Non-BCMA targeted CAR-T cell therapies for multiple myeloma

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Abstract
Despite the emergence of new strategies in recent years, multiple myeloma (MM) is still an incurable disease with poor outcome. As a new treatment, chimeric antigen receptor (CAR-) T cell therapy brought exciting news to patients with relapsed or refractory MM. B-cell maturation antigen (BCMA) is ubiquitously expressed on the surface of myeloma cells and is considered an “ideal” target of CAR-T cell. BCMA-targeted CAR-T cell therapies achieved remarkable efficacy in relapsed or refractory MM patients in several clinical trials. However, some patients had no response or relapsed after BCMA targeted CAR-T cell therapy. Myeloma cells also express other surface markers which might be used as targets for CAR-T cell therapy. Encouragingly, CAR-T cells targeting these non-BCMA markers are being tested in clinical trials or under preclinical investigation, already showing some promising results. In this review, we summarized and provided an update of these advances.

KEYWORDS
CAR-T, multiple myeloma, non-BCMA target, therapy

1 | INTRODUCTION

Multiple myeloma (MM) is one of the most common hematological tumors.1,2 The prognosis of MM patients has been improved by modern therapies such as proteasome inhibitors, lenalidomide, anti-CD38 monoclonal antibody, and autologous stem cell transplantation.3–6 However, most patients eventually relapse with poor outcomes.

Chimeric antigen receptor (CAR-) T cell therapy is a promising immunotherapeutic approach with the potential to prolong survival of patients with malignant hematological diseases including MM, lymphomas, and leukemias.7–11 The key to success of CAR-T therapy is the selection of appropriate antigen targets. Ideally, the target antigen should be expressed on the tumor cell surface but not on other cells, warranting the specificity and avoiding severe off-target side effects. Therefore, B-cell maturation antigen (BCMA) is chosen as such a candidate target of CAR-T cell therapy for MM due to its ubiquitous expression on myeloma cells. Several trials have evaluated the safety and efficacy of anti-BCMA CAR-T cells in relapsed/refractory MM and showed encouraging results.10,12,13 However, possibly due to the heterogeneous expression or therapy-induced down-regulation of BCMA antigen on myeloma cells, some patients did not respond to treatment or relapsed rapidly after response.14,15 Some patients even did not express BCMA on myeloma cells,13 which necessitating finding of new targets of CAR-T cells. At present, CAR-T cells targeting non-BCMA antigens are being tested in clinical trials or under preclinical investigation (Figure 1 and Table 1).

2 | NON-BCMA TARGETS

CAR-T cells targeting non-BCMA antigens have been proved to be clinical effective and demonstrated powerful activity against myeloma cells: Some targets is being tested in clinical trials, but data unpublished; Whereas, the other targets are under investigation in laboratory or preclinical stage (Figure 1 and Table 1).
### TABLE 1  Candidate non-BCMA targets for CAR-T therapies of multiple myeloma

