PHARMACIA

Pharmacia 72: 1–8
DOI 10.3897/pharmacia.72.e173384

Review Article

Chimeric antigen receptor (CAR) T cell therapy: current landscape, challenges, and future horizons in hematologic and solid tumors

Hany Akeel Al-Hussaniy[1], Sura Sagban Abid Ali[2], Manar Serhan Ahmed[3], Huda A. Rasheed[4], Kadhim Adnan Ali[5], Salah Hassan Zain Al-Abdeen[1,6], Zahraa Salam Al-Tameemi[1]

1 *Department of Pharmacology, College of Pharmacy, Al-Nisour University College, Baghdad, Iraq*
2 *Department of Pharmacology, College of Pharmacy, Bilad Alrafidain University, Diyala, Iraq*
3 *College of Pharmacy, Al-Farahidi University, Baghdad, Iraq*
4 *Department of Pharmacology, College of Pharmacy, Al-Bayan University, Baghdad, Iraq*
5 *Department of Anesthesia Techniques, College of Health and Medical Technologies, Al-Zahraa University for Women, Karbalaa, Iraq*
6 *Dr. Hany Akeel Institute, Iraqi Medical Research Center, Baghdad, Iraq*

Corresponding author: Hany Akeel Al-Hussaniy (Hany_akeel2000@yahoo.com)

Received 28 September 2025 ♦ **Accepted** 28 October 2025 ♦ **Published** 13 November 2025

Citation: Al-Hussaniy HA, Abid Ali SS, Ahmed MS, Rasheed HA, Ali KA, Zain Al-Abdeen SH, Al-Tameemi ZS (2025) Chimeric antigen receptor (CAR) T cell therapy: current landscape, challenges, and future horizons in hematologic and solid tumors. Pharmacia 72: 1–8. https://doi.org/10.3897/pharmacia.72.e173384

Abstract

Chimeric antigen receptor (CAR) T cell therapy has emerged as a transformative modality in cancer immunotherapy, particularly for hematologic malignancies. By genetically engineering patient-derived T cells to express synthetic receptors targeting tumor-associated antigens, CAR T cells enable precise tumor recognition and potent cytolytic activity independent of major histocompatibility complex (MHC) presentation. To date, six FDA-approved CAR-T therapies have demonstrated remarkable clinical efficacy in relapsed or refractory leukemia, lymphoma, and multiple myeloma, with durable remissions reported in otherwise treatment-resistant cases.

This review provides a comprehensive overview of CAR-T therapy development, molecular design, and mechanisms of action. It further explores clinical applications in both hematologic and solid tumors, highlighting therapeutic advances in breast, lung, and pancreatic cancers. Additionally, we discuss key toxicities, including cytokine release syndrome and neurotoxicity, and examine strategies for improving safety and efficacy. Finally, we outline future directions for CAR-T engineering and potential non-oncologic applications, underscoring the vast horizon of this personalized immunotherapy.

Keywords

chimeric antigen receptor, cytokine, immunotherapy, major histocompatibility complex

Introduction

The past decade has experienced a monumental shift in adoptive cell therapy for cancer treatment with the emergence of chimeric antigen receptor (CAR) T cells. Signaling through an antibody fragment specific for a tumor-associated antigen, on-target binding to that antigen elicits potent T-cell activation (Shaaban et al. 2023; Akunne et al.

2024). The first CAR-T therapies, targeting the B-cell lineage surface antigen CD19, received approval for the treatment of relapsed/refractory (r/r) hematologic malignancies in 2017 (Blüm and Kayser 2024). There are currently 6 FDA-approved CAR-T products for CD19-positive and B cell maturation antigen (BCMA)-positive hematologic malignancies, with other products in advanced clinical trials. Through their tremendous efficacy, second-generation CAR T cells have provided durable remissions to previously refractory diseases (Ali and DiPersio 2024; Ong et al. 2024).

