adoptive immune cells immunotherapy

Radiotherapy employed high-energy radiation to create breaks in the DNA strands in the tumor cells, leading to cell death or an inability to replicate, and radiotherapy is a common and effective treatment for various types of tumors, such as benign and malignant tumors. However, radiotherapy may cause some side effects, such as skin redness, irritation, and blistering reaction at the treatment site, gastrointestinal nausea, vomiting, and diarrhea symptoms, hair loss etc. When the tumor treated with radiotherapy, tumor blood vessels with their immature and irregularly distributed morphology experience increased permeability compared to normal vessels, and the response of tumor vasculature to radiation therapy varies significantly, hinging on factors like dose, fractionation, tumor type, and location. High doses exceeding 10 Gy led to endothelial cell death, acute vascular injury, reduced blood perfusion, and cell hypoxia [174]. Conversely, moderate to low doses stimulate vascular regeneration and normalization. Studies highlight the potential of doses ranging from 5 to 10 Gy to transiently restore vascular function by inducing NO release, improving tumor oxygenation, blood flow, and perfusion [175]. For instance, Ganss et al. demonstrated that a 10 Gy dose could normalize tumor vasculature and enhance lymphocyte infiltration in pancreatic islet tumors [176]. Fractionated regimens like 2 Gy per fraction, 5 fractions weekly, totaling 20 Gy, improved vascular maturity and reduced hypoxia in prostate cancer models without altering vascular morphology. Low-dose radiation normalizes vasculature, enhancing drug delivery into tumors. CAR immune cells would be a complimentary tool to improve the precision, effectiveness, and safety of this vital therapy.

### 4.1. 4–1. T cells in combination with radiotherapy

Combining radiotherapy with CAR T cell therapy is an emerging approach that leverages the strengths of both treatments to enhance cancer control and improve patient outcome [152]. Radiotherapy fosters a tumor microenvironment conducive to CAR T cell infiltration, overcoming many barriers. Radiotherapy can modify this microenvironment by reducing the number of immunosuppressive cells (such as regulatory T cells and M2 macrophages), and increasing pro-inflammatory signals, thus enhancing CAR T cell infiltration and

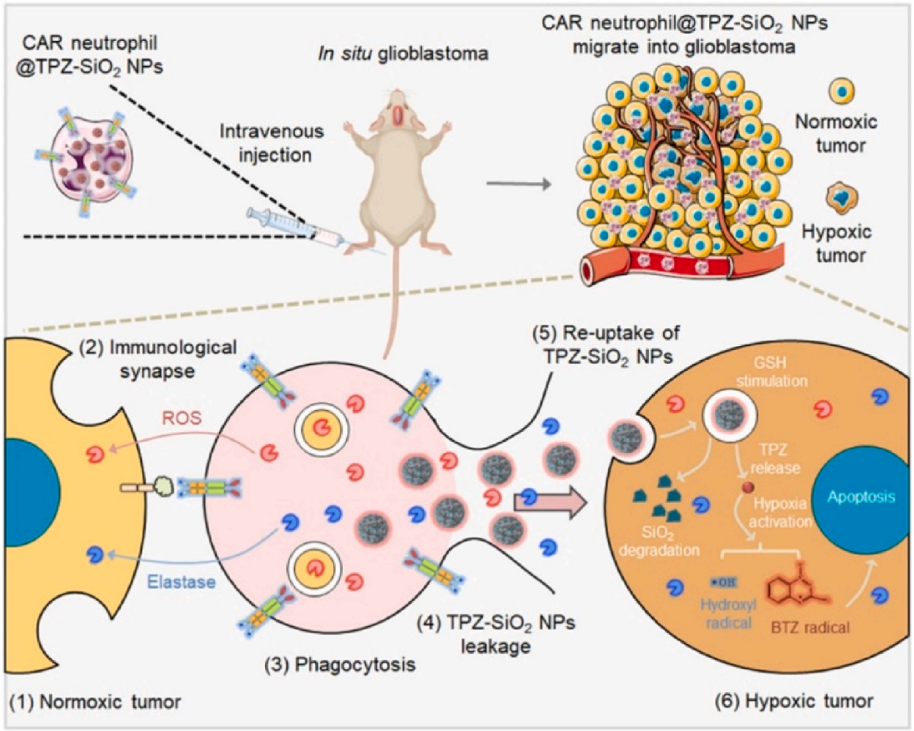


**Fig. 4.** CAR-neutrophil mediated delivery of tumor-microenvironment responsive nanodrugs for glioblastoma chemo-immunotherapy. Reproduced with permission [151]. Copyright 2023, Springer Nature.

function. Radiotherapy boosts MHC class I expression, heightening antigen presentation and recognition by cytotoxic T cells, meanwhile, radiotherapy can target diverse and heterogeneous tumor cell populations, including those that may not express the specific antigens targeted by CAR T cells, thus enhancing CAR T cell therapeutical efficacy locally and distantly (Fig. 5) [153,154]. Evidence shows radiotherapy sensitizes tumor cells to cytotoxic lymphocytes, leading to tumor cell eradication. Moreover, radiotherapy triggers pro-inflammatory cytokine release (e.g., IL-6, IL-1α/β, TNFα), along with IFNγ and DAMPs, bolstering immune effector cell entrance and function in the tumor microenvironment [155]. Local radiotherapy also ups specific chemokine expression (e.g., CXCL 1, 2, 9, 10, 16), aiding T cell entry into tumors [156].

Radiotherapy's uniqueness lies in its dual anti-tumor features. It not only stimulates local cytotoxic lymphocytes but also inhibits distant tumors, aiding regional anti-tumor growth and suppressing metastasis remotely [157,158]. CAR T cell therapy amplifies T cell responses, making combining it with radiotherapy beneficial. Numerous clinical trials have explored combining CAR T cells with radiation therapy, showing additive or synergistic effects [159]. Studies, like Weiss et al.'s, demonstrate radiotherapy's enhancement of CAR T cell function in solid tumors, potentially overcoming antigen escape [159]. Furthermore, De Selm et al. found combining low-dose radiation with CAR T cell therapy was more effective than monotherapy in treating pancreatic cancer [160,161]. This combination spurred proapoptotic trail production by activated CAR T cells, leading to better outcomes compared to CAR T cell monotherapy [162]. This underscores the synergy between radiotherapy and CAR T cells in overcoming antigen escape and eradicating tumors. Maintaining antigen presentation by dendritic cells ensures tumoricidal T lymphocyte responses persist. Given radiation's immune system enhancement, further research is warranted to explore its enhancing and synergistic effects on treatment regimens.

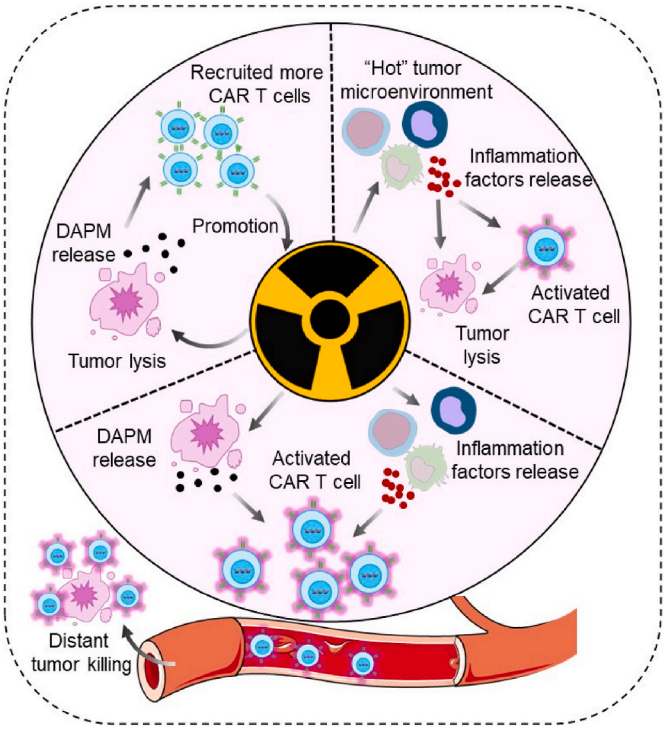


**Fig. 5.** The schematic illustration of T cell in combination with radiotherapy. Radiotherapy triggered tumor lysis, and the following damage-associated molecular patterns attracted more CAR T cells migrated into the tumor site. Radiation converted the "cold" tumor microenvironment into "hot" condition for promoted adoptive cellular therapy efficiency. Radiotherapy promoted CAR T cells for distant tumor killing.

### *4.2. 4-2. NK cells in combination with radiotherapy*

Radiotherapy also profoundly influences NK cell migration and tumor microenvironment dynamics, which has been exhibited the similar models on T cells. It also upregulates adhesion molecules (ICAM-1, VCAM-1) on endothelial cells, aiding NK cell adherence and extravasation. Combining radiation with CAR-NK cell therapy may boost homing and counteract hypoxia's inhibitory effects. Furthermore, NK cell infiltration in tumors correlates with patient prognosis. Radiotherapy amplifies this infiltration, seen in cervical, endometrial, and colorectal cancers [177]. It regulates chemokines like CXCR1, CXCR2, CXCR3, CXCR6, CCR5, and induces cytokine production (CXCL9, CXCL10, CXCL11) via cGAS/STING pathway activation, promoting NK cell migration [178]. Radiotherapy also increases MICA/B and ULBP1/2 expression on tumor cells, enhancing NK cell cytotoxicity. Moreover, it boosts ICAM1 expression, aiding NK-tumor cell adhesion and toxicity. Studies show combined radiotherapy and adoptive NK cell therapy improve survival and suppress metastasis in various cancer models [179,180]. Radiotherapy reduces tumor heterogeneity, enhancing immune cell infiltration, and response rates in CAR T cell therapy.

## 5. Oncolytic virus therapy in combination with adoptive immune cells immunotherapy

Oncolytic virus therapy is a form of cancer treatment that uses genetically modified or naturally occurring viruses to selectively infect and kill cancer cells while sparing normal cells. Oncolytic viruses are engineered to selectively infect cancer cell, exploiting the altered signaling pathways and surface receptors specific to tumor cells, once these oncolytic viruses come inside the tumor cells, the virus replicates, eventually causing the cell to lysis and release new viral particles that can infect neighboring cancer cells. Furthermore, the lysis of cancer cells by oncolytic virus releases tumor antigens, which can be recognized by the immune system, and promotes the CAR immune cell ability to target and activate the tumor immunotherapy efficiency.

