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Review:

Current advances in chimeric antigen receptor T-cell therapy for refractory/relapsed multiple myeloma

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Abstract: Multiple myeloma (MM), considered an incurable hematological malignancy, is characterized by its clonal evolution of malignant plasma cells. Although the application of autologous stem cell transplantation (ASCT) and the introduction of novel agents such as immunomodulatory drugs (IMiDs) and proteasome inhibitors (PIs) have doubled the median overall survival to eight years, relapsed and refractory diseases are still frequent events in the course of MM. To achieve a durable and deep remission, immunotherapy modalities have been developed for relapsed/refractory multiple myeloma (RRMM). Among these approaches, chimeric antigen receptor (CAR) T-cell therapy is the most promising star, based on the results of previous success in B-cell neoplasms. In this immunotherapy, autologous T cells are engineered to express an artificial receptor which targets a tumor-associated antigen and initiates the T-cell killing procedure. Tisagenlecleucel and Axicabtagene, targeting the CD19 antigen, are the two pacesetters of CAR T-cell products. They were approved by the US Food and Drug Administration (FDA) in 2017 for the treatment of acute lymphocytic leukemia (ALL) and diffuse large B-cell lymphoma (DLBCL). Their development enabled unparalleled efficacy in combating hematopoietic neoplasms. In this review article, we summarize six promising candidate antigens in MM that can be targeted by CARs and discuss some noteworthy studies of the safety profile of current CAR T-cell therapy.

Key words: Chimeric antigen receptor (CAR) T cells; Immunotherapy; Monoclonal antibody (mAb); Target antigen; Multiple myeloma

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1 Introduction

Multiple myeloma (MM) is a B-cell malignancy that displays a myriad of clinical manifestations such as hypercalcemia, anemia, renal dysfunction, and bone destruction. It leads to an overgrowth of cancerous plasma cells along with production of monoclonal protein (Kyle and Rajkumar, 2004). It has a very poor prognosis, and its occurrence increases with age, with most people being diagnosed in their mid-60s (Moreau et al., 2017).

Although MM is a relatively rare disease, it is the second most common hematological malignancy after non-Hodgkin lymphoma (Becker, 2011). The American Cancer Society (2019) estimates that in 2019, 32110 individuals will be newly diagnosed with MM, and 12960 deaths will be caused by this disease. Until the introduction of thalidomide—the milestone in MM treatment—melphalan in combination with prednisone (MP) had been the standard treatment regimen for decades. With the application of autologous stem cell transplantation (ASCT) and availability of novel agents such as immunomodulatory drugs (IMiDs),

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and subsequent proteasome inhibitors (PIs), a new therapy paradigm has led to remarkable improvements in MM (Singhal et al., 1999; Paus et al., 2005; Rajkumar et al., 2006). Notably, the median overall survival (OS) in relapsed patients has doubled from 12 to 24 months (Kumar et al., 2008). Novel strategies have significantly altered the disease trajectory such that the median survival of patients with MM has improved from three to nearly eight years (Anderson, 2012). However, relapse is inevitable in the natural course of MM, and a fraction of patients who remain unresponsive to currently available regimens, referred to as refractory individuals, have a median survival of only 13 months and progression free survival (PFS) of five months (Kumar et al., 2017). The decreasing response of relapsed/refractory multiple myeloma (RRMM) is concomitant with repetitive salvage regimens leading to clonal evolution. This has profoundly limited the benefits from treatment approaches (Cremer et al., 2005; Stewart et al., 2007), with median life expectancy ranging from six to nine months (Richardson et al., 2007). The pivotal objective of MM treatment is to achieve a durable and deep remission (Moreau et al., 2017). However, only 43% of young patients (<50 years old) and 29% of old patients (≥50 years old) have reached the goal of survival in excess of 10 years after high-dose therapy (Ludwig et al., 2008). Therefore, based on the results of previous studies which serve as a reference point, and owing to their previous success, immunotherapy modalities have been developed for RRMM, including monoclonal antibodies (mAbs) (Touzeau et al., 2017), bispecific T-cell engagers (BiTEs) (Hipp et al., 2017; Seckinger et al., 2017), and chimeric antigen receptor (CAR) T-cell therapy (Ren et al., 2019). CAR T-cell therapy involves genetically engineered T lymphocytes with CARs targeting tumor-specific antigens in the absence of the major histocompatibility complex (MHC). This new approach is increasingly being used among the different immunotherapies available (Sadelain et al., 2013), thereby aiding RRMM treatment as a salvage plan.