| Antigens            | Expression in nonmalignant cells                                                                 | Expression in MM                                                                 | Clinical trial of CAR-Ts                                                                 |
|---------------------|-------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------|----------------------------------------------------------------------------------------|
| CD19                | B cells                                                                                         | minimal expression of CD19 on myeloma plasma cell surface, CD19+ cells may represent stem cell subset,16–18 suggesting CD19 as a potential target of CAR-T cell therapy in MM. Autologous stem cell transplantation (ASCT) followed by anti-CD19 CAR-T (CTL019) infusion led to complete response with no evidence of progression in a patient with refractory MM.19 A further study reported 80% objective response rate (ORR) and more than 6 months of median progress free survival (PFS) duration in MM patients who received ASCT and anti-CD19 CAR-T cells (CTL019).20,21 | ChiCTR-OIC-17011272  
NCT03706547  
NCT03767725 |
| CD138 (syndecan-1)  | plasma cells, epithelial cells, liver, skin                                                     | expressed on myeloma cells                                                                 | NCT01886976  
NCT03672318 |
| Kappa light chain   | mature B cells                                                                                  | potential target on B cells that represent MM stem cells and that express surface immunoglobulins | NCT00881920 |
| NY-ESO-1            | not expressed or low expressed on normal tissues                                                | 60% of advanced MM patients at diagnosis and 100% of those at relapse                  | NCT03638206 |
| CD38                | red blood cells, plasma cells, precursor B cells, T cells, NK cells, muscle cells, osteoclasts, prostate cells | strong, uniform expression on myeloma cells                                                                 | NCT03464916  
NCT03767751 |
| CD44 variant 6      | activated T cells, monocytes and keratinocytes                                                  | restricted to be expressed by 43% of activated MM cases                               | NCT04097301 |
| NKG2D ligands       | rare in normal tissues                                                                          | widely expressed on hematologic malignancies including MM                               | NCT02203825  
NCT03018405 |
| SLAMF7/CS1          | plasma cells, NK cells, T cells, B cells and dendritic cells                                    | strongly expressed by myeloma cells                                                   | NCT03710421 |
| CD56                | NK cells, T cells, neurons cells                                                                 | strongly expressed in 70% of patients with myeloma                                    | NCT03473496  
NCT03271632 |
| Integrinβ7          | subpopulations of lymphocytes and immature hematopoietian cells                                 | highly expressed in most myeloma cells                                                | no report |
| CD70                | active lymphoid cells                                                                           | a portion of the myeloma cells                                                         | no report |
| GPRC5D              | hair follicle                                                                                   | highly expressed in primary MM cells                                                  | no report |
| CD229               | normal lymphocytes                                                                              | highly expressed on the myeloma cells and pre-plasma cells                            | no report |
| TACI                | plasma cells                                                                                   | highly expressed on most myeloma cells                                                | no report |
| Lewis Y             | red blood cells, epithelial cells                                                               | expressed in 52% myeloma cells                                                       | NCT01716364 |

**2.1 CD19**

CD19 is expressed on both progenitor and mature B cells, rendering it as a good target of CAR-T cell therapy in lymphocytic leukemia (ALL) and non-Hodgkin lymphoma. Physiologically, CD19 is rarely expressed on MM cells. However, some recent studies reported CD19-expressing MM clones, which are hypothesized to be myeloma-like stem cell subset,16–18 suggesting CD19 as a potential target of CAR-T cell therapy in MM. Autologous stem cell transplantation (ASCT) followed by anti-CD19 CAR-T (CTL019) infusion led to complete response with no evidence of progression in a patient with refractory MM.19 A further study reported 80% objective response rate (ORR) and more than 6 months of median progress free survival (PFS) duration in MM patients who received ASCT and anti-CD19 CAR-T cells (CTL019).20,21
This finding indicated anti-CD19 CAR-T might target MM stem cells. Prompted by this, an open, single arm clinical study (ChiCTR-OIC-17011272) was carried out to assess the safety and efficacy of combined anti-CD19 CAR-T cell and anti-BCMA CAR-T cell in treating MM, which achieved encouraging result with ORR of 95% in 21 patients.14 However, given that anti-CD19 CAR-T cell is designed for targeting "MM stem cells" but not the bulk population of MM cells, the long-term effect is challenged when anti-CD19 CAR-T cell is used alone. In a study by Garfall et al., all the ten myeloma patients have progressed at last.21 Thus, the strategy of the combined anti-CD19 CAR-T cell and anti-BCMA CAR-T cell may further improve efficacy (NCT03767725).

