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CAR T-cell Therapy of Hematologic Malignancies: An Update in Targeted Antigens

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Abstract
Immunotherapy with genetically engineered T-cells that express the chimeric antigen receptor (CAR) has raised hopes for the treatment of pediatric malignancies. Although CAR T-cell development is on a fast-moving pace and evolution, the context of exploring novel targetable antigens has been neglected. In this review study, we analyze the prominent hematologic antigens targeted by engineered T-cells in both preclinical and clinical aspects. Furthermore, we discuss the outcomes of CAR-based therapy in hematologic cancers from different viewpoints of treatment and provide some critical features for additional considerations. Almost certainly, most of the engineered T-cells redirected against hematologic disorders aim at conventional target antigens rather than targeting an ideal target antigen that is exclusively expressed on cancerous cells and restricted to normal tissues. CAR-based clinical trials in hematologic cancers have often dealt with CD19, followed by BCMA, CD22, and CD20 antigens. Besides, most of the scFvs used in the CAR structure are derived from murine antibodies, which may raise the concern about immunogenicity by reducing the persistence of modified T-cells. Nevertheless, short- and long-term life-threatening toxicities and the development of escape mechanisms that result in resistance and antigen loss are not thoroughly understood yet. The ultimate goal of using modified CAR T-cells is to make them effective and curative. Therefore, a better understanding of all the features pertaining to target antigens is imperative. Also, the methods to identify candidate target antigens and manage the associated obstacles of CAR T-cells should be evaluated and prioritized.
Keywords: Chimeric antigen receptor, Hematologic malignancies, Immunotherapy, T-cells

Introduction

Hematologic malignancies in children, such as leukemia, myeloma and lymphoma, are among the most important causes of mortality in the pediatric population of developed countries. Many patients with refractory malignancies relapse after chemotherapy or bone marrow transplantation. In recent years, chimeric antigen receptor (CAR) T-cell therapy has provided prospects for these patients (1). Immunotherapy with CAR, an artificial T-cell receptor providing strength and alertness to the host T-cells, has brought magnificent improvements in the field of cancer therapy (2). CAR is prominently defined by its extracellular domain, single-chain variable fragment (scFv). It is also derived from the antigen-recognition domain of either murine or humanized monoclonal antibody (mAb). The extracellular binding domain, scFv, is fused to the transmembrane domain via a flexible peptide linker and then connected to the intracellular domain. Upon the interaction of scFv with the interested antigen, A cascade of signaling begins in engineered T-cells to respond against the target cells (3) (Figure 1). In this regard, CAR is capable of recognizing the tumor antigen in a major-histocompatibility

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complex restricted manner, which makes the CAR T-cells superior to the conventional T-cell receptor (4). As such, encouraging outcomes have been observed in hematologic malignancies now that two CAR products, *Tisagenlecleucel* (Kymriah, CTL019, Novartis, Basel, Switzerland) and *Axicabtageneciloleucel* (Yescarta, KTE-C19, Gilead, USA) have already been included in the list of FDA-approved drugs (5). Indeed, Kymriah is specific and viable for up to 25-year-old patients with relapsed/refractory (R/R) B-cell acute lymphoblastic leukemia (B-ALL) (6). Also, Yescarta is practicable for the treatment of primary mediastinal large B-cell lymphoma (PMBCL and R/R diffused large B-cell lymphoma (DLBCL) (7). The most salient difference between these two approved engineered T-cells is in their structural components, where CD28 and 4-1BB co-stimulatory domains are exerted in Yescarta and Kymriah, respectively (8).

The data revealed that nearly 75% of the clinical trials for CAR-based therapy are focused on hematologic malignancies worldwide. The major targeted antigens in blood cancers are CD19, CD22, CD20, BCMA, and some other relevant ones (Figure 2 and Table I) (9). Despite the remarkable results in CAR-based therapy, several challenges have remained with no effective solutions, and other potential problems are emerging. Importantly, nearly 20% to 30% of patients relapse and acquire resistance after CD19 CAR T-cell infusion, which might be due to the CD19 antigen loss (10). However, the lack of an appropriate clinical target antigen significantly influences the efficacy of the T-cells engineered over cancerous cells. Therefore, discovering a new distinct antigen expressed exclusively on malignant cells and absent from healthy tissues would boost the effect of CAR-based therapy. Nevertheless, targeting or finding a single antigen does not always attack malignant cells properly. Aiming at several targetable antigens simultaneously may lead to higher specificity and lower toxicity (11).