The story of CAR began in 1980s when Zelig ESHHAR introduced an extracellular target-specific single-chain variable fragment (scFv) derived from a mAb which resulted in T-cell activation (Eshhar et al., 1993). This structure was further optimized by combining it with a CD3-ζ chain of a T-cell receptor (TCR) and a co-stimulatory moiety such as 4-1BB (CD137) or CD28, which enhanced T-cell activation. T cells are equipped with a CAR structure which typically consists of a target-recognition ectodomain, a hinge region, an anchor-function transmembrane domain, and one or more signaling endodomains (Guedan et al., 2019) (Fig. 1).

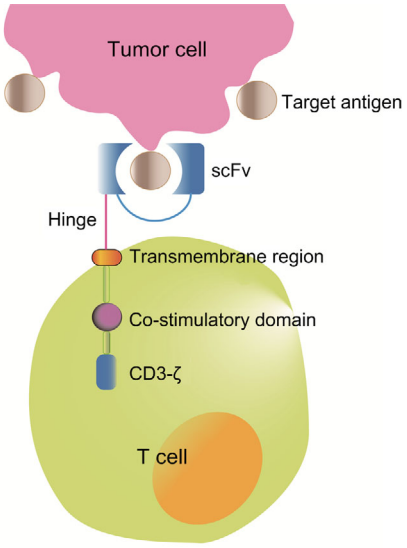

Fig. 1 Basic composition of a chimeric antigen receptor
The ectodomain of the chimeric antigen receptor (CAR) contains a single-chain variable fragment (scFv) and a hinge region. The transmembrane domain serves as a connection and a membrane anchor. The endodomain comprises the CD3-ζ signaling domain of the T-cell receptor and one or more co-stimulatory domains

The use of CAR T cells targeting CD19 is a landmark in the therapy of hematopoietic malignancies. It has been approved by the US Food and Drug Administration (FDA) for the treatment of relapsed or refractory acute lymphocytic leukemia (ALL) (Maude et al., 2015) and diffuse large B-cell lymphoma (DLBCL) (Kochenderfer et al., 2015). An ideal target is critical to develop a successful CAR with the ability to identify a tumor-associated antigen. The target antigen should have several features, such as being virtually absent from normal cells but overexpressed in malignant cells, contributing to differentiation and proliferation of malignant cells, and inducing clinical effects (Hideshima et al., 2007). For example, CD38 expressed at high epitope density on myeloma cells is involved in triggering immunosuppressive effects (Chillemi et al., 2017), enhancing T-cell activation (Quarona et al., 2013), and protecting B cells against

apoptosis (Ibrahim et al., 2001). From this, CD38 antibodies such as daratumumab and isatuximab have shown considerable efficacy as a part of combination therapies with standard regimes. Currently, in the context of RRMM, CARs such as B-cell maturation antigen (BCMA), CD38, and CD138 are being investigated in clinical trials, but no CAR T-cell therapy for MM is yet licensed by authorities. In MM patients who are heavily pretreated, ineligible for transplantation or early relapsed from transplantation, CAR T-cell therapy may provide considerable improvement. In this review, we summarize current candidate antigens that are actively being investigated (Table 1), discuss important adverse effects, and provide management strategies for CAR T-cell therapy.

2 Candidate antigens

2.1 B-cell maturation antigen

BCMA, which belongs to the tumor necrosis factor superfamily, regulates maturation and differentiation of B cells and the survival of plasma cells (O'Connor et al., 2004; Rickert et al., 2011). It is primarily expressed on normal and malignant plasma cells (Novak et al., 2004; Sanchez et al., 2012; Carpenter et al., 2013). BCMA is uniformly present on MM cells, but its expression has shown a variable intensity in clinical samples of patients (Seckinger et al., 2017). As anti-BCMA CAR T cells have exhibited robust efficacy in myeloma control in preclinical studies (Chekmasova et al., 2015), BCMA CARs have set the stage for the rapid growth of worldwide clinical trials, and they have provided the most important clinical experience to date in MM.

