World Journal of Surgical Oncology

REVIEW

Open Access

The potential of chimeric antigen receptor -T cell therapy for endocrine cancer

Ruonan Yu[1], Xiaoyu Ji[1], Ping Zhang[1], Hao Zhang[1], Huiling Qu[2*†] and Wenwu Dong[1*†]

Abstract

Endocrine cancer, a relatively rare and heterogeneous tumor with diverse clinical features. The facile synthesis of hormones further complicates endocrine cancer treatment. Thus, the development of safe and effective systemic treatment approaches, such as chimeric antigen receptor (CAR) T cell therapy, is imperative to enhance the prognosis of patients with endocrine cancer. Although this therapy has achieved good results in the treatment of hematological malignancies, it encounters diverse complications and challenges in the context of endocrine cancer. This review delineates the generation of CAR-T cells, examines the potential of CAR-T cell therapy for endocrine cancer, enumerates pivotal antigens linked to endocrine cancer, encapsulates the challenges confronted with CAR-T cell therapy for endocrine cancer, and expounds upon strategies to overcome these limitations. The primary objective is to provide insightful perspectives that can contribute to the advancement of CAR-T cell therapy in the field of endocrine cancer.

Keywords Antigen targets, CAR-T cell, Endocrine cancer, Immunotherapy, Thyroid

Introduction

Endocrine cancer represents a group of heterogeneous tumors, including thyroid cancer (TC), adrenal cancer, pancreatic cancer (PC), parathyroid cancer, and ovarian cancer (OC) [1]. The facile synthesis of hormones in certain endocrine cancers contributes to higher mortality rates, complicating the management of endocrine cancer [2]. Notably, PC is the seventh most prevalent fatal tumor worldwide, whereas OC is the eighth most deadly malignancy in women [3, 4]. Individuals afflicted by these malignancies may experience an unfavorable prognosis coupled with a heightened mortality rate [3]. Diagnosis frequently occurs at an advanced stage (Stage III or IV) in most patients with endocrine cancers. Under existing treatment modalities, PC has a 5-year survival rate of only 13% [5], while OC shows a mere 5-year survival rate of 25–47% [6]. Even in the case of the most common and generally well-prognosed endocrine malignancy, TC, a small subset still exhibits invasive behavior that is unresponsive to conventional cancer therapies [7]. In conclusion, despite the active surgical resection complemented by chemotherapy, radiotherapy, or targeted therapy, tumor recurrence remains quite common. Although these traditional treatments can effectively suppress tumor growth and extend patient survival in many cases, they are often accompanied by significant side effects [8]. Moreover, due to the heterogeneity of tumors, some patients may develop resistance to these treatment methods [9]. Therefore, it is essential to seek out more

†Huiling Qu and Wenwu Dong contributed equally to this work.

*Correspondence:
Huiling Qu
huilingqu@163.com
Wenwu Dong
dongwenwu@cmu.edu.cn
[1]Department of Thyroid Surgery, The First Hospital of China Medical University, No. 155 Nanjing North Street, Shenyang, Liaoning 110001, China
[2]Department of Neurology, The General Hospital of Northern Theater Command, 83 Wen Hua Road, Shenyang, Liaoning 110840, China

promising therapeutic strategies. The relevant data on other cancers in endocrine tumors may be insufficient, which weakens the foundation for analysis and discussion; therefore, this paper will not address this issue.

In recent years, owing to an enhanced understanding of the molecular mechanisms governing immune recognition and regulation within tumor cells [10], immunotherapy has exhibited promising therapeutic outcomes in diverse cancer types, generating substantial interest. Immune checkpoint inhibitors (ICIs) are currently approved for the treatment of many different types of cancer and have become a cornerstone of cancer therapy in various combination regimens. However, this therapy may be associated with immune-related adverse events when it involves endocrine diseases. In contrast to immune checkpoint inhibitors, CAR-T therapy not only demonstrates a unique therapeutic mechanism but also offers new hope for cancer patients [11]. The concept of T cell therapy for cancers was first elucidated by Dr. Steven Rosenberg and colleagues at the U. S. National Cancer Institute during the 1980s [12–14].

With remarkable advancements in the treatment of hematologic malignancies through adoptive T cell therapy [15], ongoing efforts are aimed at expanding this strategy to solid tumors. Consequently, researchers have developed chimeric antigen receptors (CARs) to create receptors capable of recognizing tumor antigens regardless of their MHC expression. In contrast to TCRs, CARs can identify a wider spectrum of tumor cell antigens, activate T cells without being confined to MHC restrictions, and consequently induce potent and targeted antitumor responses [16, 17]. Through advancements in gene transfer technology, researchers have incorporated CARs into T cells, giving rise to chimeric antigen receptor T cells (CAR-T cells).

This review describes the generation of CAR-T cells, explores the potential of CAR-T cell therapy for endocrine cancers, lists key antigens associated with endocrine cancers, summarizes the challenges faced by CAR-T cell therapy for endocrine cancers, and discusses strategies to overcome these challenges. The aim is to provide insights into CAR-T cell therapy for endocrine cancers and to offer assistance in this field.

Origin and preparation of CAR-T cells

In 1989, CAR-T cells were designed and engineered to treat hematologic malignancies [18]. Although the process of redirecting T cells using CARs is highly complex, it has been widely used for personalized gene-modified therapy employing autologous T cells.

In first-generation CAR-T cells, there is an extracellular ligand-binding domain and an intracellular structural domain, also known as a signaling domain. The extracellular ligand-binding domain is composed of a single-chain variable fragment (scFv) derived from antibody heavy and light chains, whereas the intracellular signaling domain consists of CD3ζ. The scFv can selectively recognize tumor antigens and activate T cells [18], whereas CD3ζ can initiate and trigger antigen-specific immune responses. However, owing to the lack of co-stimulatory signals, first-generation CAR-T cells exhibit weak or no cytotoxic function and short in vivo survival [19]. Therefore, the second and the third generations of CAR-T cells introduced one or more co-stimulatory domains, incorporating co-stimulatory molecules like 4-1BB (CD137), CD28, OX40, and CD27 to selectively modify the function of synthetic CAR-T cells [20–25], enhancing persistence and Th1 cytokine production (TNF-α, IFN-γ) [26–28]. Despite some advantages of the second and the third generations over the first, issues still exist, such as the inability to counteract immunosuppressive tumor microenvironments (TME). Fourth-generation CAR-T cells are designed to release transgenic products into tumor tissues after binding with the CAR. These locally delivered immunomodulatory molecules (such as IL-12 and IL-18) help transform the inhibitory tumor microenvironment into a state that supports immune responses [29]. However, CAR development has progressed to the fifth generation to improve the performance and safety of CAR-T cell therapies. Fifth-generation CARs build upon the foundation of second-generation CARs by incorporating a truncated cytoplasmic region of the IL-2 receptor β chain and a YXXQ motif that binds STAT3/5 (transcription factors). This design aims to achieve optimal T cell activation by simultaneously activating three signals—antigen-dependent TCR, co-stimulation, and cytokine signaling [30]. Several generations of CAR-T cells have been manufactured [31, 32], with the common feature of using scFv as the extracellular domain and incorporating costimulatory molecules in the intracellular domain, along with further modifications [33], as shown in Fig. 1.

The manufacturing process of CAR-T cells consists of several critical steps, with distinct methodologies for autologous and allogeneic CAR-T cell production [34]. For autologous CAR-T cell manufacturing, the typical procedure involves the following steps: (1) Isolation of white blood cells from the patient's peripheral blood to obtain T cells. (2) Activation of T cells using anti-CD3/anti-CD28 beads and cytokines. (3) Subsequent transduction of CAR genetic material into the activated T cells using lentiviral or retroviral vectors. (4) Notably, TCR knockout is not required for the production of autologous CAR-T cells. (5) Following transduction, the T cells are expanded in culture to increase their numbers. (6) The resulting CAR-T cells are then aliquoted into vials for storage. (7) Finally, the product is stored, frozen, and

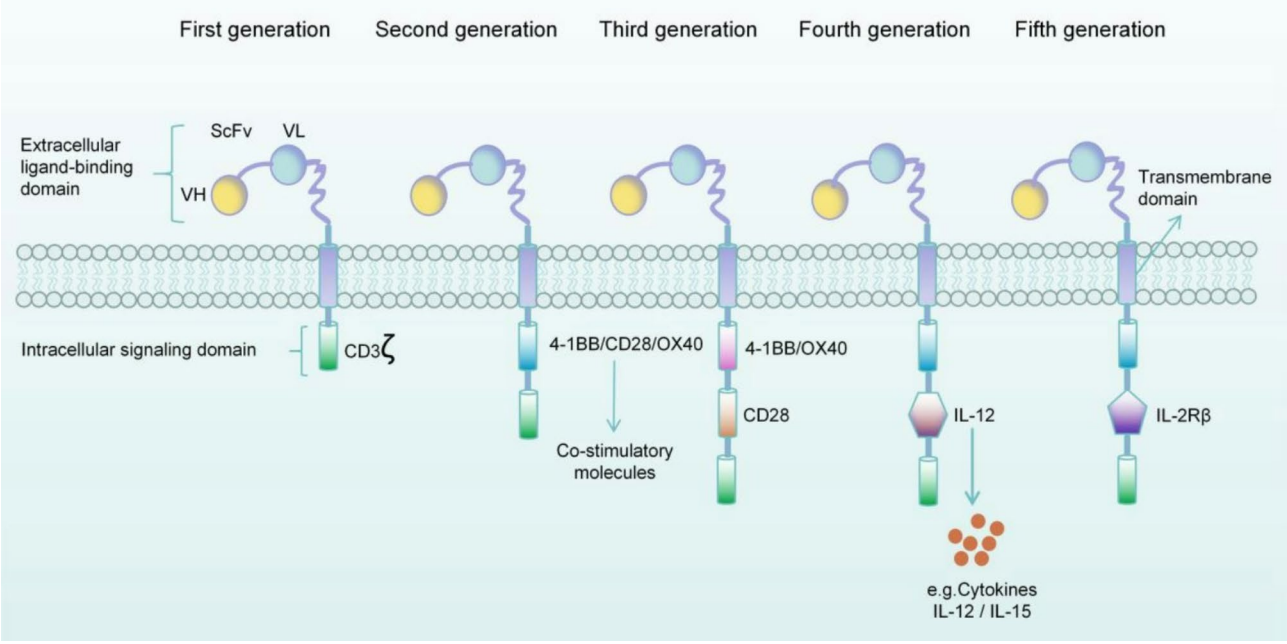

Fig. 1 Generations of CARs. CARs are constructed from a single-chain variable fragment (scFv) coupled with a CD3ζ molecule and a co-stimulatory molecule such as CD28. The scFv consists of a variable light chain domain (VL) and a variable heavy chain domain (VH). CD3ζ initiates and triggers antigen-specific immune responses. The CD28 domain promotes faster expansion of CAR-T cells. The 41BB domain is typically used to enhance in vivo persistence of the cells. IL-12 increases the survival of CAR-T cells in the immunosuppressive tumor microenvironment. The IL-2Rβ chain domain overcomes tumor-inhibitory microenvironments, enhancing the anti-tumor effects of T cells

transported to the hospital as needed, prior to infusion into the patient, as illustrated in Fig. 2 [35–37].

Unlike regular T cells, CAR-T cells express receptors with distinct biological structures. In the treatment of solid tumors, they migrate to the TME, and upon detecting tumor antigens, kill tumor cells through cytokine production and associated mechanisms [38]. The cytotoxicity of CAR-T cells is mediated by the activation of death receptors binding with fas/fas ligands and by the release of perforin enzymes that induce tumor cell lysis [39–41]. However, CAR-T cell therapy is expensive and unsuitable for all patients. There is also a risk of severe adverse events, including uncontrolled cytokine release syndrome (CRS) and neurotoxicity, as complications of CAR-T cell therapy [42].

Antigen targets

Tumor antigens are mainly classified into two categories: tumor-associated antigens (TAA) and tumor-specific antigens (TSA). TAA is expressed in both tumor and normal cells, leading to higher toxicity and more side effects when targeted. TSA, on the other hand, is specifically expressed in tumor cells, allowing for more precise targeted therapy with reduced side effects. However, current immunotherapy targets often involve one or more TAA [43], therefore, the field still requires the discovery and validation of new, truly endocrine cancer-specific antigens to minimize potential off-target effects and adverse events. In the following sections, we review antigen targets for CAR-T cell therapy in endocrine cancers, including human epidermal growth factor receptor 2 (HER2), mesothelin (MSLN), mucin 16 (MUC16), epithelial cell adhesion molecule (EpCAM), folate receptor 1 (FOLR1), and CD24 (Fig. 3).