Targeting tumor antigens is the basis of immunotherapies, such as CAR T-cell therapy. Tumor antigens fall into two major classes including tumor-specific antigens (TSAs) and tumor-associated antigens (TAAs). TSAs refer to the peptides found merely on tumor cells and often resulting from genetic mutations, while TAAs are the peptides overexpressed and/or abnormally expressed on cancer cells but expressed at lower levels on normal cells too. These tumor antigens are the biomarkers used to diagnose or excite targets in cancer treatment. Antigen targeting for cancer immunotherapy should ideally be cancer-specific and usable for all cancer patients and various cancer types. In recent years, some antigens, such as CD19, have been found to possess some of these properties for the treatment of B-cell malignancies by the CAR T-cell technology. On-target/off-tumor reactivity is one of the major challenges of antigen-depending immunotherapy. In the case of B-cell antigens, such as CD19, CD22 and BCMA, this problem is easily overcome by exogenous immunoglobulins (12, 13).

The ultimate goal of this review is to collect a set of the latest major hematologic antigens targeted by CAR T-cells. The tumor antigens to take into account here are the major antigens of hematologic neoplasms that have been targeted through CAR T-cell therapy in clinical and animal studies. Furthermore, different outcomes of both clinical and preclinical trials are discussed and compared, and the findings of the trials are provided for additional considerations.

CD19

CD19 is a 95-kDa transmembrane molecule expressed on progenitor B-cells, naive and memory B-cells, and plasmablast cells. It is comprised of an extracellular region containing two C2-type Ig-like domains divided by a smaller disulfide-linked domain. The CD19

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cytoplasmic domain with 240 amino acids possesses nine conserved tyrosine residues, which might interact with Vav, Lyn, Lck, and Fyn protein tyrosine kinases (14).

In the last decade, CAR T-cells emerged as a promising therapeutic option against CD19 antigen-positive cancers (15). As a result, the FDA approved *tisagenlecleucel* and *Axicabtageneciloleucel*, which showed remarkable anti-tumor activity in patients with R/R ALL and non-Hodgkin lymphoma (NHL), respectively (16, 17). The new challenge of antigen loss in both B-ALL and large B-cell lymphoma has greatly influenced the functionality of CD19-targeted CAR T-cells (10). Despite the well-expressed CD19 antigens on B-ALL, approximately 30% of cancer patients experience relapses after CR due to the loss of CD19 epitope (18). As found in a study (19), the mechanism of resistance in relapsed leukemias which lack the CD19 epitope on the cell surface is defined by mutations in exons 2 and 4. Subsequently, Orlando et al. (20) discovered de novo genetic alterations in exons 2-5 in patients with CD19-negative relapses. They concluded that homozygous or biallelic frameshift mutations in CD19 are the main source of CD19 loss and the acquired resistance to CTL019. In the same context, the results gained by Asnani et al. (18) corroborated the previous findings.

In another study (21), the transcriptome profiling and regulatory mechanisms of bone marrow specimens were investigated before and after CD19 CAR-engineered T-cell therapy in adult patients with refractory B-ALL. The results revealed that microRNAs and long non-coding RNAs might be in close association with transcriptional and post-transcriptional regulatory mechanisms in CAR-based immunotherapy. This suggests the key regulatory roles of these factors in CD19 CAR-engineered T-cells. Interestingly, despite the remarkable success in allogeneic hematopoietic stem-cell transplantation (alloHSCT) for advanced B-cell malignancies, most of the patients do not experience complete remission (CR); rather, they have a relapse after alloHSCT. To address such obstacles, donor-derived allogeneic CD19 CAR T-cells were redirected against the progressive malignant B-cells that were positive for CD19 antigens. According to the findings, no graft versus host disease (GVHD) occurred, and the patients had a promising CR after CAR T-cell infusion. Some controllable side effects such as fever, tachycardia and hypotension were also observed (22).

CD30

CD30 is a type I transmembrane glycoprotein. It weighs 105-120 kDa, originates from the tumor necrosis factor receptor family, and is designated as a therapeutic target for Brentuximab vedotin (23-25). The primary role of CD30 is not thoroughly identified, but it is considered to play a role in cell proliferation and survival as well as T-lymphocyte immune response and regulation. It also acts as a co-stimulatory receptor for secondary T-cell responses. CD30 expression has been corroborated on some populations of activated cells such as B, T, and natural killer cells, memory T-cells (CD45RO+), and macrophages (26).

Hombach et al. (27) proposed the first concept of using CAR T-cells against CD30 antigen. They developed and redirected the first-generation modified T-cells expressing CD30 CAR by using the scFv of HRS3 mAb against in vitro CD30+ lymphoma cells. As a result, they introduced a new path for the future clinical treatment of CD30+ Hodgkin lymphoma patients. The first clinical trial of anti-CD30 CAR T-cells in R/R Hodgkin lymphoma was conducted by Wang et al. (28). They defined the feasibility of effective trafficking to tumor sites and the safety of CD30-targeting CAR T-cells without severe toxicity in patients. In their

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trial, few patients experienced anaphylaxis and grade 3-4 toxicities, which might be due to the heavy pretreatment chemotherapy. Similarly, Ramos et al. (29) conducted a phase I dose-escalation study in which CD30 CAR T-cells infused in patients with R/R Hodgkin lymphoma or anaplastic large cell lymphoma. These enrolled patients achieved a complete response without receiving a conditioning regimen before the CAR T infusion, and no severe toxicities were observed. However, the CD30 CAR T-cells at the highest dose led to CRS in the patients.