The anti-BCMA CAR T-cell therapy clinical trial led by Kochenderfer and colleagues in 2016—the first application in humans—recruited 12 patients with RRMM and BCMA expression (Ali et al., 2016). All patients received lymphodepleting conditioning with cyclophosphamide and fludarabine before a single dose of CAR T cells. Only one patient achieved stringent complete response (sCR) with the follow-up lasting for 17 weeks, although eight patients remained in a stable disease (SD) condition. Notably—it is not quite a matter of neglecting the unsatisfactory outcome

Table 1 Selected CAR T-cell trials for multiple myeloma

Antigen	Trial site/company	Phase	Accrual	*n*	ORR (%)	CR (%)	Identifier
BCMA	NCI	I	Completed	16	81*	13	NCT02215967
	UPenn/Novartis	I	Completed	25	48	8	NCT02546167
	Celgene/Bluebird	I	Completed	33	85	45	NCT02658929
	Celgene/Bluebird	I	Ongoing	12#	83	25	NCT03274219
	Nanjing Legend	I/II	Ongoing	57	88	68	NCT03090659
	Memorial Sloan-Kettering Cancer Center/Juno	I	Ongoing	11	64	0	NCT03070327
	Fred Hutchinson Cancer Research Center/Juno	I	Ongoing	11	100	36	NCT03338972
	Celgene (ex Juno)	I/II	Ongoing	44	82	27	NCT03430011
	Poseida	I/II	Ongoing	19	43	5	NCT03288493
	Celgene	II	Ongoing				NCT03601078
	Celgene	III	Ongoing				NCT03651128
	Autolus Limited	I/II	Ongoing				NCT03287804
	Cartesian	I/II	Ongoing				NCT03448978
κ light chain	Baylor University	I	Completed	7	0	0	NCT00881920
CD138	Chinese PLA General Hospital	I/II	Completed	5	20	0	NCT01886976
	Lineberger Comprehensive Cancer Center	I	Ongoing				NCT03672318
CD38	Sorrento/Celularity	I	Ongoing				NCT03464916
	Shenzhen Geno-Immune Medical Institute, China	I/II	Ongoing				NCT03271632
SLAMF7	NCI	I	Ongoing				NCT03958656
GPRC5D			Preclinical				

CAR, chimeric antigen receptor; BCMA, B-cell maturation antigen; GPRC5D, G-protein-coupled receptor, class C group 5 member D; NCI, National Cancer Institute; UPenn, University of Pennsylvania; PLA, People's Liberation Army; ORR, overall response rate; CR, complete response. * 81% (13 of 16) ORR at the highest dose of 9×10^6 CAR T cells/kg. # All 12 subjects were treated at the lowest dose of 1.50×10^8 cells/kg

of this trial, but of rejecting its implication—the patient with sCR received only three prior lines of therapy, whereas six out of the eight patients from the SD group received more than five prior lines of therapy. Moreover, the sCR patient received the highest anti-BCMA CAR T-cell dose level (9.0×10^6 cells/kg), whereas no individuals in the SD group received doses at the highest concentration. Although not particularly successful, this clinical trial demonstrated the feasibility of anti-BCMA CAR T-cell therapy, providing directions for subsequent research.

bb2121, combined with a phosphoinositide 3-kinases (PI3K) inhibitor, an anti-BCMA CAR T-cell product, has shown superior anti-myeloma activity regardless of BCMA load, and powerful recognition capability via strong surface CAR expression. It consists of autologous T cells transduced with a lentiviral vector encoding a novel anti-BCMA CAR. An ongoing multicenter phase I study of bb2121 CRB-401 enrolled 36 heavily pretreated patients with RRMM. The latest results for the first 33 patients are encouraging (Raje et al., 2019). All patients received chemo-conditioning with cyclophosphamide and fludarabine before a single dose of CAR T-cell infusion at four dose levels (50×10^6, 150×10^6, 450×10^6, or 800×10^6 cells/kg). The objective overall response rate (ORR) was 85% (median follow-up: 10.9 months), with 9% of patients achieving complete response (CR) and 36% showing sCR. Importantly, the ORR was unlikely to have been influenced by baseline serum or tumor BCMA level and previous treatments, but a better response was observed in patients with a high-risk cytogenetic profile, progressive disease (PD) or extramedullary disease before CAR T-cell therapy.

Currently, bb2121 is the most promising front runner among its analogous candidates such as JCARH125 (NCT03430011), P-BCMA-101 (NCT03288493), and LCAR-B38M (NCT03090659) in the race for approval by authorities (Table 2). Recruitment is proceeding for a phase III study of bb2121, which should provide further reliable data (NCT03651128).

