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Current Anti-Myeloma Chimeric Antigen Receptor-T Cells: Novel Targets and Methods

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Multiple myeloma (MM) treatment becomes a major challenge once triple-class or penta-refractoriness develops. Emerging immunotherapies, including bispecific antibodies or chimeric antigen receptor (CAR)-T cell therapy, are promising options for such patients. However, the requirement for specialized expertise and staff under stringent manufacturing conditions results in high costs and restricted production. This article explores the manufacturing and clinical application of CAR T-cells in MM, highlighting their potential, limitations, and strategies to enhance efficacy.

CAR-T can be manufactured by pharmaceutical companies or accredited academic centers authorized to produce and market gene-edited cellular products. This process includes sequential steps: T cell apheresis from the patient, selection of the cells, activation, gene transfer, expansion of the produced cells, cryopreservation, and reinfusion of the cells into a lymphodepleted patient. While CD3+ T cells are typically employed for CAR-T production in clinical studies, studies have demonstrated the potential advantages of specific T cell subgroups, such as naive, central memory, and memory stem cells, in enhancing efficacy. Following T cell harvesting, the subsequent phase involves genetic modification. CAR-T cells are frequently produced by applying viral vectors such as γ-retrovirus or lentivirus. Although viral vectors are commonly used, non-viral methods-including CRISPR/Cas9 and integrative mRNA transfection methods produced by transposons-are also employed. Five different CAR-T cell generations have been developed. The myeloma-specific targets B-cell maturation antigen (BCMA), signaling lymphocyte activation molecular family 7, and G protein-coupled receptor class C group 5 member D are the most extensively studied in clinical trials. Emerging CAR-T cell targets under investigation include CD138, CD19, kappa light chain, CD56, NY-ESO-1, CD70, TACI, and natural killer G2D. In 2021, idecabtagene vicleucel, a BCMA-targeting agent, became the first CAR-T therapy approved for relapsed/refractory MM, marking a significant milestone in MM treatment. Subsequently, ciltacabtagene autoleucel has also been approved. However, CAR-T resistance is an emerging issue. Resistance mechanisms include T cell exhaustion, antigen escape (loss of BCMA), and tumor microenvironment-related inhibitors. To address these challenges, strategies such as BCMA non-targeted or dual-targeted CAR-T, memory T cells, humanized CAR-T, and rapidly manufactured PHE885 cells have been developed. To enhance specificity, ongoing investigations include bicistronic CAR/co-stimulator receptors, formation of memory-phenotype T cells, combination with immunomodulators or checkpoint inhibitors, armored CAR-T cells, cancer-associated fibroblast inhibitors, and CAR approaches that inhibit exhaustion signals.

In conclusion, studies are exploring the use of CAR-T at an earlier stage, including at diagnosis, with an aim to replace ASCT. CAR-T has introduced a new dimension to MM treatment; however, limited efficacy in high-risk MM and the emergence of resistance to CAR-T remain key challenges to be addressed.

INTRODUCTION

Immunomodulatory drugs, proteasome inhibitors, and anti-CD38 antibodies have significantly increased the depth and duration of response in multiple myeloma (MM) patients, contributing to long-term clinical success.[1] Patients exhibiting unfavorable genetic features, those categorized as high risk according to R-ISS, and those with extramedullary diseases may demonstrate inadequate responses to the best available treatments.[2] Thus, patients with triple-class (TCR) and penta-refractory represent a significant therapeutic challenge.[3] For such patients, treatment options include alkylating agent-based chemotherapy; bispecific antibodies or antibody-drug conjugates targeting B-cell maturation antigen (BCMA), FcRH5R, G protein-coupled receptor class C group 5 member D (GPRC5D); the nuclear export receptor, exportin 1 inhibitors; signaling lymphocyte activation molecular family 7 (SLAMF7) inhibitors; and the selective

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BCL-2 inhibitor venetoclax, particularly in patients with t(11;14) positivity.[4] For TCR patients, chimeric antigen receptor (CAR)-T therapy administered prior to bispecific antibodies is emerging as a promising therapy.

CAR-T therapy is an advanced immunotherapeutic approach that has exhibited efficacy in heavily pre-treated MM patients, similar to its success in other hematological malignancies in recent years. This treatment's core principle involves genetically modifying T lymphocyte-harvested from either affected or third-party healthy individuals-to express CAR, enabling them to recognize myeloma-specific receptors on tumor surfaces. CAR-T cells carry out the tumor recognition process independently of major histocompatibility antigen. Ideally, targeting antigens that are exclusively expressed on myeloma cells-and not on healthy cells-ensures tumor-specific treatment.[5] However, this treatment method's widespread adoption is being restricted by its high price, preparation time, and demand for skilled staff. This article will review the production and practical applications of CAR-T therapy, from its inception to current medical practice.