CD20

CD20 is a non-glycosylated phosphoprotein. It weighs 33–37 kDa and is present on the surface of almost all healthy and malignant B-cells but not on plasma cells and hematopoietic stem-progenitor cells. CD20 is designated as an appropriate targetable antigen for B-cell lymphoma and leukemia in which Rituximab is a therapeutic monoclonal antibody for this antigen (30).

Till et al. (31) presented the concept of anti-CD20 CAR T-cell-based therapy against B-cell malignancies. They constructed the first-generation CD20 CAR-engineered T-cells. The results of this study demonstrated the potential anti-malignancy responses, feasibility, and limited toxicities of anti-CD20 CAR T-cells in patients with R/R indolent B-cell NHL and mantle cell lymphoma (MCL). To further optimize the previous genetically-modified T-cells against relapsed indolent NHL and MCL patients, two co-stimulatory domains (CD28, 4-1BB) were added together to achieve the third-generation CAR (32). Budde et al. (33) implemented an inducible caspase 9 (iCasp9) suicide system to minimize CD20 CAR-related severe side effects. These modified T-cells effectively destroyed CD20-positive tumor cells and secreted the intended cytokines upon activation. Also, more than 90% of the engineered T-cells expressing CD20 CARs were deleted both in vivo and in vitro by a small molecule inducing a dimerized drug, AP1903. In another study (34), histone deacetylase inhibitors (HDACIs) such as romidepsin and suberoylanilide hydroxamic acid were used to escalate the CD20 antigen expression on malignant B-cells, thus augmenting the anti-tumor activity of CD20 CAR T-cells. Interestingly, the modified T-cells were ineffectual against normal B-cells, which was considered to be due to the low expression of CD20 on healthy B-cells. HDACIs pre-conditioning before CD20 CAR T-infusion led to better cytotoxicity activity and increased the function of the modified T–cells.

CD33

CD33 is a type I single-pass transmembrane protein and a 67-kD protein. It is derived from the sialic acid-binding immunoglobulin-like lectins family and serves as an ideal target for Gemtuzumabozogamicin (35). Its expression is identified on hematopoietic progenitors and myelomonocytic precursors as well as phagocytic cells such as macrophages, microglial cells, dendritic cells, and monocytes (36). Research has shown that most of the patients diagnosed with acute myeloid leukemia (AML) express CD33 antigen on their leukemic blasts (37).

Marin et al. (38) introduced CD33-CAR into cytokine-induced killer (CIK) cells and then redirected the manipulated cells against AML cells in vitro. The CD33 CAR-redirected CIK cells maintained a high level of immunostimulatory cytokine secretions and anti-leukemic cytotoxicities upon CD33+ AML cells. Most importantly, these modified-CIK cells killed some of the normal human hematopoietic progenitor cells, which raises the concern about on-target off-tumor toxicity. Subsequently, Dutour et al. (39) developed human Epstein Barr Virus-(EBV-) specific cytotoxic T-cells expressing anti-CD33 CARs. These anti-CD33-EBV-specific T-cells were exerted against CD33+ human AML-bearing

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NOD-SCID mice. This resulted in partial anti-leukemic activities and released cytokines upon engagement with the target cells. Moreover, in the in vitro model of the study, the modified T-cell had no sign of attacking the CD33+ hematopoietic progenitor cells. Consequently, Wang et al. assessed the feasibility and efficacy of anti-CD33 CAR T-cells in a patient with refractory AML. The patient was found to experience a reduction in bone marrow blasts and develope a florid disease, indicating the concern about using CD33 CAR-based therapy in refractory AML patients. Nevertheless, CART-33 cell therapy has exhibited anti-leukemic effects and a potential to control toxicities, thus providing a new therapeutic strategy for the treatment of R/R AML patients (40). Since the toxicity of CD33 CAR-engineered T-cells against the normal myeloid compartment is not thoroughly understood, Minagawa et al. (41) constructed inducible Caspase9 (iC9)-CAR.CD33 T-cells to reduce the potential side events of CAR-based therapy.

ROR1

ROR1 is a type I tyrosine kinase-like orphan receptor which acts as a receptor of Wnt-5a protein to activate the catenin-independent non-canonical Wnt signaling pathways (42). The expression of ROR1 is determined during embryonic and fetal development and observed less in the adipose tissue, pancreas, lungs, and a subset of intermediate B-cells (43). These unique patterns of ROR1 expression are considered as eminent tumor-specific targets for immunotherapy.