### 2.2 CD138 (syndecan-1)

CD138, also known as syndecan-1, is highly expressed in MM cells and considered to be an attractive target for CAR-T cell therapy.22 A preclinical study, CD138-directed CAR T cells can eliminate tumor cell lines and primary myeloma cells both in vitro and in vivo.23 In a phase 1 clinical report (NCT01886976) of five patients with R/R MM who received CD138-directed CAR-T cell therapy, four patients were in stable condition longer than 3 months and one patient had disease progression.24 In terms of safety, the patients developed cytokine release syndrome (CRS) with no epithelial cytotoxicity occurred.24 CD138 CAR-T also has potential disadvantages. CD138 also expresses on epithelial cells, possibly resulting in skin or mucosa as the target of anti-CD138 CAR-T cells.25,26 In the future, relevant strategies may be needed to avoid the targeted toxicity and maintain the potential anti-tumor effect of anti-CD138 CAR-T. Two clinical trials with CD138-directed CAR-T cells are ongoing (NCT01886976, NCT03672318).

### 2.3 Kappa light chain

Immunoglobulin light chain is a promising target because mature B-cell malignancies are often featured by κ light chain or λ light chain restricted expression.27 Thus, CAR-T cells targeting light chain are dedicated to eliminate the tumor cells expressing a certain light chain with-out causing overt immunosuppression. Although plasma cells did not express cell-surface immunoglobulins, the postulated MM "stem cells" was shown to express surface immunoglobulins,18,27 which provided a chance to target the surface immunoglobulins. Monoclonal antibody MDX-1097, which targeted cell membrane-associated κ immunoglobulin free light chains in MM, achieved encouraging efficacy and was well tolerated in clinical trials of MM patients.28 In a phase 1 clinical study (NCT00881920), anti-κ light chain CAR-T cell was used to treat seven patients with MM, of which six patients had previously received ASCT. The result showed that four of seven patients had responses and maintained stable condition for 6 weeks to 24 months.27 This trial is still recruiting subjects.

However, almost all MM cells secrete immunoglobulin, but only a few cells express immunoglobulin on cell membrane. In addition, in the development of the disease, tumor cells usually downregulate the expression of surface immunoglobulin, which may weaken the target ability of anti-κ light chain CAR-T cell.

### 2.4 NY-ESO-1

New York esophageal squamous cell carcinoma-1 (NY-ESO-1) belongs to the family of cancer/testis (CT) antigens and is another attractive target antigen for myeloma. It is expressed in several types of cancers, including 60% of advanced MM patients at diagnosis and 100% of those at relapse,29 but is not expressed or low expressed on normal tissues. NY-ESO-1 redirected CAR-T cells exhibited specific anti-tumor reaction in vitro and in vivo.30 Another study showed that NY-ESO-1 specific re-directed T cells were able to lyse target cells that endogenously express NY-ESO-1 and secrete antigen-specific IFN-γ, and showed functional activity in a MM xenograft model.31 In addition, NY-ESO-1 specific TCR-engineered T cells were shown to achieve encouraging clinical responses in MM patients, with a median PFS of 19.1 months.32 A phase 1/2a open-label clinical trial (NCT01352286) carried out in the United States showed that NY-ESO-1 specific peptide enhanced affinity receptor (SPEAR) T cell therapy in MM patients resulted in 80% ORR at day 42 and median PFS of 13.5 months in 25 patients, and no fatal serious adverse events were observed during this study.33 Another open-label clinical trial involving NY-ESO-1 CAR-T cell therapy in different malignancies including MM has been registered and ongoing (NCT03638206).

Given that NY-ESO-1 is highly expressed in a variety of malignant tumors including MM and rarely expressed in normal tissues, anti-NY-ESO-1 CAR-T should have a wide application prospect in the future with low targeted toxicity. Indeed, not only in MM, clinical trials of anti-NY-ESO-1 CAR-Ts in solid tumors are also under intense investigation.