2.2 κ light chain

Carlos RAMOS and colleagues were inspired to overcome the adverse effects of anti-CD19 CAR T-cell therapy, hypogammaglobulinemia, caused by ubiquitous expression of CD19 on all cells from B-cell lineage. They found that preservation of normal B cells may be achieved by targeting the light chain on the cell surface (Ramos et al., 2016). On mature B lymphocytes and mature B lymphoid malignant cells and myeloma cells, either the κ or λ light chain is expressed instead of both; thus, targeting the κ light chain can prevent complete B-cell ablation (Ramos et al., 2016). The first clinical trial, known as a blanket investigation, consisted of seven patients with MM and nine patients with non-Hodgkin lymphoma (Ramos et al., 2016). A modest outcome was observed—four patients had SD for up to 24 months—but three patients showed no response. This κ light chain-targeting CAR has proved elusive because light chains, which are generally secreted, present limited surface expression, which may block the CAR from targeting malignant cells and mediate CAR T-cell depletion.

2.3 CD138

CD138, a member of the syndecan family involved in cell adhesion, is the hallmark of plasma cells, being highly expressed on both malignant and healthy plasma cells, and predominantly expressed on epithelial cells (O'Connell et al., 2004; Palaiologou et al., 2014). Since the high plasma cell specificity of CD138 is well established, it is recommended that CD138 in combination with CD38 serves as the basis for identifying myeloma cells by flow cytometry (Frigyesi et al., 2014). As CD138 plays a crucial role in the pathophysiology of MM, such as cell proliferation, infiltration, or apoptosis, it is definitely a viable candidate antigen for CAR T-cell therapy (Yoo et al., 2015).

The first in-human trial of anti-CD138 CAR T-cell therapy led by Bo GUO and colleagues in 2013 comprised a small number of MM patients (n=5) with advanced disease. The trial aimed to investigate whether cytokine-induced killer cells with lentiviral vector-mediated transduction of an anti-CD138 CAR gene exert antitumor effects in myeloma cells (Guo et al., 2016). Four out of five patients met the criteria of SD, one of whom achieved up to 12 months of SD and another had PD within a month after infusion. In addition, certain visible changes were observed in the morphology of plasma cells in bone marrow aspirates of all patients, but these had no verified correlation with any immune response against myeloma cells exerted by anti-CD138 CAR T cells. All patients received cell

Table 2 Selection of ongoing and completed clinical trials of anti-BCMA CAR T cells for treatment of multiple myeloma

CAR T cell	Lymphodepletion	CAR T cell dose (cells/kg)	CRS	NT	Comment	Identifier
NCI	Flu/Cy	9×10^6	93% (15/16)	6% (1/16)	Grade 3 or 4 CRS was associated with a high level of bone marrow plasma cells and NT was limited in the setting of severe CRS	NCT02215967
UPenn (Novartis)	±Cy	Cohort 1: 1×10^8–5×10^8 CAR T cells; Cohort 2: Cy+(1×10^7–5×10^7) CAR T cells; Cohort 3: Cy+(1×10^8–5×10^8) CAR T cells	88% (22/25)	32% (8/25)	The median peak fold-increases of IL-6 and several other cytokines were 1 to 2 orders of magnitude lower than that reported in the NCI BCMA CAR T cell study	NCT02546167
bb2121	Flu/Cy	50×10^6, 150×10^6, 450×10^6, 800×10^6	76% (25/33)	42% (14/33)	CRS occurred at mostly grades 1 and 2 (70%), and NT of grade ≥3 occurred in one patient	NCT02658929
bb21217	Flu/Cy	150×10^6	67% (8/12)	25% (3/12)	All CRS and NT events were manageable and no deaths occurred on this lowest-dose cohort	NCT03274219
LCAR-B38M/ JNJ-68284528	Cy	Median dose: 0.5×10^6	90% (51/57)	2% (1/57)	CRS occurred at mostly grades 1 and 2 (83%), and NT events of grade 1 were resolved within 1 d	NCT03090659
MCARH171	Cy or Flu/Cy	1×10^6; 150×10^6, 450×10^6, 800×10^6	60% (6/10)[#]	10% (1/10)[#]	CRS of grade ≥3 occurred in 20% of patients, and no NT events of grade ≥3 were observed	NCT03070327
FCARH143	Flu/Cy	50×10^6	91% (10/11)	9% (1/11)	No CRS of grade ≥3 was observed	NCT03338972
JCARH125	Flu/Cy	50×10^6, 150×10^6, 450×10^6	80% (35/44)	25% (11/44)	CRS of grade ≥3 occurred in 9% of patients, and NT events of grade ≥3 occurred in 7% of patients	NCT03430011
P-BCMA-101[*]	Flu/Cy	0.75×10^6, 2×10^6, 6×10^6, 10×10^6, 15×10^6	10% (2/21)	5% (1/21)	Only two cases of potential CRS were reported (grades 1 and 2)	NCT03288493