The concept of adoptive immunotherapy with CAR has attracted attention and led to the generation of genetically engineered T-cells expressing ROR1 CARs. Hudecek et al. (44) successfully constructed ROR1-CAR T-cells using 2A2 mAb that targets a distal membrane epitope in the Ig-like/frizzled region of ROR1. The modified T-cells selectively destroyed the ROR1 positive primary B-CLL and the primary mantle cell lymphoma (MCL) cell lines but spared the normal resting or activated B-cells. Importantly, the study did not assess the potential attacks on healthy tissues and the corresponding side effects. Subsequently, the same research group observed that the previous ROR1 CAR, when armed with a shorter spacer length and a high-affinity scFv, could augment the function of the T-cell effector and the recognition of ROR1 positive hematopoietic tumors. Realizing the importance of optimally designed ROR1 CAR T-cells is the key to achieve satisfying results (45). Thus, to shed more light on the safety of ROR1-engineered T-cells, R12 scFv derived from the rabbit antibody was used to redirect ROR1 CAR in macaques. Although the data supported the feasibility and safety of the ROR1 engineered T-cells in a non-human primate, the study demonstrated no long-term safety due to early T-cell immune response against the CAR T cells (46). Recently, T-cells empowered with synthetic Notch (synNotch) receptors specific for EpCAM or B7-H3, which are present on ROR1 positive malignant cells, have provided a new strategy to overcome off-tumor toxicity. Indeed, exerting synNotch receptors offered a novel strategy to address the toxicities imposed by ROR1 CAR T-cells upon healthy tissues (47).

CD44v6

CD44 is a type I transmembrane glycoprotein with structural heterogeneity. It mediates the physiological and pathophysiological functions of tumor progression, lymphocyte homing, hematopoiesis, inflammation, and embryogenesis (48, 49). Different expression of CD44 isoforms have been observed during various tumor progressions, including variant CD44v6 isoform (48, 50). CD44v6 acts as a co-receptor for different cytokines such as epidermal growth factor, vascular endothelial growth factor, hepatocyte

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growth factor, and C-X-C motif chemokine (48).

Accordingly, Casucci et al. (51) generated anti-CD44v6 CAR T-cells by using scFvs derived from the humanized CD44v6-specific mAb Bivatuzumab. The modified T-cells had successful anti-malignancy responses against preclinical AML and MM without harming the normal hematopoietic stem cells and the CD44v6-positive keratinocytes. Interestingly, the predicted adverse occurrence of monocytopenia from the CD44v6 CAR-engineered T-cells made the researchers use a suicide gene system such as thymidine kinase or iC9 suicide genes to control the expected toxicities of hyperacute xenogeneic GVHD. Consistent with previous findings, CIK-expressing CD44v6 CARs were developed and redirected against high-grade soft tissue sarcomas (STS). The engineered-CIK cells proved to be anti-sarcoma without significant side effects and secreted a high amount of IL6 and IFN- γ in the STS xenograft model (52). As a benefit for future clinical applications, both studies provide new promising procedures for the adoptive treatment of CD44v6 positive tumors.

CD123

CD123 is a transmembrane α-chain of the interleukin-3 receptor (IL-3R) and a glycoprotein consisting of three extracellular domains, a transmembrane domain and a short intercellular domain (53). This 75 kD molecule is typically expressed on plasmacytoid dendritic cells and basophils at a high level and on eosinophils, monocytes, HSCs and myeloid dendritic cells at a lower level (54, 55). The CD123 expression has also been observed on some other cells such as AML blast, CD34+ leukemic progenitors, AML-LSCs, blastic plasmacytoid, dendritic cell neoplasm, B lymphoblastic leukemia, hairy cell leukemia, erythroid progenitor cells, mature granulocytes, and lymphocytes (56, 57).

To more selectively target and eliminate AML cells, Sarah et al. (58) fabricated CIK cells armed with first-generation CD123 CARs using the scFv of anti-CD123 mAb 7G3. These CD123 CAR-modified CIK cells were capable of destroying CD123+ cell lines and primary AML cells as well as sparing normal hematopoietic progenitor cells in vitro. However, slight toxicity was observed against the monocytes and normal CD123+ endothelial cells, which might be due to their lower CD123 antigen surface density. Subsequently, Mardiros et al. (59) developed T-cells expressing CD123-specific CARs with a CD28 co-stimulatory domain for CD123+ AML cells. These modified T-cells had strong anti-leukemia activity both in vitro and in a xenogeneic mouse model of AML. They did not kill healthy progenitor colony formation, which means sparing the normal hematopoietic progenitors. In contrast, these engineered T-cells significantly suppressed the development of clonogenic myeloid leukemic progenitors. Thus, the T-cells obtained from AML patients could be effectively manipulated to express CD123 CARs for the destruction of autologous blasts. Both studies highlighted the therapeutic role of CD123 CAR-modified T-cells for AML patients. In line with these results, Stevens et al. (60) redirected CD123-specific engineered T-cells against the myelodysplastic syndrome (MDS). They successfully constructed the second-generation CD123 CARs that were expressed separately on both healthy donors and MDS patient-derived T-cells. The data revealed that the modified T-cells did not target the normal hematopoietic stem and progenitor cells while killing the MDS stem cells in both in vitro and xenografts models.