THE MANUFACTURING PROCESS OF CAR-T THERAPY

Overview

Although CAR fusion protein was first created in 1989 at the Weizmann Institute of Health[6], its application in myeloma did not emerge until 2015. CAR-T cells targeting CD19 were administered 12 days after autologous stem cell transplantation with a melphalan conditioning regimen, aiming to delay or prevent relapse in patients previously treated with multiple therapy lines.[7] Subsequent identification of myeloma-specific antigens beyond CD19 has expanded the range of targets available for CAR-T cell therapy. These antigens are illustrated in adapted Figure 1.[8] In this section we will outline the technical aspects of CAR-T manufacturing with a focus on current progress to overcome the drawbacks of CAR-T therapy in general.

CAR-T MANUFACTURING

CAR-T can be manufactured either by pharmaceutical companies or by academic centers authorized to produce and *distribute* gene-edited cellular products under "good manufacturing practice" conditions. These two approaches have been developing in parallel on a global scale. This process includes the sequential steps of T cell apheresis from the patient, selection of the cells, activation, gene transfer, expansion of the produced cells, cryopreservation, and reinfusion of the cells into the patient who has undergone lymphodepletion.[9] Selecting the relevant T cells from the appropriate patient, transporting them to the laboratory, and producing CAR-T cells under optimal conditions and as rapidly as feasible require significant expenditures, trained personnel, and advanced laboratories. In this section of the article, the steps of CAR-T production and the emerging manufacturing technologies developed to overcome the barriers to effective production will be discussed.

CAR-T therapy comprises the following steps sequentially after one of the target antigens is identified. The first step involves T cell collection from the patient using leukapheresis. In addition, allogeneic CAR-T approaches are also available and will also be addressed in this article. Selecting the appropriate mature T cell subset is a critical step in CAR-T cell production.[10] Although CD3+ T cells are generally selected for CAR-T production in clinical studies, studies have demonstrated that subsets such as naïve, central memory, and memory stem T cells may offer superior efficacy.[9] The success of an adequate and effective T cell collection procedure depends on multiple factors. Leukapheresis failure occurs in approximately 7-8% of patients.[11] For example, it is crucial to ascertain the date of administration of the most recent cycle of chemotherapy and immunotherapy before the collection procedure. Factors influencing leukapheresis include the patient's performance status, disease characteristics and burden, CD3+ lymphocyte count, type of venous access, and the quality of cryopreserving and transfer conditions.[12]

Following T cell harvesting, the subsequent phase involves genetic modification. CAR-T cells are commonly manufactured by applying viral vectors such as γ-retrovirus or lentivirus.[13] The initial vector used is the γ-retroviral vector. A steady level of CAR expression is provided by the high gene transfer efficiency. This method has been employed in many studies and is considered safe and effective.[9,14] Lentiviral vectors are comparable to retroviral vectors in several aspects. However, the absence of a stable vector packaging system in lentiviruses remains a significant barrier to their production.[15] Although viral vectors are frequently used, non-viral approaches-including CRISPR/Cas9 and transposon-based integrative mRNA transfection methods-are also being employed. These non-viral methods have a larger cargo and clonality capacity.[16] There are also *ex vivo* expansion facilities. The process typically takes 1-2 weeks from the harvesting time.[17] Clinical trials employing non-viral vectors include insertion strategies such as BCMA-targeting PiggyBac [P-BCMA-ALLO1(NCT04960579)] and SLAMF7-targeting Sleeping Beauty (CARAMBA trial).

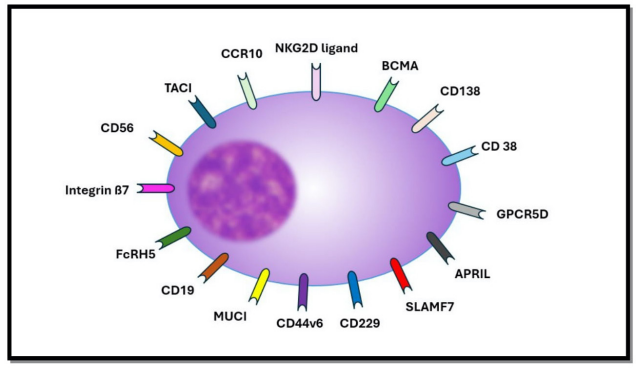

FIG. 1. Myeloma specific targets on plasma cells.[8]
NK, natural killer; BCMA, B-cell maturation antigen; GPRC5D, G protein-coupled receptor class C group 5 member D; SLAMF7, signaling lymphocyte activation molecular family 7.