### 2.5 CD38

The CD38 molecule, a single chain type II transmembrane glycoprotein, is highly expressed on malignant myeloma cells, making it a suitable therapeutic target for CAR-T cell therapy. Daratumumab (CD38
monoclonal antibody) has been approved by the US Food and Drug Administration (FDA) for the treating MM, strongly supporting CD38 as a cell surface target of MM. Anti-CD38 specific CAR-T cells are effective in eliminating primary myeloma cells from patients as well as myeloma cell lines.34 NK-92 cells expressing CD38-specific Nb-CARs have obvious anti-tumor effects in both CD38-expressing myeloma cell lines and MM cells.35 In recent years, several novel therapeutic approaches targeting CD38 have been tested for MM patients. CD38 CAR engineered T cells effectively eradicated CD38+ primary MM cells in a preclinical study, providing a promising therapeutic tool for MM patients.

However, CD38 is also expressed on muscle cells, osteoclasts, prostate cells and normal hematopoietic cells such as red blood cells, B cells, T cells, and natural killer (NK) cells,25 which increases the potential off-target effects of anti-CD38 CAR-T cell therapy in MM patients. Prompted by this, efforts to minimize off-target effect of CD38 CAR-T are being explored in recent years. Preclinical study involving caspase-9-based suicide gene demonstrated that CD38-chimeric antigen receptor transduced T cells could effectively lyse CD38+ malignant cell lines, and displayed significant anti-tumor effects in a xenotransplant model of MM tumors.36 A rational approach for reducing on-target/off-target effects of anti-CD38 CAR-T cells using affinity optimization has been generated and showed highly suitability for the generation of optimal CARs.37 These studies showed that anti-CD38 CAR-T cells were highly feasible for treating MM patients who had no other chemotherapy options. Indeed, two clinical trials of CD38 contained CAR-T cell therapy in relapsed or refractory MM patients is ongoing (NCT03464916, NCT03767751).

2.6 CD44 variant 6

CD44 variant 6 (CD44v6), an isoform of the hyaluronate receptor CD44, is overexpressed in hematological malignancies and epithelial tumors, where it contributes to the cancer stem/initiating phenotype.38 The significance of CD44v6 is not clear. CD44v6 was shown to be expressed by 43% of advanced, high risk MM cases34 and was associated with 13q14 chromosome deletions, a well-known risk factor in MM.39 The minimal expression of CD44v6 on normal cells including activated T cells, monocytes and keratinocytes38 makes CD44v6 an attractive new candidate for CAR-T cells. During a preclinical study, CD44v6-targeted CAR-T cells constructed by Casucci et al., mediate potent anti-tumor effect against MM both in vitro and in NSG mice.38 Promoted by the promising preclinical result in MM, a phase I/IIa clinical trial to assess the safety, anti-tumor activity and feasibility of CD44v6 CAR-T cells in MM patients has been registered and is currently recruiting participants (NCT04097301).

However, anti-CD44v6 CAR-T still has potential targeted toxicity due to the nonspecific expression of CD44v6 on normal cells. Besides, CD44v6-targeted CAR-T cells really caused reversible monocyteopenia although they did not recognize hematopoietic stem cells.39 Additional studies are needed to further evaluate the safety of anti-CD44v6 CAR-T.

2.7 NKG2D ligands

NKG2D is a highly conserved type II transmembrane protein which plays an important role in general active immunosurveillance by recognizing several ligands such as MICA, MICB, etc.40 NKG2D ligands are widely expressed on solid and hematologic malignancies including MM but are rarely detectable on normal tissues, which makes NKG2D an attractive target for MM CAR-T therapy.22,24 In a phase 1 study (NCT02203825) of 12 patients, of whom five had relapsed/refractory MM, were treated with NKG2DL-targeted autologous CAR-T cells. Objective clinical responses to NKG2D CAR T-cell therapy alone were not seen, and CRS or CAR-T cell-related encephalopathy syndrome was not observed in these MM patients.42 On the whole, the NKG2D-CAR approach is still in early stages of clinical development, additional studies are needed to assess the clinical efficacy of it. Indeed, a clinical study of MM patients is currently recruiting (NCT03018405).

