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Review Article

Investigation and Review of the Development and Application of Chimeric Antigen Receptor (CAR) T-Cell Therapy for Cardiovascular and Other Conditions

Kevin D Pruitt[1,2]†, Nicholas A Kerna[3,4]*†, ND Victor Carsrud[5], Hilary M Holets[6], Sudeep Chawla[7], Dabeluchi C Ngwu[8,9], John V Flores[6], Chizoba M Ani[10], Ayodeji A Ayeni[11], Cornelius I Azi[12] and Joseph Anderson II[13]

[1]*Kemet Medical Consultants, USA*

[2]*PBJ Medical Associates, LLC, USA*

[3]*Independent Global Medical Researchers Consortium*

[4]*First InterHealth Group, Thailand*

[5]*Lakeline Wellness Center, USA*

[6]*Orange Partners Surgicenter, USA*

[7]*Chawla Health & Research, USA*

[8]*Cardiovascular and Thoracic Surgery Unit, Department of Surgery, Federal Medical Center, Umuahia, Nigeria*

[9]*Earthwide Surgical Missions, Nigeria*

[10]*James Lind Institute, Switzerland*

[11]*Babcock University Teaching Hospital, Ogun, Nigeria*

[12]*Northern Care Alliance NHS Foundation Trust, UK*

[13]*International Institute of Original Medicine, USA*

***Corresponding Author:** Nicholas A Kerna, (mailing address) POB47 Phatphong, Suriwongse Road, Bangkok, Thailand 10500. Contact: medpublab+drkerna@gmail.com

† indicates co-first author

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Abstract

Treatment of cancer, especially liquid tumors, is remarkably effective when T cells carrying chimeric antigen receptors (CARs) are used. The ability to develop CARs for specific oncological applications has made them a compelling alternative to established cancer therapies such as chemotherapy or radiation therapy. CAR T cells are engineered from T cells isolated from the patient's or donor's blood. The patient then receives a second infusion of the genetically altered, enlarged T cells. CARs comprise a transmembrane domain called the spacer domain, a single chain variable fragment (scFv), one or more cytoplasmic domains, and an extracellular ligand-binding domain, usually also an scFv. These CAR T cells are then tested against cancer. Based on their pharmacodynamic and pharmacokinetic characteristics, they can be classified as first, second, third, or fourth-generation CAR T cells. Each generation showed different efficacy and safety, showing that the primary step in ACT is carefully selecting target antigens. Six CAR-T cell therapies have been approved by the US Food and Drug Administration (FDA) so far for patients with aggressive hematologic malignancies, including non-Hodgkin lymphomas (NHL), two cases of B-cell acute lymphoblastic leukemia (B-ALL), and one case of multiple myeloma (MM). Many more CAR-T cell therapies are currently in the clinical development pipeline for these and other malignancies.

Keywords: *Antigen Receptors; Chemotherapy; Genetic Alterations; Hematologic Malignancies; Oncological Applications; Radiation Therapy*

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Abbreviations

ACT: Adoptive Cell Therapy; AFP: Alpha-Fetoprotein; AIDS: Acquired Immune Deficiency Syndrome; ALL: Adult Lymphoblastic Leukemia; ASCT: Autologous Stem Cell Transplant; ASTCT: American Society for Transplantation and Cellular Therapy; B-ALL: B-Cell Acute Lymphoblastic Leukemia; BCMA: B Cell Maturation Antigen; CA: Cancer Antigen; CAAR: Chimeric Autoantibody Receptor; CAR: Chimeric Antigen Receptor; CAR T-Cell: Chimeric Antigen Receptor T Cell; CEA: Carcinoembryonic Antigen; CLL: Chronic Lymphocytic Leukemia; CR: Complete Remission; DLBCL: Diffuse Large B-Cell Lymphoma; ECOG PS: Eastern Cooperative Oncology Group Performance Status; FAP: Fibroblast Activation Protein; FDA: US Food and Drug Administration; HIV: Human Immunodeficiency Virus; IL-12: Interleukin-12; MM: Multiple Myeloma; MNC: Mononuclear Cell; NHL: Non-Hodgkin Lymphoma B Cells; PID: Primary Immune Deficiency; PR: Partial Remission; PSA: Prostate-Specific Antigen; scFv: Single Chain Variable Fragment; TIL: Tumor-Infiltrating Lymphocyte; TPS: Tissue Polypeptide-Specific Antigen; VH: Variable Sections of Heavy; VL: Variable Sections of Light

Introduction

History and background of chimeric antigen receptors (CARs)

Adoptive cell therapy (ACT) treats some chronic diseases using engineered cells. Cells are usually obtained from the patient or a compatible, healthy donor, modified *in vitro*, and then (re)infused into the patient's body. Tumor-infiltrating lymphocyte (TIL) therapy and chimeric antigen receptor T cell (CAR T-cell) therapy are two examples of ACT.

