Open Access Article

Ann. Acad. Med. Siles. (Online) 2026;80:190–194
eISSN 1734-025X
DOI: 10.18794/aams/211011
www.annales.sum.edu.pl

PRACA POGLĄDOWA
REVIEW

Dendritic cells and memory CD45RO$^+$ T cells as an optimization strategy for CAR-T cell therapy: A novel approach and challenges

Komórki dendrytyczne i komórki pamięci CD45RO$^+$ T jako strategia optymalizacji terapii CAR-T – nowe podejście i wyzwania

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ABSTRACT

Chimeric antigen receptor (CAR)-T cell therapy stands as an innovative treatment indicated for specific relapsed, refractory hematological malignancies and, increasingly, for solid tumors. Despite major therapy results in highlighted patient populations, significant limitations remain. Antigen loss, limited cell persistence, and a hostile tumor microenvironment are major issues related to the biology of the immune and cancer cells. Research that focuses on the biology of immune cells could thus contribute to improving treatment outcomes free from remission and longer-lasting immune response. Integrating dendritic cells – professional antigen-presenting cells – and memory T cell subsets, particularly those marked by CD45RO expression, is an emerging approach for significant therapy improvement. This article reviews studies that show CAR-T cell therapy's most relevant cell-derived limitations. The latest fundamental studies in immunology that justify the use of dendritic cells and memory T cells as an optimization strategy for CAR-T cell therapy are presented. Particular effort was also put into reviewing the other related clinical strategies that improve CAR-T cell therapy. Attention was also paid to studies still in progress, but with successful results. A total of 48 publications were analyzed using only PubMed sources, from which 20 papers were selected. Because of the unexplored research field and the lack of sufficient data, the review covered papers from 2007 to 2025, but with the strongest emphasis on the most recent research.

KEYWORDS

dendritic cells, memory T cells CD45RO+, CAR-T, immunotherapy

Received: 28.08.2025 **Revised:** 08.09.2025 **Accepted:** 17.09.2025 **Published online:** 23.04.2026

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Publisher: Medical University of Silesia, Katowice, Poland

STRESZCZENIE

Terapia komórkami T z chimerycznym receptorem antygenowym (*chimeric antigen receptor* – CAR) stanowi innowacyjną metodę leczenia, wskazaną w przypadku niektórych nawrotowych, opornych nowotworów hematologicznych, a coraz częściej także guzów litych. Pomimo znaczących wyników terapii w wybranych grupach pacjentów nadal ma ona istotne ograniczenia. Utrata antygenów, ograniczona trwałość komórek i nieprzyjazne mikrośrodowisko guza to główne problemy związane z biologią komórek układu odpornościowego i nowotworowych. Badania koncentrujące się na biologii komórek układu odpornościowego mogą zatem przyczynić się do poprawy wyników leczenia bez remisji i dłuższego utrzymywania się odpowiedzi immunologicznej. Integracja komórek dendrytycznych – profesjonalnych komórek prezentujących antygen – oraz subpopulacji limfocytów T pamięci, szczególnie tych charakteryzujących się ekspresją białka powierzchniowego CD45RO, to nowe podejście pozwalające na znaczną poprawę wyników leczenia. W pracy dokonano przeglądu badań wskazujących na najistotniejsze ograniczenia terapii CAR-T związane z terapiami komórkowymi. Przedstawiono najnowsze wyniki badań z dziedziny immunologii, które uzasadniają zastosowanie komórek dendrytycznych oraz limfocytów T pamięci jako strategii optymalizacji terapii CAR-T. Szczególny nacisk położono również na przegląd innych powiązanych strategii klinicznych, które udoskonalą terapię CAR-T. Ponadto zwrócono uwagę na badania nadal będące w toku, ale przynoszące pomyślne wyniki. Przeanalizowano 48 publikacji, korzystając wyłącznie ze źródeł PubMed, spośród których wybrano 20 artykułów. Ze względu na niezbadany obszar badań i brak wystarczających danych przegląd objął artykuły z lat 2007–2025, z największym naciskiem na najnowsze prace.