BCMA, B-cell maturation antigen; CAR, chimeric antigen receptor; NCI, National Cancer Institute; UPenn, University of Pennsylvania; Flu, fludarabine; Cy, cyclophosphamide; CRS, cytokine release syndrome; NT, neurotoxicity. [#] One patient required early steroids and radiation for impending cord compression and was not evaluable for toxicities; [*] P-BCMA-101 is manufactured using the "piggyback" approach, with a non-viral system for DNA delivery plus a small human fibronectin domain for BCMA. Favorable safety profile, high purity (>95% CAR^+) and a T stem cell memory (TSCM) phenotype (gradual and prolonged activity)

infusion (an average dose of 0.7563×10^7 cells/kg), and only one or two grades of cytokine release syndrome (CRS) were observed. Although it is difficult to draw a firm conclusion based on the small sample size, a respectable safety profile and limited antitumor efficiency do provide the basis for further trials with this alternative target. Because of inadequate evaluation of the efficacy and adverse effects in preclinical studies, it is difficult to obtain compelling data to support clinical trials.

The latest report that strongly supports prior clinical trials was conducted by Sun et al. (2019), who developed T cells through retroviral vector-mediated transduction of anti-CD138 scFvs from BT062, the CD138 antibody. A complete elimination of $CD138^+$ cells was observed in vitro after 3–5 d co-culture of anti-CD138 CAR T cells and MM cell lines. In a co-culture with myeloma cells from MM patients, anti-CD138 CAR T cells derived from both patients and healthy donors exhibited tumoricidal activity against not only $CD138^+$ malignant cells but also $CD138^+$ stem cells, and showed comparable cytokine secretion profiles of interferon-γ (IFN-γ) and interleukin-2 (IL-2). The significant killing capability of the anti-CD138 CAR T cells seemed unaffected even in the presence of high amounts of soluble CD138, which can neutralize CAR T cells by coupling with the scFv domain. Moreover, no lysis of epithelial and endothelial cells was observed, and no adverse effects such as diarrhea, mucositis, or stomatitis were noted in the BT062 treatment. A clinical trial (NCT03672318) of anti-CD138 CAR T-cell therapy targeting patients of RRMM, set up in January 2019, is in progress.

2.4 CD38

CD38 was first identified as a cell-surface structural marker on mouse B lymphocytes (Lund, 2006). Further research showed that in normal hematopoiesis, CD38 can be found on natural killer (NK) cells, monocytes, and lymphoid and myeloid cells (Quarona et al., 2013), and in the context of MM, CD38 is universally overexpressed on malignant plasma cells (van Dongen et al., 2012). In addition to its ubiquitous expression on myeloma cells, CD38 is being highlighted for its involvement in physiological and pathological conditions as a multifunctional enzyme (Howard et al., 1993; Deaglio et al., 2001; Chillemi et al., 2017).

The efficacy of CD38 as a target antigen was initially established in mAbs such as daratumumab (Lokhorst et al., 2015; Krejcik et al., 2016), which gained FDA approval for RRMM treatment in 2015. CD38 antibody was frequently suggested as a part of combination therapies in RRMM treatment. For example, daratumumab in combination with lenalidomide-dexamethasone (Rd) had an ORR of 92.9% (CR or better in 43.1%) and a PFS at 12 months of 83.2% (Lonial et al., 2016). Patients treated with daratumumab with bortezomib-dexamethasone (Vd) had an ORR of 82.9% (CR or better in 19.2%) and a PFS at 12 months of 60.7% (Palumbo et al., 2016), whereas daratumumab monotherapy showed an ORR of 29% (sCR in 2.8%), a median duration of response of 7.4 months, and a median PFS of 3.7 months (Lonial et al., 2016).

Mihara et al. (2012) transduced an anti-CD38 CAR gene into T cells obtained from healthy donors, reporting that anti-CD38 CAR T cells exert potent cytolytic effects in myeloma cell lines and primary myeloma cells from clinical patients. Most subsequent studies carried out in the light of this first trial have generated similar outcomes. Nevertheless, concerns have arisen regarding the role of CD38 in T-cell activation and regulation (Funaro et al., 1990). T cells containing CD38 and anti-CD38 CAR may lead to fratricide, resulting in abrogation of effector T cells. Drent et al. (2018) have developed several strategies to cope with these limitations. For example, generating lower-affinity CAR structures can decrease the recognition of T cells with CD38 expression at an intermediate level.