HER2

HER2, also known as human epidermal growth factor receptor 2 (ERBB2), is a member of the epidermal growth factor receptor family. It is a transmembrane glycoprotein involved in cell proliferation and differentiation during embryonic and adult tissue development [44]. As one of the extensively studied TAA in cancer immunotherapy, HER2 significantly contributes to the onset and clinical progression of various cancers. Notably, in the context of OC, Sun et al. [45] introduced an innovative CAR construct utilizing a humanized HER2-specific chA21 scFv (chA21-28z-CAR) that incorporates fused CD28/CD3ζ intracellular domains for robust T cell activation. Consequently, the resultant CAR-T cells effectively eliminated HER2-positive OC cells. Furthermore, considering the substantial overexpression of HER2 in approximately 7–58% of PC [46–48], along with minimal protein expression in normal tissues, HER2 has emerged as an attractive target for CAR-T cell therapy in PC. AMIT et al. [49] designed HER2-specific CAR-T cell therapy for in situ PC in immunodeficient mice and found that

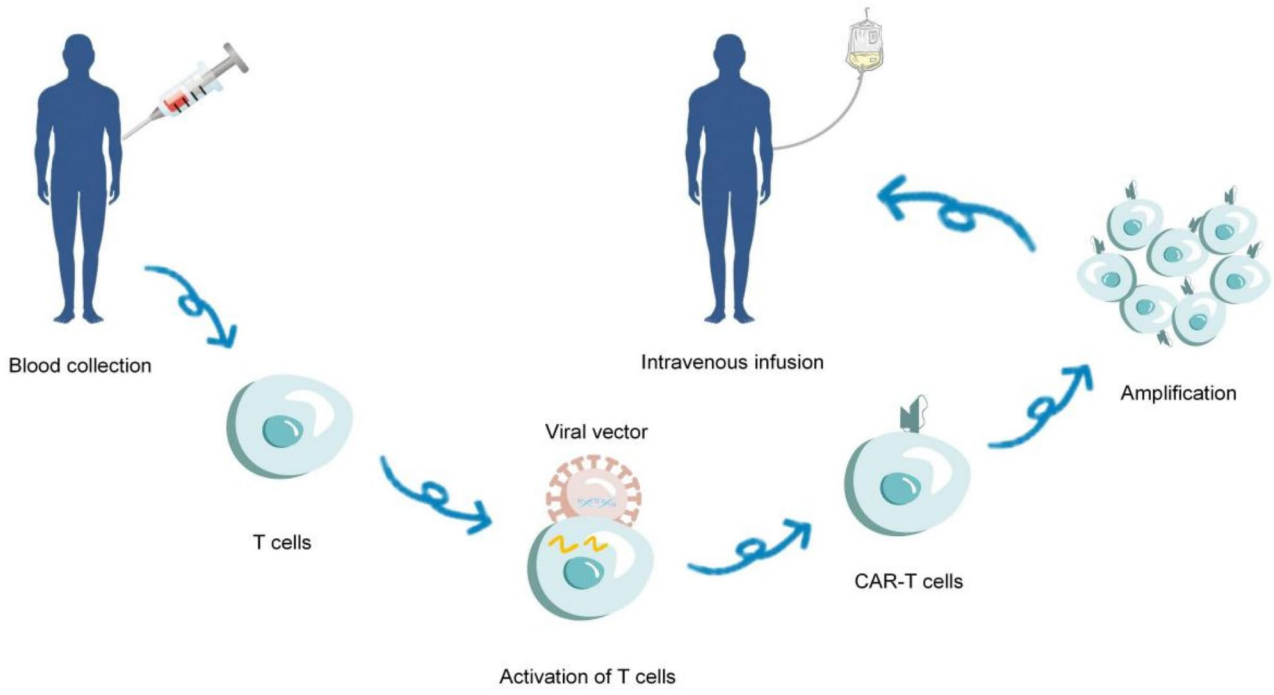

Fig. 2 Preparation process of CAR-T cells. T cells are collected from the patient's peripheral blood using leukapheresis. With the assistance of lentiviral and retroviral vectors, these T cells are transduced with CAR genetic material. The resulting chimeric antigen receptor T cells are then expanded. Subsequently, they are infused back into the patient

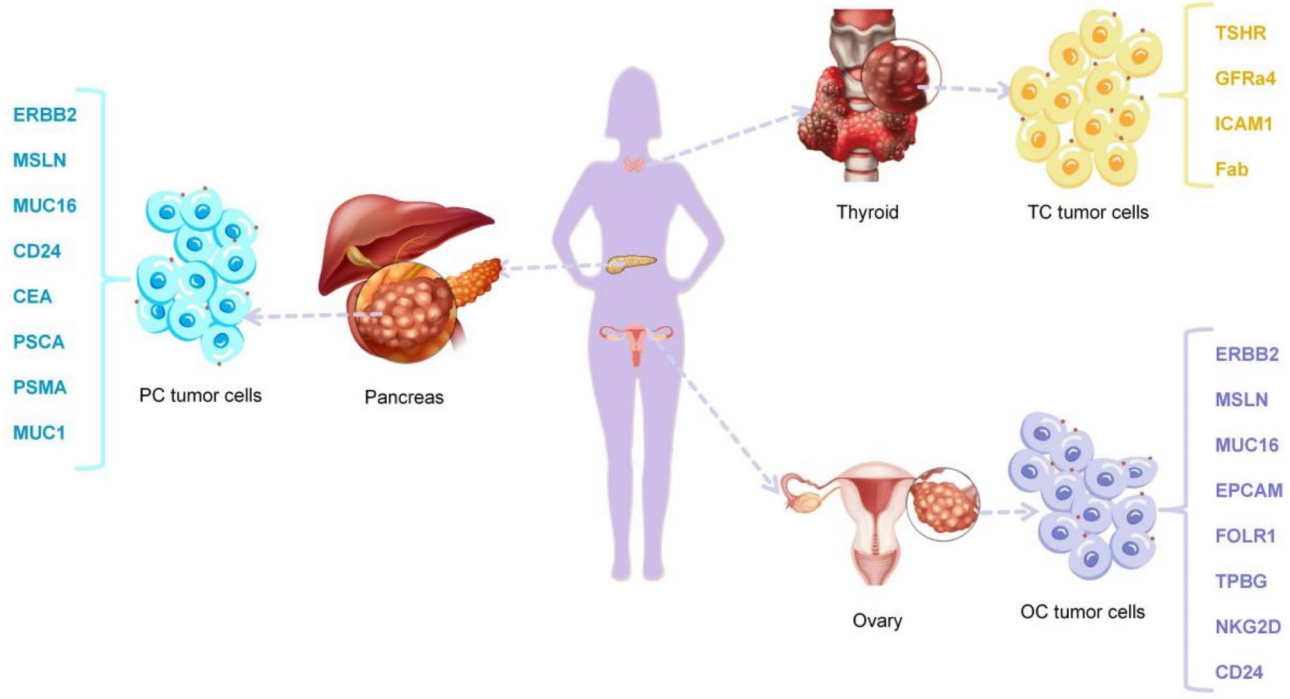

Fig. 3 Candidate target antigens for CAR-T cell therapy in endocrine cancer. Several target antigens for CAR-T cell therapy have been identified and are being studied in preclinical and clinical trials. Different tumor cells express both common and distinct antigens. For example, PC and OC tumor cells share target antigens for CAR-T therapy, including ERBB2, MSLN, MUC16, and CD24

HER2-CAR-T cells could significantly reduce the tumor burden. Despite the promising therapeutic potential of HER2-CAR-T cell therapy at preclinical stages, its application in OC and PC treatment currently remains under the scope of clinical trials.

MSLN

MSLN is a group of glycoproteins anchored to the plasma membrane through a glycosylphosphatidylinositol (GPI) linkage [49]. This antigen exists on the cell surface, initially as a 69 kDa protein, which is subsequently cleaved by furin proteinase into a soluble 32 kDa N-terminal fragment and a membrane-bound 40 kDa C-terminal fragment [50]. As most TAAs used as solid tumor targets are also present in normal cells, non-specific toxicity occurs during treatment. However, MSLN exhibits relatively high specific expression in PC and OC tissues compared to normal tissues [50–53], thus resulting in lower non-specific toxicity. Consequently, it is the most extensively studied target for PC and OC therapy.

Esther et al. [54] established an orthotopic model of OC to compare the in vivo efficacy of CAR-T cells targeting MSLN with the CD28 (M28z) or 4-1BB (MBBz) costimulatory domains. They noted that M28z-MSLN-CAR-T cells significantly extended survival yet did not provide sustained tumor control. MBBz-MSLN-CAR-T cells induced long-term remission in some mice bearing SKOV3 tumors, albeit with a lower response rate. Subsequently, Zhang et al. [55] developed MSLN-CAR-T cells with an MSLN-specific scFv, CD8 transmembrane domain, CD28 and TNFRSF9 costimulatory domains, and an activating domain CD247. In vitro, these CAR-T cells effectively killed OC cell line tumor cells. In vivo, they inhibited the growth of MSLN-positive tumors and significantly elevated T cell and cytokine levels. Similarly, Chen et al. [56] devised and constructed MSLN-CAR-T cells displaying robust cytokine secretion and cytotoxicity against OC cells, both in vitro and in vivo. These findings highlight the promising potential of MSLN-CAR-T cell therapy in OC treatment. Furthermore, Beatty et al. [57] carried out a study employing MSLN-specific CAR-T cells for treating pancreatic ductal adenocarcinoma (PDAC), revealing the safety, feasibility, and therapeutic potential of MSLN-CAR-T cell therapy for PDAC, and suggesting that MSLN could serve as a potential therapeutic tool for PDAC treatment. In conclusion, MSLN emerges as a promising target for CAR-T cell therapy in both OC and PC.

MUC16

MUC16, also known as cancer antigen 125 (CA125), belongs to the mucin-glycoprotein family. It was initially identified using the murine monoclonal antibody OC125, which is the 125th antibody generated against OC cell lines. MUC16 is the largest membrane-associated mucin glycoprotein, consisting of approximately 22,000 amino acids [58]. MUC16 plays a key role in promoting tumor initiation and proliferation, and is a well-known marker for gynecologic malignancies [59], particularly OC. Over 80% of OC cases are characterized by the overexpression of MUC16. Therefore, MUC16 is a highly attractive target for CAR-T cell therapy.

Chekmasova et al. [60] demonstrated that MUC16-CAR-T cells exert specific cytotoxic effects on MUC16 + OC cells in vitro. Furthermore, in mouse tumor models, both intravenous and intraperitoneal injections of MUC16-CAR-T cells lead to delayed OC progression or complete tumor clearance. Additionally, Mythili et al. [61] found that CAR-T lymphocytes secreting IL-12 displayed enhanced antitumor efficacy in a human OC xenograft SCID-beige mouse model. This encouraged the development of a construct (4H11-28z/IL-12) that simultaneously expressed MUC16ecto-CAR and IL-12. Compared to 4H11-28z-CAR-T cells, 4H11-28z/IL-12-CAR-T cells exhibit enhanced proliferation and IFN-γ secretion. These studies highlight the potential of MUC16 as a promising target for OC therapy.

EpCAM

EpcAM, as a type I transmembrane glycoprotein, is highly expressed in rapidly growing epithelial cell tumors and was initially identified as TAA [62]. Among these, rapidly growing epithelial tumors are OCs [63]. While the overexpression of the EpCAM antigen exhibits significant heterogeneity and is linked to processes such as cell proliferation, differentiation, and cellular signal transduction, it is crucial to address the implications of its low-level expression in normal epithelial tissues. This low expression raises valid concerns regarding the potential for off-target toxicity when targeting EpCAM therapeutically. Additionally, the heterogeneous expression of EpCAM within tumors may result in inconsistent therapeutic responses, thereby potentially limiting the overall efficacy of EpCAM-targeted therapies [64–66]. In light of these considerations, Fu et al. [67] constructed EpCAM-CAR-T cells and demonstrated their specific cytotoxicity and cytokine release against the OC cell line SKOV3 in vitro. In vivo experiments significantly reduced tumor size and improved survival rate in the OC xenograft mouse model. Therefore, although EpCAM-CAR-T cells present a promising therapeutic approach for OC, a thorough evaluation of their safety and efficacy is imperative.