SŁOWA KLUCZOWE

komórki dendrytyczne, limfocyty T pamięci CD45RO+, CAR-T, immunoterapia

Introduction

Immunotherapy has revolutionized cancer treatment. Among cell-based immunotherapies, chimeric antigen receptor (CAR)-T cell therapy is the most transformative clinical success story of the last decade, leading to unprecedented responses in hematologic malignancies such as acute lymphoblastic leukemia (ALL) and large B-cell lymphoma [1,2]. In CAR-T cell therapy, patient-derived T lymphocytes are genetically engineered to express a synthetic CAR, redirecting them to recognize and eliminate tumor cells in a major histocompatibility complex (MHC)-independent manner [3,4,5]. This approach bypasses classical antigen presentation and can overcome mechanisms of immune evasion commonly exploited by cancer cells. Adoptive cell therapy, especially CAR-T cell therapy, is revolutionizing the immunotherapy landscape [1,2]. CAR T cells, engineered to target tumor antigens independent of MHC presentation, have shown remarkable efficacy in relapsed, refractory B cell malignancies. CAR-T cell therapy still requires innovation, including its translation to solid tumors, treatment outcomes free from remission, and longer-lasting immune response. Tumor heterogeneity, immunosuppressive environments, and in vivo persistence of effector T cells are the key immune and cancer cell limitations [3,4,5]. Antigen escape and toxicities such as cytokine release syndrome or neurotoxicity add to this list of limitations [3,6]. There is a growing recognition that a "one size fits all" approach to T cell product design is insufficient. Personalized immunotherapy tends to lead to the most beneficial approach. As such, combining CAR-T cell engineering with additional immunological strategies – such as dendritic cell vaccination, the selection of memory-enriched T cell subsets, and novel manufacturing protocols – has become a major research focus [1,7]. Dendritic cells (DCs), as central orchestrators of adaptive immunity, and memory T cells, defined by CD45RO expression, present compelling opportunities to enhance antitumor immunity and improve the clinical effectiveness of CAR-T cell therapies [7,8,9]. This review integrates the latest evidence from basic science, translational research, and clinical trials to illuminate strategies that may define the future of personalized immunotherapy. Here, we review the rationale, supporting evidence, and future prospects for leveraging DCs and memory $CD45RO^+$ T cells to optimize CAR-T cell therapy in both hematologic malignancies and solid tumors.

Managing CAR-T cell therapy limitations

CAR-T cell therapy improves cancer treatment in relapsed or refractory hematologic malignancies, including B-cell ALL, diffuse large B-cell lymphoma (DLBCL), mantle cell lymphoma, follicular lymphoma, and multiple myeloma [10]. Simultaneously, CAR-T cell therapy is being developed to overcome challenges in the treatment of solid tumors [11]. The obstacles that arise in therapeutic approach can start at the cellular level due to several factors. The tumor shows clonal heterogeneity that differentiates therapy targeted antigens [12]. That leads to antigen escape and resistance to single-target therapies. The immunosuppressive tumor microenvironment creates a hostile environment for CAR-T cells [13]. The lack of a tumor-specific target antigen is a major obstacle for CAR-T cell therapy, especially in solid tumors. That leads to challenges such as potential off-target effects on healthy tissues and antigen escape, where tumors may evolve to lose the target antigen and worsen the prognosis [14]. Addressing these

challenges requires novel strategies such as multi--antigen targeting, engineering CAR-T cells to overcome suppression – particularly enriched CAR-T cells with functional agents – and developing new methods for antigen discovery.