The manufactured CAR cells consist of three components: extracellular, transmembrane, and intracellular domains.[18] The extracellular domain can interact with the intracellular domain via the transmembrane domain; this connection is vital for cancer cell eradication. The extracellular domain contains a single-chain variable fragment (scFV). This fragment is a fusion protein comprising the variable regions of an antibody, enabling the CAR-T cell to bind to the specialized target cell. Through its primary and secondary costimulatory domains, the intracellular domain-which contains immunoreceptor tyrosine activation motifs, or ITMs-contributes to T cell activation.[19] The targeted myeloma antigen activates signal production using the intracellular domain of CD3ζ.[20] Five distinct generations of CAR-T cells have been created thus far, and each new generation has brought new regulations. The comparison of these five generations of CAR-T cells is illustrated in Figure 2.[21] All five generations of CAR-T cells share the common characteristic of incorporating the CD3ζ domain within their intracellular regions. The first generation only has the CD3ζ domain with a lack of cell expansion capability. In the second generation, there exists a costimulatory domain; those incorporating 4-1BB resemble memory stem cells and exhibit enhanced persistence. Entities exhibiting CD28 have enhanced endurance as well as augmented growth ability. Other domains, such as ICOS or OX40, might exist. The most widely approved CAR-T therapies, called ide-cel and cilta-cel, belong to the second-generation CARs.[22,23] The third-generation CAR-T cells have been optimized for enhanced efficacy and prolonged persistence. Fourth-generation CAR-T cells, known as TRUCKs (T cells Redirected for Universal Cytokine-mediated Killing), and fifth-generation constructs are engineered to secrete immunomodulatory cytokines such as interleukin (IL)-12 and include IL-2Rβ domains that activate the JAK/STAT3 signaling pathway.[20,24,25] The aim of all these modifications is to establish an immune synapse with the tumor cell, resulting in cytotoxicity, apoptosis, and cytokine production.[26] Upon chemotherapy-induced lymphodepletion, reinfusion of CAR-T cells is performed.

CAR-T PRODUCTS CURRENTLY APPROVED FOR TREATMENT OF MULTIPLE MYELOMA

Overview

The CAR-T products to be utilized are defined by the myeloma-specific antigens, as shown in Figure 1. Among these targets, BCMA, SLAMF7, and GPRC5D are the most extensively studied in clinical studies. Emerging CAR-T cell targets under development include CD138, CD19, kappa light chain, CD56, NY-ESO-1, CD70, TACI, and NKG2D. Currently, the Food and Drug Administration (FDA) has approved six CAR-T cell treatments for hematological malignancies, including MM, leukemia, and lymphoma: axicabtagene ciloleucel (CD19), brexucabtagene autoleucel (CD19), ciltacabtagene autoleucel (BCMA), idecabtagene vicleucel (BCMA), lisocabtagene maraleucel (CD19), and tisagenleucel (CD19).[27] In 2021, idecabtagene vicleucel was the first CAR-T therapy to be approved for relapsed refractory MM (RRMM), a significant milestone in MM treatment. This was followed by the approval for cilta-cel in 2022, further expanding the therapeutic armamentarium for MM.

BCMA DIRECTED CAR-T PRODUCTS

BCMA is a member of the tumor necrosis factor receptor superfamily 17 (TNFRSF 17) or CD269 and is exclusively expressed on mature B lymphocytes necessary for the survival of plasmablasts and plasma cells. BCMA causes the expansion of plasma cells through interaction with B-cell activating factor and a proliferation-inducing ligand (APRIL).[29] BCMA expression is absent in hematopoietic stem cells.[30] Thus, it is a biomarker for MM that can be identified using flow cytometry or ELISA. Both expression and soluble levels of BCMA carry prognostic significance.[31]

The first CAR-T cell targeting BCMA, incorporating a murine scFV and a CD28 co-stimulatory domain, was evaluated in a trial conducted in 24 RRMM patients.[32,33] In the first of the KarMMa studies, idecabtagene vicleucel employed a CAR construct containing both a murine scFv and a 4-1BB costimulatory domain. KarMMa-1 was