Chimeric antigen receptors (CARs) are genetically modified receptors that give an immune effector cell particular abilities (e.g., a lymphocyte T cell). Viral vectors (retroviral and lentiviral) transfer the coding sequence to the receptor, giving it the specificity of a monoclonal antibody directed against a particular type of tumor cell. The term "chimeric" denotes various sources that make up the component elements of the receptor.

The immune system is redirected by T cells with modified CARs to target and destroy cancerous cells, acting as a live drug that spreads throughout the patient and maintains long-term antitumor memory [1]. Leukapheresis can be used to obtain autologous CAR T cells from patient blood, or allogeneic CAR T cells can be obtained from the blood of a healthy donor [2]. Theoretically, CAR T cells can be engineered to target virtually any tumor-associated antigen and, in general, any other antigen [3].

Progression of CARs

Israeli immunologists Zelig Eshhar and Gideon Gross created the first modified T cell with a chimeric molecule between 1989 and 1993. By joining the constant area of a tumor-specific T-cell receptor to the variable portions of a bacterial antigen-recognizing antibody, Kuwana., *et al*. 1987 published the first proof of principle of integrating antibody-type antigen specificity with T-cell signaling [4]. These early CARs had not yet demonstrated therapeutic efficacy. However, depending on their composition, CARs were immunologically modernized and technologically advanced throughout the following 30 years, becoming first, second, third, and currently fourth generation [5,6].

Original research and clinical application

A research team at the University of Pennsylvania and Children's Hospital of Philadelphia made using CAR T-cell therapy in clinical settings possible. Carl June, the immunologist, oversaw the challenge of creating CAR-T cell technology. He delivered CAR T cells to patients with chronic lymphocytic leukemia (CLL) in 2011 [10] and ALL in 2012 [11], along with David Porter and Stephan Grupp.

The first patient with acute adult lymphoblastic leukemia (ALL) to undergo therapy in 2012 was 7-year-old Emily Whitehead. She had relapsed with refractory ALL and was advised to go to hospice. She became the first child to receive CART-19 therapy. The patient went through all the severe side effects of this therapy but eventually recovered.

Generations	Features
Second	Improved antitumor activity of T cells. Improved T-cell proliferation. Resistance to apoptosis, cytokine secretion, and persistence *in vivo*.
Third	Improved effector functions and persistence in vivo than second-generation CARs [6].
Forth	Deliver a transgenic product to the targeted tumor tissues. Furthermore, antitumoral potency, cytokine activity, and costimulatory ligands and enzymes that can degrade the extracellular matrix in solid tumors [7] were further enhanced.
Smart T cells and others	These are under investigation to obtain a high safety profile [8]. Using targeted nucleases, such as regularly interspaced clustered short palindromic repeats (CRISPR), may further enhance the efficacy and safety of CAR T cells [9].

Table 1: *Characteristic features of CAR T cells of different generations*

Discussion

Generation of CAR T cells

To make CAR T cells, mononuclear cells (MNCs) from the patient's blood are extracted via leukopenterase. Following the procedures shown in figure 1 [12], T cells are isolated and transformed with CARs to express a transgene encoding a CAR that is specific for a tumor before being injected into the patient. Under ideal T-cell cultivation circumstances, CAR-modified T cells develop outside the body. The WAVE Bioreactor, G-Rex, and CliniMACS Prodigy bioreactor culture systems are utilized for culturing CAR T cells [12].