Oncolytic virotherapy is an emerging cancer immunotherapy that harnesses cancer-lysis viruses to selectively infect and kill tumor cells [163]. These oncolytic viruses (OVs) possess distinctive features such as genetic modifiability, precise cell targeting, and the ability to activate the innate and adaptive immune systems, thereby eliciting a specific immune response against tumors (Fig. 6) [164]. By exploiting these capabilities, OVT holds promise in overcoming barriers encountered by CAR T cell therapy in treating solid tumors. For instance, it can prevent antigen loss in tumors, reverse tumor-induced immunosuppression, improve CAR T cell persistence in the tumor microenvironment, and equip them with potent therapeutic molecules like chemokines [165]. Numerous preclinical studies have investigated the combination of armed OVs with CAR T cell therapy, elucidating their mechanisms and effects. Nishio et al. synergistically combined oncolytic adenoviruses with GD2 CAR T cells, along with IL-15 treatment to promote the tumor therapeutic efficiency, it showed that oncolytic adenoviruses-treated tumor microenvironment recruited more CAR T cells infiltrated into the tumor site and converted the tumor microenvironment into "hot" stage, thus improved CAR T cells' sensitivity to tumor cells and kill the tumor cells [166]. Similar results were observed with oncolytic vaccinia virus expressing CXCL11, which attracted T cells to tumor sites and enhanced tumor cell killing in vivo. Moreover, combining CAR T cells with modified oncolytic virus expressing T cell activation cytokines (such as TNFα and IL-2) showed robust anti-tumor effects, even in immunosuppressive tumor microenvironments prone to metastasis, such as pancreatic ductal adenocarcinoma (PDA) [167]. Furthermore, Tanoue research group novelly engineered oncolytic virus to express antibodies that can block immune checkpoints (such as PD-L1) [168]. This antibodies-expressing oncolytic virus combined with HER2-specific CAR T cells significantly improved anti-tumor efficacy and prolonged survival in prostate cancer models [168]. Additionally, the strategy of

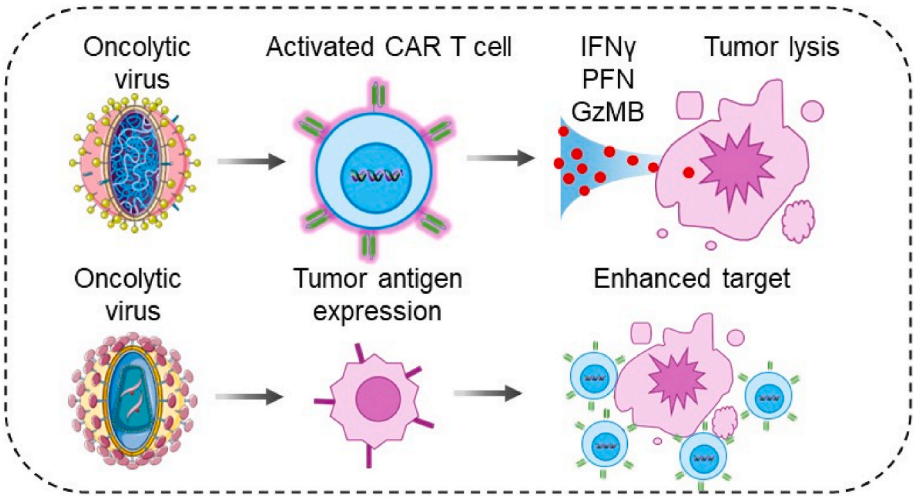


**Fig. 6.** The schematic illustration of T cell in combination with oncolytic virus therapy. Oncolytic virus activated CAR T cells for enhanced therapeutic efficiency. Oncolytic virus triggered tumor cells with tumor antigen expression and promoted the CAR T cell tumor cells targeting ability.

combining OVs that secrete pro-inflammatory cytokines like IL-12p70 along with checkpoint inhibitors has shown promise in controlling bulky and metastatic tumors, surpassing the efficacy of individual therapies. Addressing challenges like tumor antigen heterogeneity and loss, Park et al. developed an OV expressing a truncated CD19 variant to enhance CD19 CAR T cell activity selectively against tumor cells [169]. In conclusion, OVT combined with CAR T cell therapy represents a multifaceted approach to overcoming obstacles in treating solid tumors, offering enhanced antigen presentation, immune modulation, and targeted tumor cell eradication, ultimately improving therapeutic outcomes.

## 6. Immunomodulation agents (cytokines, priming agents, and checkpoint inhibition) in combination with CAR immune cells

### *6.1. 6-1. T cells combination therapy with cytokines*

Cytokines are versatile immunological signaling molecules integral to modulate various immune processes, which can enhance body's natural immune response to cancer or improve the efficacy of adoptive immune cellular therapy, making them attractive for co-treatment with CAR T cells [170]. Tumor immune evasion, often mediated by immunosuppressive cytokines such as IL-4, highlights the necessity for IL-4 resistant CAR T cells to enhance therapeutic efficacy [171]. Inverted cytokine receptors (ICRs) counteract the immunosuppressive effects of IL-4 in IL-4 positive tumors. IL-7 enhances effector immune responses by specifically promoting the growth of memory and naïve T cell. This effect does extend to regulatory T cells (Tregs) due to their lack of IL-7Rα receptors [172]. IL-15 is another potent immunostimulant against tumors [173]. IL-7 is pivotal in bolstering effector immune responses by selectively fostering memory and naive T cell growth. Treg cells, lacking the IL-7Rα receptor, are unresponsive to IL-7, hindering Treg cell expansion (Fig. 7A) [174]. Consequently, IL-7 can selectively enhance T cell anti-tumor responses while preserving Treg cell immunosuppressive activities. Engineering CAR T cells to maintain IL-7 responsiveness, particularly through IL-7Rα receptor subunit expression (IL-7Rα--transgenic/CAR-redirected Epstein Barr virus T cells), has been explored [175]. These engineered cells exhibited augmented immune responses against neuroblastoma cells, demonstrating enhanced antitumor function, expansion, and persistence, without affecting Treg cells. Similarly,

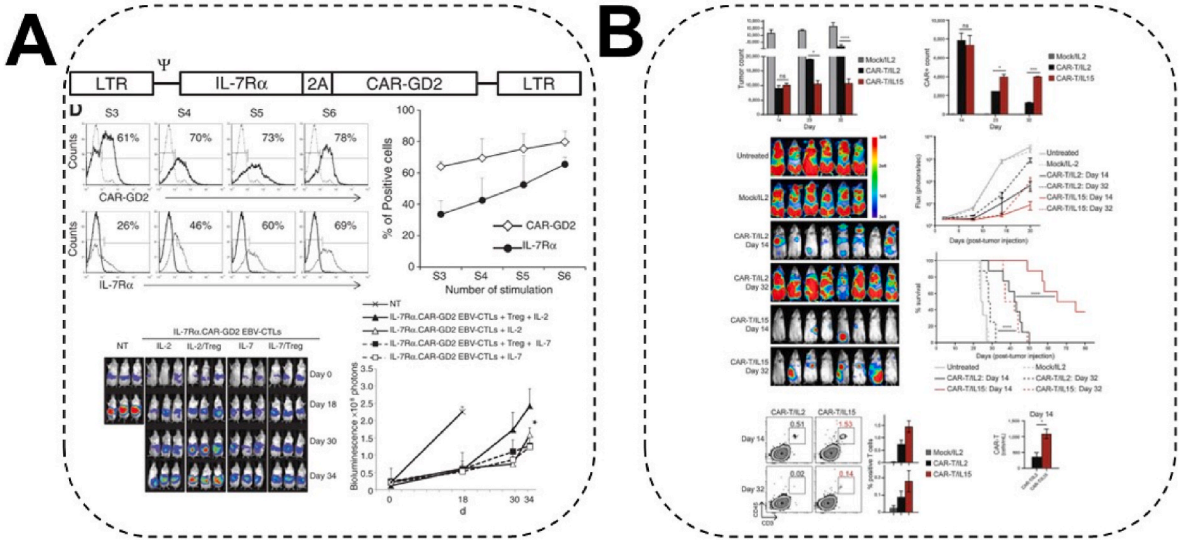


**Fig. 7.** CAR T cells combination therapy with cytokines. (A) Interleukin-7 mediates selective expansion of tumor-redirected cytotoxic T lymphocytes. Reproduced with permission [174]. Copyright 2014, American Association for Cancer Research. (B) IL15 enhances CAR T cell antitumor activity by reducing mTORC1 Activity. Reproduced with permission [177]. Copyright 2019, American Association for Cancer Research.

