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Review Article

A Description of Chimeric Antigen Receptor-Modified T Cells in Cancer Immunotherapy

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Abstract

Chimeric Antigen Receptor (CAR)-modified T cells, or CAR-T cell therapy, is emerging as a promising new strategy for immunotherapy, and by modifying T cells in vitro to add a CAR that specifically recognizes tumor antigens, CAR-T cell immunotherapy improves tumor-specific killing. This immune cell therapy has the advantages of good targeting and killing power, and it enables effective activation and proliferation of T cells independent of MHC molecules, which is a very effective new strategy for immune killing. In this paper, we will introduce the composition of CAR, the basic principles of CAR-T cell immunotherapy and the preparation aspects of CAR-T cells, and highlight an overview of the use of CAR-T cell immunotherapy in various tumor treatments in recent years.

Keywords: Car-T therapy; Oncology; Immune cells; Targeted therapy; Immunotherapy

Introduction

Among the basic methods of treating tumors, radiotherapy and chemotherapy still occupy an important position, but the accompanying toxic side effects cannot be ignored, which seriously affect the daily life of patients. To solve these problems, researchers have gradually turned to research on the role of immune cells and inflammatory factors in the tumor microenvironment, hoping to use the normal body immune system to monitor and kill cancer cells. So immune cell therapy has begun to be used in the treatment of tumors [1].

Among them, chimeric antigen receptor T-cell immunotherapy (CAR-T), which introduces Chimeric Antigen Receptors (CARs) into T cells, has a specific killing effect on cancer cells by using modified CAR-T to specifically recognize and bind to Tumor Associated Antigens (TAAs) on the surface of cancer cells, thus achieving specific treatment for cancer [2-4]. This method can be used for specific treatment of cancer cells. At the same time, this method can show better anti-tumor effects because it does not require the participation of antigen-presenting cells (APCs) and is therefore not limited by the major histocompatibility complex (MHC) [5]. In the clinical treatment of hematologic tumors, CAR-T cell immunotherapy has achieved better results, especially in CD19-positive B-cell leukemia and lymphoma, with an overall remission rate of more than 80%, which has again increased the interest of researchers in modifying T-cell immunotherapy and gradually extending it to clinical treatment of various tumors [6,7].

In this paper, we first describe the basic components and principles of CAR-T, then review the progress of CAR-T cell immunotherapy for various tumors in recent years, and finally summarize the future of CAR-T cell immunotherapy.

CAR-T cell immunotherapy

Composition of CAR

The key site in CAR-T cell immunotherapy is the chimeric antigen receptor (CAR), which consists of three main components, namely the extracellular antigen-binding domain, the hinge region and the intracellular structural domain, and is a fusion protein expressed on T cells [8,9]. The extracellular antigen binding domain can be composed of a monoclonal antibody heavy chain and a light chain with a single variable fragment, and this binding domain can determine the target of CAR-T cell attack through its antigen specificity [10]. The hinge region, as a transmembrane spatial domain with a certain degree of toughness, mainly functions as a link between the extracellular antigen binding domain and the intracellular structural domain, which determines the stability and signalling function of CAR, and thus facilitates the binding of CAR-T cells to target cells [10,11]. The intracellular structural domains are mainly divided into co-stimulatory structural domains and T cell activation structural domains, which serve to trigger and activate antigens to generate specific immune responses and transmit first and second signals to influence the activation, proliferation and killing of T cells [12]. Currently, researchers have conducted research on the design of CARs for their structure and have reached the fifth generation. The first-generation CARs consist of an extracellular single-chain variable fragment scFv, a transmembrane region and a single intracellular activation signal molecule [13]. These CARs lack the second signal molecule to induce T-cell activation, and can only transmit the activation signal to the cell, causing a short period of T-cell proliferation and a small amount of cytokine secretion, which is not conducive to the long-term anti-tumor activity of CAR-T cells in patients [14]. The second-generation CARs add co-stimulatory molecules to the original ones, which can enhance the killing and toxic function of T cells on tumor cells by activating the second signal. The third-generation CARs add multiple costimulatory molecules, which interact with each other to enhance multiple signaling pathways in T cells, resulting in more significant enhancement of T cells in various aspects of anti-tumor cell functions, prolonging T cell proliferation activity, survival cycle and promoting the release of multiple cytokines. The fourth-generation CAR, on the other hand, adds selectable markers to multiple co-stimulatory molecular structures, allowing T-cell activity to be enhanced by the genes encoding CARs, inducing them to secrete cytokines and chemokines, recruiting and activating their own intrinsic immune cells, and improving T-cell survival in the tumor microenvironment. Fifth-generation CART cells are general-purpose CAR-T cells designed on the basis of gene editing technology to recognize more target proteins and improve the flexibility of CART cells to treat different cancers. Its genes are designed to prevent rejection by the body and to pre-prepare allogeneic T cells for patients for ready supply, but so far, fifth-generation CAR-T cells have not been widely used [15] (Figure 1).