2.8 SLAMF7/CS1

Signaling-lymphocyte-activating molecule (SLAM)F7, a cell surface glycoprotein, also known as CS1, is widely and highly expressed on the surface of bone marrow myeloma cells but not in epithelial tissues and hematopoietic stem cells, making it a promising alternative antigen for MM CAR-T therapy. SLAMF7 is being extensively studied as a target for immunotherapy of MM. In vitro, SLAMF7 CAR-T cells can promote the rapid dissolution of previously untreated and R/R primary myeloma cells. Some normal tissues also expressed SLAMF7, including plasma cells, NK cells, T cells, B cells, and dendritic cells.43 Compared with CD38 and CD138, SLAMF7 was less expressed in normal tissues.43 Preclinical work has demonstrated the efficacy of anti-SLAMF7 CAR-T in MM cells. Anti-SLAMF7 CAR T cells exerted complete cytolytic effector activity in xenograft models.44 Wang et al. showed that anti-SLAMF7CAR-T exhibited efficient anti-tumor activity in a mouse model.45 Chu et al.46 Constructed SLAMF7 specific labeled CAR-NK cells, and tested the effect of SLAMF7-CAR-NK cells on the eradication of human MM cells with orthotopic MM xenograft mouse model. The results showed that SLAMF7-CAR-NK could effectively eliminate human myeloma cells and prolong mice survival, thus proving the specificity of SLAMF7 as a target for the treatment of MMA phase 1 clinical trial of SLAMF7 is underway (NCT03710421).

SLAMF7 is another attractive target of CAR-T cell for MM, because it is not expressed on non-hematologic tissues.45 However, whether the expression of SLAMF7 on NK cells limits clinical application in MM still need further clinical verification in the future.

2.9 CD56

CD56 is a specific marker of MM and strongly expressed by malignant plasma cells in 70% of myeloma patients.47 With the progression of
the disease, the loss of CD56 indicates extramedullary infiltration of MM and plasma cell leukemia. In a preclinical trial, CAR-T cells targeting CD56 in a xenograft model of myeloma effectively cleared the tumor of MM mice and showed powerful anti-tumor efficacy. Therefore, CAR T-cell therapy targeting CD56 has paved the way for clinical trials in combination with another target antigen (NCT03473496, NCT03271632).

However, CD56 is also expressed on some normal cells such as central neurons and NK cells, so the potential neurotoxicity may limit the application of CD56 CAR-T cell therapy.

2.10 | Integrin β7

Because integrin β7 is highly expressed in most myeloma cells and has an active conformer, researchers have developed anti-MMG49 CAR-T cells using fragments from MMG49 monoclonal antibodies, which could specifically recognize a subset of integrin β7. T cells transduced with MMG49-derived CAR specifically recognize and kill MM cells, exert powerful activity against MM without damaging normal hematopoietic cells. Thus, active conformer of integrin β7 can serve as a promising target against MM.

2.11 | CD70

CD70, a member of tumor necrosis factor receptor superfamily, has the ability to regulate the activation, proliferation, and differentiation of T cells and B cells, and plays an important role in maintaining the immune response of human body. Meanwhile, CD70 is highly expressed in a variety of hematological malignancies including lymphoma and MM. A preclinical study also supported the feasibility and safety of a CD27-containing CAR targeting CD70-expressing tumors, of which dramatic anti-tumor reactivity was observed both in vitro and in vivo. Furthermore, few in vitro “fratricide” occurred in this type of CAR-T response.

In recent years, CD70-targeted CAR-T therapies were reported to have robust anti-tumor responses in solid tumors. While engineered anti-CD70 antibody showed cell-mediated anti-tumor activities in malignant cells lines including MM, the suitability of CD70-targeted CAR-T cells in MM patients was still not reported yet.