DCs and memory T cells – Biology and role in immunotherapy

DCs are specialized antigen-presenting cells essential for initiating, modulating, and sustaining immune responses. A key aspect of DC biology is their ability to navigate the tumor immunity. Through cytokine secretion (including interleukin 12 [IL-12], IL-15, and type I interferons [IFN-I]), DCs can polarize T cell differentiation toward cytotoxic, helper, or regulatory phenotypes. Conventional DC1s (cDC1s) are especially critical for cross-presenting tumor antigens to $CD8^+$ T cells, making them indispensable in antitumor immunity [7]. However, tumors can actively subvert DC function, leading to impaired antigen presentation, immune exclusion, and local immunosuppression [1]. Recent single-cell omics studies have identified diverse DC subpopulations with specialized roles in tumor immunity, including cross-presenting cDC1s and regulatory DC subsets that modulate T cell response [7]. The functional state of DCs is influenced by the tumor microenvironment, often resulting in DC dysfunction, reduced antigen presentation, and T cell exclusion in solid tumors.

To overcome these limitations, DC-based vaccines and adjuvant therapies have been developed. The clinical potential of DCs has long been recognized. DC-based cancer vaccines aim to "jumpstart" the immune response by loading autologous DCs with tumor antigens ex vivo and re-infusing them into patients [7,9]. Sipuleucel-T, the first Food and Drug Administration (FDA)-approved DC vaccine, prolonged survival in men with metastatic prostate cancer [15]. However, responses remain limited in solid tumors and research is ongoing to optimize DC maturation, antigen loading, and combination strategies (e.g., with CAR-T cells or immune checkpoint inhibitors). Over 300 DC vaccine trials are presently registered [16]. Notably, DCs are key producers of IFN-I, which not only enhance direct antigen presentation, but also upregulate MHC and co--stimulatory molecules on other immune cells, further boosting the antitumor immune milieu [8,9].

Memory T cells – defined by the expression of CD45RO – are essential for robust, durable immune surveillance. Upon antigen encounter, naïve T cells differentiate into effector and memory subsets. $CD45RO^+$ memory T cells exhibit rapid recall responses upon re-exposure to an antigen, greater persistence and longevity, superior tissue trafficking due to upregulated adhesion molecules, increased cytokine secretion, and cytotoxic activity [5,6].

Importantly, memory T cells display increased resistance to apoptosis, are less prone to exhaustion than terminal effector T cells, and may persist for years, supporting long-term protection [4,5]. Preclinical and clinical evidence demonstrates that CAR-T cells manufactured from memory-enriched populations show enhanced in vivo expansion, tumor infiltration, and antitumor activity compared to bulk or terminally differentiated cells [2].

The manipulation and enrichment of memory T cells, especially the stem cell memory (T-SCM) subset, is now a major focus of next-generation CAR-T cell engineering [4,6].