CD22

CD22 is a 140-kDa single-spanning membrane glycoprotein in the family of sialoadhesin proteins family. It is selectively expressed on mature B-cells as

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well as precursor B-cells at a lower level, but it has no expression in mature plasma cells (61). CD22 is expressed in 60-80% of B-cell lymphomas, including hairy cell leukemia, chronic lymphoblastic leukemia, NHL, and ALL (62). So far, several therapeutic monoclonal antibodies such as Epratuzumab, Inotuzumab, Ozogamicin, Moxetumomab and Pasudotox have been used to target the CD22 antigen (63).

Haso et al. (64) genetically engineered some T-cells that expressed CD22 CARs with different antigen-recognition domains. In a preclinical model, it was found that the second-generation CD22 CAR T-cells possessing the proximal CD22 epitope-specific scFv of m971 mAb have much better anti-leukemic response than the other modified T-cells with similar affinity to target different epitopes. Additionally, neither adding one extra co-stimulatory domain to the second-generation CAR nor extending the distance between the CD22 epitope and the T-cell surface could augment the anti-tumor response. The results highlighted the applicability of CD22 CAR-based therapy in ALL patients. Subsequently, CD22 CAR T-cells were redirected against B-cells in ALL patients including the patients with dim or negative CD19 (65). The data denoted the potent anti-leukemic activity of CD22 CAR T-cells with no substantial sign of off-target toxicity, severe neurotoxicity or CRS. However, in this trial, the density of CD22 reduced down to a complete loss. This gave leukemia a chance of escaping from CD22 CAR-engineered T-cells that could then lead to a high rate of relapse. Likewise, in another study (66), CD22 CAR T-cells were redirected against R/R B-ALL in pediatric and adult patients whose previous CD19 CAR-based therapies were ineffectual. Interestingly, CD22 CAR-modified T-cells induced a high rate of complete remission in these patients, and no sign of a significant association was observed between the relapse and the loss or mutation of the CD22 antigen.

CD5

CD5 (Leu-1) is a 67-kD glycoprotein and a member of the scavenger receptor cysteine-rich superfamily. It takes part in the TCR/CD3 complex and B-cell receptors and is expressed on thymocytes, T-lymphocytes and a small subset of B-cells (67, 68). This receptor has been shown to be an immunological synapse between T-cells and antigen-presenting cells, a positive/negative regulator of TCR signaling, and a negative regulator of BCR signaling (69). Mamonkin et al. (70) transduced T-cells with CD5 CARs using the scFv of clone H65 to achieve a substantial depletion in CD5-positive malignant T-cells and the least fratricide. The anti-CD5 CAR T-cells were capable of recognizing and destroying malignant T-cells and primary T-ALL blasts with limited fratricide, but no complete tumor eradication was observed in this study.

BCMA

B-cell maturation antigen (BCMA) is a member of the TNFR superfamily. It is a cell-surface protein predominately expressed by mature B-lymphocytes, plasma cells, and most cases of multiple myeloma (MM) (71, 72). BCMA is designated as an ideal immunotherapeutic target for myeloma and shown to be expressed in malignant plasma cells. It is a critical factor for the survival of normal bone marrow plasma cells, but, importantly, it is absent in the early development of B-cells and the other bone marrow cell populations (73).

Ali et al. (71) performed a dose-escalation clinical trial for the BCMA CAR-based treatment of patients with MM. They demonstrated the limited anti-myeloma activity of modified T-cells. Some patients experienced mild toxicity, but the others had negative bone marrow plasma cells and entered CR for a few weeks before relapse. In a similar context, Brudno et al. (74) treated R/R MM patients with a chemotherapy regimen of

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cyclophosphamide and fludarabine before anti-BCMA CAR T-cell infusion. The trial achieved significant anti-malignancy responses such as the eradication of wide bone marrow myeloma although there was considerable toxicity in some of the patients. However, further investigation is required to enhance CAR proliferation, survival, persistence, and exertion of humanized scFv (75) to subside the possibility of immunogenicity. Recently, a few studies have developed BCMA CAR T-cells against MM disorders (76, 77).