The first phase I clinical study (NCT03464916) for a USA-based anti-CD38 CAR T-cell therapy was conducted in 2018 at the University of Pennsylvania and Roger Williams Medical Center. The aim was to evaluate the efficacy and safety of CAR2 anti-CD38 A2 CAR T cells in patients with RRMM, and to shed light on further measures.

2.5 SLAMF7

SLAMF7 (aliases CD319, CRACC, CS-1) is a member of the signaling lymphocytic activation molecule (SLAM) family, first identified on NK cells (Boles and Mathew, 2001). It is expressed on a fraction of T cells, B cells, macrophages, and dendritic cells, and its expression in more than 95% of normal

and malignant plasma cells of MM has been documented (Hsi et al., 2008). However, the mechanism underlying the upregulated SLAMF7 has not been entirely elucidated (Calpe et al., 2008; Schwartzberg et al., 2009; Wu and Veillette, 2016). It may be correlated with the formation of the immunosuppressive bone marrow milieu that aids the harboring of myeloma cells (Tai et al., 2008).

The introduction of elotuzumab—the first humanized SLAMF7 antibody—has laid the foundation for studies of the further utility of SLAMF7 as a target for CAR T-cell therapy (Friend et al., 2017). Gogishvili et al. (2017) designed the anti-SLAMF7 CAR T cell by obtaining scFvs from elotuzumab. $CD8^+$ anti-SLAMF7 CAR T cells promptly exert tumoricidal effects, leading to >90% lysis of myeloma cell lines after a 20-h co-culture. As for $CD38^+$ $CD138^+$ $SLAMF7^+$ malignant cells obtained from MM patients, anti-SLAMF7 CAR T cells have exhibited rapid eradication of all myeloma cells in 4 h regardless of antigen load. Furthermore, in xenograft models with extramedullary invasion, anti-SLAMF7 CAR T cells were capable of exerting anti-myeloma activity in systematic infiltration. In addition, engineered T cells derived from MM patients and healthy donors displayed similar oncolytic effects both in vivo and in vitro.

The concern surrounding anti-SLAMF7 CAR is its expression in a fraction of functional cells. $CD8^+$ anti-SLAMF7 CARs are able to elicit fratricide via coupling with SLAMF7, which is present at a high level in T cells (Gogishvili et al., 2017). Reduction of effector T cells is observed wherein elotuzumab produces the adverse effect of lymphopenia. However, a proportion of lymphocytes with moderate SLAMF7 expression can be preserved, and the residual T cells can maintain the capability of eliciting an immune response toward certain viral pathogens (Gogishvili et al., 2017).

Furthermore, SLAMF7 serves as a pro-phagocytic signal on macrophages, which perform essential phagocytosis in hematopoietic tumors compared with other tissue-derived tumors (Chen et al., 2017). A recent study indicates that SLAMF7 is not a prerequisite for killing diffuse large B cell lymphoma (DLBCL) cells (He et al., 2019). However, macrophages are likely to mediate endogenous elimination of myeloma cells via surface SLAMF7 signaling, which may be impaired by anti-SLAMF7 CAR T cells.

A phase I clinical trial of anti-SLAMF7 CAR T-cell therapy is open for recruiting in May 2019 in the USA and CARs will be designed to express both anti-SLAMF7 antibody and a suicide gene (NCT03958656).

2.6 GPRC5D

Orphan G-protein-coupled receptor, class C group 5 member D (GPRC5D) was once a candidate for distinguishing MM cells because its elevated transcript level correlates with poor prognosis of MM (Atamaniuk et al., 2012). It is now a potential alternative option for MM treatment.

According to previous in situ hybridization studies, GPRC5D expression in MM patients is restricted to three anatomical locations—hair follicles (Inoue et al., 2004; Gao et al., 2016; Kim et al., 2017), lung tissue, and bone marrow (Atamaniuk et al., 2012; Cohen et al., 2013). Although the expression of GPRC5D mRNA was confirmed by previous studies (Atamaniuk et al., 2012), the protein product of GPRC5D could not be detected on plasma cells in samples from patients with MM (Smith et al., 2019). Gene chip profiling has demonstrated that GPRC5D expression on malignant and normal plasma cells in bone marrow is substantially higher (at least 500-fold) than that on plasma cells in the peripheral blood (Smith et al., 2019).

Previous research has revealed the likelihood that GPRC5D expression is independent of BCMA expression (Smith et al., 2019). Analysis of $CD138^+$ plasma cells obtained from 83 clinical trial samples from patients with primary MM under the cutoff ≥50% target antigen expression showed 65% of samples with GPRC5D expression, 74% with BCMA expression, and 88% with co-expression of GPRC5D and BCMA (Smith et al., 2019).