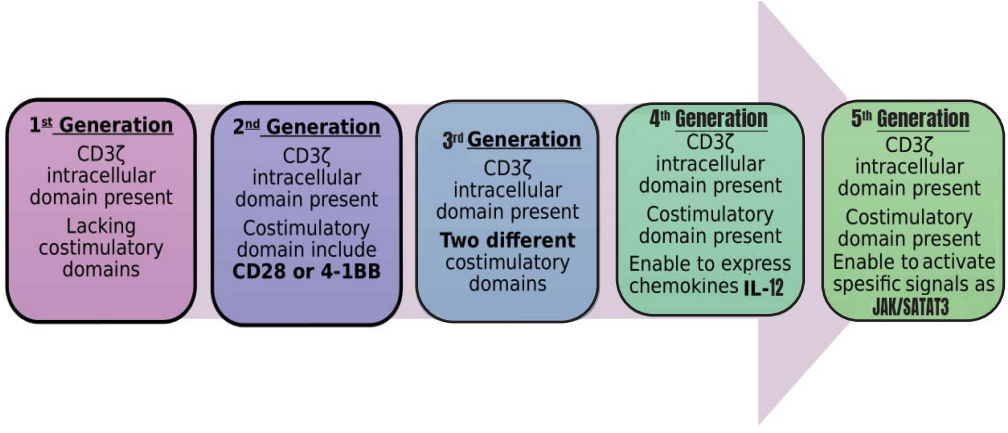

FIG. 2. The Features of five generations of CAR-T cells.

CAR-T, chimeric antigen receptor-T; CRISPR, clustered regularly interspaced short palindromic repeats; FAP, fibroblast activation protein; iPSC, induced pluripotent stem cell; NK, natural killer; Tscm, T- stem cell memory; TRUCK, T cell redirected for universal cytokine-mediated killing.

conducted in 128 RRMM patients receiving at least three previous regimens, demonstrating an ORR of 81% and a CR rate of 39%.[34] The FDA authorized the medication for RRMM in 2021 based on the study's findings. In the KarMMA-2 trial there were several cohorts, and cohort 2a included early relapsed patients.[35] After these phase 2 trials, the KarMMa-3 trial investigated the efficacy of ide-cel compared to standard of care treatments.[36] The phase 1 KarMMa-4 study, which includes newly diagnosed MM (NDMM) patients, has finished accrual but has not yet published results yet.[37]

In another BCMA-targeted CAR-T study, CARTITUDE-1, the efficacy of ciltacabtagene autoleucel was examined. Here, 97 RRMM patients were included. The ORR was 98%, and the stringent CR response was reported as 98%. The CARTITUDE-2 cohort A[38] and CARTITUDE-4[39] research included patients who had received 1-3 lines of treatment, in contrast to the earlier studies. The results of the subsequent CARTITUDE-2[40] and CARTITUDE-4[39] studies resulted in the approval of cilta-cel in 2022. The ongoing phase 3 CARTITUDE-5 and CARTITUDE-6 studies are designed for NDMM patients.[41]

There are still many ongoing clinical trials beyond those currently approved by the FDA. For example, LCAR-B38M is an anti-BCMA CAR-T cell developed in China, characterized by high specificity. It includes two camelids and demonstrates high affinity for BCMA. In the LEGEND-2 study, its efficacy was investigated in 57 RRMM patients, and an ORR of 88% and a CR rate of 74% were reported.[42]

To enhance access to CART, universal CAR-T (UCAR-T) and CAR-T γδ cells have been introduced as alternatives to autologous CAR-T cells, which require 3-4 weeks for manufacturing. Although obtaining these cells from a healthy donor reduces the risk of tumor contamination, these allogeneic cells carry a potential to induce graft-versus-host disease, which may be mitigated through *CD52* gene manipulation.[43] The list of anti-BCMA targeting products is presented in Table 1.[23,42,44-69]

RESISTANCE TO CELLULAR IMMUNOTHEREAPY IN MM

Overview

Despite yielding profound responses even among TCR MM patients with CAR-T, disease relapses still occur. There are various factors that impede the success of CAR-T therapy. Among factors impacting treatment success, patient-related factors (i.e. cachexia, cytopenia, gut microbiota disrupted by antibiotics), disease-related factors, and the host's immune system play pivotal roles. Intensive treatments prior to CAR-T can exacerbate these factors.[70] In addition, there may be factors connected to the CAR-T product. The quality and function of T lymphocytes might be influenced by prior therapies; hence, it is imperative to confirm that the patient has not received intensive treatments, including steroids, immunosuppressive drugs, or chemotherapy, prior to the T cell harvesting to minimize T cell exhaustion.[71] The CD4/CD8 ratio has been demonstrated to predict T cell fitness. Consequently, several studies considered conforming to a CD4/CD8 ratio of 1:1.[72]