CD138

CD138 is a member of the syndecan family and the most widely studied heparan sulfate proteoglycan. Syndecan-1 is significantly present on the basolateral surface of epithelial cells despite being expressed at different stages of differentiation in normal lymphoid cells (pre-B) and mesenchymal cells during the development of mature plasma B-cells. CD138 takes part in cell adhesion, migration, proliferation, signaling, cytoskeleton, and extracellular matrix interactions. The aberrant expression of this protein often correlates with the malignant phenotypes of the cells that are linked to increasing cell angiogenesis, survival, metastasis, and invasion (78-80).

Guo et al. (81) conducted adoptive immunotherapy with second-generation CD138 CAR-modified T-cells in patients with advanced and chemotherapy-refractory MM. Although the study provided a feasible, well-tolerated and safe mode of treatment for these patients, long-term outcomes and potential toxicity needed to be followed up. Furthermore, anti-CD138 CAR T-cells were redirected for a 52-year-old male MM patient with extensive extra-medullary involvement. The use of CD138-modified T-cells was found as a potential therapeutic strategy for this type of malignancy. However, the patient died due to the lung infection, implying the need for further evaluation of CD138 CAR-based therapy (82). Similarly, Sun et al. (83) constructed the second-generation CD138 CAR using the scFv of the BT062 chimeric antibody. The CD138 CAR-modified T-cells exhibited significant anti-MM activity with no on-target off-tumor toxicity both in vitro and in a xenograft mouse model.

CD7

Human CD7 molecules are expressed on thymocytes, T and NK cells as well as the progenitors of lymphoid and a subset of myeloid progenitor in the cord blood of healthy individuals. The exact physiological functions of CD7 have not been thoroughly understood. However, the expression of CD7 has been found to be 30% on AML and 95% on lymphoblastic leukemias and lymphomas. CD7 expression might be in close association with resistance to the standard treatment and the aggressive and progressive forms of the disease. Moreover, CD7 positivity is linked to the poor prognosis of myelodysplastic syndromes, treatment resistance, and the high incidence of relapse after stem cell-transplant (84-86).

To enhance the efficacy of CD7-based therapy in patients afflicted with T-cell malignancies, some researchers developed CD7 CAR-engineered T-cells for a preclinical model of T-cell malignancies. However, the concern about the fratricide of CD7 CAR-transduced T-cells due to the very existence of CD7 in the T-cell population should not be neglected (87). Therefore, Gomes et al. (ibid) used a genome-editing technique such as CRISPR/Cas9 to disrupt the CD7 gene before CAR expression. They demonstrated that the CD7 CAR-modified T-cells whose CD7 was knocked out had a substantially reduced rate of fratricide and a robust anti-tumor activity against T-malignancies. However, the manipulated T-cells showed cytotoxic activity for healthy T and NK cells. Consistent with these data, Cooper et al. (88) developed "off-the-shelf fratricide-resistant" CAR T-cells where the expressions of both CD7

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and a T-cell receptor alpha chain (TRAC) were expunged simultaneously via the CRISPR/Cas9 system. These CD7 and TRAC-deleted CAR T-cells efficiently destroyed human T-ALL cell lines and patient-derived primary T-ALL with no sign of xenogeneic GVHD. In contrast, Png et al. (89) blocked the CD7 expression in T-cells by transducing the protein expression blocker (PEBL) in anti-CD7 scFvs to boost the success of CD7 CAR T-cells and reduce the fratricide by abrogating the CD7 expression. The CD7 PEBL-CAR-modified T-cells yielded remarkable anti-leukemic responses in patient-derived T-ALL xenografts.

Table I: Some of the current clinical trials of CAR-based therapy in hematologic malignancies