As the most critical initial step, manufacturing the GPRC5D target scFvs provides the basis for effective and specific CAR T-cell therapy. A preclinical investigation generated anti-GPRC5D CARs via retroviral vector-mediated transduction after selecting scFvs with high GPRC5D-specific affinity from a human B-cell-derived phage display (Smith et al., 2019). Preliminary outcomes have shown that anti-GPRC5D CAR T cells exhibit anti-myeloma activity comparable to that of anti-BCMA CAR T cells in vitro and in vivo, and similar secretion profiles of cytokines

such as elevated IFN-γ, tumor necrosis factor-α (TNF-α), and granulocyte-macrophage colony-stimulating factor (GM-CSF) were observed. Notably, even in relapsed xenograft models with BCMA loss after BCMA-specific CAR T-cell therapy, anti-GPRC5D CAR T cells can eliminate malignant cells, thereby inhibiting disease progression (Smith et al., 2019).

GPRC5D is highly expressed on the hair follicles of hairy animal models such as monkeys and mice, but with no alopecia or other visible damage observed, which may be caused by the immune-privileged site of hair follicles (Westgate et al., 1991; Paus et al., 2005; Wang et al., 2014). Laboratory data on GPRC5D as a potential target have provided a stepping stone for further clinical trials.

3 Controlling toxicities in CAR T-cell treatment of MM

Apart from non-specific side effects such as infusion reactions, infection, or tumor lysis syndrome, CRS and neurotoxicity (NT) are two major adverse effects observed after CAR T-cell therapy. The first sign of CRS, occurring in up to 90% of patients within the first week after infusion, is a high fever along with a cluster of other manifestations such as fatigue, nausea, myalgia, and anorexia (Lee et al., 2014; Brudno and Kochenderfer, 2016). Although most CRS is mild to moderate within a self-limiting course, severe CRS can rapidly progress and evolve into life-threatening complications including severe hypotension, dysoxia, or multiple organ dysfunction (Brentjens et al., 2010; Lee et al., 2014). CRS is driven by an excessively high level of pro-inflammatory cytokines, such as IL-6, IFN-γ, and granulocyte macrophage-colony stimulating factor (GM-CSF), and is associated with the expansion and activation of CAR T cells (Lee et al., 2014). Notably, tocilizumab, an IL-6 receptor antagonist with FDA approval for rapid CRS resolution (Le et al., 2018) based on data from anti-CD19 CAR T-cell therapy, has demonstrated potent efficiency for treating severe CRS without limiting CAR T-cell efficacy (Grupp et al., 2013). The dose of tocilizumab recommended by FDA is 8 mg/kg (12 mg/kg for patients weighing less than 30 kg) (Le et al., 2018). For patients with a poor response to the initial dose of tocilizumab, clinical situations may improve with a second administration and/or addition of corticosteroids (Neelapu et al., 2018). To date, siltuximab, which prevents IL-6 from binding to its receptor by forming an affinity complex with IL-6, is administered only under the condition of CRS being refractory to tocilizumab and corticosteroid (Mahmoudjafari et al., 2019). CAR T-cell therapy-associated NT frequently presents with a new onset of neural symptoms within three weeks after infusion (Davila et al., 2014). Although representative NT generally appears after high-grade CRS for some reasons, atypical NT events which can occur independently have also been observed. Clinical manifestations, usually self-limiting, include headache, apraxia, ataxia, dysgraphia, seizures, and myoclonus (Grupp et al., 2013; Kochenderfer et al., 2015; Maude et al., 2018). Unlike CRS, NT responds poorly to intervention with tocilizumab (Lam et al., 2016; Gauthier and Turtle, 2018). Corticosteroids are the frontline management drugs for NT to date, although no robust data are available to support this practice (Porter et al., 2018).

"On-target but off-tumor" toxicity, which refers to the adverse effects of the target antigen on normal tissue, is also a major concern. For example, CD38 is expressed on plasma cells, NK cells, monocytes, healthy T cells and B cells, and a fraction of hematopoietic progenitor cells (Terstappen et al., 1991). CD38 is upregulated with T cell activation (Dianzani et al., 1994); therefore, CD38-specific CAR T-cell therapy may result in a persistent cytopenia and T-cell fratricide.