studies on anti-AXLCART cells against AXL-positive triple-negative breast cancer (TNBC) found that co-expressing the IL-7 receptor (C7R) enhanced CAR T cell expansion and cytotoxicity. This improvement overcame barriers in solid tumor treatment compared to anti-AXL CAR T cells lacking the IL-7 receptor. This approach holds promise for improving CAR T cell efficacy against solid tumors [176]. IL-15, a potent immunostimulatory cytokine, is crucial role for trafficking, persistence, and generation of memory in $CD8^+$ T cells (Fig. 7B) [177]. Combining IL-15 gene with an inducible caspase-9-based suicide gene has created safe iC9/CAR.19/IL-15+T cells for lymphoma and leukemia treatment. This approach enhances CAR T cell antitumor activity, reduces tumor growth, and prevents exhaustion by downregulating PD-1 [178]. Alizadeh and colleague's study on IL-15 combined CAR T-cells demonstrated decreased mTORC1 activity. This resulted in the preservation of CAR T cells' stem cell memory phenotype and improved their function, survival, proliferation, and resistance to exhaustion and apoptosis [179]. IL-12, a pro-inflammatory cytokine with potent tumor-suppressive properties, is a promising candidate for combinatorial immunotherapy. It can directly enhance the persistent cytotoxic activity of T cells, improve antigen presentation, counteract antigen-negative escape, and reprogram endogenous immune inhibitory cells within the tumor microenvironment [180]. Agliardi et al. demonstrated that CAR T cells targeting the tumor-specific epidermal growth factor receptor variant III (EGFRvIII), when combined with a single, locally delivered dose of IL-12, can achieve durable anti-glioblastoma responses [181]. Similarly, Lee et al. reported that CAR T cells targeting tumor-associated glycoprotein-72, in conjunction with an optimized membrane-bound IL-12 (mbIL-12), exhibited robust in vivo efficacy in human ovarian cancer xenograft models [182]. IL-18 was initially characterized as an inducer of interferon-γ (IFN-γ) expression in T cells and has been shown to activate lymphocytes and monocytes without causing severe dose-limiting toxicity in clinical trials [183]. Hu et al. demonstrated that IL-18-secreting human CAR T cells significantly enhanced CAR T cell proliferation and effectively augmented antitumor effects in mice with B16F10 melanoma [184]. Jaspers and colleagues reported that the expression of IL-18 in CAR T cells greatly increased the potency of DLL3-targeting CAR T cell therapy [185]. IL-21 plays a critical role in the development and maintenance of memory $CD8^+$ T cells by promoting an early differentiation phenotype. Tumor-reactive T cells generated under the influence of IL-21 exhibit a superior antitumor effect in vivo compared to T cells cultured with other cytokines [186]. Li et al. demonstrated that IL-21 can be effectively targeted to tumor-reactive T cells by fusing it with an anti-PD-1 antibody, significantly enhancing the efficacy of CAR T cell therapy [187]. Additionally, Zhu et al. reported that the antitumor function of AFP-specific T cell receptor-engineered T cells was augmented by exogenous IL-21 both in vitro and in vivo [188].

A 2021 study compared the impact of different ex vivo cytokines treatments on BCMA-CAR T cell function and persistence in a murine model of multiple myeloma (MM). The three conditions tested were IL-15 alone, IL-2 alone, and a combination of IL-15 and IL-7. The results indicated that BCMA-CAR T cells cultured with IL-15 exhibited limited differentiation and dysfunction, leading to improved survival and efficacy compared to cells cultured with IL-2 or IL-15/IL-7 combination [189]. This suggests IL-15 is a superior candidate for enhancing MM CAR T cell therapy. Additionally, IL-15 was found to enhance the metabolic profile of CAR T cells, decrease the expression of inhibitory molecules, preserve the stem cell memory (SCM) phenotype, and promote durable persistence and activity. These effects collectively prevent CAR T cell exhaustion, and enhance their metabolic function, contributing to more effective and long-lasting anti-tumor activity. Table 2 summarized the clinical trials involving CAR T and CAR NK cells in combination with immunomodulation agents.

**Table 2**
Summary of CAR T and CAR NK cell combination with immunomodulation agent clinical trials for cancer treatment (ClinicalTrials.gov).

| Immune cells | Immunomodulating agent | CAR Target | Phase | Reference |
|---|---|---|---|---|
| CAR T | Decitabine | CD19 | I | NCT04850560 |
| | | CD20 | I, II | NCT04697940 |
| | Lenalidomide | BCMA | I | NCT03070327 |
| | Durvalumab | CD19 | I | NCT02706405 |
| | Nivolumab | CD30 | I | NCT04134325 |
| | Pembrolizumab | CD19 | I, II | NCT02650999 |
| | | EGFRvIII | I | NCT03726515 |
| | PD-1 mAb | MUC1 | I, II | NCT03525782 |
| | Tislelizumab | CD19 | II | NCT04539444 |
| | Ibrutinib | CD19 | I, II | NCT03960840 |
| | Acalabrutinib | CD19 | I, II | NCT04257578 |
| | Rimiducid | PSMA | I | NCT04249947 |
| | Aldesleukin (IL-2) | CD19 | I, II | NCT00924326 |
| | | CD22 | I, II | NCT03098355 |
| NK or CAR NK | Trastuzumab | No target | I, II | NCT02030561 |
| | Bevacizumab | No target | I, II | NCT02857920 |
| | Nimotuzumab | No target | I | NCT03554889 |
| | Anti-GD2 Antibody | No target | I | NCT03242603 |
| | Cetuximab | No target | I | NCT02845856 |
| | Rituximab | No target | I | NCT00383994 |
| | Penostatin, Rituximab | No target | II | NCT01181258 |
| | Trastuzumab | No target | I, II | NCT02844335 |
| | Elotuzumab, Lenalidomide | No target | II | NCT01729091 |
| | Pembrolizumab | PD L1 | II | NCT04847466 |

### 6.2. 6-2. T cell combination therapy with checkpoint inhibition

Checkpoint signaling regulates immune responses, downregulating excess activity to prevent autoimmunity. This has sparked interest in checkpoint blockade for cancer immunotherapy (Fig. 8) [190]. Tumor-derived checkpoint ligands evade immunity, but checkpoint inhibitors enhance immune function, leading to promising outcomes in combined CAR T cell and PD-1 blockade therapy [191,192]. (1) Combining extrinsic checkpoint blockade (PD-1/PD-L1 axis blocking antibodies) with CAR T cell therapy shows promise in enhancing T cell immunity and tumor eradication. Studies have shown that the co-administration of pembrolizumab, an immune checkpoint inhibitor, with CAR T cells significantly increased the production of TNF-α and IFN-γ. These cytokines play crucial roles in immune response modulation. The elevated levels of TNF-α and IFN-γ resulted in enhanced persistence and function of CAR T cells, leading to improved therapeutic outcomes in patients with metastatic melanoma [193]. Additionally, combining anti-PD-1 checkpoint blockade with CAR T cells improved therapeutic outcomes in murine breast cancer models by enhancing tumor eradication. Anti-PD-1 therapy works by blocking the PD-1 pathway, which tumors exploit to evade the immune system, thereby reactivating T cells to attack the cancer. Despite concerns about the adverse effects and high cost associated with systemic PD-1-blockade, targeted delivery of checkpoint blockade via CAR T cells could mitigate these issues. This targeted approach could reduce systemic exposure, minimizing side effects and potentially lowering costs by using smaller does. Furthermore, preconditioning CAR T cells in specific cytokine environments, such as those containing IL-7 or IL-15, may further enhance therapeutic efficacy. IL-7 and IL-15 are known to support the growth, survival, and function of T cells. By preconditioning CAR T cells with these cytokines, their effectiveness could be increased, allowing for lower does and reducing the likelihood of adverse event. This strategy aims to improve the persistence and potency of CAR T cells, ultimately leading to better clinical outcomes [194]. (2) Dominant-negative receptor and short hairpin RNA (shRNA) techniques were employed for CAR T combination therapy [195]. These techniques help in modulating gene expression and function to enhance the efficacy

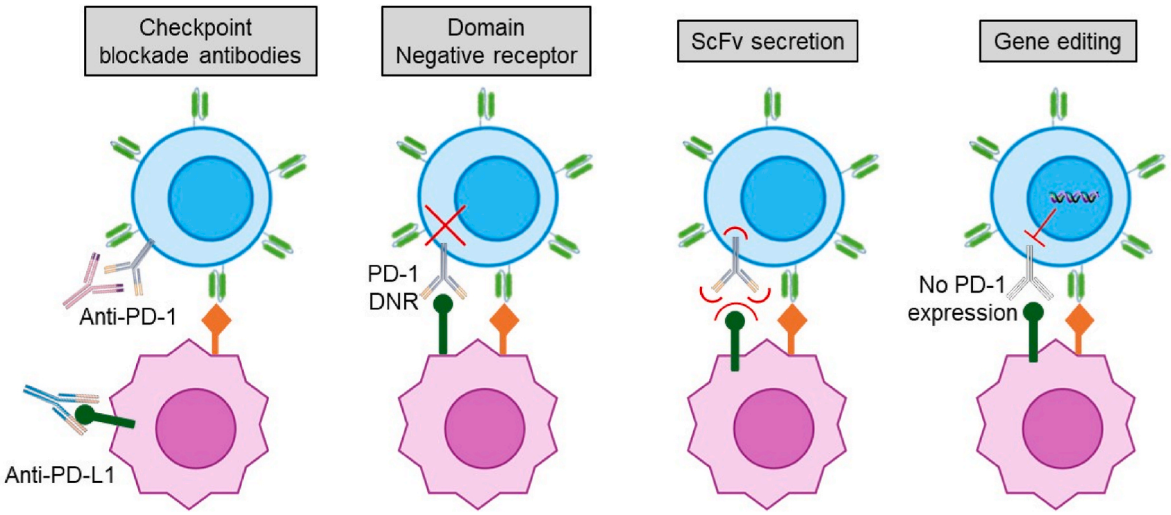


**Fig. 8.** Schematic illustration of T cell combination therapy with checkpoint inhibition.

of CAR T cells. Both CD28 and 4-1BB CAR T cells exhibited increased persistence upon encountering antigens, which is crucial for sustained immune response against tumors. Notably, 4-1BB CAR T cells showed resistance after repeated antigen exposures, maintaining their potency and cytotoxicity levels. This means that even after exposed to tumor antigens multiple times, these cells remained effective in killing cancer cells. They were particularly effective in tumor eradication even at low doses, highlighting their robustness and potential for dose reduction in therapy [195]. Conversely, CD28 CAR T cells demonstrated lower cytotoxicity, which was attributed to the overexpression of the PD-1 receptor. Cherkassky et al. designed and evaluated second-generation mesothelin-specific CAR T cells incorporating both CD28 and 4-1BB costimulatory signaling domains [196]. These dual-costimulatory domains aim to combine the benefits of both signaling pathways, potentially enhancing the CAR T cells' overall efficacy, persistence, and resistance to exhaustion. They enhanced CD28 CAR T cells using anti-PD-1 checkpoint blockade, demonstrating improved functionality. To further counteract PD-1-mediated immunosuppression, they engineered CD28 CAR T cells to express PD-1 dominant-negative receptor, effectively neutralizing the inhibitory effects of PD-1 on T cells. Additionally, PD-1 shRNAs were used to silence PD-1 expression, which enhanced CAR T cell function. This approach also targeted adenosine receptors (A2Ars) and CTLA-4, leading to increased cytokine production and enhanced anti-tumor efficacy. These strategies proved more efficient than PD-1 antibodies or shRNA alone. These combined strategies proved more efficient than using PD-1 antibodies or shRNA alone, providing a robust approach to overcoming immune suppression in the tumor microenvironment. (3) Gene editing using CRISPR/Cas9, a novel genome editing technique, targets immune checkpoint receptor gene loci to improve the efficacy of CAR T cells. In 2019, CRISPR/Cas9-mediated editing enhanced CAR T cell cytotoxicity and cytokine secretion against PD L1 positive cells, leading to better tumor control in vivo [197]. Similarly, this approach increased the cytotoxicity and anti-tumor responses of CD19 CAR T cell against LAG-3 in lymphoma xenografts, demonstrating its potential in treating various cancers by overcoming immune checkpoint-mediated resistance.