The promise of CAR T cells for treating solid tumors has yet to be fulfilled. Although there has always been an awareness of the unique challenges posed in treating solid tumors – such as antigen heterogeneity, trafficking to disease sites, and prolonged on-target/off-tumor toxicity – clinical experience with the solid tumor agent axicabtagene ciloleucel has highlighted the potentially life-threatening toxicities of CAR-T treatments (Adwan and Al-Rekabi 2025). Toxicities now span the gamut of possible organ systems, including the central and peripheral nervous systems, and have necessitated the recognition and management of syndromes beyond the best-described cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS) associated with CD19-directed products (Srivastava et al. 2024).

Mechanism of action

The mechanism of CAR-T immunotherapy resembles the innate machinery of T cells. CARs are genetically engineered receptors with an antigen-binding domain for antigen recognition, a hinge/spacer to separate the outer and transmembrane domains, a transmembrane domain to anchor the receptor to the membrane, and an activating cytoplasmic domain involved in intracellular signaling cascades (Du et al. 2023). To mimic the TCR's ability to recognize antigens, CARs are transduced predominantly into T cells. However, CARs are also being expanded in a variety of other immune cells, including natural killer (NK), natural killer T (NKT), and γδ T cells. Once infused into the patient, CAR T cells penetrate the blood–brain barrier, infiltrate the tumor, and induce direct cytolysis of the cancer cells, bypassing MHC-dependent antigen presentation (Wang et al. 2021; Almeida et al. 2023). Additionally, CAR T cells bolster B-cell antibody production and promote the recruitment of immune cells to the tumor microenvironment (Sengsayadeth et al. 2022; Srivastava et al. 2024).

The therapeutic mechanism of CAR T cells begins with targeting their tumor-specific antigen through an scFv either built in or purposely expressed. Generation 2.0 was developed using a combination of two single-chain variable fragments of antibodies (scFv) linked by a natural flexible polypeptide chain that keeps the variable regions (~7 kDa) at an adjustable distance (10–44 Å), which appears to make specific binding of the tandem scFv more adaptable and eliminates the cell–scFv mismatch by recognizing two targeted tumor antigens simultaneously (Li et al. 2021). This mechanism avoids tumor escape caused by antigen loss or antigen heterogeneity, and tandem CAR-T cells can prevent fratricide in the case of CD5- or CD7-targeted CAR-T cells because only one of the CARs needs to bind its targeted antigen for T-cell activation. The tandem mechanism can also reduce cytokine release syndrome (CRS) by generating weaker cytokine secretion when interacting with a single antigen. Another strategy, the dual-signaling (DS) mechanism – baseline CAR-T cells and inducible CAR-T cells – was developed to avoid severe off-target effects when two signals occur sequentially in the tumor microenvironment (Wolf et al. 2023). This mechanism involves two CARs expressed separately within the same T cells; one CAR provides signal 1 to activate the T cells when recognizing antigen A, and the second CAR provides signal 2 with an inducible IL-12 cassette to reduce the adverse side effects of indiscriminate cytokine secretion, such as CRS or cytokine-related encephalopathy syndrome (CRES). DS CAR-T cells show an increased ability to kill tumor cells, as Palmieri et al. demonstrated with A20 lymphoma in vivo. Delving further into the mechanism, Zhang et al. discovered that the hinge length of DS CAR-T cells with a CD28 costimulatory domain affects tumor-tropic ability and that shortening the CD8a hinge in CAR0 enhances tumor recognition, resulting in greater tumor regression and longer survival (Palmieri et al. 2010; Zhang et al. 2021). Enhancing the scFv-based recognition mechanism, Loss Damage Apache Score (LDAS) CAR-T cells were developed by expressing tandem scFv linked to the light chain of HLA-DRB1* and DS CAR linked to the heavy chain of HLA-DRB1*. Finally, Nie ve hizo maś developed a triple scFv mechanism by adding an anti-CD16 scFv to the tandem CAR structure, which enables activation by targeting tumor cells or by binding to different isotypes of immune cells (Al-hussaniy et al. 2025).