Various approaches have been proposed to minimize the off-tumor effects of CAR T-cell therapy. The strategy of optimizing the ectodomain and then screening for CARs with a lower affinity for normal tissue allows for generation of CAR T cells that are highly specific for malignant cells owing to their excessive antigen density (Drent et al., 2017). Moreover, incorporation of the suicide gene by editing technologies such as transcription activator-like effector nuclease (TALEN) and clustered regularly interspaced palindromic repeats (CRISPR)-Cas9 mediates toxicities in a more controllable status (Straathof et al., 2005; Philip et al., 2014; Drent et al., 2016). In view of this, the doxycycline (DOX)-regulated Tet-on system can maximize antitumor activity while alleviating "off-tumor" effects. Drent et al. (2018) designed CAR T cells with a DOX-induced structure. The cells are

devitalized without DOX administration and revived after a high dose of DOX.

4 Conclusions

Immunotherapy with CAR-expressing T cells has shown encouraging success in patients with RRMM; even a small nudge can yield remarkable lessons for others. In this review, we have highlighted several promising candidate antigens in RRMM treatment, including those in some stages of clinical trials, as well as a novel antigen. However, while CAR T-cell therapy has laid down a treatment pattern for RRMM, a myriad of challenges have emerged. One challenge is to reduce "off-target" toxicities. For instance, although CD56 is expressed on malignant plasma cells and not on healthy ones, it is present on major organs such as myocardial tissue, so CAR T-cell therapy may lead to heart dysfunction. Such issues can be addressed by targeting ideal antigens, optimizing CAR constructs, and incorporating the suicide gene. Another important problem to cope with is minimizing CAR T-cell therapy-related toxicities. Whereas for CRS, IL-6 blockage has been regarded as the first-line management strategy with rapid symptom control, no credible agents are available for resolving NT. Future in-depth research is needed at the pathophysiological level, aiming to facilitate management of NT and to establish a consensus on treatment regimens. To emulate traditional modalities, scientists are already setting their sights farther afield.

Contributors

He HUANG took the lead in writing the manuscript. Heng-wei WU wrote and edited the manuscript. Yong-xian HU contributed to shaping the tables and figures. All authors read and approved the final manuscript and, therefore, had full access to all the data in the study and take responsibility for the integrity and security of the data.

Compliance with ethics guidelines

He HUANG, Heng-wei WU, and Yong-xian HU declare that they have no conflict of interest.

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

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中文概要

题　目：嵌合抗原受体 T 细胞在治疗难治/复发多发性骨髓瘤中的新进展

概　要：多发性骨髓瘤被认为是一种无法治愈的血液系统恶性疾病，其特征为恶性浆细胞的克隆性增殖。尽管在过去的几十年中，自体干细胞移植（ASCT）的应用及新型药物（蛋白酶体抑制剂和免疫调节药）的问世，将患者的中位生存时间由原来的 4 年提高到了 8 年，但复发与难治仍然是多发性骨髓瘤疾病进程中难以逾越的鸿沟。为了获得长期持续的缓解，免疫治疗开始在多发性骨髓瘤中崭露头角，其中嵌合抗原受体（CAR）T 细胞治疗就是最有潜力的一颗新星。通过在基因层面改造患者自己的 T 细胞，使 T 细胞表达一种特定的受体（人造的融合蛋白），该受体可以识别并结合肿瘤相关抗原，并活化 T 细胞启动后续的杀伤过程。Tisagenlecleucel 和 Axicabtagene 是两个针对 CD19 抗原的 CAR T 产品，用于治疗 B 细胞来源的急性淋巴细胞白血病（B-ALL）和弥漫大 B 细胞淋巴瘤（DLBCL），并于 2017 年被美国食品药品监督管理局（FDA）批准。这两个产品的发展极大推动了 B 细胞来源的恶性血液系统疾病的治疗，并刷新了对于传统治疗的认知。基于之前 CAR T 治疗的成功经验，寻找如 CD19 一样的特定靶点能为 CAR T 治疗多发性骨髓瘤打下基础。本综述介绍了数个在骨髓瘤细胞上的肿瘤靶抗原，如 B 细胞成熟抗原（BCMA）和 CD38。这些针对抗原的 CAR T 治疗有些还在实验室阶段，而有些已经进入了 3 期的临床试验，很有可能成为下一个被批准的 CAR T 产品。另外，本综述也介绍了在 CAR T 治疗中出现的毒副反应以及相应的管理和处理方法。

关键词：嵌合抗原受体（CAR）T 细胞；免疫治疗；单克隆抗体；靶抗原；多发性骨髓瘤