### 6.3. 6-3. T cell combination therapy with immunomodulatory agents

The combination treatment of CAR T cells with immunomodulatory drugs is widely recommended for efficient tumor cell eradication. These combinations enhance several critical aspects of CAR T cell therapy (Fig. 9), such as proliferation, persistence, and cytokine production within the tumor microenvironment [198]. (1) Lenalidomide, a commonly used immunomodulatory drug, enhances T cell activity through multiple mechanisms. It stimulates T cell proliferation, leading to an increase in the number of active T cells. Additionally, lenalidomide upregulates the expression of NF-κB nuclear factor, a protein complex that plays a critical role in regulating the immune response. Furthermore, lenalidomide promotes phosphorylating CD28 costimulatory

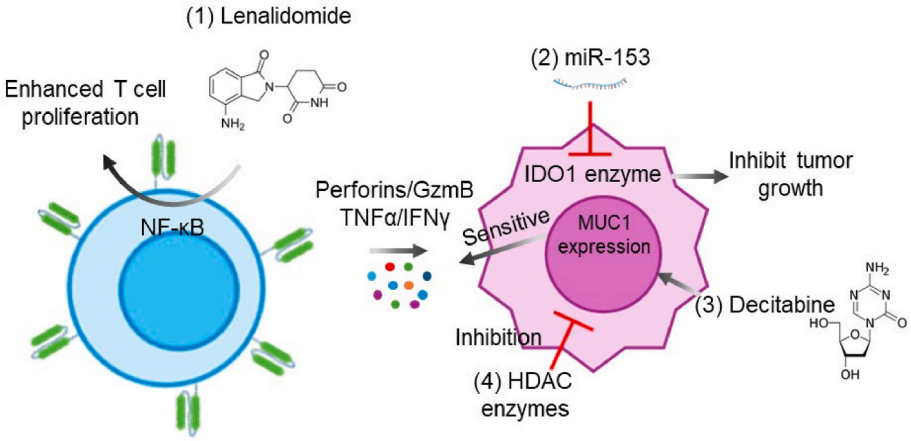


**Fig. 9.** Schematic illustration of T cell combination therapy with immunomodulatory agents.

molecules on T cells, which is essential for their full activation and function. These combined effects contribute to a more robust and effective immune response [199]. (2) Non-coding miRNAs such as miR-153 function as epigenetic immunomodulators, influencing cellular processes in naïve, effector, and memory T cells in distinct ways. These miRNAs do not code for proteins but regulate gene expression post-transcriptionally, thereby affecting the behavior and function of immune cells. For instance, miR-153 has been found to suppress the expression of the IDO1 enzyme in colon cancer. IDO1 is involved in the production of immunosuppressive metabolites like kynurenine, which can inhibit T cell function and promote tumor immune evasion. By downregulating IDO1, miR-153 reduces these immunosuppressive metabolites, thereby enhancing the immune system's ability to target and destroy cancer cells and promoting antitumor effects [200]. (3) Decitabine, another immunomodulatory agent, increases the expression levels of MUC1 on tumor cells by demethylating DNA. This process of DNA demethylation removes methyl groups from the DNA, reversing epigenetic silencing and allowing previously suppressed genes to be expressed. By regulating MUC1 expression, decitabine makes tumor cells more susceptible to being attacked by MUC1-CAR T cells. This enhances the effectiveness of MUC1 CAR T cell therapy against tumors [201]. (4) HDAC enzymes, which compact chromatin and suppress gene transcription, can be inhibited by HDAC inhibitors (HDACis) to enhance target gene expression on tumor cells. This has been observed in Burkitt's lymphoma with treatments like Romidepsin. HDAC inhibitors help de-compact chromatin, making DNA more accessible for transcription, thus increasing the expression of genes that can make tumor cells more recognizable to the immune system [202] SMAC mimetics (SMs) target inhibitor of apoptosis protein (IAPs), leading to increased TNF-α expression and caspase 8 activation, which promotes apoptosis in target cells. By neutralizing IAPs, SMs enable the activation of apoptotic pathways, thereby enhancing the ability of immune cells to kill cancer cells. Combining cyclophosphamide with CD19-CAR T cells can strengthen antitumor cytotoxicity by targeting the IDO enzyme. Cyclophosphamide depletes regulatory T cells and reduces immunosuppressive mechanisms in the tumor microenvironment, thus enhancing the effectiveness of CD19 CAR T cells against tumors expressing IDO enzyme [203]. Overall, combining CAR T cells with various immunomodulatory drugs and inhibitors presents a promising approach for improving cancer treatment efficacy and overcoming tumor cell evasion mechanisms.

### 6.4. 6-4. NK cell combination therapy with priming agents

The mechanism of action for NK priming agents involves providing factors like IL-15 or IL-2, or their modified variants, to support NK cell survival, activation, and sustained cytotoxic function. The IL-2 diphtheria toxin conjugate Denileukin Diftitox (IL2DT) selectively depletes CD25-expressing regulatory T cells, as shown in Fig. 10A [204]. This depletion facilitates the expansion and function of peripheral blood (PB)-NK cells [205]. Similarly, the IL-15/IL-15Rα fusion protein ALT-803 [206], depicted in Fig. 10B, is an IL-15 super agonist used with PB-NK cells [207] and NK-92 derived products [208]. ALT-803 enhances NK cell function by improving their proliferation and cytotoxicity. Additionally, ALT-801 and Hu14.8-IL-2 fusion proteins, which target specific complexes and tumor cells, have also been combined with PB NK cells to boost NK cell function against specific tumor types [209].

### 6.5. 6-5. NK cell combination therapy with antibodies

Combining monoclonal antibodies (mAbs) with non-engineered and engineered NK cell products represents the most extensively researched combination option in clinical settings. These antibodies play a pivotal role in enhancing NK cell function and improving tumor targeting through various mechanisms. (1) Elotuzumab, a monoclonal antibody that targets glycoprotein CS1 (also known as SLAMF7/CD319) [210], is a significant component of the SLAM family receptors, consisting of 9 members that are highly expressed on myeloma cells. This antibody can exert its effects through two main mechanisms, antibody-dependent cell-mediated cytotoxicity (ADCC), elotuzumab can mediate ADCC against CS1-expressing myeloma cells by engaging NK cells. NK cells recognize the antibody-bound CS1 on myeloma cells and subsequently induce their destruction through cytotoxic mechanisms. Elotuzumab can also directly activates NK cells by binding to their own CS1 [211]. A phase II clinical trial (NCT01729091) is currently underway to investigate the combination of NK cells with elotuzumab in myeloma treatment. In this trial, 72 patients received elotuzumab followed by

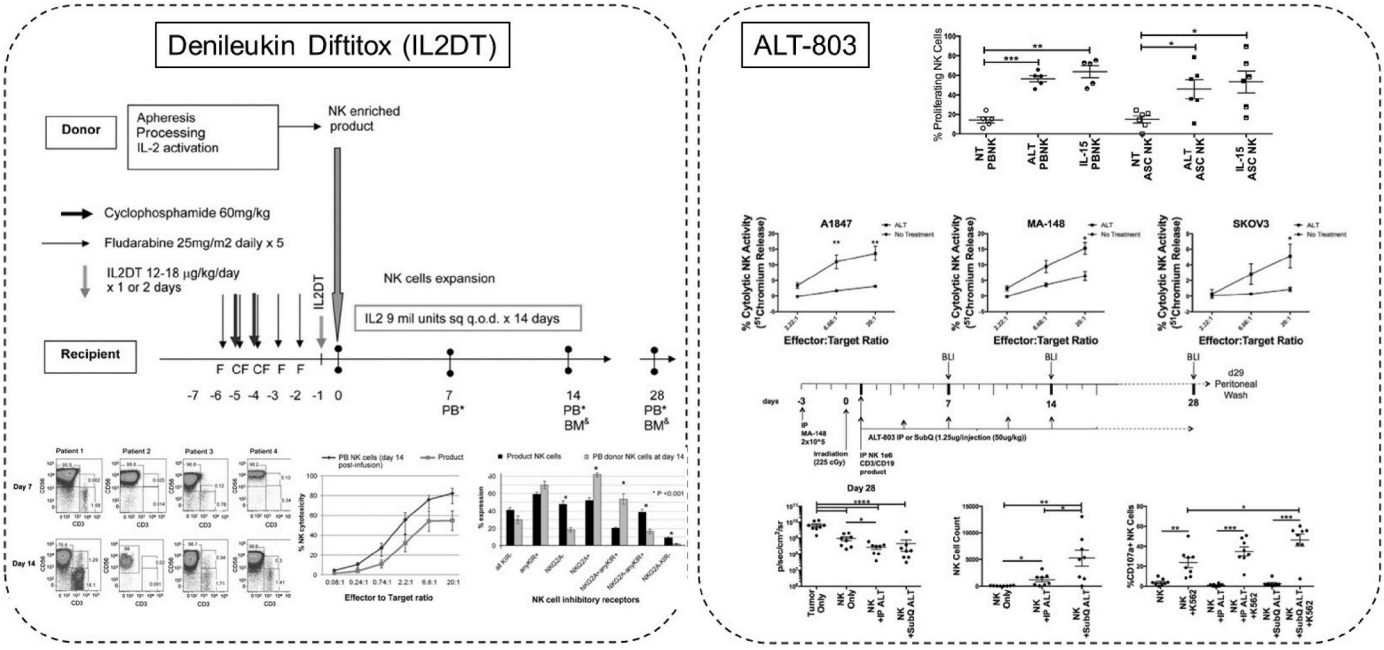


**Fig. 10.** NK cell combination therapy with priming agents. (A) The IL-2 diphtheria toxin fusion protein enhanced the clearance of acute myeloid leukemia through NK cell activity. Reproduced with permission [204]. Copyright 2014, Blood. (B) IL-15 super-agonist (ALT-803) enhances natural killer (NK) cell function against ovarian cancer. Reproduced with permission [207]. Copyright 2017, ELISEVIER.