Additional contributing factors to CAR-T therapy failure include the tumor's inability to release adequate antigens (antigen escape, BCMA loss)[73], the failure of trogocytosis (the lymphocyte killing by the tumor through contact at the tumor cell surface)[74], and the inadequate persistence of CAR-T cells or exhaustion. Also, tumor milieu can hinder the optimal functioning of CAR-T cells through the production of inhibitory immune checkpoint inhibitors or immunosuppressive cytokines.[75] To overcome resistance, such as antigen escape, strategies include the use of dual- or multi-targeted CAR-T products. To reduce CAR-T cell exhaustion and enhance persistence, approaches such as incorporating memory T cells, optimizing intracellular signaling domains, and developing armored CAR-T cells to counter the immunosuppressive tumor microenvironment have been explored.[8] Other targets except BCMA and dual targets are presented in Table 1. Beyond its current approval for RRMM, CAR-T therapy is also being investigated as a first-line treatment for high-risk patients whose T cells have not been exhausted by previous treatments. Conversely, while immunotherapies or ASCT given may serve as bridging therapies to increase efficacy, it would be prudent to avoid using anti-BCMA bispecific treatments as a bridge here, as they may downregulate antigen expression and contribute to T cell exhaustion.[76] Nevertheless, considering that patients with a high tumor burden have a high risk of relapse, bridging therapies are essential.

One way to overcome the barrier against optimal autologous T cell harvesting could be obtaining allogeneic CAR-T. Since this product is obtained from a completely healthy individual, it mitigates the likelihood of T cell exhaustion or contamination with a tumor. For example, in a study, T cells obtained from a patient with monoclonal gammopathy of uncertain significance were demonstrated to be more immunologically active compared to those obtained from symptomatic MM patients.[77] In addition, CAR-natural killer (NK) could serve as an alternative for patients refractory to CAR-T therapy. NK cells exhibit a different cytokine profile compared to T cells, and the risk of cytokine release syndrome is lower with these products. In this context, the CAR construct is designed to address the relatively limited persistence of NK cells.[78]

For individuals who do not benefit from CART cellular immunotherapy, new approaches are still required in spite of all these coping mechanisms. It has been demonstrated that the combination of CAR-T therapy with previously ineffective anti-BCMA bispecifics provides 15-18 months of OS advantages.[79,80] The relatively decreased success rate of CAR-T therapy among patients who had previously received belantamab mafodotin or bispecifics mandates temporal sequencing of targets and effectors.[81]

During CAR-T cell production, safety, purity, potency, identity, and persistence play crucial roles. To optimize all these features, novel CAR-T technologies are being developed. These include dual-targeted therapies, bicistronic CAR, tandem CAR utilizing two scFV constructs, and ligand-based CAR technologies designed to boost efficacy. In addition, to enhance efficacy or suppress the inhibitory microenvironment, combining CAR-T therapy with various drugs or ASCT and adding proteasome inhibitors and gamma secretase inhibitors have also been explored by clinical research. To improve specificity, there are approaches such as the use of bicistronic CAR/co-stimulator receptors, induction of memory-phenotype T cells, combination with immunomodulators or checkpoint inhibitors, armored CAR-T cells, cancer-associated fibroblast inhibitors, and CAR designs that block exhaustion signals. Moreover, the application of non-viral transfections, such as the CRISPR-Cas9 technique, is under investigation.[21]

TABLE 1. The List of Anti-BCMA and Non-BCMA and Dual CAR-T Cell Products.