2.12 | GPRC5D

The human orphan G protein-coupled receptor, class C group 5 member D (GPRC5D), highly expressed in CD138+ primary MM cells from bone marrow samples, is another feasible target antigen of MM. In a preclinical study, GPRC5D-targeted CAR-T cells were shown to exhibit significant anti-tumor effects on MM cell lines and myeloma cell murine xenograft model. In particular, GPRC5D-targeted CAR-T cells still showed activity in a murine model of BCMA escape mediated relapse. Overall, these results suggest that GPRC5D could play an important role in CAR-T therapy of MM patients.

2.13 | CD229

The surface antigen CD229, also known as SLAMF3, is not only commonly and strongly overexpressed on the malignant plasma cells but also highly expressed on pre-plasma cells carrying the phenotype of myeloma-propagating and chemotherapy-resistant cells in RRMM patients. CD229 CAR-T cells have been reported in a preclinical study with dramatic ability eradicating MM cells including MM-propagating cells without fratricide, indicating that targeting CD229 maybe a promising target for patients with MM.

2.14 | TACI

Transmembrane activator and CAML interactor (TACI), a member of the tumor necrosis factor receptor (TNFR) superfamily, was found to be expressed on MM cells, making it an alternative strategy for CAR-T therapy.

It has been showed that a proliferation-induced ligand (APRIL) -based CAR-T (ACAR-T cells) could target both BCMA and CAML activator (TACI) in myeloma cells, and still had anti-tumor activity even when BCMA was downregulated, thus reducing the risk of antigen negative escape. Further, in mouse intramedullary myeloma model, tumor regression could be induced within 2 days by ACAR cells. Recently, a study using APRIL-based, a novel trimeric CAR that targeted both BCMA and TACI, exhibited enhanced targeted cytolytic activity against MM lines in vitro and in vivo xenograft models, thus making this type of CAR a promising therapeutic approach for MM.

2.15 | Lewis Y

Lewis-Y (LeY) antigen is a part of Lewis blood group system. LeY antigen is moderately expressed in 52% malignant plasma cells of patients with MM. A preclinical study showed that anti-LeY CAR-T cells could target LeY-positive MM cells and exerted anti-tumor effects both in vitro and in myeloma mouse model, suggesting LeY antigen as a potential target for CAR-T cell therapy in myeloma. An early phase I clinical trial of LeY specific CAR-T in MM patients (NCT01716364) is registered.

3 | MULTI-TARGETS STRATEGIES FOR MM

Tumor recurrence caused by antigen loss and escape have become one of the major challenges for long-term disease control after CAR-T cell therapy of MM patients. Multi-targets strategies may eliminate poorly differentiated MM cells and increase the response of relapsed or refractory MM patients to CAR-T cells. The structures of multi-target CARs are mainly divided into the following types: (1) Two antigen recognition regions are expressed in tandem on the same expression vector; (2) CAR-T cells carrying two kinds of CARs are prepared by bicistronic expression vector; (3) Two or more CAR-T cells targeting different target antigens are infused successively or simultaneously; and
CONCLUSION

In recent years, CAR-T cell therapy has emerged as one of the great advances in relapsed/refractory MM patients who had poor responses to other therapies including chemotherapy. Anti-BCMA CAR-T was commonly used in clinical treatment of relapsed/refractory MM and got encouraging results. However, there were still some patients who had no response or relapsed after BCMA CAR-T therapy. In addition, CAR-T related toxicities such as CRS and neurologic toxicity, remain challenging. In this review, we summarized the candidate non-BCMA targeted CAR-T therapies such as CD38, CD138, SLAMF7, etc., most of which are under clinical studies and got promising results in MM. In addition, multi-targets strategies, which are currently under way or in development, may have the potential to reduce the recurrence and enhance treatment efficiency, thus highlighting the great potential benefit of CAR-T cell therapies. More clinical studies are needed to optimize the targets of CAR-T cell therapies for patients with MM in the future.

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CONFLICTS OF INTEREST

All the authors declare no financial competing interests.

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