Target Antigen	Disease*	Status	Phase	Estimated Enrollment	Start date	Finish date	Sponsor	NCT
NA	HM	Not Yet Recruiting	NA*	600	Dec, 2019	Mar, 2035	Assistance Publique - Hôpitaux de Paris	**NCT04209829**
CD4	MM	R	1	12	Nov, 2019	Oct, 2021	iCell Gene Therapeutic	**NCT04162340**
BCMA, CD38, CD56, CD138	MM	R	1/2	20	July, 2017	Dec, 2020	Shenzhen Geno-Immune Medical Institute	**NCT03271632**
NA	HM	By Invitation	2	500	Aug, 2018	Dec, 2032	Autolus Limited	**NCT03628612**
BCMA AND CD19	MM	R	1	20	Dec, 2019	Dec, 2020	The First Affiliated Hospital of Nanchang University	**NCT04194931**
NA	HM	R	1/2	50	Aug, 2017	Aug, 2023	Hebei Senlang Biotechnology Inc., Ltd.	**NCT03312205**
BCMA	Myeloma	R	1	15	Apr, 2018	Apr, 2020	Henan Cancer Hospital	**NCT03664661**
Dual CD38/ BCMA	MM	R	1/2	80	Dec, 2018	Dec, 2022	Chinese PLA General Hospital	**NCT03767751**
BCMA	MM	R	1	10	Mar, 2019	Mar, 2021	PersonGenBioTherapeutics (Suzhou) Co., Ltd.	**NCT04186052**
CD38	MM	R	1	72	Apr, 2018	Sep, 2020	Sorrento Therapeutics, Inc.	**NCT03464916**
CD138	MM	R	1	33	Jan, 2019	Oct, 2032	UNC Lineberger Comprehensive Cancer Center	**NCT03672318**
CD20	NHL	R	1/2	30	Dec, 2017	Nov, 2037	Fred Hutchinson Cancer Research Center	**NCT03277729**
CS1	PCM	R	1	30	Feb, 2019	Dec, 2021	City of Hope Medical Center	**NCT03710421**
CD123-CD33	HM	R	1	20	Mar, 2018	Sep, 2020	iCell Gene Therapeutics	**NCT04156256**
Kappa Light Chain	HM	R	1	54	Jul, 2009	Jul, 2034	Baylor College of Medicine	**NCT00881920**
CD19	AML	R	1/2	15	Oct, 2017	Jan, 2022	Shanghai Unicar-Therapy Bio medicine Technology Co.,Ltd	**NCT03896854**
CD38	ALL	R	1/2	80	Nov, 2018	Nov, 2022	Chinese PLA General Hospital	**NCT03754764**
CD30	Lymphoma	Active	1	10	Oct, 2011	Dec, 2030	UNC Lineberger Comprehensive Cancer Center	**NCT01316146**

*Abbreviations: Not Available (NA), Recruiting (R), Multiple Myeloma (MM) Acute Lymphoblastic Leukemia (ALL), Hematologic Malignancy (HM), Plasma Cell Myeloma (PCM), Acute Myeloid Leukemia (AML), Non-Hodgkin Lymphoma (NHL), Hodgkin Lymphoma (HL).

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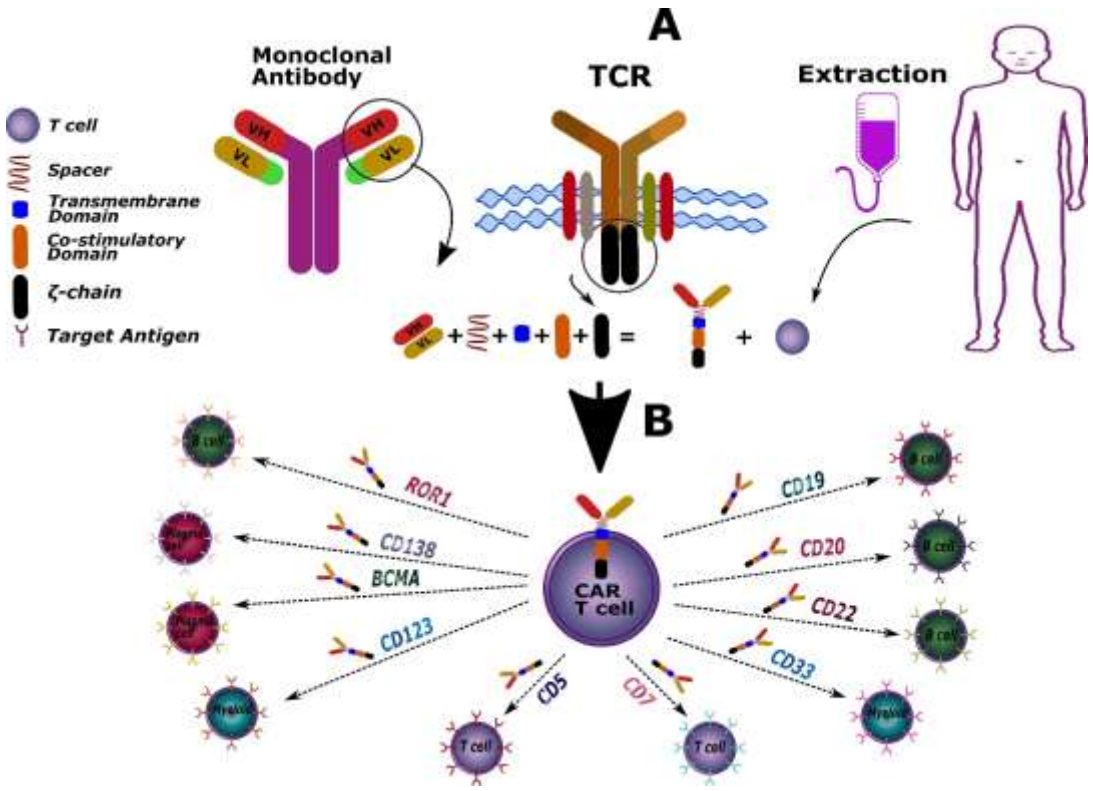

Figure 1. A schematic display of CAR construction and its target antigens: (A) CAR is derived from different types of proteins such as CD28 and CD8α specific for hinge and transmembrane domains. There are CD244, CD28, OX40 and ICOS for a co-stimulatory domain as well as CD3 ζ, DAP10 and DAP12 for an intracellular signaling domain. The scFv of CAR mainly originates from either the murine model of monoclonal antibody or its humanized form. (B) The isolated T-cells then undergo a modification process to express the desired CAR. The engineered T-cells can target various types of biomarkers in hematiologic malgnancies. These potential targetable antigens are not tumor-specific antigens, meaning that they are present on healthy cells as well.