Optimize the recognition ability of CARs

Chimeric antigen receptors are genetically engineered to endow T cells with the capability of specifically attacking tumor cells, based on the antigenic profile of target cells. However, antigen loss or escape remains a significant limitation, leading to tumor relapse. Recent advances in CAR design involve the introduction of two single-chain fragment variable domains (double scFvs), both tandem CARs and dual-signaling CARs, as well as the use of three scFvs, all of which can reduce the risk of relapse and improve the survival of patients undergoing CAR T-cell therapy.

First-generation CARs consist of an scFv linked to a hinge and transmembrane domain, as well as CD3ζ. Second-generation CARs add one costimulatory domain, such as CD28 or 4-1BB. Third-generation CARs include two costimulatory domains. Current clinical practice demonstrates that second-generation CARs are very useful for treatment. To further optimize CARs, the distal CD8a hinge region should be shortened to enhance CAR recognition of low-density PD-L1 cancer cells.

Double scFvs

Double scFvs (DbCARs) are CAR T cells expressing two different single-chain variable fragments (scFvs) in order to recognize two different tumor antigens simultaneously. Hematologic malignancies present higher heterogeneity of tumor-associated antigens in tumor cells (TES) compared to normal cells (TENS). Due to this heterogeneity of TES, first-generation CAR T cells targeting a single tumor antigen can neither remove all tumor cells nor prevent relapse. DbCAR T cells can bypass this limitation by recognizing two different tumor antigens, thereby killing not only double antigen-expressing tumor cells but also single antigen-expressing tumor cells. However, deviation of scFv orientation affects the fold and affinity of the newly expressed tandem scFv, which subsequently hampers the efficacy of DbCAR T cells.

Simultaneous targeting of two different tumor antigens has been found to overcome the limitation of antigen escape. Additionally, because each scFv can function as an independent structural entity, DbCAR T cells could provide a greater antigen density of each targeted antigen when antigen expression is low. This could also allow for efficient killing of tumor cells with low levels of a tumor antigen in vivo. On the downside of simultaneous targeting of two different tumor antigens, limitations include high levels of cytokine release, which may result in severe cytokine release syndrome (CRS), off-target/on-target toxicity, and neurotoxicity. Thus, the specificity of antigen-binding regions is an important parameter for therapeutic application.

The Tandem CAR (TanCAR)

The so-called tandem CAR (TanCAR) is a bispecific receptor with two linked scFv fragments for antigen recognition. While tandem bispecific antibodies do not always bind two antigens simultaneously, TanCAR has been shown to bind two antigens simultaneously and achieve a synergistic effect. TanCAR T has been used to treat hematologic cancers such as B-cell acute leukemia and lymphoma to offset the inherent heterogeneity in CD19 expression and to restore immune surveillance in cancers resistant to individual antigen-specific immune therapies. It has also been applied to solid tumors such as glioblastoma to reduce the likelihood of errors in CAR T antigen recognition and cross-reactivity. Targeting glioblastoma multiforme (GBM), the most aggressive primary brain tumor, CAR T cells based on TanCAR were engineered to target EGFRvIII and IL13Rα2 but at different intervals on the extracellular structural domain. Significant shortening of the CD8a hinge from 45 to 22 amino acids increased the flexibility of the CAR-T cells, with enhancement in the level of cytokine release and tumor control observed both in vitro and in vivo. Narrowing the interval between the two scFv fragments also increased CAR T cell activity.

TanCAR can interact with two tumor-associated antigens and activate CAR T cells when only one antigen is present. The construct allows for the survival and proliferation of many tumor-specific CAR T cells without the need to recognize both antigens (independent bivalent activation). However, the independent bivalent activation may be weaker than the synergistic bivalent activation triggered by recognition of two antigens. Furthermore, different types of CAR T cells for tumor treatment are being actively studied, including triple scFv CAR T cells. The introduction of triple scFv fragments in CAR structure aims to further improve the sensitivity and specificity of CAR T cells and enhance their antitumor effects.