chemotherapy, then infusion of umbilical cord blood (UCB)-derived NK cells five days before an autologous stem cell transplant [212]. The combination of elotuzumab with NK cells in the context of myeloma treatment represents a promising therapeutic approach that leverages both antibody-mediated and cellular immune mechanisms against cancer cells. The ongoing clinical trial aims to validate and optimize this strategy for improved patient outcomes. (2) Daratumumab is a human IgG1κ antibody targeting CD38, a 46 kDa type II transmembrane glycoprotein highly expressed on myeloma cells and [213], to a lesser extent, on immune effector cells such as natural killer (NK) cells. These NK cells play a vital role in daratumumab-mediated antibody-dependent cellular cytotoxicity (ADCC) [214]. Ochoa et al. demonstrated the benefits of combining anti-CD137 with daratumumab treatment [215], showing reduced tumor growth and enhanced survival in animal models. This suggests an advantage in co-stimulating the NK cell activation pathway to boost anti-CD38 therapeutic efficacy. (3) The Anti-CD20 monoclonal antibodies, such as Rituximab and Obinutuzumab, are utilized to treat various B cell malignancies that express CD20 [216]. The anti-lymphoma effects of these antibodies are partly due to the increased degranulation of NK cells they induce. Obinutuzumab, a humanized IgG1K monoclonal antibody, has been engineered to have its core fucose removed in the Fc portion. This modification enhances its binding affinity to CD16 (FcγRIIIa) receptors on NK cells, thereby improving ADCC [217]. Bachanova et al. conducted two studies involving patients treated with haploidentical NK cells, rituximab, and IL-2 [218]. The first study, a phase I/II clinical trial (NCT00625729), enrolled six patients with non-Hodgkin lymphoma or chronic lymphocytic leukemia. The primary objective was to evaluate whether allogeneic NK cells, infused following chemoimmunotherapy, could be safely expanded in vivo using IL-2 (Aldesleukin) [219]. The second study, a phase II clinical trial (NCT01181258) involving 16 patients, demonstrated that the treatment regimen was well-tolerated. Remarkably, one out of four patients with refractory non-Hodgkin lymphoma achieved remission within two months. Additionally, the majority of patients displayed transient yet highly functional CD16-expressing NK cells, while autologous NK cells exhibited poor functionality [220]. (4) Cetuximab, a chimeric IgG1 monoclonal antibody, targets the extracellular domain of the epidermal growth factor receptor (EGFR), which is commonly overexpressed in colorectal carcinoma, breast cancer, and non-small cell lung cancer (NSCLC) [221]. Its mechanism of action extends beyond ADCC, involving interactions with immune cells [222]. In a Phase I trial involving 9 patients with gastric or advanced colorectal cancer, researchers evaluated the safety, toxicity, and immunological response to administering autologous NK cells in combination with Trastuzumab or Cetuximab [223]. NK cells were expanded using IL-2, frozen prior to administration, and infused into patients three times at triweekly intervals, starting three days after monoclonal antibody administration and a capecitabine-based chemotherapy. (5) Trastuzumab binds to the extracellular domain of the HER2 receptor, inhibiting HER2 homodimerization and thus halting HER2-mediated signaling. This mechanism promotes enhanced HER2 degradation and subsequent inhibition of the MAP kinase pathway, resulting in suppressed cell proliferation. Trastuzumab's efficacy is further augmented by the recruitment of natural killer (NK) cells and the induction of antibody-dependent cellular cytotoxicity (ADCC). This has been demonstrated in vitro and is evidenced by the increased presence of NK cells within tumors following trastuzumab treatment [224]. Animal models, specifically FcγRIII receptor knockout mice, underscore the crucial role of ADCC in trastuzumab's anti-tumor activity [225]. Building on these preclinical findings, a clinical trial (NCT02844335) was conducted to assess the benefits of combining cryoablation, allogeneic KIR-mismatched NK cells, and trastuzumab in 48 patients. The participants were divided into three groups: cryoablation alone, cryoablation with NK cells, and cryoablation with the anti-HER2 antibody trastuzumab [226]. Compared to cryoablation alone, this combination therapy significantly improved anti-tumor effects and enhanced patients' immune function. (6) The anti-GD2 monoclonal antibody targets GD2, which is prominently expressed on neuroblastoma cells [227]. Modak et al. discovered that, in the presence of this antibody, unlicensed NK cells lacking killer immunoglobulin-like receptors (KIRs) for self-HLA molecules could effectively mediate robust antibody-dependent cellular cytotoxicity (ADCC). This finding highlights the crucial anti-tumor role these NK cells play in patients undergoing anti-GD2 therapy [228]. This underscores the advantage conferred by the absence of the KIR ligand in these patients.

Bi- and trispecific killer engagers (BiKE and TriKE) represent the next evolution in monoclonal antibody therapy, distinct from full-length antibodies [229]. These compact molecules consist of a variable portion of one antibody linked to one (BiKE) or two (TriKE) variable portions of another antibody. The pioneering product in this domain is AFM13-NK by Affirmed, comprising non-engineered umbilical cord blood (UCB) NK cells precomplexed with AFM13 tetravalent bispecific antibodies [230]. These bispecific antibodies target a tumor-associated antigen on tumor cells and CD16a on NK cells, demonstrating potential in a Phase I trial at the MD Anderson Cancer Center, focusing on patients with Hodgkin's lymphoma or non-Hodgkin's lymphoma (HL or NHL) by targeting CD30 on tumor cells [231]. Another notable development is the NKp46/CD16-based NKCE IPH6101/SAR443579 from Innate Pharma, now in clinical development in collaboration with Sanofi [232]. This candidate has shown significant anti-tumor activity in preclinical models and aims to enhance the specificity of NK cell engagement by targeting NKp46, potentially minimizing interactions with other immune cell types in vivo. Chang et al. evaluated eight CAR constructs using anti-PD-L1 nanobody and/or universal anti-FITC scFv to enhance NK-92 cell proliferation and cytotoxicity against solid tumors (Fig. 11) [229]. We then engineered hPSCs with optimized CARs, yielding functional dual CAR-NK cells. The anti-PD-L1 CAR promoted hPSC-NK cell activity through intracellular signaling pathways. FITC-folate adapter further boosted anti-tumor responses, suggesting our platform as a feasible off-the-shelf CAR-NK immunotherapy strategy.

### *6.6. 6-6. Adoptive macrophage combination therapy with immune checkpoint inhibitors*

Numerous immune checkpoint blockade therapies have been reported to date, with anti-PD-1 and anti-PD-L1 therapies being the most widely used in clinical settings. Unlike traditional methods that simply bolster immune responses, cancer immunotherapy based on inhibiting immune checkpoints like CTLA-4 and PD-1 aims to alleviating immune suppression. Blocking the PD-1/PD-L1 pathways using inhibitors to enhance T cell cytotoxic function, leading to significant progress in combating malignancies. In addition to T cell-associated immune checkpoints, several checkpoints primarily linked to macrophages have also been identified. For instance, CD47, a protein expressed on the surface of tumor cells, serves as a "don't eat me" signal by interacting with SIRPα on macrophages. This interaction inhibits the macrophages' ability to phagocytose, or engulf and destroy, the tumor cells, thereby helping the tumor cells evade immune clearance. CD47 is considered a poor prognostic factor because its presence on tumor cells is associated with a decreased likelihood of the immune system effectively targeting and eliminating the cancer [233]. Inhibiting CD47 has been shown to promote macrophage-mediated tumor inhibition. CD47 is a "don't eat me" signal expressed on tumor cells that, when blocked, allows macrophages to recognize and phagocytose the tumor cells more effectively. Moreover, the inhibitory receptor LILRB1 on macrophages plays a critical role in preventing tumor cell phagocytosis by interacting with the beta-2 macroglobulin (β2M) subunit of the MHC class I complex. This interaction sends a signal to macrophages to inhibit their phagocytic activity, thereby protecting the tumor cells from being engulfed and destroyed. By targeting LILRB1 or its interaction with β2M, it is possible to overcome this inhibition and enhance the immune system's ability to

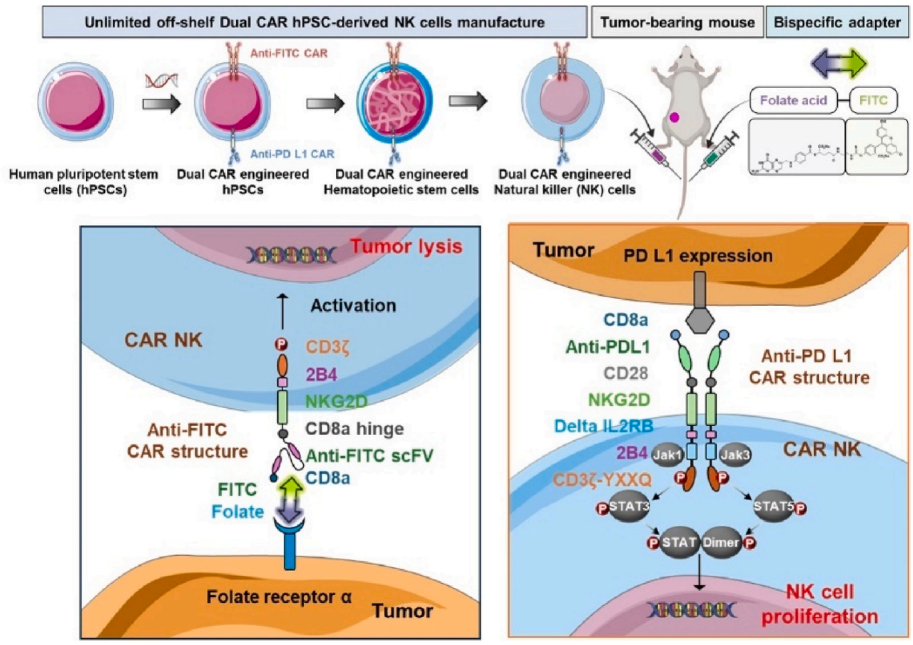


**Fig. 11.** Engineered human pluripotent stem cell-derived natural killer cells with universal anti-FITC scFv for enhanced immunotherapeutic efficacy. Reproduced with permission [229]. Copyright 2023, ELISEVIER.

clear tumor cells. (Fig. 12) [234]. The CD24-Siglec-10 axis plays a crucial role in immune evasion by inhibiting macrophage phagocytosis, which is an essential process for clearing cancer cells. When this axis is active, it hampers the ability of macrophages to engulf and eliminate tumor cells, allowing cancer cells to evade immune surveillance more effectively. Targeting immune checkpoints such as the CD24-Siglec-10 axis has shown remarkable advancements in cancer immunotherapy. By blocking or modulating these checkpoints, the immune system can be unleashed to recognize and attack cancer cells more effectively. This approach has significantly improved the efficacy of cancer treatments, leading to better outcomes for patients [235].