The rationale for integrating DCs and memory T cells in CAR-T cell therapy

Integrating DCs and memory T cells in CAR-T cell therapy is rooted in immunological synergy. DCs, particularly when matured and pulsed with tumor antigens, can potentiate the expansion and functional quality of memory T cells ex vivo, generating CAR-T cell products with superior persistence and efficacy [3,7]. DCs secrete IFN-I and IL-12, enhancing T cell cytotoxicity and creating a more supportive microenvironment for CAR-T cell function [8]. Using memory-enriched T cells for CAR engineering leads to better expansion, survival, and anti-tumor responses, as confirmed in clinical trials [4,5]. Preclinical studies incorporating DCs for T cell priming and antigen presentation during CAR-T cell production yield superior in vivo tumor clearance, greater persistence, and reduced exhaustion [7]. Patients treated with CAR-T cells manufactured from memory-enriched populations ($CD45RO^+$ or T-SCM) experience longer--lasting remissions and fewer relapses. Multiple ongoing clinical trials are evaluating combinations of DC vaccines and CAR-T cells, as well as the selective use of memory T cell subsets for CAR-T cell production [16]. Early-phase studies are also exploring the role of allogeneic (donor-derived) memory T cells for "off-the-shelf" CAR-T therapies [1,3]. Memory T cells arise following antigen exposure and persist long-term, enabling rapid and robust responses upon re-exposure. The surface marker CD45RO identifies memory T cells, distinguishing them from naïve T cells ($CD45RA^+$) [4,5,6]. Compared to naïve or terminally differentiated effector T cells, $CD45RO^+$ memory T cells exhibit enhanced persistence and self-renewal, especially for T-SCM and T central memory (T-CM) cells. CD45RO+ memory T cells are also superior in getting through to the lymphoid and peripheral tissues. This may be promising in solid tumor therapies. Memory T cells are also responsible for rapid recall and cytokine production. They perform greater resistance to apoptosis and exhaustion. Recent work shows that the initial composition of the T cell product, particularly the proportion of T-SCM and T-CM, strongly influences CAR-T cell expansion, persistence, and clinical outcomes [4,6]. CAR-T cells manufactured from memory-enriched or T-SCM-purified populations have shown increased in vivo proliferation, longer persistence, and improved antitumor activity compared to bulk T cell or effector-rich products [2,5,6].

The manufacturing of CAR-T cells traditionally involves leukapheresis to collect peripheral blood mononuclear cells, followed by T cell activation (usually with anti-CD3/CD28 beads or antibodies), gene transfer (often via lentiviral or retroviral vectors), and ex vivo expansion. Increasingly, protocols are being developed to preferentially expand memory T cells, either by cytokine selection (IL-7, IL-15, or IL-21), surface marker-based cell sorting, or optimizing stimulation protocols [4].

Clinical studies demonstrate that products with higher proportions of $CD45RO^{+}$ memory T cells, especially T--SCM, correlate with better response rates and persistence [5]. Next-generation CAR-T cell manufacturing may include magnetic enrichment or flow cytometry sorting for memory T cells as a routine step.

Novel CAR-T cells are engineered not only to recognize tumor antigens, but also to secrete cytokines (such as IL-12, IL-18, or IL-15), resist exhaustion, or overcome suppressive signals in the tumor microenvironment [1,7]. Some constructs co-express checkpoint blockade (PD-1 dominant-negative, PD-1/CD28 switch), or even incorporate suicide switches for safety. The addition of DC-activating signals (such as CD40L or granulocyte-macrophage colony-stimulating factor [GM-CSF]) is being tested to boost endogenous antigen presentation and epitope spreading.

One promising approach is the sequential or simultaneous use of DC vaccines and CAR-T cells. DC vaccination can prime the endogenous immune system, facilitate antigen spreading, and overcome tumor escape by broadening the antitumor T cell repertoire [1,7,9]. Early-phase trials are now testing CAR-T cell therapy in combination with DC vaccines loaded with tumor lysates or neoantigens. Some evidence suggests that DCs may also support the persistence and fitness of infused CAR-T cells via cytokine secretion and cross-talk. Another method is to co-culture autologous DCs with T cells ex vivo prior to CAR transduction. This can bias expansion toward memory phenotypes, improve stemness, and produce a CAR-T product with enhanced in vivo function [3].

The use of allogeneic (donor-derived) memory T cells for “off-the-shelf” CAR-T cell therapies is gaining traction [7]. Memory T cells are less alloreactive and may present lower risks of graft-versus-host disease. Universal CAR constructs using gene editing to knock out endogenous T-cell receptor and human leukocyte antigen molecules are now entering the clinic.

Solid tumors present unique challenges for adoptive cell therapies. The tumor microenvironment is rich in immunosuppressive cytokines (transforming growth factor β or IL-10), regulatory cells (Tregs or myeloid--derived suppressor cells), and metabolic constraints (hypoxia or adenosine) [7]. These factors impair DC function and drive T cell exhaustion.