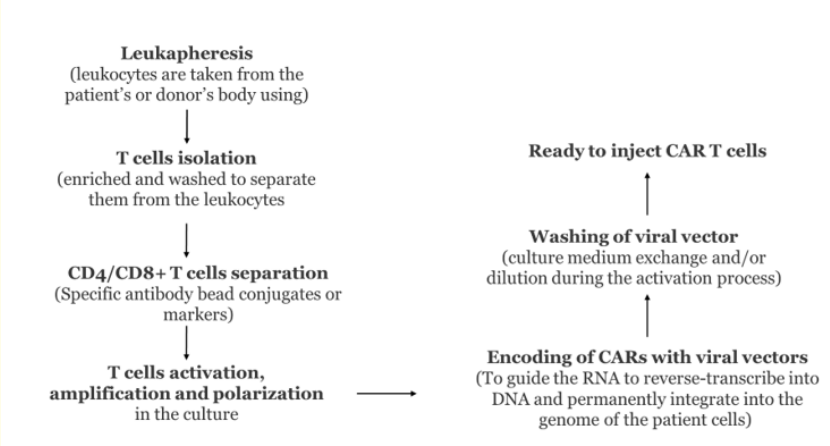

Figure 1: *Different steps involved in the production of CAR T cells*

The flask opening required for cell inoculation is the primary disadvantage of the first two techniques. On the other hand, the CliniMACS Prodigy®system consists of a single apparatus that can efficiently enrich, activate, transduce, and grow cells. Cells are collected once they have sufficient quantities for clinical applications. After harvesting, the completed product is dose-formulated. Quality and product release tests are conducted to ensure that the infusible product is safe to transfuse into patients.

How does CAR T-cell therapy work?

Throughout the body, T cells seek to combat disease and infection. An antigen-recognition receptor exists in every T cell (proteins or molecules recognizable by the immune system). The immune system tries to remove aberrant or foreign antigens when it finds them. Cancer cells, however, sometimes have antigens that the body cannot recognize as abnormal. As a result, the immune system does not send T cells to fight cancer cells. In other instances, T cells might be unable to destroy cancer cells. CAR T cells have undergone genetic engineering to develop a unique receptor that enables them to function as antibodies bind to antigens in tumor cells and kill them [13]. Antigens differ among distinct cancer types. Each CAR T cell therapy is made to target a specific tumor antigen. Because of this, a CAR T cell therapy created for one type of cancer will not work against a different type of cancer.

Depending on the relationship between tumors and their antigens, the antigens are distinct, meaning they do not exist in normal tissue cells or can exist but are overexpressed in cancer cells. These antigens are closely related to the prognosis and recurrence of cancer because they protect tumor cells from treatment stresses and are essential for better diagnosis, tracking the course of the disease, and proposing a prognosis via altered serum TAA concentrations [14].

Tumor-associated antigens: The TAAs in tumor cells are structurally similar to normal cells but present at higher concentrations. TAAs, such as alpha-fetoprotein (AFP), carcinoembryonic antigen (CEA), cancer antigen (CA), tissue polypeptide-specific antigen (TPS), prostate-specific antigen (PSA), and others, are currently widely used as biomarkers for several cancers [14]. In addition, searching for "unique" antigens in tumors can help create new therapeutic strategies such as vaccines, antibodies, and radioimmunoconjugates [15].

Tumor-specific antigen: TSAs are proteins or other molecules exclusive to cancer cells and are absent in healthy cells. TSAs may also be used in laboratory tests to help diagnose some types of cancer [16]. In addition, they can aid the body's immune response against cancer cells.

Single-chain variable fragment (scFv): The single-chain variable fragment (scFv) is a recombinant antibody form and an essential component of artificial CAR T cells [17,18]. To preserve the antigen-binding properties of the corresponding IgG antibody, ScFvs are synthetic constructs made of variable sections of heavy (VH) and light (VL) immunoglobulin chains joined by a flexible peptide linker [19]. The extracellular scFv portion of the receptors recognizes an antigen of interest. In contrast, the intracellular T cell receptor portion of the CAR facilitates signal transduction and the release of cytotoxic granules from the T cell [19].

Therapeutic applications of CAR T cells

While most TCR-modified T-cell studies concentrate on solid malignancies, CAR-modified T cells are generally used in B-cell malignancies such as lymphoma, leukemia, and multiple myeloma (MM). The CAR targeting CD19, a protein expressed by most B-cell malignancies, has shown the most encouraging clinical outcomes. Depending on the antigens present in the tumor cells, CAR T cells are modified and tested preclinically and clinically to evaluate their efficacy. Figure 2 represents the clinical efficacy of CAR T cells and the antigens targeted for each type of malignancy [20-22].

Acute lymphoblastic leukemia (ALL) and chronic lymphoblastic leukemia (CLL)

To date, CAR T-cell therapy is more effective in treating ALL, particularly deadly relapsed/refractory (r/r) B-ALL [23]. Adults and children with r/r B-ALL demonstrated encouraging complete remission (CR) and partial remission (PR) rates when treated with CD19-targeted CAR T cells [24].