FOLR1

FOLR1 is a GPI-anchored membrane protein. It is minimally expressed in normal tissues but is overexpressed in epithelial-derived malignancies, including OC, lung cancer, and breast cancer [68]. Moreover, this overexpression

is associated with increased tumor aggressiveness and poor prognosis [69], making it an attractive target for immunotherapy. In a study by Zuo et al. [70], FOLR1-specific CAR-modified cytokine-induced killer (CIK) cells were investigated to evaluate their antitumor immune effects in OC. They found that FOLR1-CAR-CIK cells augmented antitumor immunity against FOLR1-positive OC. Liang et al. [71] demonstrated that FOLR1-CAR-T cells effectively recognize and target FOLR1-positive tumor cells, resulting in significant anti-tumor effects. Furthermore, these CAR-T cells exhibited high cytotoxicity in vitro, efficiently killing FOLR1-positive cells, and demonstrated the ability to delay tumor growth in in vivo mouse models. Additionally, the fully human FOLR1-CAR-T cells developed by Maria et al. not only showed remarkable anti-tumor activity but also exhibited a certain degree of persistent survival in vivo, allowing for sustained anti-tumor responses that contributed to the delay in tumor progression. Overall, FOLR1 holds promise as a potential target for CAR-T cell therapy for OC.

5T4

The cancer/testis antigen 5T4 (also known as trophoblast glycoprotein, TPBG) is highly expressed on the cell surface of numerous solid tumors [72], making it an attractive target for adoptive cell immunotherapy. Guo et al. developed second-generation CAR-T cells specific to 5T4. They demonstrated that these CAR-T cells secreted cytotoxic cytokines such as IFN-γ, IL-2, and GM-CSF, induced tumor cell lysis, and substantially delayed tumor formation in intraperitoneal and subcutaneous animal models [73]. However, it is important to note that the expression of the 5T4 antigen in normal tissues raises concerns about the potential for unintended immune attacks, which must be carefully evaluated in clinical applications. The ability of 5T4-CAR-T cells to circulate, target tumors, expand, and exert antitumor effects underscores their potential for effective OC therapy. This study also establishes a theoretical foundation for future clinical trials of OC immunotherapy [73].

CD24

A significant contributor to the heightened invasiveness of PC and OC is the existence of cancer stem cells (CSCs), which are characterized by robust self-renewal abilities and high resistance to chemotherapy [74–76]. CSCs are implicated in tumor initiation, invasion, metastasis, and recurrence. Commonly recognized CSC markers in PC and OC include CD44 and CD24. Heightened expression of these markers correlates with unfavorable clinical outcomes in patients with PC and OC [74]. Given its minimal expression in normal tissues, CD24 emerges as a highly promising therapeutic target. Maliar et al. engineered second-generation CD24-specific CAR-T cells that effectively eradicated CD24 + tumor cells in a human PC xenograft model [49]. This implies that CD24 holds promise as a potential target for CAR-T cell therapy in PC. Furthermore, Klapdor et al. [77] utilized lentiviral transduction to equip the human NK cell line NK-92 with an anti-CD24 CAR, resulting in the creation of a novel anti-CD24-CAR termed CD24-CAR-NK-92. This third-generation, optimized CAR equipped with a high-affinity scFv SWA11 targeting CD24 exhibited selective cytotoxicity against OC cell lines. In conclusion, CD24 shows promise as a target for CAR-T cell therapy in both PC and OC.

TAG72

Tumor-associated glycoprotein 72 (TAG72) antigen is a sialylated glycoprotein, with approximately 90% of epithelial OCs being TAG72 positive, indicating its abundant presence in various histological subtypes of OC [78]. Murad et al. [79] developed a humanized TAG72 specific CAR that includes a 4-1BB intracellular co stimulatory signal domain (TAG72-BB ζ). TAG72-BBζ-CAR-T cells, composed in this manner, demonstrated potent cytotoxicity against TAG72 + OC cell lines and the ability to stimulate the production of cytokines in vitro. Furthermore, upon intraperitoneal infusion into mice, these cells significantly inhibited tumor cell proliferation and prolonged overall mouse survival. Although TAG72-BBζ-CAR-T cell therapy exhibits favorable effects on OC, the decreased expression of TAG72 in recurrent tumor cells considerably diminishes the efficiency of treating recurrent tumors [79]. In summary, TAG72-CAR-T cell therapy could be a suitable strategy for CAR-T cell treatment of OC, yet further experimental research is warranted.

TM4SF1

Transmembrane 4 L6 family member 1 (TM4SF1) is a cell surface protein characterized by four transmembrane domains, and it is classified within the tetraspanin superfamily. Gao et al. reported that TM4SF1 exhibited notably higher rates of positive expression (90.90%) in epithelial OC tissues compared to normal ovarian tissues (31.25%) [80]. Moreover, TM4SF1 assumes a pivotal role in driving the progression, migration, and invasion of OC. Shen et al. [81] engineered third-generation CAR-T cells targeting TM4SF1 as part of an OC therapy approach. These cells exhibited selective cytotoxicity against TM4SF1-positive OC cell lines in in vitro settings and effectively suppressed tumor growth in a xenograft mouse model derived from SKOV3 cells. Consequently, TM4SF1 holds significant potential as a therapeutic target for OC, underscoring its promise as a foundation for CAR-T cell-based immunotherapeutic interventions targeting TM4SF1.

CEA

Carcinoembryonic antigen (CEA) is a 180-kDa GPI-linked glycoprotein typically found on the colonic surface. Its expression experiences an exponential increase during the process of carcinogenesis. Moreover, it can be released into the bloodstream and serves as a serum marker employed to monitor gastrointestinal malignancies [59]. Furthermore, its elevated expression is notably associated with unfavorable prognoses in patients with PC [82]. Hence, CEA holds the potential to be a valuable target for CAR-modified T cell therapy in the context of PC. Chmielewski et al. conducted a study to assess the effectiveness of CAR-T cells targeting CEA in the treatment of mice with orthotopic PC. Their findings revealed that 67% of the mice experienced long-term tumor eradication, thereby exemplifying the cytotoxic impact of CEA-CAR-T cells within a mouse model of PC [83]. Nonetheless, a separate study assessing these cells was prematurely terminated due to respiratory complications, underscoring the potential risks associated with CEA-CAR-T cell therapy [84]. While CEA demonstrates promise as a potential target for the treatment of PC, additional research is imperative to address these aforementioned concerns.

Table 1 Recent completed or ongoing research experiments on CAR-T cell therapy for endocrine cancers

Target antigens	Receptor type (other specificity)	Type of cancer	Country of the study	Author	Year
ERBB2	chA21-ScFV-CD8a-CD28-CD3ζ	Ovarian cancer	China	Meili Sun	2014
CD24	ScFV-CD28–4–1BB-CD3ζ	Ovarian cancer	Germany	Rüdiger Klapdor	2019
TAG72	ScFV–4–1BB-CD3ζ	Ovarian cancer	USA	John P. Murad	2018
EpCAM	ScFV-CD8a-CD8-CD28–4–1BB-CD3ζ	Ovarian cancer	China	Juan FU	2020
MSLN	ScFV–4–1BB-CD3ζ	Ovarian cancer	China		2021
TM4SF1	ScFV-CD8-CD28–4–1BB-CD3ζ	Ovarian cancer	China	Yijie Shen	2023
CLDN18.2	ScFV-CD8a–4–1BB-CD3ζ	Pancreatic cancer	China	Changsong Qi	2022
CEA	SCA431scFv-IgG1-CD4-CD28-CD3ζ	Pancreatic cancer	Germany	Markus Chmielewski	2012
MUC1	ScFV–4–1BB-CD3ζ	Pancreatic cancer	USA	Posey	2016
Trop2	2F11scFv-CD8–4–1BB-CD3ζ	Pancreatic cancer	China	Hongjia Zhu	2022
EGFR		Pancreatic cancer	China	Yang Liu	2020
SSEA–4	ScFV-CD28-CD3ζ	Pancreatic cancer	China	Chih-Wei Lin	2021
TSHR	ScFV-CD28–4–1BB-CD3ζ	Thyroid cancer	China	Hanning Li	2021
ICAM–1	ScFV-CD28–4–1BB-CD3ζ	Thyroid cancer	USA	Irene M. Min	2017
GFRa4	ScFV-CD137-CD3ζ	Thyroid cancer	USA	Vijay G. Bhoj	2020

EGFR

Epidermal growth factor receptor (EGFR) is expressed in roughly 70–90% of patients with metastatic PC and is linked to unfavorable prognoses, thereby substantiating its potential as a target for addressing metastatic PC [85–88]. Liu et al. [89] conducted a Phase I clinical trial to evaluate the safety and efficacy of autologous CAR-T cells targeting anti-EGFR (EGFR-CAR-T) in patients afflicted with metastatic PC. Their findings demonstrated that anti-EGFR-CAR-T cells not only displayed specific antitumor activity but also successfully infiltrated tumor tissues. This study provided evidence showcasing the safety and efficacy of CAR-T cell therapy targeting EGFR in patients dealing with metastatic PC.

Trop2

Tumor-associated calcium signal transducer 2 (Trop2), also designated as TACSTD2, is a member of the TACSTD family [90]. Trop2 is extensively overexpressed as a tumor-associated antigen in diverse cancers, positioning it as a promising target for the immunotherapy of PC. Zhu et al. [91] engineered CAR-T cells featuring a fully human scFv specifically targeting Trop2. These CAR-T cells exhibited both substantial expansion and selective cytotoxicity against Trop2-positive PC cell lines in vitro settings, alongside the secretion of elevated levels of cytotoxic cytokines. Furthermore, they demonstrated sustained circulation, transient expansion within tumor tissues, and the substantial inhibition or eradication of pancreatic tumor xenografts in mice. These findings propose that CAR-T cells equipped with a fully human scFv targeting Trop2 hold promise as a prospective strategy for treating PC.

MUC1

Mucin 1 (MUC1) is a transmembrane glycoprotein expressed on the apical surface of epithelial cells and has been designated as the second-largest target antigen by the National Cancer Institute [92]. Its overexpression in roughly 90% of PDAC patients suggests its potential as a diagnostic, prognostic, and therapeutic marker for PDAC [84]. Table 1 is an innovative monoclonal antibody with selective affinity for tumor-associated MUC1 (tMUC1), while sparing recognition of the normal MUC1 form [93, 94]. Yazdanifar et al. [95] engineered CAR-T cells targeting anti-tMUC1 using the highly specific Table 1 and demonstrated that these CAR-T cells effectively restrained the growth of pancreatic tumors. While

many PDAC tumor cells can be effectively destroyed by CAR-T cells, there are still some PDAC tumor cells that exhibit high levels of drug resistance. This is not surprising, as PDAC is known to be immunoresistant and difficult to treat. Thus, while the MUC1 antigen presents substantial potential for CAR-T cell therapy in PDAC, a deeper understanding of mechanisms underlying PDAC immune resistance is imperative to enhance treatment safety and efficacy.

CLDN18. 2

Claudin18. 2 (CLDN18. 2) is a gastric-specific membrane protein that, together with occludin, forms a critical component of tight junctions. It is notably elevated in malignant tumors, including PDAC [96, 97]. Liu et al. [98] have developed CAR-T cells targeting CLDN18. 2, which were found to recognize tight junction proteins highly expressed in PDAC and exhibit anti-tumor effects. Moreover, preliminary data from a Phase I clinical trial (NCT03874897) suggest that CLDN18. 2-CAR-T cells are safe and demonstrate some anti-tumor activity in advanced gastrointestinal tumors, including PDAC [99]. These studies indicate that CLDN18. 2-CAR-T cells could show certain effectiveness in the treatment of PDAC.

TSHR

The thyroid-stimulating hormone receptor (TSHR) is a transmembrane glycoprotein receptor situated on chromosome 14q31, constituting a member of the G protein-coupled receptor subfamily [100]. TSHR is persistently elevated in a majority of differentiated thyroid cancers (DTCs), with expressions of 90. 8% in papillary thyroid carcinoma (PTC), 89. 2% in follicular thyroid carcinoma (FTC), 78. 2% in neck lymph node metastases, and 86. 7% in radioactive iodine-refractory (RAI-R) disease. These attributes underscore the potential of TSHR as a viable target for CAR-based therapy in thyroid carcinoma [100, 101]. Zhou et al. [102] engineered a TSHR-targeting CAR-T cell using second-generation CAR technology and substantiated its viability for addressing TSHR-positive TCs through in vitro experiments. Li et al. [103] additionally demonstrated the safety and effectiveness of TSHR-CAR-T cell therapy in both in vitro and in vivo settings. The findings revealed its capacity to proficiently eradicate TSHR-positive DTC tumor cells in vitro and xenograft models, all while not provoking substantial toxicity. Moreover, Ding et al. [104] employed TSHR + CD19-CAR-T therapy in a patient with relapsed and refractory TC, employing a fusion of second-generation CAR constructs targeting both TSHR and CD19. They noted substantial expansion of antitumor CAR-T cells in the patient, resulting in partial remission within three months and well-tolerated effects. These observations posit CAR-T therapy as a conceivable strategy for managing relapsed and refractory TC.