Anti-BCMA			Other targets	Dual targets
Standard	**Humanized**	**Novel**		
Murine scFV (11D5-3) CD28 co-stim. domain Retroviral vector	**KITE-583 Human anti-BCMA** scFV CD28 costimulatory domain	**P-BCMA 101** Non-viral piggyBac DNA mod system using transposons and rimiducid[43]	**CTL019 (Tisa-cel, Kymriah, Novartis) CD19** scFV (FMC63) 4-1BB co-stimulatory domain Lentiviral vector	**BCMA/CD38** Bispecific CAR-T cells Lentiviral vector
CRB (bb2121/Ide-cel) 4-1BB co-stim. Domain Lentiviral vector	**PHE885 T-charge platform** Enables *in vivo* CAR-T expansion and manufacture < 2 days Human anti-BCMA scFV 4-1BB co-stimulatory domain Lentiviral vector	**ALLO-715** Second gen scFV with TALEN knockout of T cell receptor alpha constant and CD52 with rituximab safety switch[40]	**MCARH109 GPRC5D scFV** Lentiviral vector	**BCMA/CD38 Hela cells**
JNJ-4528 (Cilta-cel) 2 camelid variable heavy chain domains 4-1BB co-stimulatory domain Lentiviral vector	**MCARH171** Human scFV 4-1BB co-stimulatory domain tEGFR safety switch Lentiviral vector	**ddBCMA** Anitocabtagene Autoleucel Synthetic antigen-binding domain with reduced immunogenicity and improved CAR stability[52]	**AUTO2 Truncated form of APRIL** Recognizes BCMA and TACI OX40 co-stimulatory domain Gamma retroviral vector RQR8 safety switch	**Combined humanized anti-BCMA and anti-CD38 CAR-T cell**
CRB402 (bb21217) **Murine scFV (11D5-3) 4-1BB** Phosphoinositide 3 kinase inhibitor added to enrich memory-like T cells Lentiviral vector	**JCARH125 (Orva-cel)** Human scFV 4-1BB co-stimulatory domain Lentiviral vector	**BRD015** Murine BCMA ScFv, CD3ζ, and CD28 domains derived from mice Lentiviral vector (ChiCTR-OPC-16009113)	**Human NKG2D** Gamma retroviral	**Combined humanized anti-BCMA and anti-CD19 CAR-T cells**
LCAR-B38M 2 camelid variable heavy chain only domains 4-1BB co-stimulatory domain Lentiviral vector	**CT103A** Human scFV 4-1BB co-stimulatory domain Lentiviral vector	**DESCARTES-08** CD8+ CAR T anti BCMA mRNA transfection (NCT03448978)	**CAR2 Anti-CD38 A2 CAR-T** (NCT03464916)	**Combined humanized anti-BCMA and anti-CD19 CAR-T cells** Lentiviral vector
	FHVH33-CD8BBZ Human heavy chain variable domain (FHVH33) 4-1BB co-stimulatory domain Gamma retroviral vector		**ATLCAR Anti-CD138 CAR-T** (NCT03672318)	**Combined anti-BCMA and anti-CD19 FasTCAR-T Cells (GC012F)**
	CT053 (Zevor-cel) Human scFV (25C2) 4-1BB co-stimulatory domain Lentiviral vector		**Sleeping Beauty gene transfer** SLAMF7 (NCT03958656)	**Combined humanized anti-BCMA and anti-CD19 CAR-T cells (huCART19)**

TABLE 1. continued

Anti-BCMA		Other targets	Dual targets
	CT103A (median persistence: 307.5 days) (ChiCTR1800018137)	**CD138-CAR-T** Indatuximab scFv of anti-CD138 antibody linked to 41BB and CD3ζ Lentiviral vector	**BCMA/CS1 (7A8D5 clone) Bispecific CAR-T cells**
		Kappa- CAR-T (NCT00881920) scFv of anti-κ light chain antibody linked to CD28 Lentiviral vector	
		NY-ESO-1-CAR T scFv of anti-NY-ESO-1 antibody linked to 4-1BB and CD3ζ s Lentiviral vector	
		CD56-CAR T (NCT03473496 and NCT03271632)	
		CD70-CAR T scFv (XW-208) of anti-CD70 antibody linked to CD3ζ subunit Lentiviral vector	
		Anti-TACI CAR-T (CB-P24) h(CD28-CD3ζ) Lentiviral vector	

CAR-T, chimeric antigen receptor-T; BCMA, B-cell maturation antigen; GPRC5D, G protein-coupled receptor class C group 5 member D; scFV, single-chain variable fragmen.

To improve persistence, completely humanized (CT053, CT103A) or synthetic (CART-ddBCMA) constructs have been introduced.[60,82,83] Furthermore, CAR-T cells characterized by central memory and/or stem cell memory phenotypes (nbb21217, P-BCMA-101, MCARH171, and JCARH125/orva-cel) with superior persistence capacity have been developed (23,46,57). The most recent CAR-T cell strategies (GC012F, PHE885, and CC-98633) feature rapid manufacturing timelines, allowing more patients to gain access to CAR-T therapy.[63,84,85] PHE885 is rapidly manufactured (< 2 days) and permits *in vivo* T-cell expansion.[48] Combination therapies play a key role in enhancing T cell activity. Some of CAR-T efficacy improvement methods are illustrated in the adapted Figure 3[62], and the novel manufacturing CAR-T technologies are displayed in adapted Table 2.[27,86]

NON-BCMA CAR-T INVESTIGATIONAL PRODUCTS

An alternative to BCMA depletion or resistance is non-BCMA focused immunotherapies. Figure 1 illustrates the novel CAR-T cell therapies targeting several antigens. Mechanisms of CAR-T efficacy enhancement are illustrated in Figure 2, CAR-T therapies employ dual antigen targeting, allogeneic sources, and CRISPR-Cas9 technologies and exhibit significant potential. While clinical trials targeting CD138, CD38, CD19, CD56, CD70, kappa, GPRC5D, SLAMF7, and integrin β7[49,55,59,61] (NCT03778346) have been initiated, many of these treatments are still in the preclinical research stage. In this section of the article, all these multifaceted targets will be covered in detail.