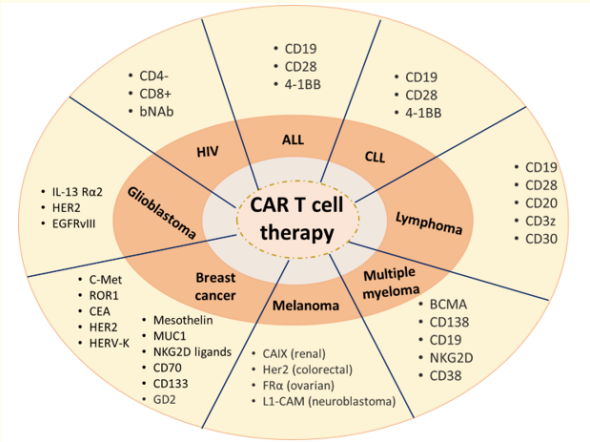

Figure 2: *The indications of CAR T cells and the different antigens against which these are modified*

Large B-cell lymphomas

For non-Hodgkin lymphoma B cells (NHL) that have relapsed or are resistant to chemotherapy, CAR T cells are among the most recent and cutting-edge immunotherapies, with anti-CD19 CAR T cells being the oldest and most established [25]. Several researchers are currently using first-generation anti-CD20 CAR T cell therapy.

Multiple myeloma (MM)

In early-phase clinical trials, individuals with MM exhibited substantial response rates to CARs targeted with B cell maturation antigen (BCMA) [26]. Although relapses have been seen regularly, responses are typically only transitory. The result of a clinical trial using second-generation anti-CD138 CAR T cell treatment showed that this cell therapy for MM is well tolerated and potentially has antitumor immunity [27].

Melanoma

Due to the immunosuppressive tumor microenvironment, the efficacy of CAR T cells in solid tumors is still poor, despite the unprecedented response rates with CD19 CAR T cells in hematologic malignancies. This barrier can be removed by other genetically altering T cells to express tumor-specific chemokine receptors, a transforming growth factor dominant negative receptor, or by combining CAR treatment with antiangiogenic drugs [28]. Another potential strategy to improve T cell reactivity is blocking PD-1 [29]. The ability to develop CAR T cells that only activate when two tumor antigens are binding at once (tandem/split CARs) or that contain a safety switch or safety gene may open the door to CAR T-cell therapy for melanoma [29,30].

Glioblastoma

Recent clinical studies have demonstrated CAR T cell therapy's efficacy, feasibility, and safety for glioblastoma. IL-13 Rα2 expression is present in more than 75% of glioblastoma. IL-13 Rα2–directed CAR T cells in patients with recurrent glioblastoma showed promising efficacy and early signs of anti-glioma [31]. Anti-IL-13 zeta kine CAR and anti-HER2 CAR T cell therapy are also effective [32,33].

Breast cancer

The cell surface molecule c-Met, expressed in ~50% of breast tumors, led to the construction of the anti-cMet CAR T cell. Intratumoral injections of anti-cMet CAR T cells are well tolerated and elicit an inflammatory response within tumors [34]. Furthermore, CAR T cells targeting HER2, MUC-1, and EGFR are potent and specific in suppressing breast cell growth [35].

Human immunodeficiency virus (HIV) infection (AIDS)

Currently, the CD4 receptor [36] and bNAbs [37] are used to construct anti-HIV CARs. Therefore, equipping CD8+ T cells with a CAR capable of recognizing various HIV antigens is critical to curing HIV. In the trial with active viral replication, CAR T cells showed a mean decrease >0.5 logs for at least 14 days in rectal tissue-associated HIV RNA, suggesting the antiviral activity of these CAR T cells against this important tissue reservoir of HIV [38].

Indications of CAR T cell therapy

Since 2017, the Food and Drug Administration (FDA) has approved six CAR T cell therapies. The go-ahead to treat blood disorders such as lymphomas, some types of leukemia, and, most recently, MM has been given to all of them. The US FDA has approved six CAR T cell treatments to date for the treatment of cancer (Table 2). According to the U.S. National Institute of Health clinical trial registration, numerous clinical trials using CAR T cell treatment are now being carried out for various malignancies, including MM, CNS tumors, hepatocellular carcinoma, and lung cancer [39].