GFRa4

Glial cell-derived neurotrophic factor (GDNF) family receptor alpha 4 (GFRa4) has been posited as a prospective antigen target for CAR-based therapy in metastatic medullary thyroid carcinoma (MTC) [105]. Vijay et al. [106] discovered significant expression of GFRa4 in metastatic MTC, thyroid parafollicular cells derived from MTC, and the normal thymus. They isolated two scFv targeting GFRa4 subtypes a and b via antibody phage display. Subsequently, they constructed a CAR incorporating CD3ζ and CD137 co-stimulatory domains, engineered to target GFRa4. This CAR-T immunotherapy, aimed at GFRa4, exhibited cytotoxicity, cytokine production, and substantial therapeutic impact against tumors derived from metastatic MTC TT cell lines in vitro, as well as in xenograft models of immunodeficient mice. In summary, this investigation has recognized and validated GFRa4 as a promising and validated therapeutic target for treating metastatic MTC.

ICAM1

Intercellular adhesion molecule 1 (ICAM1, CD54) is a cell surface glycoprotein belonging to the immunoglobulin superfamily. Its expression can be induced by cytokines [107]. ICAM-1 RNA and protein expression levels correlate positively with the invasive capacity of TC [108, 109], thereby rendering it a conceivable biomarker and intervention target for TC treatment. Min et al. formulated a third-generation CAR targeting ICAM-1, resulting in ICAM-1-CAR-T cells that displayed robust cytotoxicity against cell lines of PTC and anaplastic thyroid carcinoma (ATC) in vitro. Furthermore, notable therapeutic outcomes were witnessed in an animal model harboring tumors derived from ATC patients [110]. Additionally, they noted that sustained ICAM-1 expression on tumor cells heightened their susceptibility to destruction mediated by CAR-T cells [111]. Subsequently, Vedvyas et al. [112] designed CAR-T cells targeting ICAM1 that displayed specificity against TC tumor cells. Their findings indicated that tumors showing elevated ICAM-1 expression within or proximate to tumor tissues could potentially be more receptive to CAR-T cell-mediated elimination, facilitated by T-cell cytokines such as IFN-γ inducing ICAM-1 expression.

Challenges in CAR-T cell therapy

Although CAR-T cell therapy has proven effective in hematologic malignancies and demonstrated relative success in preclinical investigations of certain solid cancers, several challenges remain in the context of treating endocrine cancers. These challenges encompass issues such as

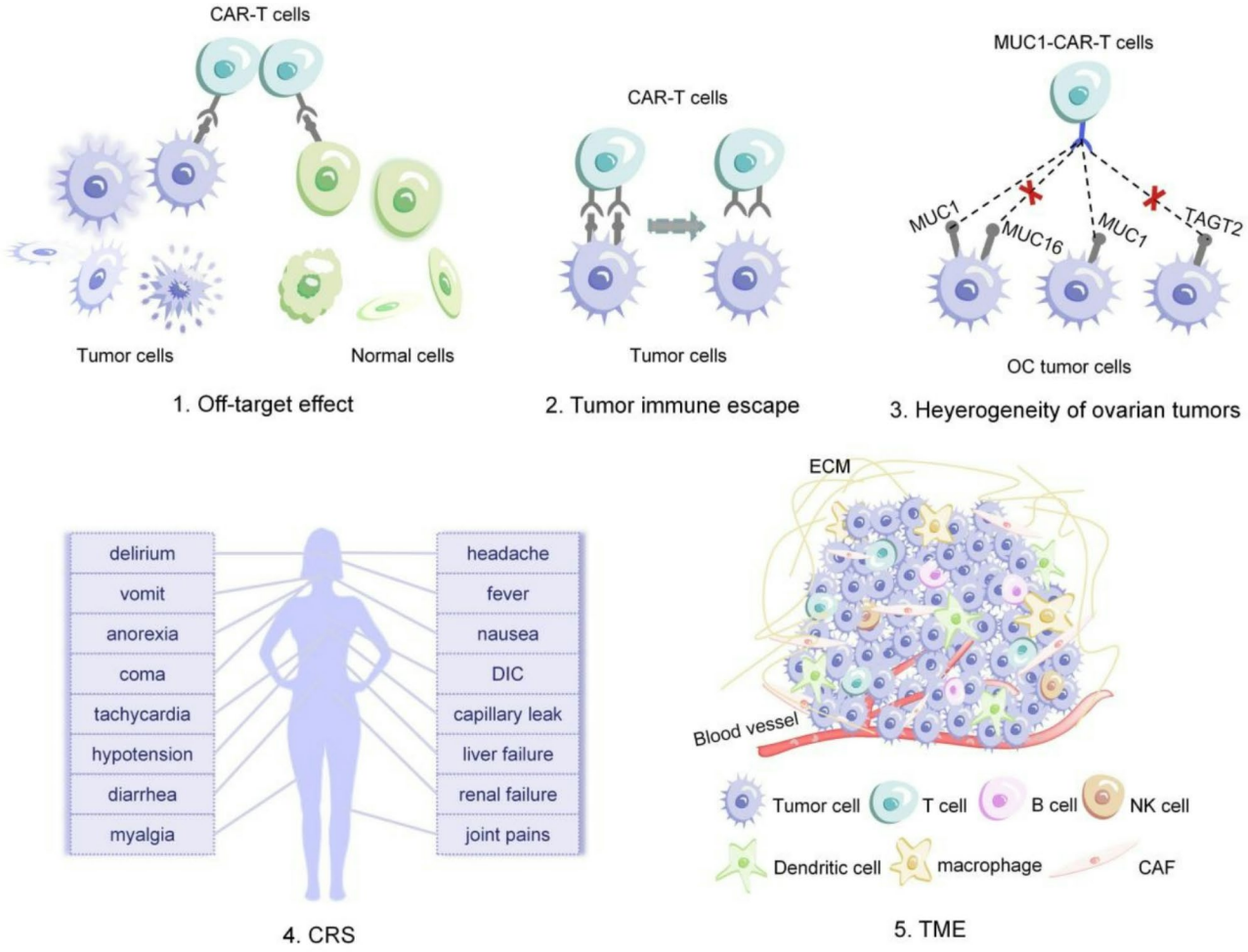

Fig. 4 The figure illustrates the main challenges associated with CAR-T cell therapy for various endocrine cancers. These challenges include off-target effects, tumor antigen escape, tumor heterogeneity, cytokine release syndrome, and the immunosuppressive tumor microenvironment (TME)

off-target effects, tumor antigen escape, tumor heterogeneity, cytokine release syndrome, and the presence of an immunosuppressive TME, as illustrated in Fig. 4.

Off-target effects

The optimal target for CAR-T cell therapy should exclusively reside on tumor cells, enabling CAR-T cells to efficiently recognize and eliminate them. As a result, when both tumor and non-tumor tissues harbor the target cells, CAR-T cells may inadvertently eradicate normal cells alongside tumor cells. This situation heightens the potential for immune-mediated toxicity [59]. This phenomenon represents an off-target effect. For instance, since MSLN is expressed in both tumor cells and certain normal tissues, such as the pleura and peritoneum, CAR-T cells targeting MSLN may trigger off-target effects that negatively impact healthy tissues [113]. Furthermore, due to the limited availability of accessible TSAs, the TAAs currently employed in CAR-T cell therapy predominantly derive from overexpressed endogenous cell surface proteins. This overlap in antigen expression can lead CAR-T cells to inadvertently recognize the same antigens present on healthy tissues, resulting in off-target toxicity [114]. Therefore, if the target protein of CAR-T cells is expressed in normal epithelial cells, it could lead to severe consequences [115].

Tumor immune escape

The effectiveness of CAR-T cell therapy for solid tumors is suboptimal, primarily attributed to immune evasion mechanisms within the TME of solid tumors [116]. Within the realm of solid tumors, heightened expression of immune checkpoints dampens T cell immune responses [117], thereby facilitating tumor cell proliferation, invasion, and metastasis—a phenomenon termed immune evasion. Engineered T cells, including CAR-T cells, are also susceptible to immune checkpoint blockade, particularly via the PD-1/PD-L1 pathway [118, 119]. This results in compromised T cell expansion and persistence, leading to either weak or no response to CAR-T

cell therapy in patients [120, 121]. Nonetheless, immune evasion instigated by the TME is an inevitable occurrence within the body [122]. Consequently, guided by the mechanisms of tumor antigen evasion, investigators have delved into diverse strategies to thwart immune evasion. These strategies encompass bispecific CAR-T cells, tandem CAR-T cells, combinatorial drug therapy with CAR-T cells, and co-transduced CAR-T cells [35].

Tumor heterogeneity

Following the eradication of antigen-positive target cells, the intrinsic heterogeneity of tumors permits the unabated proliferation of antigen-negative tumor cells [123]. The heterogeneity in the expression of tumor antigens stands as a noteworthy concern across all CAR-T cell-based cancer therapies, representing a pivotal impediment to effective CAR-T cell function within solid tumors [124]. As an illustration, the scrutiny of MUC1, MUC16, and TAG72 expression in diverse subtypes of patient samples with OC accentuates the antigenic heterogeneity inherent to this malady, unveiling aberrant profiles of cell surface glycoprotein expression [79]. This makes it challenging for a single type of CAR-T cells to effectively kill all tumor cells, leading to issues in selecting TSAs. This difficulty also poses a limiting obstacle to the specificity and widespread application of CAR-T cells.

CRS

CRS represents a potential, profoundly systemic toxicity reaction that emerges subsequent to CAR-T cell therapy. CRS is incited by the activation and proliferation of T cells, leading to heightened circulating levels of cytokines, encompassing C-reactive protein, interleukin-6 (IL-6), and interferon-gamma [3]. Swift escalation of cytokine levels can prompt mild manifestations in CRS patients, encompassing fever, fatigue, headache, rash, and joint pain, alongside pronounced symptoms such as systemic inflammatory response, shock, multi-organ failure, vascular leakage, disseminated intravascular coagulation, and potentially mortality. Consequently, CRS assumes substantial prominence, demanding adept teams for recurrent patient monitoring within intensive care units [125, 126].

Immunosuppressive nature of TME

The immunosuppressive nature of the TME, particularly in the case of PC [127], stands as a paramount impediment in CAR-T cell therapy for solid tumors. Mounting evidence underscores the characterization of the TME in PDAC by immune expansion and a suboptimal active matrix, encompassing constituents such as cancer-associated fibroblasts (CAFs), tumor vasculature, immune cells, and extracellular matrix (ECM) [128]. Within these components, CAFs, fundamental constituents of the PDAC TME, emerge as salient and dynamic entities [128]. Abundant studies have consistently showcased the establishment of an adversarial TME by CAFs, aimed at circumventing tumor immunity, which encompasses counteraction against cytotoxic T cell assaults [128–130]. Moreover, CAFs initiate immune crosstalk via the secretion of chemokines and cytokines, disrupting T cell functionality and attracting tumor-associated macrophages (TAMs), regulatory T cells (Tregs), and myeloid-derived suppressor cells (MDSCs) [129, 131]. Furthermore, within the context of immune evasion by PC, the TME assumes a substantial role in constructing immune surveillance barricades and imposing immune inhibitory attributes [127, 132]. This compromises the persistence and function of the transplanted T cells [133–135]. For instance, PDAC is typified by an extensively immunosuppressive TME, which confines T cell infiltration and triggers a deterioration in T cell function, culminating in the arduous survival of CAR-T cells and, consequently, a reduction in their therapeutic efficacy. Additionally, the biochemical attributes of the tumor stroma, encompassing hypoxia, nutrient deficiency, and reduced pH values, impede the chemotactic prowess of CAR-T cells and, as a result, undermine their anti-tumor efficacy [136, 137].

Methods to enhance the efficacy of CAR-T cell therapy

The effectiveness of CAR-T cell therapy is significantly compromised by the immunosuppressive TME and off-target effects. In order to enhance the anti-tumor effectiveness of CAR-T cell therapy, researchers have undertaken various strategies to tackle these challenges. For example, approaches aimed at countering the immunosuppressive TME have been investigated to bolster the survival, migration, and endurance of CAR-T cells in PDAC [138]. Several preclinical investigations grounded in this principle are presently underway. This section will provide an overview of different strategies currently under evaluation in clinical trials, as depicted in Fig. 5.