### *6.7. 6-7. Adoptive macrophage combination therapy with antibodies*

The efficacy of CAR macrophage therapy is notable in targeting tumor cells and enhancing phagocytosis, though not universally or completely effective. Patients unresponsive to single immunotherapy agents or resistant to treatments may not benefit significantly from CAR macrophages alone. However, combining CAR macrophages with antibodies can enhance anti-tumor capabilities. (1) CD40, a crucial costimulatory receptor found on antigen-presenting cells such as dendritic cells (DCs) and macrophages, plays a significant role in immune activation. It interacts with its ligand, CD40L (CD40 ligand), which is expressed on activated T cells and B cells. This interaction is a key step in initiating and sustaining immune responses. When activated T cells encounter antigens presented by DCs or macrophages, they upregulate CD40L expression. CD40L then binds to CD40 on the antigen-presenting cells, leading to a cascade of signaling events that enhance immune cell activation and function. This includes promoting antigen presentation, cytokine production, and the generation of effector T and B cell responses [236]. Activating CD40 boosts antigen-presenting cell activity, subsequently enhancing cytotoxic T cell function against tumors and reversing immunosuppressive microenvironments. CD40 agonists exhibit synergistic effects when combined with various immunomodulators, such as TLR agonists, cytokines like IFN and IL-2, adoptive immunotherapy, and chemotherapy. When a CSF-1R blocker is combined with a CD40 agonist, it leads to a significant improvement in antitumor efficacy and survival rates in mice. This combination strategy reduces Ly-6ClowF4/80+ TAMs (tumor-associated macrophages) and shifts the remaining macrophages towards a proinflammatory

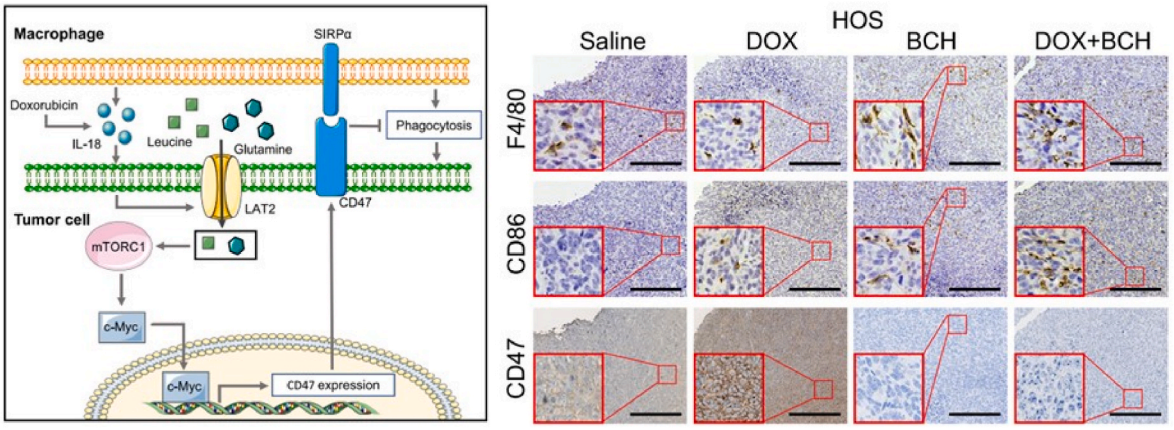


**Fig. 12.** Metabolic control of CD47 expression through LAT2-mediated amino acid uptake on macrophage. Reproduced with permission [234]. Copyright 2023, Springer Nature.

phenotype characterized by MHC-II high, $CD80^+$, and $CD86^+$ expression. This underscores the importance of both inhibitory cell removal and immune cell activation in enhancing the immune response against tumors [237]. (2) Targeting Toll-like receptors (TLRs) involves engaging a class of pattern recognition receptors that play a crucial role in enhancing immune function. TLRs accomplish this by initiating NF-κB signaling, which is pivotal for activating immune responses and regulating the secretion of key cytokines such as TNF-α, various interleukins (ILs), and interferon-alpha (IFN-α) [238]. Imiquimod (INN), a Toll-like receptor 7 (TLR7) agonist, has demonstrated success in combating skin tumors. It achieves this by inducing cytokine secretion and enhancing adaptive immune activity through TLR7-MyD88 signaling, a crucial pathway in the immune response against cancer. Toll-like receptors (TLRs) are a family of pattern recognition receptors that play a vital role in recognizing pathogen-associated molecular patterns (PAMPs) and initiating innate immune responses. TLRs like TLR3 (e.g., dsRNA, poly(I:C)), TLR4 (e.g., picibanil, LPS), TLR7 (e.g., imiquimod), TLR7/8 (e.g., R848), and TLR9 (e.g., CpG-oligonucleotide) are explored for innate immune targeting against cancer [239,240]. Exploring these TLRs and their respective agonists provides insights into harnessing the innate immune system's capabilities to target and combat cancer. These investigations contribute to the development of novel immunotherapeutic strategies that leverage the innate immune response to enhance anti-tumor activity.

## 7. Cancer vaccine and bispecific engagers in combination with adoptive immune cells immunotherapy

### 7.1. 7-1. T cell in combination with cancer vaccines

Cancer vaccines, a form of immunotherapy designed to stimulate the immune system to recognize and attack cancer cell, are powerful tools in immunotherapy, enhancing immune responses by targeting tumor-associated epitopes and activating adaptive immune systems [241]. Unlike the traditional vaccines that prevent infectious diseases, tumor vaccines are therapeutic, aiming to treat existing cancer by enhancing the body's natural defenses against malignancies. Combining cancer vaccines with CAR T cells offers a promising solution to address certain limitations of cancer vaccine or CAR T cell therapy, separately (Fig. 13). For example, tumor vaccine can introduce a wider array of tumor associated antigens or neoantigens to the immune system, potentially expanding the repertoire of targets for CAR T cells, this broadens the scope of tumor cells that can be recognized and attacked, overcoming the limitations of CAR T cells that target a single antigen. There are two primary approaches to boost CAR T cells using vaccines [242,243]. First, stimulating CAR T cells through antigen-presenting cells (APCs) or human leukocyte antigen (HLA)-dependent pathways by the peptide or protein vaccine. Second, directly activating dual or bi-specific CAR T cells within the tumor microenvironment. (1) Cellular vaccines utilize whole cells or cellular components as antigen sources and carriers, targeting APCs for immune activation. Various cell types, including irradiated tumor cells expressing the tumor antigen, and engineered dendritic cells with antigen expression, can be harnessed for cellular vaccines. A pioneering study by Caruana et al. employed a K562 tumor cell line expressing CMV-pp65, enhancing cross-presentation of viral epitopes on APCs and engineering dual CAR T cells specific to GD2 and CMV [244]. This approach demonstrated enhanced in vivo anti-tumor effects without significant side effects in neuroblastoma models. In a phase I/II trial by Rossig et al., EBV-specific cytotoxic CD19 CAR T cells were combined with irradiated EBV-transformed lymphoblastoid cellular vaccine, carefully integration of tumor vaccines with CAR T cell therapy can be optimized to enhance anti-tumor immunity and improve clinical outcomes for patients [245]. This strategy bolstered CAR19 T cell persistence and expansion, showing promise in augmenting CAR T cell therapy. Dendritic cell (DC)-based vaccines, DCs were pre-activated ex vivo with specific antigens, which holds the great ability to induce immunological memory and combat tumor relapse. Combining CAR T cells with DC-based vaccines, as demonstrated by Wu et al. using Eps8-DCs and CD19 CAR T cells, resulted in prolonged CAR T cell in vitro persistence, enhanced expansion, and stronger anti-tumor effects of both treatments together [246]. (2) Molecular vaccines offer alternative avenues, utilizing peptides, RNA, or DNA to load antigens into APCs and stimulate T cells [242]. Chan et al. utilized a nanoparticulate as vaccination platform to deliver OVA peptides to APCs, synergizing with dual-specific CAR T cells to achieve durable remission in solid tumors [247]. Similarly, Reinhard et al. combined liposomal antigen-encoding RNA with CAR T cells, enhancing CAR T cell expansion and tumor control in vivo [248]. (3) Viral-based vaccines, leveraging viral antigens to activate virus-sensitive T cells, have also shown promise. Wang et al. engineered CD19 CAR redirected CMV-specific T cells, enabling activation through both CAR engagement and CMV peptide antigens [249].