Brand Name	Kymriah	Yescarta	Tecartus	Breyanzi	BCMA	Carvykti
Target	CD19				BCMA	
Disease	B-cell acute lymphoblastic leukemia B-cell non-Hodgkin lymphoma	B-cell non-Hodgkin lymphoma Follicular lymphoma	B-cell acute lymphoblastic leukemia Mantle cell lymphoma	B-cell non-Hodgkin lymphoma	Multiple myeloma	
Patients	Patients (children or young adults) with refractory or relapsed B-cell acute lymphoblastic leukemia Adults with relapsed or refractory B-cell non-Hodgkin lymphoma	Adults with relapsed or refractory B-cell non-Hodgkin lymphoma Adults with relapsed or refractory Follicular lymphoma	Adults with relapsed or refractory Mantle cell lymphoma Adults with relapsed or refractory B-cell acute lymphoblastic leukemia	Adults with relapsed or refractory B-cell non-Hodgkin lymphoma	Adults with relapsed or refractory Multiple myeloma	
Generic Name	Tisagenlecleucel	Axicabtagene Ciloleucel	Brexucabtagene Autoleucel	Lisocabtagene Maraleucel	Idecabtagenevicleucel	Ciltacabtagene autoleucel

Table 2: *FDA-approved CAR T-cell therapies*

Universal eligibility and contraindications of CAR T cell therapy

Along with the indications of the disease, the patient's performance status and comorbidities are critical considerations for the eligibility for CAR T cell therapy. In an expert panel opinion of the American Society for Transplantation and Cellular Therapy (ASTCT), Jain., *et al*. (2019) recommend that eligibility evaluation should consider renal function (GFR, Cr), liver function (AST/ALT, bilirubin), cardiac status (LVEF), pulmonary status (dyspnea, pulse ox), hematologic status (ANC, ALC, platelets), baseline neurologic examination and evaluation, presence of autoimmune diseases and use of immunosuppressive agents, presence of active or uncontrolled infection [40].

Pregnancy, members receiving immunosuppressive therapy for an autoimmune disorder, any active and uncontrolled infection, uncontrolled human immunodeficiency virus (HIV) infection, active hepatitis b or hepatitis c infection for lymphomas, active infection with hepatitis b, hepatitis c, or CMV for MM, hepatitis b or c infection, active graft vs. host disease (allogeneic hematopoietic stem cell transplant patients), primary central nervous system lymphoma, solid tumors are considered contraindications to CAR T cell therapy regardless of the product [41].

Mechanism of action of CAR T cells

A CAR is a synthetic construct that can bind to target cell surface antigens. Each CAR is created for a particular cancer antigen since many malignant neoplasms have various antigens. For example, carcinogenic cells in some types of leukemia or lymphoma express the antigen CD19. The CAR T cell treatments used to treat these tumors are designed to bind to the CD19 antigen and will not be effective against cells lacking this antigen. However, evidence suggests CAR T-cell therapies stimulate a T-cell response against antigen-expressing cells, including healthy and malignant cells. The external targeting domain binds to the antigen, activating the CAR T cell. Once activated, CAR T cells release cytokines and other soluble mediators that may play a role in killing antigen-expressing target cells and normal cells [42].

To develop the best CAR T cells, four generations of CAR T cells have been created through the continuous exploration and improvement of the effects of intracellular signaling domains that modulate action in target cells [43]. The first generation of CAR T cells binds to target cells through a single chain variable fragment (scFv) recognition domain.

This ligand recognition domain is an intracellular signaling module composed of a portion of the differentiation cluster (CD) -3 zeta (3ζ) chain to induce T-cell activation upon antigen binding [44]. The CD3ζ chain provides the signals required for T-cell activation, target cell lysis, regulation of IL-2 secretion, and antitumor immunoregulatory activity. However, the antitumor action of first-generation CAR T cells was limited *in vivo*, and the decrease in T cell proliferation ultimately led to T cell apoptosis.

Second and third-generation CAR T cells add costimulatory signals to cells [45]. The commonly used costimulatory molecule is CD28 or the 4-1BB receptor (CD137). This costimulatory signal, propagated by the phosphoinositide 3-kinase PI3K (in the case of CD28), is required for the complete physiological activation of T cells [46]. In addition, CD28 exhibits improved antitumor activity, and the advantage of 4-1BB is to prolong the survival of T cells and maintain their anticancer effects.