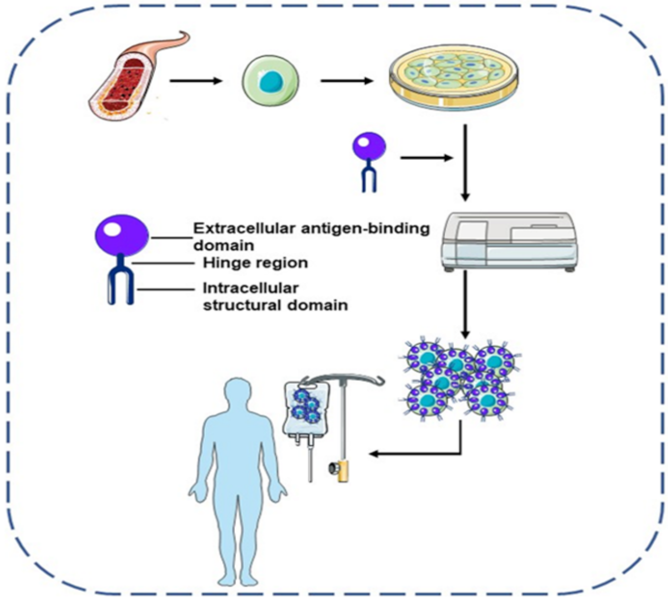

Figure 1: The way of Car-T cell therapy in human.

Principles of CAR-T cell immunotherapy

Activation signalling of T cells and tumor-specific recognition are the basic principles of CAR-T cell immunotherapy [16]. A dual signalling pathway induces T-cell activation, consisting of antigen-specific signals, i.e., the binding of T-cell receptors (TCRs) to major histocompatibility complexes (MHCs) - antigenic peptides, as the first signalling pathway, and antigen-nonspecific signals, consisting of the binding of T cells to CMs on the surface of antigen-presenting cells (APCs), as the second signalling pathway [17]. The activation and cascade of T cells are informed by both signalling pathways, with the ultimate goal of converting T cells into cytotoxic T cells (CLT). This binding can induce the production of perforin, which can lyse tumor cells, or release a large amount of cytokines, which can change the living environment of tumor cells, thereby directly killing them or inhibiting their growth [18-20]. CAR-T cell immunotherapy, on the other hand, utilizes the combination of the effect of CLT on target cell toxicity and the specific recognition of antigens by antibodies to enable CAR to kill tumor cells by generating activated T cells through the specific recognition of antigens that target tumor cells [21]. In this treatment, most of the T cells are derived from the peripheral blood of the patient, and by introducing the designed exogenous gene into the T cells, a stably expressed CAR-T cell can be obtained, then the stably expressed CAR-T cells are cultured and proliferated in vitro, and finally the proliferated CAR-T cells are injected back into the patient to kill the tumor cells.

Preparation of CAR-T

Firstly, T cells are isolated from the patient's peripheral blood cells, and then the T cells are cultured and proliferated in vitro. And secondly, the CAR gene is introduced into the patient's isolated T cells by electroporation, lentivirus or retrovirus transduction, so that the T cells are modified to express the CAR gene to obtain stably expressed CAR-T cells. The retroviral transduction method has a wide range of application and high transduction efficiency, but has a high risk of tumorigenicity due to the loss of the ability to infect non-dividing cells due to the small DNA fragments carried by the transduction method. For safety reasons, electroporation is safe, but has the disadvantage of transient expression, which requires multiple injections [22-24].

Current status of research on CAR-T therapy for various types of cancer treatment

Chimeric antigen receptor (CAR) T-cell technology was originally proposed by Eshhar and Gross in the 1980s with the idea of directing T-cell responses through genetic editing of T-cell receptors (TCRs) to enable them to play a greater role in the immune response and fight against tumors. In recent years, various gene editing techniques have enabled CAR-T cells to be targeted to different sites, thus greatly improving the therapeutic effect on various types of cancers [12].