### 7.2. 7-2. T cell combination therapy with bispecific T cell engager

Human antibodies are typically monospecific, meaning they target a single antigen. In contrast, bispecific antibodies, such as bispecific T cell engagers (BiTEs) (Fig. 14A), can simultaneously target multiple antigens [250]. This dual-targeting capability allows BiTEs to link T cells to cancer cells, enhancing the immune system's ability to recognize and

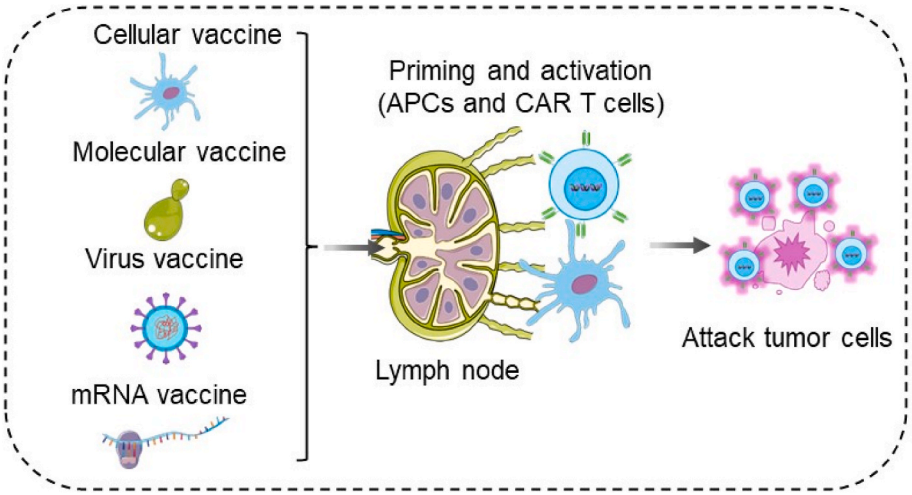


**Fig. 13.** The schematic illustration of T cell in combination with cancer vaccines. Tumor vaccine activated the CAR T cells for enhanced tumor lysis ability.

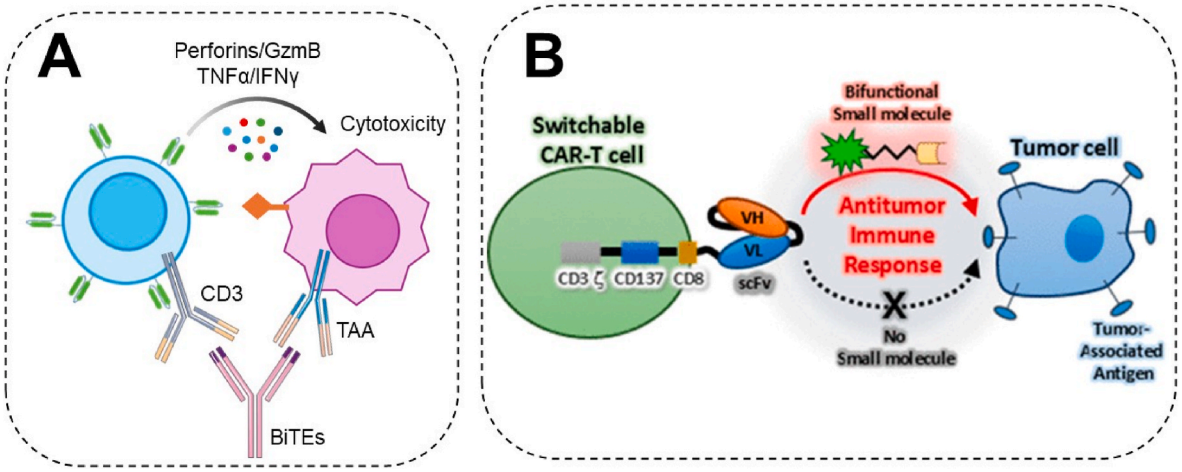


**Fig. 14.** Schematic illustration of T cell combination therapy with bispecific T cell engager. (A) bispecific T cell engagers (BiTEs) bridged CAR T cell and tumor cell. (B) Folate conjugated to fluorescein isothiocyanate bridged CAR T cell and tumor cell. Reproduced with permission [257]. Copyright 2015, American Chemical Society.

destroy tumor cells. BiTEs recruit T cells into the tumor microenvironment, significantly enhancing the efficacy of tumor combat. These antibodies are dual-specific, comprised of two single-chain variable fragments (scFvs) derived from different antibodies [251]. They engage both T cells and tumor cells by binding to CD3 on chimeric antigen receptor (CAR) or bystander T cells, and a target antigen on tumor cells. And this dual engagement promotes a focused immune attack on the tumor. BiTEs offer advantages, unlike many other immune therapies, BiTEs link T cells and tumor cells without the need for major histocompatibility complex (MHC) restriction, making them broadly applicable across various patients; by directly binding to T cells and tumor cells, BiTEs efficiently activate T cells, promoting their proliferation and enhancing their cytotoxic function; BiTEs facilitate the connection between CAR T cells and various tumor cells, leading to more effective tumor cell eradication [252]. For instance, Choi et al. developed and assessed EGFRvIII-specific CAR T cells that secrete EGFR-specific BiTE antibodies against glioblastoma in a mouse model [253]. This approach showed potential efficacy without significant toxicity. Combining BiTEs with other therapies has yielded promising results. Co-administration of blinatumomab, a BiTE, with anti-CD22 CAR T cells resulted in complete tumor cell eradication and prolonged patient survival post-relapse after anti-CD22 CAR T cell monotherapy [254]. In another study, CD3/EGFR BiTEs combined with anti-EGFRVIII CAR T cells effectively targeted neuroblastoma cells expressing EGFR [255]. In cases like relapsed/refractory B-ALL with CD19 loss after anti-CD19 CAR T cell therapy, adding blinatumomab induced CAR T cell expansion, persistence, and cytokine production, resulting in potent tumor cell elimination. Using bispecific adapters like anti-biotin CAR T cells with biotinylated bispecific antibodies against CD19 or CD20 has been shown to enhance CAR T cell function and tumor eradication [256]. Moreover, armored BiTE CAR T cells, produced by transfecting BiTE and CAR encoding sequences into T cells, effectively target heterogeneous tumor cells. Utilizing small molecule switches like folate-fluorescein isothiocyanate (FITC) conjugates allows for the control CAR T cell function at tumor sites targeting folate receptor (FR)-expressing tumors (Fig. 14B) [257]. In summary, BiTEs are a versatile and powerful addition to cancer immunotherapy, enhancing the effectiveness of CAR T cells and other treatments through direct and potent activation of T cells, leading to improved tumor cell targeting and destruction.

## 8. Metabolic modulators in combination with adoptive immune cells immunotherapy

### *8.1. 8-1. T cell combination therapy with metabolic modulators*

Altering the metabolic environment of tumor microenvironments and adjusting the metabolic profiles of effector T cells represent promising therapeutic avenues, particularly for solid tumors. Effective T cell activity requires metabolic adaptations to support crucial functions such as proliferation, cytotoxicity, and cytokine production. However, the abnormal tumor microenvironment hinders T cell function. This is caused by the heightened metabolic activity of tumor cells, which leads to a hypoxic, acidic environment lacking essential nutrients and amino acids. T cells need to adjust their metabolic profiles to sustain their activities, including rapid proliferation, efficient killing of target cells, and secretion of cytokines to modulate immune responses. The tumor microenvironment is characterized by increased metabolic demands from rapidly dividing cancer cells. This leads to a scarcity of oxygen (hypoxia), increased acidity (acidosis), and depletion of crucial nutrients and amino acids. The hostile tumor microenvironment negatively impacts T cell function by impairing their metabolic capabilities. T cells struggle to survive and function optimally in this harsh environment. Reduced T cell function can compromise the immune system's ability to recognize and eliminate cancer cells effectively. This phenomenon contributes to immune evasion by tumors. Additionally, within the tumor microenvironment, inhibitory enzymes like arginase and IDO-1, originating from both tumor cells and immunosuppressive cells, contribute to a suppressive milieu. Arginase depletes arginine, and IDO-1 depletes tryptophan amino acids. Both arginine and tryptophan are essential for T cell function and proliferation. The scarcity of these amino acids further suppresses effector T cell activity. Targeting these inhibitory enzymes, altering T cell metabolic profiles to adapt to nutrient limitations, and improving nutrient availability within the tumor microenvironment are essential strategies. By doing so, we can enhance effector T cell efficacy against tumors and overcome the immunosuppressive barriers imposed by the tumor microenvironment. Genetic modifications in T cells, such as enhancing mitochondrial function through the expression of PPAR-γ coactivator 1-alpha (PGC1α), knocking out ACAT1 to enhance effector function, and inducing catalase for resistance against hypoxia, represent highly effective reprogramming strategies. This genetic modification improves mitochondrial function, leading to increased energy production and overall cellular fitness. Mitochondria play a crucial role in providing energy for T cell activities such as proliferation and cytokine production. By knocking out

ACAT1, T cells can boost their effector functions. ACAT1 inhibition has been shown to enhance the production of cytokines and cytotoxic molecules, improving the T cells' ability to recognize and eliminate target cells, such as cancer cells. Hypoxia, or low oxygen levels, can impair T cell function and survival in the tumor microenvironment. Inducing catalase expression helps T cells resist the detrimental effects of hypoxia, allowing them to maintain their functionality and effectiveness in oxygen-deprived environments [258,259]. Moreover, incorporating different costimulatory molecules in CAR T cell structures directs cells to distinct metabolic profiles, influencing cell function [260]. For example, CD28 in CAR structures promotes aerobic glycolysis [261], while 4-1BB enhances fatty acid oxidative breakdown and mitochondrial biogenesis.

### *8.2. 8-2. Adoptive macrophage combination therapy with cellular metabolism modulation*

Metabolic reprogramming is pivotal for macrophage plasticity and polarization, especially upon their recruitment to the tumor microenvironment (TME), where they must adapt metabolically to survive. Arginine metabolism plays a crucial role in macrophage function and polarization; M1 macrophages utilize arginine for iNOS, generating NO and citrulline and suppressing oxidative phosphorylation (OXPHOS) while enhancing glycolysis [223]. In contrast, M2 macrophages utilize arginine for Arg1, favoring oxidative glucose metabolism (fatty acid oxidation) over glycolysis [224]. Understanding the metabolic changes in the TME and tumor-associated macrophages (TAMs) is vital for developing novel therapeutic strategies aimed at enhancing innate immune cell phagocytosis. Two key areas of focus are: (1) Glucose metabolism modulation: LPS stimulation of TLR4 triggers macrophage polarization towards M1, shifting glucose metabolism from OXPHOS to glycolysis [225]. Compounds like chelidamic acid inhibit HIF-1α degradation in M1 macrophages, promoting glycolytic metabolism. Exogenous succinic acid stabilizes HIF-1α expression, further enhancing macrophage glycolysis [226]. (2) Lipid metabolism modulation: Lipid metabolism plays a crucial role in influencing macrophage phagocytosis by regulating membrane fluidity and providing energy for cellular processes [227]. Excessive cholesterol uptake disrupts cholesterol metabolism in macrophages, leading to pathological changes. Increased endoplasmic reticulum membrane and free cholesterol promote cholesterol acyltransferase 1 (ACAT1) activity, generating more free cholesterol and triggering inflammatory signals via lipid rafts, notably TLR and NF-κB pathways [228].