Further developments in fourth- or fifth-generation CAR T cells included signaling domains from cytokine receptors or inducible expression of inflammatory cytokines, such as interleukin-12 (IL-12) or IL-18 [47].

CAR T cell therapy versus standard cancer therapies

Radiation, chemotherapy, and surgical tumor excision are standard cancer treatments. Chemotherapy medications come in many varieties, and all work differently. These include antibiotics that fight tumors, nitrosoureas, antimetabolites, and alkylating drugs. Disease treatments, including chemotherapy and CAR T-cell therapy, a sort of immunotherapy, try to stop cancer from spreading in different ways. Through immunotherapy, the immune system is strengthened to better attack cancer cells. Immunotherapy is a treatment that boosts the immune system and allows it to locate and target cancer cells in the body, in contrast to chemotherapy, which directly affects cancer cells and prevents them from multiplying [48].

Patient identification for CAR T cell therapy

In contrast to autologous stem cell transplant (ASCT), CAR T cell therapy is typically an autologous therapy that may have different patient selection criteria. These criteria include prior therapies, maximum age, patient fitness, the severity of comorbidities, and chemoresistance status [49]. Patients' CAR T cell therapy eligibility is frequently determined by their Eastern Cooperative Oncology Group

performance status (ECOG PS). The exact eligibility requirements depend on the type of cancer treated, the therapy plan or protocol, and the CAR T cell product [50]. General eligibility requirements for CAR T cell therapy are mentioned in box 1 [50].

- Tumour expressing a CAR target
- An adequate number of T cells for collection
- No active and uncontrolled infections, including hepatitis B, hepatitis C, or HIV
- Adequate Performance Status and Organ Function
- Absence of clinically relevant comorbidities (e.g., select cardiovascular, neurologic, or immune disorders)

Box 1: *Eligibility requirements for CAR T cell therapy*

CAR T cell therapy administration

Patients approved for CAR T cell therapy will undergo the following treatment process represented in figure 3 [12].

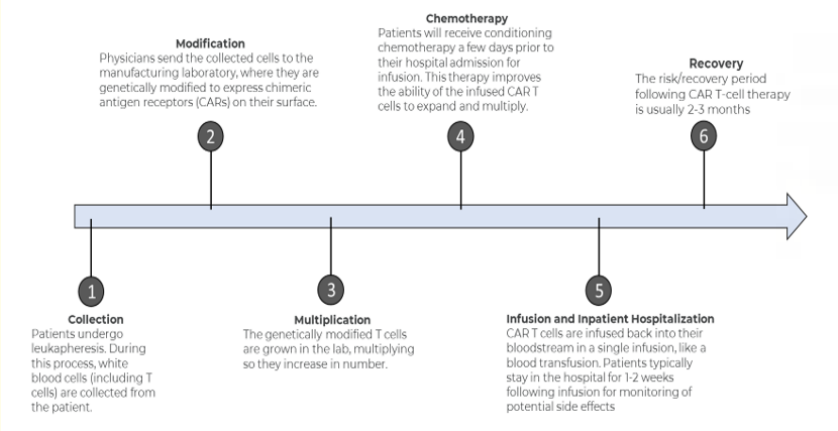

Figure 3: *CAR T cell therapy treatment process*

Status of tumor-specific CAR T-cell immunotherapy

Cancer treatment is increasingly dependent on immunotherapy. With five FDA approvals, CAR T cell therapy has demonstrated significant effectiveness in treating hematologic malignancies such as diffuse large B-cell lymphoma (DLBCL), acute B-cell lymphoblastic leukemia (B-ALL), and MM. The ideal approach would be CAR T cells, which have the benefits of immunotherapy and can be used to suppress cancer cells that have become resistant to chemotherapy, regardless of the underlying oncogenic driver mutations. Additionally, if CAR T cells are maintained for a few years, and the tumor antigen does not change, they could stop the tumor from recurring.

Hematologic malignancies: Five CAR-T cell therapies have been available since the first FDA approval in 2017 [51].