CAR-T cell immunotherapy for head and neck squamous cell carcinoma

Head and neck squamous cell carcinomas (HNSCCs), as malignant lesions of the mucosal epithelium of the oral cavity, pharynx and larynx, account for 90% of all head and neck cancers and are among the sixth most common malignancies worldwide(25-27). Surgery with conventional radiotherapy, chemotherapy and immunotherapy is the basis of treatment for squamous cell carcinoma of the head and neck [28]. However, tumor recurrence and metastasis remain at a high level with these treatment modalities. There is growing evidence that chimeric antigen receptor T (CAR-T) cells have promising antitumor effects in the treatment of HNSCC [29,30].

Currently, investigators are approaching the treatment of squamous cell carcinoma of the head and neck through three main areas: preclinical studies, clinical studies, and the search for potential targets [30,31] (Table.1).

Preclinical study target	**Reference**
EGFR	[1]
MUCI	[2]
B7-H3	[3]
HER2	[4]
CD70	[5]
Clinical trial target	**Reference**
ERBb2/HER2	[6]
NKG2DL	[6]
EpCAM	[6]
LMP1	[6]
Potential target	**Reference**
NKGD2	[7]
HER3	[8,9]
FAP	[10-13]

Table 1: The treatment of squamous cell carcinoma of the head and neck.

In preclinical studies, investigators found that HER2 expression was detectable in 0-47% of HNSCC patient tissues and that HER2 overexpression was often associated with a poorer prognosis for HNSCC patients [44,45]. Warren et al. developed specific CAR-T cells targeting HER2 for the treatment of HNSCC and their results showed that anti-HER2 CAR-T cells resulted in a 56% reduction in tumor size, suggesting that HER2 may be a potential target for CAR-T cells to treat HER-positive HNSCC [38,46,47]. Similarly, overexpression of CD70, a ligand for tumor necrosis factor, which is highly expressed in HNSCC, is associated with a reduction in CD8+ T cells and can induce immunosuppression TME [48]. Park et al. analysed nine proteins highly expressed in HNSCC cells as potential CAR-T cell targets and demonstrated that compared to the untreated group, anti-CD70 CAR-T cells could effectively eradicate HNSCC cells [38,49]. In addition to this, EGFR was overexpressed in hypopharyngeal cancer, which accounts for about 5% of HNSCC [50]. Thus, Dong et al. developed CAR-T cells targeting EGFR to limit the growth of EGFR-positive hypopharyngeal cancer cells. The results showed that the cytokine secretion and lysis rates of hypopharyngeal cancer cells were significantly increased after co-culture of hypopharyngeal cancer cells with CAR-T cells [32].

For clinical studies in the treatment of HNSCC, Sophie Papa et al. conducted a phase I clinical trial for the treatment of HNSCC in combination with intra-tumor injection of the binary lysing adenovirus CAdVEC to investigate the safety and cytotoxic effects of CAR-T cell immunotherapy targeting HER2 in the treatment of HNSCC [30].

In conclusion, in the treatment of HNSCC, researchers have been searching for its new targets to enhance the specificity of CAR-T cells, reduce the side effects of CAR-T cells, and continuously promote the transformation of CAR-T cell immunotherapy to clinical applications.

CAR-T cell immunotherapy for breast cancer

Breast cancer is the leading cancer in women. Approximately 20-30% of breast cancer patients develop invasive or metastatic disease after radical surgical resection and eventually die [51,52]. Despite advances in chemotherapy, endocrine therapy and molecular targeted therapy, there are still some breast cancer patients who are less sensitive to treatment. Treatment resistance and tumor recurrence or metastasis also develop as treatment proceeds [53]. Therefore, investigators need to explore more favourable treatment strategies. Chimeric antigen receptor-modified T cells have made some progress in immunotherapy for breast cancer by exploring breast cancer-related targets [54-56]. For example, for HER-2-positive breast cancer, a subtype that affects approximately one quarter of breast cancer patients, HER-2 gene amplification or protein overexpression underlies HER-2-positive breast cancer [57,58]. HER-2 can be used as a recognition molecule for constructing HER-2-specific CAR-T cells for immunotherapy of HER2-positive breast cancer [59]. li et al. used CAR-T cells targeting HER-2 cells in combination with PD-1 blockers to kill Herceptin-resistant breast cancer cells [60]. seyedmirzaei et al. used HER-2-specific CAR-T cells to eliminate tumors and improve survival of trastuzumab-resistant breast tumor cells in mice [61]. meili et al. prepared chA21 scFV-based HER-2-specific CAR-T cells and it was shown to recognize and kill HER-2-positive breast cancer cells in vitro, as well as to induce breast cancer regression in vivo [62].