Multi-antigen targeting CAR-T cells

The advancement of CAR-T cells poses challenges due to their targeting of distinctive antigens present on tumor cells. With the goal of improving target specificity and mitigating immune escape, scientists have developed CAR molecules featuring tandem architectures that simultaneously target two antigens [139]. Both CAR constructs displayed anti-tumor activity without disruption. Moreover, bispecific CAR-T cells have also been formulated. In vitro studies showcased robust cytotoxic impacts of both bispecific and single-specific CAR-T cells against diverse iterations of OVCAR-3 cells, particularly under elevated E/T ratios. Although no notable disparities in

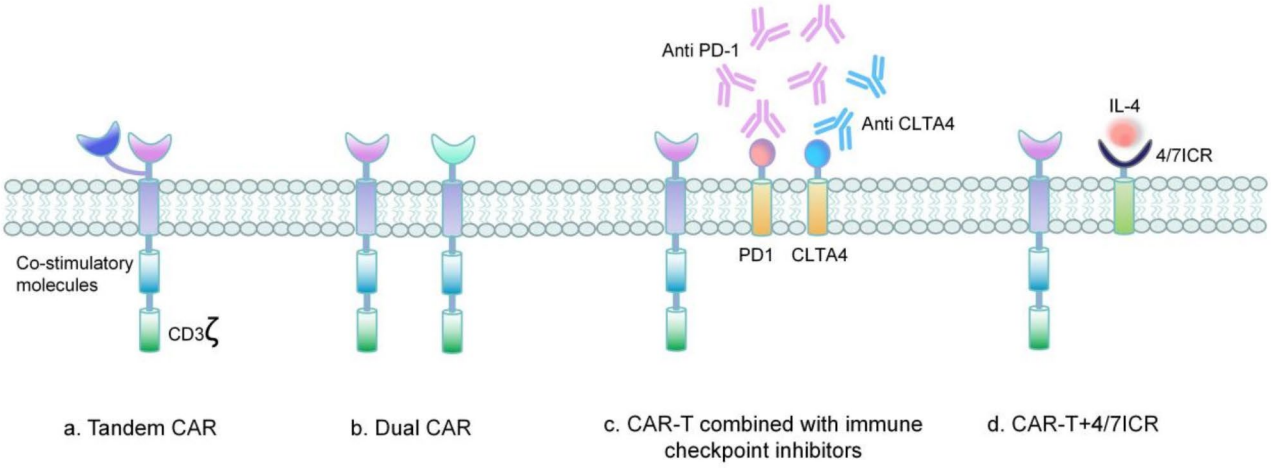

Fig. 5 Enhancing the Efficacy of CAR-T Cell Therapy for Endocrine Cancer. Various strategies have emerged to improve the effectiveness of CAR-T cell therapy. The tandem structure of CAR molecules targeting two antigens can enhance specificity and reduce immune escape. Dual CAR-T cells are anticipated to heighten the specificity of CAR-T therapy. Combined treatment of CAR-T cell therapy with monoclonal antibody immune checkpoint inhibitors holds promise for preserving CAR-T cell functionality in the tumor microenvironment (TME). CAR-T cells expressing inverted cytokine receptors (ICRs) exhibit augmented anti-tumor activity

cytotoxicity and cytokine generation emerged between bispecific and single-specific CAR-T cells, the bispecific CAR-T cells proved incapable of efficiently rousing CAR-T cells or inducing anti-tumor effects upon interaction with each antigen in isolation. This underscores the heightened specificity inherent in CAR-T cell therapy. In summation, methodologies encompassing tandem configurations [140, 141] or bispecific CAR-T cells [122, 142] have been devised to confer heightened and sustained therapeutic responses against profoundly antigenic and heterogeneous tumors.

Combination with checkpoint inhibitors

CAR-T cells can be influenced by suppressive immune checkpoint signals within the TME, including cytotoxic T lymphocyte-associated protein 4 (CTLA-4) and the programmed cell death PD-1 ligand PD-L1. Monoclonal antibodies that target these inhibitory receptors or ligands have the ability to obstruct their interaction, thus alleviating suppression of T-cell activity. For example, ipilimumab, an antibody against CTLA-4, has demonstrated promising outcomes in the treatment of advanced melanoma [143]. Notably, monotherapy employing checkpoint inhibitors has displayed constrained effectiveness in PC; however, the amalgamation with CAR-T cell therapy presents a strategy to overcome these challenges [144]. Because both approaches entail immunotherapies that target tumor cells through distinct mechanisms, the integration of CAR-T cells and checkpoint inhibitors (e.g., anti-PD-1, anti-PD-L1, anti-TIM-3, anti-LAG-3 antibodies, particularly anti-PD-1 antibodies) augments anti-tumor responses by obstructing immune inhibitory functions [145] within the tumor immune system, substantially advancing the efficacy of solid tumor therapy. Numerous preclinical investigations [146–148] have showcased a synergistic impact arising from the combination of CAR-T cell therapy and PD-1 blockade, culminating in extended survival devoid of detrimental repercussions. Gargett et al. [149] communicated that the concurrent application of PD-1 checkpoint inhibitors and CAR-T cells had the potential to magnify patient responses and augment the endurance of CAR-T cells. In addition to these strategies, investigations involving the conjunction of immune checkpoint inhibitors with CAR-T cells targeting mesothelin are currently underway.

Treatment for CRS

CRS represents a systemic inflammatory response, and multiple strategies have been devised to monitor and mitigate this adverse outcome. Therapeutic interventions generally encompass high-dose steroids, respiratory assistance, vasopressors, and administration of anti-IL-6 receptor antibodies (such as tocilizumab), which have demonstrated clinical efficacy in certain patients [150]. In the initial management of CRS, tocilizumab is frequently employed. This humanized monoclonal antibody specifically targets the IL-6 receptor and is administered to ameliorate fever, hypotension, and severe hypoxia; however, its efficacy in reversing neurological effects has not been substantiated [151, 152]. Should CRS persist despite treatment, administering cetuximab becomes a viable option for eradicating CAR-modified T cells. Cetuximab is an FDA-approved drug that targets EGFR and is known for its favorable tolerability and safety profile. Individuals experiencing exacerbation of CRS within a

12-hour period or exhibiting no clinical amelioration within 24 h following cetuximab administration are subjected to intravenous dexamethasone treatment. Due to dexamethasone's robust and non-discriminatory immunosuppressive effects, its application is anticipated to result in the eradication of any remaining CAR-modified T cells following cetuximab therapy [153–155]. Diminished cytokine levels will promote alleviation of CRS symptoms in patients; nevertheless, timely intervention, suitable reversal modalities like tocilizumab or suicide gene triggers embedded in CAR-T cell structures, and a heightened awareness of potential toxicity are imperative [125, 126].

Selection of feasible tumor antigens

The majority of patients with DTC typically undergo total thyroidectomy or near-total thyroidectomy as the primary treatment approach [156]. While thyroid hormone replacement therapy can effectively sustain thyroid function, the scope of antigen selection can be expanded to encompass thyroid-specific proteins that are co-expressed in both normal thyroid tissue and DTC. This expansion goes beyond the realm of TSAs or TAAs. For example, the TSHR, primarily prevalent in normal thyroid follicular epithelial cells, exhibits partial expression in orbital and tibial anterior fibroblasts of certain patients with Graves' disease [157]. In the context of DTC, substantial data have showcased persistent TSHR expression, encompassing findings from PCR [158], ligand binding [159], and immunohistochemistry (IHC) [160]. Hence, TSHR emerges as a viable candidate for targeting by CAR-T cell therapy against DTC.

Overcoming immunosuppression in TME

The immunosuppressive TME hinders the function and persistence of CAR-T cells. To enhance the resilience of CAR-T cells against the TME, a custom-designed inverted cytokine receptor (ICR) can be engineered. This involves combining the extracellular domain of the IL-4 receptor with the intracellular domain of the IL-7 receptor (4/7 ICR). CAR-T cells that express the ICR have demonstrated heightened anti-tumor activity. In addition, other methods have also emerged, including the utilization of gene-modified oncolytic adenoviruses (OAds). These OAds selectively express therapeutic transgenes within the confines of the TME. These viruses locally express therapeutic genes, thereby counteracting tumor-induced immune suppression. This mechanism offers a viable strategy, particularly when used in conjunction with secondary T-cell transfer. An additional strategy to manipulate the TME in support of adoptive T-cell therapy involves locally administering recombinant cytokines. The targeting of FAP with CAR-T cells has been reported as a method to modulate the TME. This approach led to the expansion and activation of native T cells within the tumor tissue [161], resulting in a notable reduction in the abundance of CAFs, ECM content, and vessel density in the stroma of PDAC. As a consequence, PDAC growth was constrained. Nevertheless, the exclusive targeting of FAP using CAR-T cells exhibits limitations, rendering the anti-tumor effect limited or short-lived [161, 162]. The anti-tumor effect can be enhanced through multiple injections of CAR T cells, using CAR T cells lacking diacylglycerol kinase, or in combination with vaccines [162]. A recent study conducted using a glioblastoma model demonstrated that intratumoral administration of IL-12 led to the restructuring of the immunosuppressive TME and a notable increase in CAR-T cell cytotoxicity [71]. Moreover, the concurrent application of gemcitabine and rosiglitazone among PDAC patients resulted in a reduction of tumor progression, metastasis, and an enhancement in overall survival. The introduction of rosiglitazone brought about modifications in tumor-inhibitory mediators, consequently rendering the TME more immunogenic [163]. Likewise, metformin was observed to elevate CD8 + tumor-infiltrating lymphocytes (TILs) within the TME [164]. Hence, the concurrent utilization of CAR-T cell therapy along with rosiglitazone or metformin is anticipated to mitigate the immunosuppressive attributes of the TME and bolster therapeutic effectiveness.

Cellular redirection

To overcome the challenge of inadequate trafficking of CAR-T cells to the TME, multiple studies have implemented targeting strategies to guide these cells towards prominent cell surface molecules linked with PC [138]. For example, the chemokine receptor CCR2 has been effectively introduced into meso-CAR-T cells. When contrasted with conventional CAR-T cells, meso-CAR-T cells demonstrated augmented T-cell infiltration and heightened anti-tumor activity. Likewise, FAP has garnered attention as a prospective target antigen for CAR-T cells. Tran et al. [165] devised an innovative CAR-T cell strategy that steers the cells towards engagement with FAP. Subsequently, these cells were introduced into murine models featuring diverse subcutaneous tumors, encompassing PC. It is noteworthy, however, that this approach could potentially lead to cachexia and fatal bone toxicity, thereby curtailing its applicability as a universally applicable target for CAR-T cell therapy.

Novel fab-CAR design

Conventional CARs consist of a scFv and intracellular signaling domains. Preliminary clinical data indicate the significant potential of conventional CAR-T cells in managing leukemia or lymphoma [64, 114, 166]. Nonetheless, various unknown factors underlie the relatively limited ability of conventional CAR-T cells to elicit

comprehensive tumor responses and the emergence of off-target effects [167–170]. A plausible explanation for these unsatisfactory outcomes might be the relatively modest affinity of scFv and swift decline in peripheral blood CAR-T cells after administration. To surmount these challenges, Duan et al. engineered an innovative CAR by combining antibody Fab fragments with intrinsic TCRsignaling domains [171]. Data indicate that T cells expressing membrane-bound Fab-CARs efficiently eliminate tumor cells while consistently releasing cytokines such as IL-2 and IFN-γ. This enhanced efficacy is attributed to the superior stability and affinity of Fab fragments compared to single-chain variable fragments (scFv). By employing Fab in place of scFv, we can effectively mitigate issues related to scFv aggregation while preserving robust antigen recognition. Consequently, the innovative Fab-CAR has the capability to recognize MHC-independent tumor antigens, extend the longevity of CAR-T cells, and yield enduring clinical effects.

iPSC-derived CAR-T cells

CAR-T cell therapy has become an important approach for treating certain cancers. However, traditional sources of CAR-T cells, such as peripheral blood T cells, often face issues like TCR-mediated autoimmune responses and functional instability [172]. Induced pluripotent stem (iPS) cells, due to their unlimited proliferation and pluripotency, have emerged as a new research direction for generating specific types of CAR-T cells [173]. Currently, research teams have successfully generated CAR-T cells that lack TCR but express CD8αβ by utilizing iPS cells, employing precise gene editing techniques to remove the TCR gene and specific cell differentiation strategies. The modified CAR-T cells demonstrated good proliferation capacity and anti-tumor effects [174]. iPS cells provide new ideas and methods for the research and development of CAR-T cells, with the potential to enhance the efficacy and safety of CAR-T therapies in the future, thereby promoting the advancement of precision medicine.