- Tisagenlecleucel (tisa-cel, Novartis: refractory and relapsed (r/r) B-ALL, r/r DLBCL, CD19-41BB-CD3z CAR-T, cryopreserved PBMC)
- Axicabtagene ciloleucel (axi-cel, Kite Pharma: r/r DLBCL, CD19-CD28-CD3z CAR T, fresh PBMC)
- Brexucabtagene autoleucel (brex-cel, Kite Pharma: r/r mantle cell lymphoma, CD19-CD28-CD3z CAR T, enriched T cell)
- Lisocabtagene maraleucel (liso-cel, Juno Therapeutics & Bristol Myers Squibb: r/r DLBCL, CD19-41BB-CD3z CAR T, 1:1 mixture of CD4: CD8 T cell)
- Idecabtagene vicleucel (ide-cel, Bristol Myers Squibb: r/r MM, BCMA-41BB-CD3z CAR T, CD8 T cell).

MM is the second most frequently diagnosed hematologic malignancy. Recently, BCMA CAR-T therapy showed outstanding results in patients with heavily pretreated MM, leading to FDA approval of idecabtagene vicleucel (ide-cel, Bristol-Myers Squibb) [52].

Solid tumours: Approximately 200 clinical trials of CAR T cells against solid tumors have been launched worldwide. CAR T cell therapy is less effective in solid tumors than in hematologic malignancies [53].

Lung cancer: CAR T-cell therapy is being investigated in phase I and II clinical trials, mainly for NSCLCs [54]:

PSCA CAR-T (NCT03198052)

GPC3 CAR-T (NCT02876978)

Mucin 1 (MUC1) CAR-T (NCT02587689)

CEA CAR-T (NCT02349724)

MSLN CAR-T (NCT02414269).

Brain tumor: The evaluation of CAR-T cell therapy in glioblastoma multiforme has been carried out intensively, with promising results in preclinical models; however, a lack of efficacy has been reported in clinical trials with CAR-T cell monotherapy [55].

CAR T-cell therapy for autoimmune diseases and viral infections

The enormous success of this strategy in treating cancer could be used to treat other diseases, as the list of possible targets suitable for CAR T cell therapy is rapidly growing. For example, some cancer-related disorders have pathogenic characteristics that may make treating them with CAR T cells possible—including a particular disease-related cellular element that identifies infected, hyperactive, or enlarged cells. Furthermore, CAR T cells frequently work as a potent substitute for the human immune system, which is often compromised by disease [56]. Table 3 shows the disorders in which CAR T cell therapy is being investigated [56].

Autoimmune disorders: Mechanisms underlying the loss of immunological self-tolerance in AID include activating autoreactive B cell clones that produce autoantibodies that promote tissue damage and suppress cytotoxic or regulatory T cells. The chimeric autoantibody receptor (CAAR), also known as the B cell antibody-targeting receptor, represents a variety of modified CARs that are used to eliminate autoreactive clones of immune cells. Unlike the scFv domain, CAAR is a target for autoreactive B cells. It defines the selective cytotoxicity of CAAR T cells only against immune cells that carry receptors to a specific autoantigen without inducing immunosuppression [57].

Allergy and asthma: IgE produced by B cells plays a vital role in the pathogenesis of allergic diseases and may be targeted by CAR T cells [58].

Disease	The target for CAR-T cell
Autoimmunity and allergy	
Pemphigus Vulgaris	Keratinocyte adhesion protein Dsg3
Haemophilia A	Anti-FVIII antibody
Type 1 diabetes	Insulin-B chain
Multiple sclerosis	Myelin Oligodendrocyte glycoprotein
Ulcerative colitis	Carcinoembryonic antigen
Allergy	The transmembrane form of IgE
Allergic asthma	Carcinoembryonic antigen
Infectious Diseases	
HBV	Domain S domain of HBsAg
HCV	Glycoprotein E2
HCMV	Glycoprotein B
Aspergillus	Carbohydrates of the cell surface
Influenza A	M2e protein
HIV	gp120, gp41, Oligomannose patch on Envs
SARS-CoV-2	S protein
In clinical trials	
Mucosal-dominant Pemphigus Vulgaris	Clone-specific anti-Dsg3 CAAR-T (NCT04422912)
Generalized Myasthenia Gravis	Nonspecific anti-BCMA CAR-T (NCT04146051)
Systemic Lupus Erythematosus	Nonspecific anti-CD19 CAR-T (NCT03030976)
Neuromyelitis Optica Spectrum Disorder	Nonspecific tandem anti-CD19 and anti-CD20 CAR-T (NCT03605238)
	Nonspecific anti-BCMA CAR-T (NCT04146051)
Human Immunodeficiency Virus	Anti-gp120 BNAbs-based CAR-T (NCT03240328)
	Anti-gp120 dual CAR-T (NCT04648046)
COVID-19	CAR-NK bispecific anti-ACE2 and anti-NKG2D (NCT04324996)

Table 3: *The list of diseases that can potentially be treated with CAR T cell therapy and the respective target molecules*

Infectious diseases: The primary function of CD8+ T cells is their ability to eliminate foreign cells and agents, making them attractive CAR T cells for treating infectious diseases [59]. Different studies are in progress to test the efficacy of CAR T cell therapy against chronic hepatitis B virus, chronic hepatitis C, human cytomegalovirus, influenza A, human immunodeficiency, type 1, and coronavirus infection [56].