Numerous clinical trials are now underway to test these combined and optimized strategies [16]. For example, phase I/II studies are exploring CAR-T cell plus DC vaccines in glioblastoma, ovarian cancer, and lymphomas. Early results indicate improved immune infiltration, increased antigen spreading, and enhanced durability of responses compared to monotherapy [17]. Long-term follow-up from CD19 CAR-T cell trials demonstrates that the persistence of memory T cell clones correlates with durable remissions. Conversely, relapse is often associated with a loss of CAR-T cells, antigen escape, or T cell exhaustion [6,17]. Integrating DC and memory T cell principles into CAR-T cell product design is expected to further improve these outcomes.

Integrating memory CD45RO+ cells can limit antigen loss. In patients with neuroblastoma, integrating CD4+ cells with CD45RO+/CD62L+ showed high concordance with the length of persistence of CAR-T cells [18]. Another study showed that due to the properties of memory T cells, thanks to which they can undergo dynamic adaptations in response to environmental signals, there is an antigen-guided shift in memory cell phenotype that can optimize vaccine design and adoptive T cell therapy [19].

Challenges and prospects

Despite the significance mentioned above, there are manufacturing and regulatory hurdles. Manufacturing personalized, memory-enriched CAR-T cell products at scale presents challenges of logistics and costs. Batch-to-batch variability, regulatory requirements for product release, and the need for robust potency assays are all significant barriers to widespread adoption [15]. The isolation and expansion of pure memory T cell populations and the maturation of DCs remain technically challenging and costly [7,17]. Regulatory pathways approved in FDA guidance and oversight for novel cell therapies are presently evolving. Therefore, the safety and consistency of cellular products are paramount [15]. When it comes to safety concerns, augmenting CAR-T cell activity via DC co-stimulation or memory T cell enrichment may heighten risks of cytokine release syndrome, neurotoxicity, or off-tumor effects. Careful dosing, safety switches, and split-dosing regimens are being developed to mitigate risks [1,6].

Another challenge comes from antigen escape mechanisms and tumor microenvironment properties. Tumor heterogeneity and immunosuppressive microenvironments remain substantial barriers. The FDA and European Medicines Agency have established guidance for CAR-T cell and DC vaccine products, emphasizing safety, consistency, and traceability. Post--marketing surveillance and risk evaluation and mitigation strategies are now standard for cell therapy approvals [15]. Novel strategies, such as armored

CAR-T cells, gene editing to resist exhaustion, and combination regimens with checkpoint inhibitors or oncolytic viruses, are under investigation [1,6]. They project the direction for precision medicine: personalized CAR-T cell and DC-based regimens [2]. The future of CAR-T cell therapy can integrate regimens with DC vaccines, products derived from memory T cells, checkpoint blockade, and tumor-targeted adjuvants. Armored and multi-specific CARs can therefore address antigen escape and microenvironmental suppression. Using synthetic biology and gene editing can significantly endow T cells and DCs with novel functions.

Conclusions

The integration of DCs and memory CD45RO$^+$ T cells into CAR-T cell therapy is justified in clinical studies. It provides an opportunity to overcome current barriers in cancer immunotherapy. By harnessing the strengths of these two cell types – antigen presentation and immune memory – next-generation therapies may achieve greater efficacy, persistence, and safety. Continued innovation in cell processing, clinical trial design, and combination regimens will define the future of personalized cancer immunotherapy.

Authors' contribution

Study design – M. Greniuk

Data collection – M. Greniuk, H. Raś, P. Kubicki

Manuscript preparation – M. Greniuk, H. Raś, P. Kubicki

Literature research – M. Greniuk, K. Jankowska

Final approval of the version to be published – M. Greniuk, H. Raś, P. Kubicki, K. Jankowska

Funding statement

This study did not receive special funding.

Institutional Review Board Statement

Not applicable

Informed Consent Statement

Not applicable

Data Availability Statement

Not applicable

Conflict of interest

All authors declare no conflict of interest.

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