CD19, a surface antigen expressed on mature B cells, serves as a key therapeutic target in several B cell malignancies. Although CD19 is lacking in most myeloma cells, a minor subset may continue to express this antigen. The CTL019 study evaluated the efficacy of combining CTL019 with standard myeloma therapy in a cohort of twelve patients. This trial involved ASCT administration in conjunction with CAR-T therapy, utilizing a high-dose melphalan conditioning regimen in addition to the induction therapy. In this study, progression-free survival improved significantly.[87]

Alternatively, there are investigations focusing on CD56, an antigen that is frequently expressed on myeloma cells. Given that both central and peripheral nervous system cells may express CD56, neurological toxicities are concerning.[88] The study investigating the efficacy of anti-CD56 was discontinued (NCT03473496).

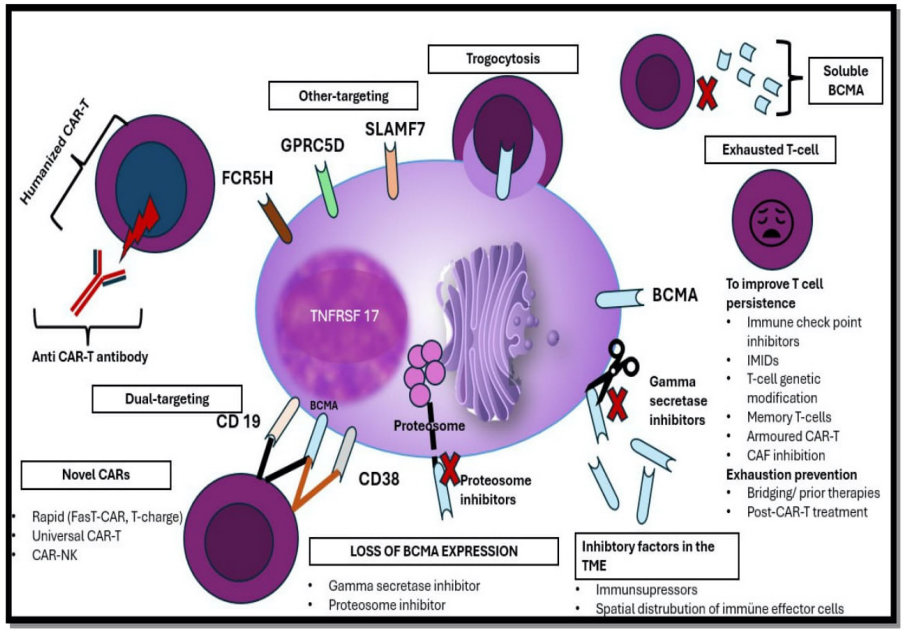

FIG. 3. The Improvement of CAR-T Efficacy.
CAF, cancer associated fibroblast; TME, tumor microenvironment; CAR-T, chimeric antigen receptor-T.

BMS-936561 and SGN-75 are drugs designed to target CD70, another anti-myeloma target. Although it appears to be effective and safe, the insufficient CD70 expression on myeloma cells is seen as an obstacle to the widespread adoption of the treatment.[68]

In this context, CD138, which is expressed on several myeloma cells, may be a more rational therapeutic target. CD138 is a member of the syndecan family of heparan sulfate proteoglycans. It is widely acknowledged to be overexpressed, particularly in refractory disease.[89] Apart from the generation of anti-CD138 CAR-T cells, research is being conducted to evaluate the combination of anti-CD138 medications [BT062 (indatuximab)].[90]

Today, the CD319 molecule, known as SLAMF, also plays a key role in phagocytosis and is frequently expressed by immune cells. The anti-SLAMF7 medication elotuzumab is already authorized as an anti-myeloma medication.[91] In ongoing clinical trials, it has been demonstrated that SLAMF7 CAR-T cells contain scFV, memory-enhanced T cells, and the truncated EGFR molecule (NCT03710421). The lack of specificity of this target to myeloma cells not only reduces efficacy but also leads to side effects. CAR-T cells may not achieve the desired level of disease control in all patients.[92]