Cardiac fibrosis: The potency of CAR T cells that target activated heart fibroblasts through recognition of fibroblast activation protein (FAP) in mice is assessed [60]. These anti-FAP CAR T cells induce significant reductions or even complete elimination of cardiac fibrosis and cause a partial rescue of systolic and diastolic cardiac functions with no adverse effects.

Primary immune deficiency (PID): The application of CAR T cell technology is eagerly awaited to treat viral infections in patients with PID [61].

CAR T-cell therapy approval process

The US Food and Drug Administration (FDA) approves CAR T cell therapies to treat certain lymphomas and leukemias. Numerous additional CAR T cell therapies (and related types of therapy) are currently being investigated in clinical studies to treat other types of cancer. CAR T cell therapies hold the promise of more effective and customized cancer treatments after decades of study. However, as with many ground-breaking drugs, these new medicines' regulatory and developmental pathways are only sometimes wholly established. As a result of these new approvals, regulatory bodies have had to modify their way of thinking. There are several approaches to solving these difficulties that must be taken into account when considering CAR T cell therapy. Limited FDA guidance, logistics for production and distribution, product safety, and long-term follow-up are possible obstacles to CAR T cell development. However, the regulatory tools available and ongoing research will increase your chances of success and help get your product on its way to commercialization.

Possible side effects of CAR T cell therapy

CAR T cell therapy can be very effective against certain hard-to-treat cancers but can sometimes cause severe or life-threatening side effects. Because of this, it must be administered in a medical center that is specially trained in its use, and patients must be closely monitored for several weeks after receiving CAR T cells. As CAR T cells multiply, they can release large amounts of chemicals called cytokines into the blood, which can hyperactivate the immune system and cause several adverse events (Table 4).

Cytokine release syndrome (CRS)	Nervous system problems	Other serious side effects
High fever and chills Trouble breathing Severe nausea, vomiting, or diarrhea Feeling dizzy or lightheaded Headaches Fast heartbeat Feeling very tired Muscle and joint pain	Headaches Changes in Consciousness Confusion or agitation Seizures Shaking or twitching (tremors) Trouble speaking and understanding Loss of balance	Allergic reactions during infusion Abnormal levels of minerals in the blood (K^+, Na^+, Ph, levels) A weakened immune system Low blood cell counts, fatigue, and bleeding or bleeding

Table 4: *Adverse effects of CAR-T therapy*

Future perspectives of CAR T-cell therapy

Although CAR T-cell therapy is evolving rapidly and has much potential, several problems remain. For example, the capacity of CAT T cells to penetrate solid tumor tissues, the specificity with which they can be used to treat different solid tumors, and their resistance to immunosuppressants should be improved. The ultimate objective of adoptive cell therapy is to develop a customized cellular product aimed at cancerous cells while minimizing adverse effects. Possible combinations with immunomodulatory drugs, checkpoint inhibitors, or other CAR T cells modified to incorporate suicide genes or switches, now being evaluated in preclinical and clinical investigations, are future directions to improve efficacy and safety. Currently, more than 100 clinical trials are recruiting participants. Additionally, the importance of adoptive T-cell therapy in the fight against cancer will eventually be determined by developments in CAR T-cell biology throughout the ensuing years regarding safety, dependability, and efficacy against nonhematopoietic tumors.

Conclusion

Immunotherapy is more effective against cancer and more targeted at specific cancer cells when compared to conventional therapy. Additionally, thanks to ongoing scientific advancements, the field of immunotherapy is expanding quickly. In conclusion, CAR T cells represent a state-of-the-art, personalized immunotherapeutic strategy that has advanced significantly in recent years.

Conflict of Interest Statement

The authors declare that this paper was written without any commercial or financial relationship that could be construed as a potential conflict of interest.

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