## 9. Allogeneic hematopoietic cell transplantation (alloHCT) in combination with T cell therapy

Allogeneic hematopoietic cell transplantation (alloHCT) and CAR T cell therapy are potent adoptive cellular therapy (ACT) strategies [262]. Combining allo-HSCT with CAR T cells enhances tumor cell-killing activity and durable remission. However, comprehensive data on the synergistic effect of CAR T cells with allo-HSCT in cancers is lacking and warrants further research [263]. CAR T cell therapy has demonstrated efficacy in achieving MRD-negative complete remission in relapsed/refractory (R/R) B-ALL patients with minimal residual disease (MRD), paving the way for successful allo-HSCT [264]. Co-treatment with allo-HSCT (allogeneic hematopoietic stem cell transplantation) has been shown to significantly reduce leukemia relapse rates and improve leukemia-free survival when compared to CAR T cell monotherapy. This combined approach is particularly beneficial in the context of relapsed/refractory (R/R) B-cell acute lymphoblastic leukemia (B-ALL). Clinical trials have provided robust evidence supporting the use of consolidative allo-HSCT following CD19 CAR T cell therapy in R/R B-ALL cases. These trials have demonstrated promising outcomes in terms of disease control and overall survival, with an acceptable safety profile [265]. CD22 CAR T cell therapy combined with allo-HSCT (allogeneic hematopoietic stem cell transplantation) has shown enhanced responses and favorable safety profiles in treating B-cell malignancies. Allo-HSCT involves using stem cells from a donor (typically a family member or unrelated matched donor) to replace the patient's diseased or damaged bone marrow, offering a potential cure for certain blood cancers. Integrating allo-HSCT after CAR T cell therapy is particularly recommended for eligible high-risk patients. These are individuals who have a higher likelihood of cancer recurrence or progression despite initial treatment with CAR T cells. The rationale behind this recommendation is to consolidate the gains made with CAR T therapy and further strengthen the immune system's ability to combat cancer cells. By reducing the chances of relapse, this combined approach can significantly improve the overall survival rates for these patients [266]. The clinical value of CAR T cell therapy combined with allo-HSCT should be further evaluated for cancer treatment.

## 10. Current challenges for further clinical applications

Adoptive cellular immunotherapy (ACT) has emerged as a promising approach in cancer treatment, leveraging the patient's own immune cells to target and eliminate malignant cells. Despite its success, several challenges hinder its widespread clinical application, necessitating further research and innovation. One significant challenge is the limited immune cell source. Obtaining enough functional immune cells for therapy can be challenging, especially for patients with compromised immune systems or those with rare cell types. This scarcity of cells limits the feasibility of personalized cellular therapies tailored to each patient's unique immune profile and disease characteristics. Patient-specific variability poses another hurdle. Each patient's immune system and tumor biology are distinct, requiring customized therapeutic strategies. However, this individualized approach is often constrained by the limited availability of suitable donor cells for allogeneic therapies, particularly for rare cell types or specific genetic backgrounds. Manufacturing scalability is a critical issue in adoptive cellular therapy. Scaling up cell production to meet clinical demand while ensuring consistent quality and potency is a complex task, especially when working with limited cell sources. Maintaining the efficacy and safety of cell therapies during large-scale manufacturing processes is essential for successful clinical outcomes. Moreover, tumors exhibit significant heterogeneity, comprising diverse cell populations with distinct genetic and molecular profiles. This heterogeneity presents challenges in targeting all cancer cells effectively with a single therapy. Heterogeneous tumors can employ immune escape mechanisms, such as downregulating antigen expression or altering immune cell recognition, thereby reducing the efficacy of adoptive cellular immunotherapy. Subpopulations of cancer cells within heterogeneous tumors may also develop resistance to immunotherapy, leading to treatment failure and disease progression. Overcoming these challenges requires a deep understanding of tumor heterogeneity, immune evasion mechanisms, and the development of innovative strategies to enhance tumor infiltration and improve the effectiveness of adoptive cellular immunotherapy across various tumor types and patient populations.

Optimizing synergistic therapeutic multimodal approaches faces several challenges. One major hurdle is the task of identifying the most effective combination of therapies, which often involves integrating CAR T cells, checkpoint inhibitors, and various immunomodulators. The challenge lies in the diverse responses that different patients exhibit to these therapies, as well as the potential interactions between them. Determining the optimal combination requires extensive research and clinical trials to evaluate efficacy and safety. The tumor microenvironment further complicates synergistic therapy. It is characterized by its heterogeneity and dynamic nature, presenting barriers such as immune suppression, hypoxia, and stromal components that impede the effectiveness of combined therapies. Tumors also employ immune evasion strategies, such as upregulating inhibitory checkpoints or inducing immune tolerance, which can undermine the efficacy of immunotherapies. Moreover, combining multiple therapies increases the risk of off-target

toxicity, potentially causing adverse effects on healthy tissues and organs. For instance, chemotherapy can target rapidly dividing cells, which may also lead to damage in healthy cells that also divide quickly, such as those in bone marrow, gastrointestinal tract, and hair follicles. This can result in side effects like anemia, nausea, and hair loss. Radiotherapy, which uses high-energy radiation to kill cancer cells, can cause collateral damage to nearby healthy tissues, potentially leading to issues such as fibrosis, organ dysfunction, or secondary cancers. Oncolytic virus therapy, designed to selectively infect and kill cancer cells, may sometimes infect healthy cells, particularly if the virus spreads beyond the tumor sites. The combination of these therapies increases the cumulative burden on the body, making it more challenging for the immune system to distinguish between healthy and cancerous cells. This underscores the importance of carefully balancing therapeutic doses and monitoring for any unintended side effects. Careful monitoring and precise targeting of therapies are essential to minimize these risks while maximizing the therapeutic benefits. Another challenge is the development of resistance mechanisms by tumors. Some tumors may adapt and become resistant to immunotherapies or other treatments over time. This necessitates continuous adaptation and modification of therapeutic strategies to overcome resistance and maintain efficacy. From a logistical and administrative perspective, coordinating and integrating different therapeutic modalities, managing treatment schedules, and navigating regulatory requirements for combination therapies can pose significant hurdles. Collaboration among researchers, clinicians, regulatory bodies, and industry partners is crucial to streamline these processes and ensure compliance with regulatory standards. Furthermore, individual patient characteristics play a significant role in treatment outcomes. Factors such as immune status, genetic makeup, and tumor heterogeneity can greatly influence responses to therapy, emphasizing the need for personalized approaches. Tailoring treatment plans to each patient's unique profile can enhance therapeutic efficacy and minimize adverse effects. Addressing these multifaceted challenges requires a comprehensive approach that includes ongoing research, innovative technologies, robust preclinical and clinical studies, and collaborative efforts among stakeholders. This collaborative endeavor is essential for advancing synergistic therapeutic approaches and improving outcomes for patients with complex diseases.

Considering these factors, optimizing synergistic therapeutic approaches with CAR immune cells for personalized medicine requires a tailored strategy that maximizes therapeutic efficacy while minimizing off-target toxicity. To tailor treatment plans to each patient's unique profile, genomic and proteomic analyses should be conducted to examine the tumor at the molecular level. Understanding the genetic mutations, protein expressions, and immune landscape of the tumor allows for the identification of specific targets and pathways most relevant to the individual's cancer. For customized CAR design, the CAR structure should be specific to antigens highly expressed on the patient's tumor cells while minimally expressed on healthy tissues, in alignment with the patient's unique profile. Where possible, CAR constructs should incorporate safety mechanisms, such as suicide genes or inducible kill switches, which can be activated if severe toxicity occurs, providing a means to quickly halt the therapy. Adaptive dosing strategies based on real-time monitoring of the patient's response can further personalize treatment. In some cases, sequential administration of therapies may reduce toxicity, while in others, concurrent administration may enhance synergistic effects. Additionally, advanced imaging techniques and molecular diagnostics should be utilized to track tumor response and adjust the treatment plan accordingly. After treatment, personalized monitoring protocols should be established to detect any recurrence early and manage potential late-onset toxicities. By integrating these strategies, it is possible to create a personalized, multimodal treatment plan that leverages the strengths of CAR immune cells alongside other therapies, achieving a more effective and safer cancer treatment tailored to each patient's unique needs.

## 11. Conclusion

In conclusion, the strategic integration of adoptive immunotherapy with synergistic multimodal treatments represents a pivotal advancement in cancer therapeutics. This holistic approach leverages the strengths of adaptive immunotherapy while addressing its limitations, such as complex preparation processes and challenges within the tumor microenvironment. The synergy achieved offers promising prospects for significantly improving therapeutic outcomes and precision in personalized therapy. Moving forward, continued research efforts should prioritize refining treatment protocols, identifying optimal sequencing strategies, and deepening our understanding of immune-tumor interactions. As this synergistic paradigm evolves, its successful translation into clinical practice has the potential to revolutionize cancer treatment, ushering in a new era of more effective and tailored therapeutic interventions.

## Ethics approval and consent to participate

This review article does not require any ethical approval or allied consents for publication.

## Declaration of competing interest

We declare no conflict of interest.

## CRediT authorship contribution statement

**Yun Chang:** Writing – review & editing, Writing – original draft, Supervision, Conceptualization. **Mingyang Chang:** Validation. **Xiaoping Bao:** Writing – review & editing. **Cheng Dong:** Writing – review & editing, Writing – original draft, Supervision, Conceptualization.

## Acknowledgments

This worked was supported by start-up package funding from The Hong Kong Polytechnic University (Y.C.).

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