Another target is the transmembrane activator and CAML interactor (TACI), a member of the TNFRSF13B superfamily. A proliferation inducing ligand (APRIL) and B cell activating factor are key drivers of myelomagenesis, and research indicates that CAR-T cells targeting APRIL can also influence BCMA and TACI signaling. TACI is expressed on both myeloma cells and regulatory T cells. Consequently, cytotoxicity may manifest with greater intensity.[93] A study demonstrated the effectiveness of second-generation CAR-T cells targeting TACI.[69] NY-ESO-1-CAR-T cells also appear promising in cancers that express this molecule. It has played a significant role in both enhancing tumor cytotoxicity and in the persistence of memory CAR-T cells. One of the adverse outcomes, monocytopenia, is largely curable. It is also believed to reduce CRS. It main limitation is its non-specificity toward myeloma cells.[94,95]

Immunotherapy may target light chains secreted by myeloma cells as a therapeutic strategy. To investigate this, a phase 1 study on kappa-positive RR lymphomas and myeloma was conducted. In this study, all prior treatments were discontinued at least four weeks before CAR-T cell infusion in the cohort of 16 patients. Although the authors correlate treatment response with light chain production in myeloma cells, further research is required.[96] Additional target-based products are also presented in Table 2.

In addition to single antigen-targeted therapies, dual-targeted therapies have also shown promise. This strategy can be implemented either by targeting two distinct antigens or by employing a single CAR-T cell-or two separate CAR-Ts-expressing different scFvs simultaneously, as in tandem CAR-T constructs.[97] The extracellular domain of third-generation CAR-T cells includes both anti-BCMA and anti-CD19 scFV. Ongoing studies are investigating BCMA/CD38, BCMA/CS1 bispecific cells, anti-BCMA with anti-CD38, or anti-CD19/FasTCAR T combined therapies-either administered concurrently or after ASCT-as presented in Table 1.

CAR-T therapies are currently being used as a successful advance in MM treatment, demonstrating efficacy in heavily pretreated, high-risk, and early-relapsing patients. Currently, studies are being conducted to use CAR-T at an earlier stage, even at diagnosis, with an aim to replace ASCT. CAR-T therapy has transformed MM treatment; however, limited efficacy in high-risk patients and emerging resistance remain challenges to be addressed. As the biology of the tumor can be complex and patient-specific, it is essential to understand the escape mechanisms well and to develop novel strategies. In addition, safety and success rely on timely access to CART. Global access remains a major challenge, which may be alleviated by expanding manufacturing capacity, particularly through selected academic centers alongside pharmaceutical producers.

TABLE 2. The Novel Manufacturing CAR-T Technologies.

The novel CAR-T technologies
The fifth-generation CARs
Multiantigen CARs with "OR" logic gate
Pooled CAR-T cells
Universal CARs
On-switch CARs
Off-switch CARs
Suicide gene
Suicide receptor (antibody-mediated depletion)
CAR-T cells with tumor-associated chemokine receptors
FAP-specific CARs
Modify CAR-T cells to express heparinase by gene editing
Dual CARs with "NOT" logic gate: inhibitory CARs (iCARs)
Dual CARs with "AND" logic gate: synNotch receptor system
Dual CARs with "AND" logic gate: split CARs (Combination CARs)
Armoured CAR-T cells
The fourth-generation CARs (TRUCKs)
mRNA transfections
CRISPR-Cas9/Cas12a technique (allogeneic)
ARCUS (allogeneic)
TALEN (allogeneic)
Memory-like T PI3K inhibitor
Earlier employment
Transposon Tscm, Cas-CLOVER, allogeneic
ShRNA/hairpin, allogeneic
Combination therapies
Artificial antigen-presenting cells (AAPCs)
Bi-specific T cell engagers (BiTEs)
Hematopoietic stem cell transplantation after remission
Cytokine inhibitors
Dasatinib to inhibit CD3ζ downstream signal
Antibodies for depleting suppressive immune cells/cytokines
Immune checkpoint inhibitors (ICIs)
Gamma secretase inhibitors
Other strategy
Regional delivery
NK-92, Cord blood-NK, NK-iPSCs, allogeneic NK

CAR-T, chimeric antigen receptor-T; CRISPR, clustered regularly interspaced short palindromic repeats; FAP, fibroblast activation protein; iPSC, induced pluripotent stem cell; NK, natural killer; Tscm, T- stem cell memory; TRUCK, T cell redirected for universal cytokine-mediated killing.

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