In addition, CAR-T cell immunotherapy is being further investigated by researchers in triple-negative breast cancer (TNBC) and other types of breast cancer (Table 2).

Brest cancer subtype	Target	Intervention (CAR-T)	NCT Number
HER-2 positive	HER2	HER2-CAR T cells	NCT02547961, NCT03696030
		Anti-HER2 CAR-T	NCT02713984
		CAdVEC	NCT03740256
		HER2-targeted dual-switch CAR-T cells	NCT04650451
HER2-negative	Mesothelin	Mesothelintargeted T cells	NCT02792114
TNBC	MUC1	anti-MUC1 CAR T Cells	NCT02587689
	Mesothelin	CART-meso cells	NCT02580747
	ROR1	ROR1 CAR-T cells	NCT02706392
		ROR1-targeted CAR T cells	NCT05274451
	NKG2DL	NKG2DL-targeting CAR- ch CAR-T	NCT04107142
	c-Met	mRNA c-Met-CAR T cell	NCT01837602
Other types	CEA	Anti-CEA CAR T cells	NCT02349724, NCT03682744
		CEA CAR-T cells	NCT04348643
	Mesothelin	iCasp9M28z T cell infusions	NCT02414269
	EpCAM	EpCAM CAR-T	NCT02915445
	CD70	Anti-hCD70 CAR transduced PBL	NCT02830724
	HER2/Gd2/ CD44v6	Multiple 4SCAR T cells	NCT04430595

Table 2: CAR-T cell immunotherapy in TNBC and other types of breast cancer.

CAR-T cell immunotherapy for HIV

CAR-T cell immunotherapy has been applied in clinical trials for a variety of cancers with promising results, which have demonstrated the safety, feasibility, efficacy and durability of CAR-T cell immunotherapy [63,64]. Based on these results, the HIV field has begun to view CAR-T cell immunotherapy as a promising HIV cure strategy [65,66]. Unlike other strategies for treating HIV, CAR-T cell immunotherapy would be a targeted, curative tool designed to completely eliminate the HIV reservoir from the patient's organism [67-69]. Table 3 summarizes the clinical trials of investigators using CAR-T cell immunotherapy for HIV treatment over the last two decades.

Start Date	Study Title	NCT Number	Reference
2001	A phase I/II study of the safety, survival, and trafficking of autologous CD4-ζ gene-modified T cells with and without extension Interleukin-2 in HIV infected patients	NCT01013415	-14
2017	The effect of CAR-T cell therapy on the reconstitution of HIV-specific immune function	NCT03240328	-15
2019	A pilot study of T cells genetically modified by Zinc Finger Nucleases SB-728mR and CD4 chimeric antigen receptor in HIV-infected subjects	NCT03617198	Ongoing
2021	Safety and anti-HIV activity of autologous CD4+ and CD8+ T cells transduced with a lentiviral vector encoding bispecific anti-gp120 CAR molecules (LVgp120duoCAR-T) in anti-retroviral drug-treated HIV-1 infection	NCT04648046	Ongoing

Table 3: CAR-T cell immunotherapy for HIV treatment.