Conclusion

The remarkable outcomes of CAR-T cell therapy in hematological malignancies and the promising initial results in endocrine tumors, such as PC, OC, and TC, have catalyzed numerous clinical trials in these medical conditions. CAR-T cell therapy introduces a novel avenue for treating endocrine cancers, providing a viable alternative for diverse treatment-resistant endocrine tumors. Nonetheless, owing to the intricacy of human physiology and the existence of multiple unidentified variables, hurdles such as the absence of appropriate CAR-T cell targets, tumor antigen evasion, immunosuppressive cells within the TME, and off-target effects impede the effectiveness of endocrine cancer treatment. Enhanced comprehension of the TME, enhanced approaches to mitigate off-target effects of CAR-T cell therapy, analysis of the underlying causes of monotherapy immunotherapy shortcomings, and integration of novel drugs with CAR-T cell therapy hold the potential to bolster the effectiveness of endocrine cancer treatment. The expansion of CAR-T cell therapy into the realm of endocrine cancers is in its nascent stages, marked by swift advancements in this domain. We maintain an optimistic perspective that in the imminent future, CAR-T cell therapy, whether as standalone therapy or in combination, will ameliorate the prognosis and survival of individuals afflicted by endocrine cancers.

Acknowledgements

Thanks are due to Huiling Qu and Wenwu Dong for valuable discussion.

Author contributions

All the authors materially participated in this work; have read and approved the final manuscript. RY is the first authors for this study. WD is the corresponding author supervising this work. RY, XJ and PZ performed analysis on all data interpretation from literature review. RY, HZ and WD reviewed the manuscript. We acknowledge that all authors participated sufficiently in the work and take public responsibility for its content.

Funding

No specific funding source was used in this study.

Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethical approval

This article does not contain any studies with human participants or animals performed by any of the authors.

Consent for publication

All authors read and approved the final manuscript for publication.

Competing interests

The authors declare no competing interests.

Received: 20 December 2024 / Accepted: 7 March 2025
Published online: 22 April 2025

References

1. Correa P, Chen VW. Endocrine gland cancer. Cancer. 1995;75:338–52.
2. Geurts JL, Strong EA, Wang TS, Evans DB, Clarke CN. Screening guidelines and recommendations for patients at high risk of developing endocrine cancers. J Surg Oncol. 2020;121:975–83.
3. Yan W, Hu H, Tang B. Advances of chimeric antigen receptor T cell therapy in ovarian Cancer. Onco Targets Ther. 2019;12:8015–22.
4. Webb PM, Jordan SJ. Epidemiology of epithelial ovarian cancer. Best Pract Res Clin Obstet Gynaecol. 2017;41:3–14.
5. Wedig J, Jasani S, Mukherjee D, et al. CD200 is overexpressed in the pancreatic tumor microenvironment and predictive of overall survival. Cancer Immunol Immunother. 2024;73:96.
6. Zhang F, Xu Y, Ye W, Jiang J, Wu C. Circular RNA S-7 promotes ovarian cancer EMT via sponging miR-641 to up-regulate ZEB1 and MDM2. Biosci Rep 2020;40.
7. Malaguarnera R, Morcavallo A, Giuliano S, Belfiore A. Thyroid cancer development and progression: emerging role of cancer stem cells. Minerva Endocrinol (Torino). 2012;37:103–15.

8. Yu WD, Sun G, Li J, Xu J, Wang X. Mechanisms and therapeutic potentials of cancer immunotherapy in combination with radiotherapy and/or chemotherapy. Cancer Lett. 2019;452:66–70.
9. Dagogo-Jack I, Shaw AT. Tumour heterogeneity and resistance to cancer therapies. Nat Rev Clin Oncol. 2018;15:81–94.
10. Yan L, Liu B. Critical factors in chimeric antigen receptor-modified T-cell (CAR-T) therapy for solid tumors. Onco Targets Ther. 2019;12:193–204.
11. Wright JJ, Powers AC, Johnson DB. Endocrine toxicities of immune checkpoint inhibitors. Nat Rev Endocrinol. 2021;17:389–99.
12. Boon T, Cerottini JC, Van den Eynde B, van der Bruggen P, Van Pel A. Tumor antigens recognized by T lymphocytes. Annu Rev Immunol. 1994;12:337–65.
13. van der Bruggen P, Traversari C, Chomez P, et al. A gene encoding an antigen recognized by cytolytic T lymphocytes on a human melanoma. Science. 1991;254:1643–7.
14. Yang JC, Rosenberg SA. Adoptive T-Cell therapy for Cancer. Adv Immunol. 2016;130:279–94.
15. Met Ö, Jensen KM, Chamberlain CA, Donia M, Svane IM. Principles of adoptive T cell therapy in cancer. Semin Immunopathol. 2019;41:49–58.
16. Sadelain M, Brentjens R, Rivière I. The basic principles of chimeric antigen receptor design. Cancer Discov. 2013;3:388–98.
17. Geldres C, Savoldo B, Dotti G. Chimeric antigen receptor-redirected T cells return to the bench. Semin Immunol. 2016;28:3–9.
18. Zhang C, Liu J, Zhong JF, Zhang X. Engineering CAR-T cells. Biomark Res. 2017;5:22.
19. Mazinani M, Rahbarizadeh F. CAR-T cell potency: from structural elements to vector backbone components. Biomark Res. 2022;10:70.
20. Frigault MJ, Lee J, Basil MC, et al. Identification of chimeric antigen receptors that mediate constitutive or inducible proliferation of T cells. Cancer Immunol Res. 2015;3:356–67.
21. Guedan S, Chen X, Madar A, et al. ICOS-based chimeric antigen receptors program bipolar TH17/TH1 cells. Blood. 2014;124:1070–80.
22. Guedan S, Posey AJ, Shaw C et al. Enhancing CAR T cell persistence through ICOS and 4-1BB costimulation. JCI Insight 2018;3.
23. Knochelmann HM, Smith AS, Dwyer CJ, Wyatt MM, Mehrotra S, Paulos CM. CAR T cells in solid tumors: blueprints for Building effective therapies. Front Immunol. 2018;9:1740.
24. Shen CJ, Yang YX, Han EQ, et al. Chimeric antigen receptor containing ICOS signaling domain mediates specific and efficient antitumor effect of T cells against EGFRvIII expressing glioma. J Hematol Oncol. 2013;6:33.
25. Zhang H, Snyder KM, Suhoski MM, et al. 4-1BB is superior to CD28 costimulation for generating CD8+cytotoxic lymphocytes for adoptive immunotherapy. J Immunol. 2007;179:4910–8.
26. Chen H, Wei F, Yin M, et al. CD27 enhances the killing effect of CAR T cells targeting trophoblast cell surface antigen 2 in the treatment of solid tumors. Cancer Immunol Immunother. 2021;70:2059–71.
27. Chacon JA, Wu RC, Sukhumalchandra P, et al. Co-stimulation through 4-1BB/CD137 improves the expansion and function of CD8(+) melanoma tumor-infiltrating lymphocytes for adoptive T-cell therapy. PLoS ONE. 2013;8:e60031.
28. Zuccolotto G, Penna A, Fracasso G, et al. PSMA-Specific CAR-Engineered T cells for prostate cancer: CD28 outperforms combined CD28-4-1BB Super-Stimulation. Front Oncol. 2021;11:708073.
29. Abreu TR, Fonseca NA, Gonçalves N, Moreira JN. Current challenges and emerging opportunities of CAR-T cell therapies. J Control Release. 2020;319:246–61.
30. Kagoya Y, Tanaka S, Guo T, et al. A novel chimeric antigen receptor containing a JAK-STAT signaling domain mediates superior antitumor effects. Nat Med. 2018;24:352–9.
31. Siddiqi HF, Staser KW, Nambudiri VE. Research techniques made simple: CAR T-Cell therapy. J Invest Dermatol. 2018;138:2501–4.
32. Kim DW, Cho JY. Recent advances in allogeneic CAR-T cells. Biomolecules 2020;10.
33. Luangwattananun P, Junking M, Sujjitjoon J, et al. Fourth-generation chimeric antigen receptor T cells targeting folate receptor alpha antigen expressed on breast cancer cells for adoptive T cell therapy. Breast Cancer Res Treat. 2021;186:25–36.
34. Lv Z, Luo F, Chu Y. Strategies for overcoming bottlenecks in allogeneic CAR-T cell therapy. Front Immunol. 2023;14:1199145.
35. Zhang XW, Wu YS, Xu TM, Cui MH. CAR-T cells in the treatment of ovarian cancer: A promising cell therapy. Biomolecules 2023;13.
36. Conroy T, Desseigne F, Ychou M, et al. FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer. N Engl J Med. 2011;364:1817–25.
37. Jindal V, Arora E, Masab M, Gupta S. Chimeric antigen receptor T cell therapy in pancreatic cancer: from research to practice. Med Oncol. 2018;35:84.
38. Brudno JN, Kochenderfer JN. Chimeric antigen receptor T-cell therapies for lymphoma. Nat Rev Clin Oncol. 2018;15:31–46.
39. Yasukawa M, Ohminami H, Arai J, Kasahara Y, Ishida Y, Fujita S. Granule exocytosis, and not the Fas/fas ligand system, is the main pathway of cytotoxicity mediated by alloantigen-specific CD4(+) as well as CD8(+) cytotoxic T lymphocytes in humans. Blood. 2000;95:2352–5.
40. Hombach A, Köhler H, Rappl G, Abken H. Human CD4 + T cells lyse target cells via granzyme/perforin upon circumvention of MHC class II restriction by an antibody-like immunoreceptor. J Immunol. 2006;177:5668–75.
41. Silbert S, Yanik GA, Shuman AG. How should we determine the value of CAR T-Cell therapy?? AMA J Ethics. 2019;21:E844–51.
42. June CH, Sadelain M. Chimeric antigen receptor therapy. N Engl J Med. 2018;379:64–73.
43. Ma S, Li X, Wang X, et al. Current progress in CAR-T cell therapy for solid tumors. Int J Biol Sci. 2019;15:2548–60.
44. Cho HR, Choi HS. Effects of anticoagulant from Spirodela polyrhiza in rats. Biosci Biotechnol Biochem. 2003;67:881–3.
45. Sun M, Shi H, Liu C, Liu J, Liu X, Sun Y. Construction and evaluation of a novel humanized HER2-specific chimeric receptor. Breast Cancer Res. 2014;16:R61.
46. Nam AR, Kim JW, Cha Y, et al. Therapeutic implication of HER2 in advanced biliary tract cancer. Oncotarget. 2016;7:58007–21.
47. Zhang Z, Oyesanya RA, Campbell DJ, Almenara JA, Dewitt JL, Sirica AE. Preclinical assessment of simultaneous targeting of epidermal growth factor receptor (ErbB1) and ErbB2 as a strategy for cholangiocarcinoma therapy. Hepatology. 2010;52:975–86.
48. Yan M, Schwaederle M, Arguello D, Millis SZ, Gatalica Z, Kurzrock R. HER2 expression status in diverse cancers: review of results from 37,992 patients. Cancer Metastasis Rev. 2015;34:157–64.
49. Maliar A, Servais C, Waks T, et al. Redirected T cells that target pancreatic adenocarcinoma antigens eliminate tumors and metastases in mice. Gastroenterology. 2012;143:1375–84.
50. Chang K, Pastan I. Molecular cloning of mesothelin, a differentiation antigen present on mesothelium, mesotheliomas, and ovarian cancers. Proc Natl Acad Sci U S A. 1996;93:136–40.
51. Morello A, Sadelain M, Adusumilli PS. Mesothelin-Targeted cars: driving T cells to solid tumors. Cancer Discov. 2016;6:133–46.
52. Argani P, Iacobuzio-Donahue C, Ryu B, et al. Mesothelin is overexpressed in the vast majority of ductal adenocarcinomas of the pancreas: identification of a new pancreatic cancer marker by serial analysis of gene expression (SAGE). Clin Cancer Res. 2001;7:3862–8.
53. Pastan I, Hassan R. Discovery of mesothelin and exploiting it as a target for immunotherapy. Cancer Res. 2014;74:2907–12.
54. Schoutrop E, El-Serafi I, Poiret T, et al. Mesothelin-Specific CAR T cells target ovarian Cancer. Cancer Res. 2021;81:3022–35.
55. Zhang Q, Liu G, Liu J, et al. The antitumor capacity of mesothelin-CAR-T cells in targeting solid tumors in mice. Mol Ther Oncolytics. 2021;20:556–68.
56. Chen J, Hu J, Gu L, et al. Anti-mesothelin CAR-T immunotherapy in patients with ovarian cancer. Cancer Immunol Immunother. 2023;72:409–25.
57. Beatty GL, O'Hara MH, Lacey SF, et al. Activity of Mesothelin-Specific chimeric antigen receptor T cells against pancreatic carcinoma metastases in a phase 1 trial. Gastroenterology. 2018;155:29–32.
58. Felder M, Kapur A, Gonzalez-Bosquet J, et al. MUC16 (CA125): tumor biomarker to cancer therapy, a work in progress. Mol Cancer. 2014;13:129.
59. Varghese AM. Chimeric antigen receptor (CAR) T and other T cell strategies for pancreas adenocarcinoma. Chin Clin Oncol. 2017;6:66.
60. Chekmasova AA, Rao TD, Nikhamin Y, et al. Successful eradication of established peritoneal ovarian tumors in SCID-Beige mice following adoptive transfer of T cells genetically targeted to the MUC16 antigen. Clin Cancer Res. 2010;16:3594–606.
61. Koneru M, Purdon TJ, Spriggs D, Koneru S, Brentjens RJ. IL-12 secreting tumor-targeted chimeric antigen receptor T cells eradicate ovarian tumors in vivo. Oncoimmunology. 2015;4:e994446.
62. Huang L, Yang Y, Yang F, et al. Functions of EpCAM in physiological processes and diseases (Review). Int J Mol Med. 2018;42:1771–85.
63. Spizzo G, Went P, Dirnhofer S, et al. Overexpression of epithelial cell adhesion molecule (Ep-CAM) is an independent prognostic marker for reduced survival of patients with epithelial ovarian cancer. Gynecol Oncol. 2006;103:483–8.
64. Dalerba P, Dylla SJ, Park IK, et al. Phenotypic characterization of human colorectal cancer stem cells. Proc Natl Acad Sci U S A. 2007;104:10158–63.