Conjectures

The best way to kill tumor cells is to make a CD19-directed CAR T cell. To protect the CAR T cells from anti-CD19 CAR-T treatment, CD19 can be disrupted through gene editing so that it is protected from the lysis effect. The affinity of the scFv is another factor to be considered, as it can help decrease immune toxicity during treatment. In a recent study, the use of a CD8a hinge instead of CD8b in CAR-T cells led to longer persistence and controlled release of cytokines in patients with lung cancer. Similarly, the recognition by CAR-T can be further optimized by the use of double scFvs, tandem CAR, dual-signaling CAR, and triple scFvs. Cherry Huang et al. used the hyper scFv (multiple scFvs from different clones connected) to show that clone selection plays an important role in the functionality of hyper scFv.

Breast cancer is one of the most common cancers that affect women worldwide and is responsible for high mortality and morbidity despite available treatment options. A meta-analysis showed that breast cancer patients face a substantially higher risk of severe COVID-19. In a recent study, CAR-T targeting mesothelin (MSLN) with varied intracellular domains showed that shortening of the CD8a hinge from 45 to 22 amino acids is effective in controlling cytokine release and tumor lysis effects. The efficacy of CAR-T in hematologic malignancies has already been established using CD19 (Elia et al. 2023). CD19-directed CAR T-cell therapy has been approved by the United States Food and Drug Administration (FDA) for lymphoma, mantle cell lymphoma, and acute lymphoblastic leukemia. Loop CAR-T has been developed through structural optimization of the CAR by shortening the distance between the two chains of scFv. Current evidence indicates that Loop CAR19 T is comparable to conventional CD19 CAR T for relapsed/refractory B-cell malignancy.

Dual-signaling CARs

Chimeric antigen receptor (CAR) T cell therapy has recently emerged as a promising immunotherapeutic strategy for hematologic and solid tumors. Engineered CAR-T cells are capable of recognizing and killing tumor cells through recognizing antigen peptides on the surface of tumor cells. CAR structure can be optimized to improve tumor-specific recognition ability, which can be achieved by employing different types of single-chain variable fragments (scFvs). Dual-signaling CARs combine two individual CAR molecules: one provides the T cell activation signal (recognizing tumor-associated antigen 1), while the other delivers the costimulatory signal (recognizing tumor-associated antigen 2). Cytotoxicity assays have confirmed that dual-signaling CARs are more sensitive to target tumor cells and can recognize a wider range of tumor cells than conventional CARs (Lei et al. 2024).

CAR-T therapy has been authorized for use in the treatment of hematologic malignancies, with excellent efficacy achieved in most patients, especially in acute lymphoblastic leukemia (ALL). To broaden its applications, CAR-T therapy is combined with other therapies, and the backbone of the CAR is further modified. These directions expand the indications of CAR-T therapy to treat other hematologic malignancies and solid tumors and also potentiate the antitumor activity of CAR-T cells in the tumor microenvironment of hematologic and solid tumors. Besides significant advances in the treatment of breast and lung cancer, the therapeutic potential of CAR-T therapy against pancreatic cancer, which is highly aggressive, has attracted increasing attention. Altering the length of the CD8α hinge in CARs affects antigen-specific recognition, subpopulation balance, and T cell activation of Teb chimeric antigen receptor T cells (Fiorenza and Turtle 2021).

Triple scFvs (arranged in tandem)

The selection of scFvs together with the optimum length of each domain creates double scFv CARs that target two different tumor-associated antigens. While so far only two clinical trials of double scFv CARs have been initiated for solid tumors, tandem CARs seem to increase the cytotoxicity of CAR T cells. Other approaches have been used to improve the antitumor abilities of CAR T cells – for example, a CH2 domain was introduced in the hinge part of second-generation CARs to increase persistence, and the size of the CD8α hinge in second-generation CARs was altered to optimize the antitumor ability of CAR T cells. In addition, tandem CARs targeting two different antigens could prolong the progression-free survival of lymphoma patients compared with axicabtagene ciloleucel (Axi-cel) (Locke et al. 2022).