CAR-T cell immunotherapy for ovarian cancer

Ovarian cancer (OC), one of the most common gynecologic malignancies, has a poor prognosis and high mortality rate [72]. Most patients are diagnosed at advanced stages (stage III or IV), with a global 5-year survival rate of 25% to 47%. Surgical resection and first-line chemotherapy are the main treatment modalities for OC [73]. However, due to resistance to chemotherapy, patients usually relapse within a few years of initial treatment. Cell-based therapy, chimeric antigen receptor T (CAR-T) cell therapy, represents an alternative immunotherapeutic approach with great potential for the immunotherapy of ovarian cancer [74,75]. Ovarian tumors typically lack TSA, and therefore, the target of immunotherapy is usually one or more tumor-associated antigens [7]. Researchers are currently constructing CAR-T cells that target different targets on the surface of ovarian cancer to achieve ovarian cancer immunotherapy [5,19]. For example, erb-b2 receptor tyrosine kinase 2 (ERBB2) [62,76], programmed cell death-ligand 1 (CD274) [73,77], programmed cell death 1 (PDCD1) [78-80], epithelial cell adhesion molecule (Ep-CAM) [81], anti-Müllerian hormone receptor type 2 (AMHR2) [82], annexin A2 (ANXA2) [83], trophoblast glycoprotein (TPBG) [74], folate receptor alpha (FOLR1) [84,85], mesothelin (MSLN) [72,86-88], mucin 16 (MUC16) [89,90] and CD24 [75], among others (Figure 2).

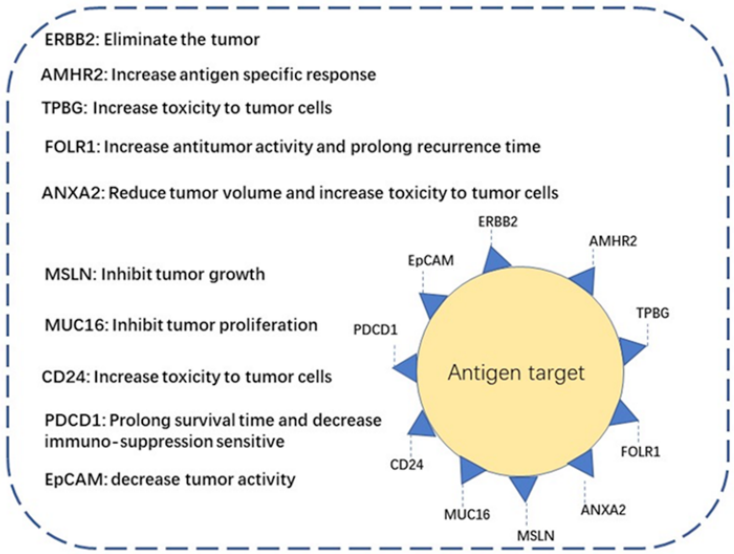

Figure 2: Constructing CAR-T cells that target different targets on the surface of ovarian cancer to achieve ovarian cancer immunotherapy.

ERBB2, also known as human epidermal growth factor receptor 2 (HER2), is a proto-oncogene with gene amplification and overexpression associated with OC and negative or very low protein expression in normal tissues. Sun et al. [62] have developed a HER2-CAR-T-cell treatment and found that novel MSLN is a group of glycoproteins anchored to the plasma membrane by the phosphatidylinositol region (GPI) and is normally expressed in pleural, peritoneal, pericardial and mesothelial cells and is highly expressed in 30% of OCs are highly expressed. Due to the low non-specific toxicity of MSLN, researchers have identified it as a potential target for the treatment of OC [87,86,91]. Recently, Zhang et al.(88)developed MSLNCAR containing MSLN-scFv, CD8 transmembrane structural domain, CD28 and TNFRSF9 co-stimulatory structural domains, and activation structural domain CD247. In vitro experiments showed that MSLN-CAR was able to specifically kill tumor cells in OC cell lines and release cytokines.

Muc16, also known as cancer antigen 125 (CA125), is characterized by overexpression of MUC16 in more than 80% of OCs and serves as an important indicator for early diagnosis of OC [89]. Studies have shown that MUC16-CAR-T cells specifically kill MUC16+ OC cells in vitro. In mouse tumor models, intravenous or intraperitoneal injection of MUC16-CAR-T cells also delayed the progression of OC and even completely cleared tumors. Similarly, Ep-CAM is overexpressed in OC cells and can be targeted by CAR-T cells [90]. Fu et al. [81] developed a third-generation Ep-CAM- CAR containing an EpCAM- SCFV fragment, a CD8 transmembrane structural domain, stimulatory structural domains of CD28 and TNFRSF9, and a CD247 activation structural domain. The CAR was then transferred into T cells using lentivirus. Finally, it was also well demonstrated by in vivo and in vitro experiments that Ep-CAM-CAR-T cells could effectively inhibit OC tumor activity.