65. Herlyn M, Steplewski Z, Herlyn D, Koprowski H. Colorectal carcinoma-specific antigen: detection by means of monoclonal antibodies. Proc Natl Acad Sci U S A. 1979;76:1438–42.
66. Maetzel D, Denzel S, Mack B, et al. Nuclear signalling by tumour-associated antigen EpCAM. Nat Cell Biol. 2009;11:162–71.
67. Fu J, Shang Y, Qian Z, et al. Chimeric antigen receptor-T (CAR-T) cells targeting epithelial cell adhesion molecule (EpCAM) can inhibit tumor growth in ovarian cancer mouse model. J Vet Med Sci. 2021;83:241–7.
68. Matsunaga Y, Yamaoka T, Ohba M et al. Novel Anti-FOLR1 Antibody-Drug conjugate MORAb-202 in breast Cancer and Non-Small cell lung Cancer cells. Antibodies (Basel) 2021;10.
69. Kurosaki A, Hasegawa K, Kato T, et al. Serum folate receptor alpha as a biomarker for ovarian cancer: implications for diagnosis, prognosis and predicting its local tumor expression. Int J Cancer. 2016;138:1994–2002.
70. Zuo S, Wen Y, Panha H, et al. Modification of cytokine-induced killer cells with folate receptor alpha (FRα)-specific chimeric antigen receptors enhances their antitumor immunity toward FRα-positive ovarian cancers. Mol Immunol. 2017;85:293–304.
71. Liang Z, Dong J, Yang N, et al. Tandem CAR-T cells targeting FOLR1 and MSLN enhance the antitumor effects in ovarian cancer. Int J Biol Sci. 2021;17:4365–76.
72. Owens GL, Sheard VE, Kalaitsidou M, et al. Preclinical assessment of CAR T-Cell therapy targeting the tumor antigen 5T4 in ovarian Cancer. J Immunother. 2018;41:130–40.
73. Guo C, Dong E, Lai Q et al. Effective antitumor activity of 5T4-specific CAR-T cells against ovarian cancer cells in vitro and xenotransplanted tumors in vivo. MedComm (2020) 2020;1:338– 50.
74. Shah MM, Landen CN. Ovarian cancer stem cells: are they real and why are they important? Gynecol Oncol. 2014;132:483–9.
75. Garson K, Vanderhyden BC. Epithelial ovarian cancer stem cells: underlying complexity of a simple paradigm. Reproduction. 2015;149:R59–70.
76. Burgos-Ojeda D, Rueda BR, Buckanovich RJ. Ovarian cancer stem cell markers: prognostic and therapeutic implications. Cancer Lett. 2012;322:1–7.
77. Klapdor R, Wang S, Morgan M et al. Characterization of a novel Third-Generation Anti-CD24-CAR against ovarian Cancer. Int J Mol Sci 2019;20.
78. Chauhan SC, Vinayek N, Maher DM, et al. Combined staining of TAG-72, MUC1, and CA125 improves labeling sensitivity in ovarian cancer: antigens for multi-targeted antibody-guided therapy. J Histochem Cytochem. 2007;55:867–75.
79. Murad JP, Kozlowska AK, Lee HJ, et al. Effective targeting of TAG72(+) peritoneal ovarian tumors via regional delivery of CAR-Engineered T cells. Front Immunol. 2018;9:2268.
80. Gao C, Yao H, Liu H, Feng Y, Yang Z. TM4SF1 is a potential target for anti-invasion and metastasis in ovarian cancer. BMC Cancer. 2019;19:237.
81. Shen Y, Liu G, Zhang Q, Tian X, Ouyang L, Zhang L. Construction of CAR-T cells targeting TM4SF1 and its anti-tumor capacity in ovarian cancer. Immunol Lett. 2023;255:1–9.
82. Li T, Li H, Li S, et al. Research progress and design optimization of CAR-T therapy for pancreatic ductal adenocarcinoma. Cancer Med. 2019;8:5223–31.
83. Chmielewski M, Hahn O, Rappl G, et al. T cells that target carcinoembryonic antigen eradicate orthotopic pancreatic carcinomas without inducing autoimmune colitis in mice. Gastroenterology. 2012;143:1095–107.
84. Gilham DE, Anderson J, Bridgeman JS et al. Adoptive T-cell therapy for cancer in the United kingdom: a review of activity for the British Society of Gene and Cell Therapy annual meeting 2015. Hum Gene Ther. 2015;26:276– 85.
85. Xiong HQ, Rosenberg A, LoBuglio A, et al. Cetuximab, a monoclonal antibody targeting the epidermal growth factor receptor, in combination with gemcitabine for advanced pancreatic cancer: a multicenter phase II trial. J Clin Oncol. 2004;22:2610–6.
86. Cascinu S, Berardi R, Labianca R, et al. Cetuximab plus gemcitabine and cisplatin compared with gemcitabine and cisplatin alone in patients with advanced pancreatic cancer: a randomised, multicentre, phase II trial. Lancet Oncol. 2008;9:39–44.
87. Fjällskog ML, Lejonklou MH, Oberg KE, Eriksson BK, Janson ET. Expression of molecular targets for tyrosine kinase receptor antagonists in malignant endocrine pancreatic tumors. Clin Cancer Res. 2003;9:1469–73.
88. Ueda S, Ogata S, Tsuda H, et al. The correlation between cytoplasmic overexpression of epidermal growth factor receptor and tumor aggressiveness: poor prognosis in patients with pancreatic ductal adenocarcinoma. Pancreas. 2004;29:e1–8.
89. Liu Y, Guo Y, Wu Z, et al. Anti-EGFR chimeric antigen receptor-modified T cells in metastatic pancreatic carcinoma: A phase I clinical trial. Cytotherapy. 2020;22:573–80.
90. Lenárt S, Lenárt P, Šmarda J, Remšík J, Souček K, Beneš P. Trop2: Jack of all trades, master of none. Cancers (Basel) 2020;12.
91. Zhu H, Fang X, Tuhin IJ, et al. CAR T cells equipped with a fully human ScFv targeting Trop2 can be used to treat pancreatic cancer. J Cancer Res Clin Oncol. 2022;148:2261–74.
92. Cheever MA, Allison JP, Ferris AS, et al. The prioritization of cancer antigens: a National cancer Institute pilot project for the acceleration of translational research. Clin Cancer Res. 2009;15:5323–37.
93. Roy LD, Dillon LM, Zhou R, et al. A tumor specific antibody to aid breast cancer screening in women with dense breast tissue. Genes Cancer. 2017;8:536–49.
94. Moore LJ, Roy LD, Zhou R, et al. Antibody-Guided in vivo imaging for early detection of mammary gland tumors. Transl Oncol. 2016;9:295–305.
95. Yazdanifar M, Zhou R, Grover P et al. Overcoming immunological resistance enhances the efficacy of A novel Anti-tMUC1-CAR T cell treatment against pancreatic ductal adenocarcinoma. Cells 2019;8.
96. Niimi T, Nagashima K, Ward JM, et al. claudin-18, a novel downstream target gene for the T/EBP/NKX2.1 homeodomain transcription factor, encodes lung- and stomach-specific isoforms through alternative splicing. Mol Cell Biol. 2001;21:7380–90.
97. Wöll S, Schlitter AM, Dhaene K, et al. Claudin 18.2 is a target for IMAB362 antibody in pancreatic neoplasms. Int J Cancer. 2014;134:731–9.
98. Jiang H, Shi Z, Wang P, et al. Claudin18.2-Specific chimeric antigen receptor engineered T cells for the treatment of gastric Cancer. J Natl Cancer Inst. 2019;111:409–18.
99. Qi C, Gong J, Li J, et al. Claudin18.2-specific CAR T cells in Gastrointestinal cancers: phase 1 trial interim results. Nat Med. 2022;28:1189–98.
100. Davies T, Marians R, Latif R. The TSH receptor reveals itself. J Clin Invest. 2002;110:161–4.
101. Rowe CW, Paul JW, Gedye C, et al. Targeting the TSH receptor in thyroid cancer. Endocr Relat Cancer. 2017;24:R191–202.
102. Zhou J, Chen J, Huang Y, et al. Signaling dynamics of TSHR-Specific CAR-T cells revealed by FRET-Based biosensors. Front Cell Dev Biol. 2022;10:845319.
103. Li H, Zhou X, Wang G, et al. CAR-T cells targeting TSHR demonstrate safety and potent preclinical activity against differentiated thyroid Cancer. J Clin Endocrinol Metab. 2022;107:1110–26.
104. Ding J, Li D, Liu X, et al. Chimeric antigen receptor T-cell therapy for relapsed and refractory thyroid cancer. Exp Hematol Oncol. 2022;11:59.
105. Airaksinen MS, Titievsky A, Saarma M. GDNF family neurotrophic factor signaling: four masters, one servant? Mol Cell Neurosci. 1999;13:313–25.
106. Bhoj VG, Li L, Parvathaneni K, et al. Adoptive T cell immunotherapy for medullary thyroid carcinoma targeting GDNF family receptor alpha 4. Mol Ther Oncolytics. 2021;20:387–98.
107. Gray KD, McCloskey JE, Vedvyas Y, et al. PD1 Blockade enhances ICAM1-Directed CAR T therapeutic efficacy in advanced thyroid Cancer. Clin Cancer Res. 2020;26:6003–16.
108. Buitrago D, Keutgen XM, Crowley M, et al. Intercellular adhesion molecule-1 (ICAM-1) is upregulated in aggressive papillary thyroid carcinoma. Ann Surg Oncol. 2012;19:973–80.
109. Zhang KE, Ge SJ, Lin XY, et al. Intercellular adhesion molecule 1 is a sensitive and diagnostically useful immunohistochemical marker of papillary thyroid cancer (PTC) and of PTC-like nuclear alterations in Hashimoto's thyroiditis. Oncol Lett. 2016;11:1722–30.
110. Min IM, Shevlin E, Vedvyas Y, et al. CAR T therapy targeting ICAM-1 eliminates advanced human thyroid tumors. Clin Cancer Res. 2017;23:7569–83.
111. French JD, Haugen BR. Thyroid cancer: CAR T cell therapy - potential in advanced thyroid cancer? Nat Rev Endocrinol. 2018;14:10–1.
112. Vedvyas Y, McCloskey JE, Yang Y, et al. Manufacturing and preclinical validation of CAR T cells targeting ICAM-1 for advanced thyroid cancer therapy. Sci Rep. 2019;9:10634.
113. Beatty GL, Haas AR, Maus MV, et al. Mesothelin-specific chimeric antigen receptor mRNA-engineered T cells induce anti-tumor activity in solid malignancies. Cancer Immunol Res. 2014;2:112–20.
114. Kalos M, Levine BL, Porter DL, et al. T cells with chimeric antigen receptors have potent antitumor effects and can Establish memory in patients with advanced leukemia. Sci Transl Med. 2011;3:95ra73.
115. Haubner S, Mansilla-Soto J, Nataraj S, et al. Cooperative CAR targeting to selectively eliminate AML and minimize escape. Cancer Cell. 2023;41:1871–91.