Third-generation CAR T cells round up the CAR generations by introducing two costimulatory domains that enhance the persistence of the cells. It is hypothesized that CARs with dual costimulatory domains may allow the generation of less differentiated memory T cell subsets through less intense immediate activation. These cells are capable of persisting longer under certain tumor microenvironmental stimuli. Most importantly, stable long-term carcinoma remission can be achieved after a single infusion of third-generation (3G) CD19-directed CAR T cells. Triple CARs have also been constructed by functional tandem scFvs linked to the spacer domain of second-generation CARs (Gómez-Melero et al. 2025).

According to the structure of the anti-CD19 scFv, recognition functions and cytokine secretion may be improved further with second-generation (2G) CAR T cells containing three scFvs in tandem linked to the hinge domain of CARs with a short CD8 hinge (Zoine et al. 2024).

Types of CAR T cells

CAR constructs with one, two, or three antigen-stimulating fragments are classified as first-, second-, or third-generation CARs. The inclusion of more costimulatory molecule components is thought to modulate CAR-T expansion, persistence, and efficacy in vivo. A pilot clinical trial suggested that using a second-generation CAR with one costimulatory molecule was better than using the first-generation CAR without a costimulatory molecule in terms of antitumor efficacy and cellular persistence. In preclinical models of hematologic malignancies, third-generation CARs incorporating two costimulatory molecules promoted cellular proliferation and prolonged persistence, whereas only one trial in chronic lymphocytic leukemia demonstrated that the third-generation CAR was more efficient than the second-generation CAR (Derigs et al. 2024).

In CAR constructs, costimulatory signaling is transmitted via the hinge and transmembrane domains, but details of the intracellular portion of the CAR construct have been relatively neglected. The optimal hinge and transmembrane domains in a CD19-specific CAR construct remain controversial; these components typically originate from CD28 or CD8α receptors. A recent study demonstrated that shortening the length of a CD8α hinge improved antitumor efficacy and increased CAR-T cell survival in a preclinical pancreatic cancer model. Hinge shortening also has potential drawbacks, such as decreased cytokine secretion. The exploration of additional CAR structures remains a promising area for optimizing CD19-specific CARs and CARs targeting solid tumors (Yi et al. 2022).

First-generation CARs

Chimeric antigen receptors are engineered antibody–T cell receptor chimeric proteins that couple an antibody's antigen-recognizing properties with T-cell function and the ability to be genetically modified. First-generation CAR T cells have an extracellular tissue-targeting domain and an intracellular T-cell signaling domain. The tissue-targeting domain consists of a single-chain variable fragment (scFv) that specifically antibodies the tumor-associated antigen. The intracellular T-cell signaling domain consists of the TCR CD3ζ chain that transduces a signal to activate T cells upon antigen binding. First-generation CAR T cells target CD19, a pan-B lineage marker expressed on normal and malignant B cells. First-generation CAR T cells are the simplest combination of a chimeric receptor (Teppert et al. 2022; Abbasi et al. 2023; Minguet et al. 2025).

The design provides CAR T cells with unique specificity for antigen, thereby redirecting T-cell cytotoxicity toward tumor targets in a natural MHC-independent fashion. However, CAR T cells of this generation lack coreceptors needed for complete activation of the physiologic T-cell response and interact with negative regulators of immune activation. These conditions alter the therapeutic activity of CAR T cells and can result in suboptimal immune responses. Early clinical trials of first-generation CAR T cells demonstrated good tolerability and early signals of efficacy, but persistent responses remained limited. These observations provided insight for the next generation of CAR T cells (Kampouri et al. 2023).