The use of cell-derived vesicles in cancer therapy

The selection and exploration of potential targets for CAR-T cell immunotherapy in targeting various types of cancers should be guided by the following two prerequisites: (1) proteins targeted by CAR-T cells have been reported for use in certain cancers, such as FAP and GD2; and (2) proteins that are highly expressed on the surface of the cancer cells of interest for treatment and little or no expression in normal tissues.

Mucin-1

An abnormal glycoform large-size protein, mucin-1 of the cell membrane (MUC1), capable of overexpression is present in a large number of adenocarcinomas [91,92]. Researchers designed a CAR based on mAb (5E5) that can effectively target the MUC1 glycopeptide to kill pancreatic tumor cells [93,94]. Meanwhile, because IL-4 is closely linked to the pathophysiology and treatment of cancer, the researchers used the IL-4 receptor outer structural domain to modify MUC1CAR-T cells, which allowed CAR-T cells to gain further viability in the treatment of cancer and significantly enhanced resistance to immunosuppressive cytokines, greatly improving the anti-tumor effect [95-97].

GD2

As a tumor-associated carbohydrate surface antigen, the ganglioside GD2, unlike other gangliosides expressed in most normal tissues, is preferentially overexpressed in the vast majority of neuroblastomas, melanomas, retinomas, and Ewing's sarcomas [98-100]. GD2 not only promotes tumor development by inducing cell proliferation, migration, and anti-apoptosis, but also exhibits immunosuppressive properties when released into the circulation, it can impede T-cell activation and dendritic cell maturation [101-103]. The researchers prepared Epstein-Barr virus (EBV) specific CAR T-cells targeting GD2 and delivered them to eight patients with neuroblastoma, showing necrosis and regression of tumor cells in four patients [104-106].

NKG2D

Natural killer group 2D (NKG2D), a key regulator of effector immune cell function, is able to activate a potent cytotoxic pathway against its target cells even in the presence of normal concentrations of inhibitory MHC-I molecules [107]. Since the ligand of NKG2D is overexpressed on tumor cells, the NKG2D-CAR-T constructed using its ligand as a target has functional significance in innate and adaptive immunity against infected cells and malignant cells.

B7H3

B7H3 (CD276), an immune checkpoint molecule, enhances immune escape and metastasis of tumors and is associated with poor prognosis [108,109]. Recently, investigators have constructed B7H3-CAR-T cells and used them in preclinical models of various solid tumors, and the results of the study have demonstrated their potent anti-tumor effects, such as neuroblastoma, childhood malignancies and ovarian cancer [110,111].

GPC3

Glypian-3 (GPC3) belongs to the Glypian family of proteoglycans and is attached to the cell surface via glycosylphosphatidylinositol (GPI) anchors [112]. GPC3 is essential for cell differentiation, proliferation and migration and it has been shown that GPC3 is abundantly expressed in hepatocellular carcinoma HCC and is not expressed in normal tissues, so it can be used as a specific target for hepatocellular carcinoma [113]. The investigators infused the prepared GPC3-CAR-T cells back into 13 patients and studied their safety and preliminary efficacy [114-116]. The results showed that GPC3-CAR-T cells were effective and safe for the treatment of GPC3-positive HCC patients, and when combined with lymphodepleting conditioning, GPC3-CAR-T cells showed strong anti-cancer potential.

Conclusion

CAR-T cell therapy can cause a range of immunopathological reactions due to its "targeted, off-tumor" toxicity, including fever, hypotension, hypoxia, neurotoxicity, skin toxicity, gastrointestinal toxicity, and multi-organ damage. The immunopathological reactions may include fever, hypotension, hypoxia, neurotoxicity, skin toxicity, gastrointestinal toxicity and multi-organ damage. In severe cases such as cytokine release syndrome or tumor lysis syndrome, it may even cause death of the patient. Coupled with its high cost and complicated operation, the clinical application of CAR-T cell immunotherapy has been limited. Therefore, in addition to enhancing antitumor efficacy, methods to eliminate complications of CAR-T cell immunotherapy, reduce its cost, and optimize operational steps are also a major challenge for the clinical application of CAR-T cell immunotherapy. In summary, despite the many obstacles, with the study and in-depth exploration of precision medicine research, more and more researchers are joining the research on CAR-T cell immunotherapy, and CAR-T cell immunotherapy is likely to elevate the treatment of various types of cancer to a new level in the future and will play a more important role in cancer immunotherapy.

Disclosure

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