116. Majzner RG, Mackall CL. Tumor antigen escape from CAR T-cell therapy. Cancer Discov. 2018;8:1219–26.
117. Zhou K, Guo S, Li F, Sun Q, Liang G. Exosomal PD-L1: new insights into tumor immune escape mechanisms and therapeutic strategies. Front Cell Dev Biol. 2020;8:569219.
118. Leone RD, Emens LA. Targeting adenosine for cancer immunotherapy. J Immunother Cancer. 2018;6:57.
119. Marin-Acevedo JA, Soyano AE, Dholaria B, Knutson KL, Lou Y. Cancer immunotherapy beyond immune checkpoint inhibitors. J Hematol Oncol. 2018;11:8.
120. Aqbi HF, Wallace M, Sappal S, Payne KK, Manjili MH. IFN-γ orchestrates tumor elimination, tumor dormancy, tumor escape, and progression. J Leukoc Biol 2018.
121. Melero I, Navarro B, Teijeira A, Coukos G. Cancer immunotherapy full speed ahead. Ann Oncol. 2017;28:xii1–2.
122. Wilkie S, van Schalkwyk MC, Hobbs S, et al. Dual targeting of ErbB2 and MUC1 in breast cancer using chimeric antigen receptors engineered to provide complementary signaling. J Clin Immunol. 2012;32:1059–70.
123. Leong L, Tan HL, Cua S, Yong K, Chen Q, Choo A. Preclinical activity of embryonic Annexin A2-Specific chimeric antigen receptor T cells against ovarian Cancer. Int J Mol Sci 2020;21.
124. Li N, Quan A, Li D, et al. The IgG4 hinge with CD28 transmembrane domain improves V(H)H-based CAR T cells targeting a membrane-distal epitope of GPC1 in pancreatic cancer. Nat Commun. 2023;14:1986.
125. Jackson HJ, Rafiq S, Brentjens RJ. Driving CAR T-cells forward. Nat Rev Clin Oncol. 2016;13:370–83.
126. Maude SL, Barrett D, Teachey DT, Grupp SA. Managing cytokine release syndrome associated with novel T cell-engaging therapies. Cancer J. 2014;20:119–22.
127. Hong M, Clubb JD, Chen YY. Engineering CAR-T cells for Next-Generation Cancer therapy. Cancer Cell. 2020;38:473–88.
128. Hosein AN, Brekken RA, Maitra A. Pancreatic cancer stroma: an update on therapeutic targeting strategies. Nat Rev Gastroenterol Hepatol. 2020;17:487–505.
129. Sahai E, Astsaturov I, Cukierman E, et al. A framework for advancing our Understanding of cancer-associated fibroblasts. Nat Rev Cancer. 2020;20:174–86.
130. Chen Y, McAndrews KM, Kalluri R. Clinical and therapeutic relevance of cancer-associated fibroblasts. Nat Rev Clin Oncol. 2021;18:792–804.
131. von Ahrens D, Bhagat TD, Nagrath D, Maitra A, Verma A. The role of stromal cancer-associated fibroblasts in pancreatic cancer. J Hematol Oncol. 2017;10:76.
132. Martinez M, Moon EK. CAR T cells for solid tumors: new strategies for finding, infiltrating, and surviving in the tumor microenvironment. Front Immunol. 2019;10:128.
133. Rabinovich GA, Gabrilovich D, Sotomayor EM. Immunosuppressive strategies that are mediated by tumor cells. Annu Rev Immunol. 2007;25:267–96.
134. Leen AM, Rooney CM, Foster AE. Improving T cell therapy for cancer. Annu Rev Immunol. 2007;25:243–65.
135. Peggs KS, Quezada SA, Allison JP. Cancer immunotherapy: co-stimulatory agonists and co-inhibitory antagonists. Clin Exp Immunol. 2009;157:9–19.
136. Xu X, Gnanaprakasam J, Sherman J, Wang R. A metabolism toolbox for CAR T therapy. Front Oncol. 2019;9:322.
137. Berahovich R, Liu X, Zhou H et al. Hypoxia selectively impairs CAR-T cells in vitro. Cancers (Basel) 2019;11.
138. Akce M, Zaidi MY, Waller EK, El-Rayes BF, Lesinski GB. The potential of CAR T cell therapy in pancreatic Cancer. Front Immunol. 2018;9:2166.
139. Li T, Wang J. Therapeutic effect of dual CAR-T targeting PDL1 and MUC16 antigens on ovarian cancer cells in mice. BMC Cancer. 2020;20:678.
140. Hegde M, Mukherjee M, Grada Z, et al. Tandem CAR T cells targeting HER2 and IL13Rα2 mitigate tumor antigen escape. J Clin Invest. 2016;126:3036–52.
141. Zah E, Lin MY, Silva-Benedict A, Jensen MC, Chen YY. T cells expressing CD19/CD20 bispecific chimeric antigen receptors prevent antigen escape by malignant B cells. Cancer Immunol Res. 2016;4:498–508.
142. Hegde M, Corder A, Chow KK, et al. Combinational targeting offsets antigen escape and enhances effector functions of adoptively transferred T cells in glioblastoma. Mol Ther. 2013;21:2087–101.
143. Carlino MS, Sandhu S. Safety and efficacy implications of discontinuing combination ipilimumab and nivolumab in advanced melanoma. J Clin Oncol. 2017;35:3792–3.
144. Royal RE, Levy C, Turner K, et al. Phase 2 trial of single agent ipilimumab (anti-CTLA-4) for locally advanced or metastatic pancreatic adenocarcinoma. J Immunother. 2010;33:828–33.
145. Morgan MA, Schambach A. Engineering CAR-T cells for improved function against solid tumors. Front Immunol. 2018;9:2493.
146. John LB, Devaud C, Duong CP, et al. Anti-PD-1 antibody therapy potently enhances the eradication of established tumors by gene-modified T cells. Clin Cancer Res. 2013;19:5636–46.
147. Liu X, Ranganathan R, Jiang S, et al. A chimeric Switch-Receptor targeting PD1 augments the efficacy of Second-Generation CAR T cells in advanced solid tumors. Cancer Res. 2016;76:1578–90.
148. Cogdill AP, Andrews MC, Wargo JA. Hallmarks of response to immune checkpoint Blockade. Br J Cancer. 2017;117:1–7.
149. Gargett T, Yu W, Dotti G, et al. GD2-specific CAR T cells undergo potent activation and deletion following antigen encounter but can be protected from activation-induced cell death by PD-1 Blockade. Mol Ther. 2016;24:1135–49.
150. Grupp SA, Kalos M, Barrett D, et al. Chimeric antigen receptor-modified T cells for acute lymphoid leukemia. N Engl J Med. 2013;368:1509–18.
151. Frey NV, Porter DL. CAR T-cells merge into the fast lane of cancer care. Am J Hematol. 2016;91:146–50.
152. Lee DW, Gardner R, Porter DL, et al. Current concepts in the diagnosis and management of cytokine release syndrome. Blood. 2014;124:188–95.
153. Diaz-Buxo JA, Chandler JT, Farmer CD, Walker PJ. Intraperitoneal infusion of non-absorbable steroids in the treatment of Ascites and sterile peritonitis. J Dial. 1980;4:43–50.
154. Jenkin RP, Bamford R, Patel V, Kelly L, Stern S. The use of intraperitoneal triamcinolone acetonide for the management of recurrent malignant Ascites in a patient with non-Hodgkin's lymphoma. J Pain Symptom Manage. 2008;36:e4–5.
155. Mackey JR, Wood L, Nabholtz J, Jensen J, Venner P. A phase II trial of triamcinolone hexacetanide for symptomatic recurrent malignant Ascites. J Pain Symptom Manage. 2000;19:193–9.
156. Chen W, Li J, Peng S, et al. Association of total thyroidectomy or thyroid lobectomy with the quality of life in patients with differentiated thyroid Cancer with low to intermediate risk of recurrence. JAMA Surg. 2022;157:200–9.
157. Agretti P, De Marco G, De Servi M, et al. Evidence for protein and mRNA TSHr expression in fibroblasts from patients with thyroid-associated ophthalmopathy (TAO) after adipocytic differentiation. Eur J Endocrinol. 2005;152:777–84.
158. Wang ZF, Liu QJ, Liao SQ, et al. Expression and correlation of sodium/iodide symporter and thyroid stimulating hormone receptor in human thyroid carcinoma. Tumori. 2011;97:540–6.
159. Carayon P, Thomas-Morvan C, Castanas E, Tubiana M. Human thyroid cancer: membrane Thyrotropin binding and adenylate cyclase activity. J Clin Endocrinol Metab. 1980;51:915–20.
160. Liu TR, Su X, Qiu WS, et al. Thyroid-stimulating hormone receptor affects metastasis and prognosis in papillary thyroid carcinoma. Eur Rev Med Pharmacol Sci. 2016;20:3582–91.
161. Wang LC, Lo A, Scholler J, et al. Targeting fibroblast activation protein in tumor stroma with chimeric antigen receptor T cells can inhibit tumor growth and augment host immunity without severe toxicity. Cancer Immunol Res. 2014;2:154–66.
162. Kakarla S, Chow KK, Mata M, et al. Antitumor effects of chimeric receptor engineered human T cells directed to tumor stroma. Mol Ther. 2013;21:1611–20.
163. Bunt SK, Mohr AM, Bailey JM, Grandgenett PM, Hollingsworth MA. Rosiglitazone and gemcitabine in combination reduces immune suppression and modulates T cell populations in pancreatic cancer. Cancer Immunol Immunother. 2013;62:225–36.
164. Eikawa S, Nishida M, Mizukami S, Yamazaki C, Nakayama E, Udono H. Immune-mediated antitumor effect by type 2 diabetes drug, Metformin. Proc Natl Acad Sci U S A. 2015;112:1809–14.
165. Tran E, Chinnasamy D, Yu Z, et al. Immune targeting of fibroblast activation protein triggers recognition of multipotent bone marrow stromal cells and cachexia. J Exp Med. 2013;210:1125–35.
166. Maude SL, Frey N, Shaw PA, et al. Chimeric antigen receptor T cells for sustained remissions in leukemia. N Engl J Med. 2014;371:1507–17.
167. Lamers CH, Sleijfer S, Vulto AG, et al. Treatment of metastatic renal cell carcinoma with autologous T-lymphocytes genetically retargeted against carbonic anhydrase IX: first clinical experience. J Clin Oncol. 2006;24:e20–2.
168. Kershaw MH, Westwood JA, Parker LL, et al. A phase I study on adoptive immunotherapy using gene-modified T cells for ovarian cancer. Clin Cancer Res. 2006;12:6106–15.

169. Park JR, Digiusto DL, Slovak M, et al. Adoptive transfer of chimeric antigen receptor re-directed cytolytic T lymphocyte clones in patients with neuroblastoma. Mol Ther. 2007;15:825–33.
170. Parkhurst MR, Yang JC, Langan RC, et al. T cells targeting carcinoembryonic antigen can mediate regression of metastatic colorectal cancer but induce severe transient colitis. Mol Ther. 2011;19:620–6.
171. Duan H, Huang H, Jing G. An antibody fab Fragment-based chimeric antigen receptor could efficiently eliminate human thyroid Cancer cells. J Cancer. 2019;10:1890–5.
172. Xue D, Lu S, Zhang H, et al. Induced pluripotent stem cell-derived engineered T cells, natural killer cells, macrophages, and dendritic cells in immunotherapy. Trends Biotechnol. 2023;41:907–22.
173. Ueda T, Shiina S, Iriguchi S, et al. Optimization of the proliferation and persistency of CAR T cells derived from human induced pluripotent stem cells. Nat Biomed Eng. 2023;7:24–37.
174. van der Stegen S, Lindenbergh PL, Petrovic RM, et al. Generation of T-cell-receptor-negative CD8αβ-positive CAR T cells from T-cell-derived induced pluripotent stem cells. Nat Biomed Eng. 2022;6:1284–97.

Publisher's note