Second-generation CARs

Many costimulatory molecules were introduced to optimize the function of CAR T cells, such as 4-1BB, CD28, OX40, CD27, and inducible costimulator (ICOS) (Han et al. 2021). Second-generation CARs (fig. 7) consist of an scFv, a transmembrane domain, and one costimulatory domain. Adding one costimulatory domain can improve antitumor function in vivo and increase proliferation ability and cytokine production in vitro compared with first-generation CARs. Costimulation is a crucial mechanism for overcoming the anergy and exhaustion states of T cells (Huang et al. 2022).

Second-generation CAR T cells enhance antitumor effects compared with first-generation CAR T cells because the inclusion of costimulatory domains enhances expansion potential, cytokine secretion, antitumor function, and persistence. The FDA has approved two commercialized second-generation CAR-T products for clinical use: Kymriah (Novartis, Basel, Switzerland) and Yescarta (Kite Pharma, Santa Monica, CA, USA). Kymriah contains 4-1BB as the costimulatory domain, whereas Yescarta contains a CD28 domain as the costimulatory domain. Using different costimulatory domains may affect the clinical outcome of CAR-T therapy in hematologic malignancies because of differences in expansion capacity and persistence (Haslauer et al. 2021; Khan et al. 2024).

Third-generation CARs

Accumulating evidence demonstrates that the use of a single scFv in CAR T cells leads to tumor cell antigen escape and immunotherapy resistance. Therefore, triple scFvs have recently been identified as a means of intensifying the efficacy of CAR T-cell therapy (Sterner and Sterner 2021). A universal CAR T (UniCAR) platform adopting bispecific antibodies (BsAbs) has recently been developed. The effects of third-generation UniCARs on tumor killing have been tested and compared with those of CD19- and PSCA-specific second-generation UniCARs, as well as target-specific CD19 CAR T cells in two xenograft mouse models of acute lymphoblastic leukemia (ALL) and prostate cancer (PCa) (Feldmann et al. 2017; Shah and Fry 2019).

Third-generation UniCAR T cells recognizing B-cell leukemia via αCD19 sBsAbs show the greatest cytotoxic effects among the CAR T cell types tested. The CD19 and PSCA bispecific BsAb also directs third-generation UniCAR T cells to PCa cells more efficiently than the corresponding monospecific target BsAbs. Notably, third-generation UniCAR T cells induce less cytokine release during therapy in the PCa model, with upregulated β2 integrin expression potentially involved in this process (Al-Hussaniy 2023).

Clinical applications in hematologic malignancies

The first clinical use of genetically engineered T cells involved designing chimeric antigen receptors (CARs) that redirected cytotoxic T cells' specificity to the surface antigen of malignant B cells, the CD19 molecule. In contrast, the second-generation CAR added a second-generation costimulatory signal, such as 4-1BB or CD28, to enhance T-cell proliferation, cytokine secretion, and persistence. Cellular therapy with CD19 CAR T cells is a therapeutic option for B cell malignancies. Currently, hematopoietic cells remain the central focus of CAR T-cell research, as clinical trials have shown a potential curative effect in various CD19-positive lymphoma subtypes, including diffuse large B-cell lymphoma, B-cell acute and chronic lymphoblastic leukemia, mantle cell lymphoma, Burkitt lymphoma, follicular lymphoma, multiple myeloma, chronic lymphocytic leukemia, and Richter transformation (Zhang et al. 2022; Rojas-Quintero et al. 2024).

Clinical applications in solid tumors

Breast cancer

Novel immunotherapy treatments in breast cancer are required. Seven antigens appear to be attractive targets: mucin 1, receptor cMet, receptor tyrosine kinase-like orphan receptor 1, epithelial cell adhesion molecule, alpha-folate receptor, HER2, and carcinoembryonic antigen (CEA) (Bandara and Raveendran 2025). CAR T-cell therapies for breast cancer are still under development, and no products have been approved so far (Bharti et al. 2023). The CAR T-cell Therapy Database shows that only eight clinical trials have been completed and published, accounting for only 2.09% of the total number of clinical trials with CAR T cells. The limited clinical results obtained so far reinforce the value of this useful and easy-to-apply tool (Al-hussaniy 2022; Al-hussaniy and Al-Zobaidy 2024).

Lung cancer

Recently, a novel autonomous switch-mediated CAR-T therapy designed to controllably target B7-H3 in lung cancer (SK1-SCAR-T) has shown potential to improve tumor killing and T-cell infiltration (Zugasti et al. 2025). Exploring the use of combinatorial strategies also holds promise. Activated H69 CAR-T cells combined with cisplatin showed excellent killing efficiency. Cisplatin plays a role in enhancing the expression of GD2 and NCAM on the surface of small-cell lung cancer (SCLC) cells, facilitating the targeting and killing of residual SCLC cells by H69 CAR-T cells. The killing effect of combinatorial treatment on SCLCs was significantly superior to that of either treatment alone. Adoptive immunotherapy with CAR-T cells is expanding the field of exploration for lung cancer treatment. Ongoing research seeks more suitable targets, a better understanding of the tumor microenvironment barriers, and strategies employing combinatorial approaches to enhance lung cancer treatment (Al-hussaniy 2022).

Pancreatic cancer

The prognosis of pancreatic carcinoma (PC) is known to be very poor. Currently, CAR-T approaches have targeted different antigens in pancreatic cancer treatment. MSLN is a cell surface glycoprotein with limited expression in mesothelial cells of the pleura, peritoneum, and pericardium, but it is overexpressed in pancreatic cancers. MUC1 (mucin 1) belongs to the family of glycoproteins overexpressed in cancer. MUC1, with modified glycosylation, is involved in several interactions in the tumor microenvironment and regulates cell growth, differentiation, and apoptosis. C-met is the receptor of hepatocyte growth factor (HGF), and it regulates the biological behavior of tumor cells. CAR-T cells against CEA (carcinoembryonic antigen) can specifically recognize and destroy CEA-positive solid tumors such as pancreatic carcinoma. The CEA receptor CAR-T cells found in the inflammatory tumor conditions displayed significant antitumor activity (Al-Zobaidy et al. 2024; Abdulla et al. 2025).

Conclusion

The construction of a novel CAR T cell product requires a deep understanding of CAR molecular structure and tumor treatment. The application of gene delivery technology, including viral and non-viral gene delivery, helps safely engineer CAR structure. Meanwhile, elucidation of the role of costimulatory molecules in T cell activation contributes to next-generation CAR design. A novel CAR T cell product could eliminate the tumor while avoiding fatal side effects. Besides tumor recognition, expansion, and memory development are also critical for sustaining antitumor ability. Additionally, the application of CAR T-cell therapy has been explored in various other diseases beyond tumors, such as human immunodeficiency virus (HIV) infection.

Additional information

Conflict of interest

The authors have declared that no competing interests exist.

Ethical statements

The authors declared that no clinical trials were used in the present study.

The authors declared that no experiments on humans or human tissues were performed for the present study.

The authors declared that no informed consent was obtained from the humans, donors or donors' representatives participating in the study.

The authors declared that no experiments on animals were performed for the present study.

The authors declared that no commercially available immortalised human and animal cell lines were used in the present study.

Use of AI

No use of AI was reported.

Funding

No funding was reported.

Author contributions

All authors have contributed equally.

Author ORCIDs

Hany Akeel Al-Hussaniy https://orcid.org/0000-0003-2647-8574
Sura Sagban Abid Ali https://orcid.org/0009-0008-4273-2409
Manar Serhan Ahmed https://orcid.org/0000-0002-4949-6743
Huda A. Rasheed https://orcid.org/0000-0002-2084-939X
Kadhim Adnan Ali https://orcid.org/0009-0006-4607-5309
Salah Hassan Zain Al-Abdeen https://orcid.org/0000-0002-5685-481X
Zahraa Salam Al-Tameemi https://orcid.org/0009-0004-7026-5263

Data availability

All of the data that support the findings of this study are available in the main text.

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