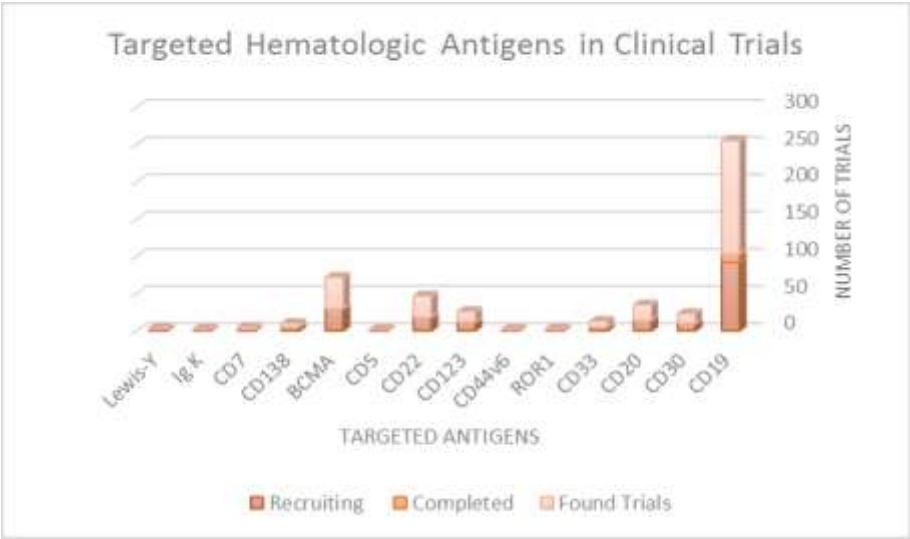

Figure 2. The number of CAR T-cell-based therapeutic trials against hematologic antigens: The data were obtained from the studies registered at http://clinicaltrials.gov/. Most of the trials targeted the CD19, CD22, CD123, CD20, CD30 and BCMA antigens more than the other antigens. This indicates the therapeutic roles of these antigens for hematologic malignancies, while other potential targetable antigens have been neglected and are needed to be investigated for the further success of treating such malignancies.

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Conclusion

Despite the current state of the art in therapeutic agents, substantial numbers of patients with high-risk hematologic malignancies have remained incurable. As a novel practical therapeutic strategy, CAR-based therapy is a promising treatment option for both leukemia and lymphoma patients. In contrast, the other approaches against solid tumors are ineffectual and challengeable due to various identified and unidentified physiological factors (10). In this regard, short and long-term life-threatening toxicities and the development of escape mechanisms that result in resistance and antigen loss are still under evaluation.

CAR-based therapy is at a fast pace of development and design, while the issue of potential antigen discovery for clinical purposes is restricted and neglected. Indeed, several critical concerns are needed to be addressed. Most scFvs are derived from murine antibodies rather than humanized models, which may cause the development of immunogenicity and reduce the persistence of modified T-cells. CARs predominantly target the surface antigens; therefore, characterizing the optimal affinity and avidity of the interaction between the CAR and its corresponding ligand can alter the treatment outcomes (90). Furthermore, selecting the most proper epitope of a targeted antigen and realizing whether to design a high-affinity or low-affinity binding domain would boost the therapeutic use of CAR T-cells. Besides, the spacer or the hinge region of CAR appears to be a significant component in reaching the desired epitope. The lack of defined optimal length of spacer whether to use a longer or shorter spacer in CAR construction could hinder the success of therapy (91).

Almost certainly, the majority of the CAR T-cells used against leukemia and lymphoma disorders targeted the conventional tumor antigens rather than exploring innovative targetable antigens. This approach may almost always lead to the same results and problems such as low-level persistence and the corresponding side effects of CAR T-cells. Therefore, a new outlook on the antigen of interest is imperative to optimize the treatment and make it more effective for such malignancies. In the context of antigens, multiple potential antigens have been investigated to provide significant immunogenic epitopes and thus to accelerate the therapeutic success of CAR T-cells (92). These tumor-specific and the associated antigens are classified as neoantigens, overexpressed antigens, viral antigens derived from oncogenic viruses, shared self-antigens, tumor-associated carbohydrate antigens, and peptides derived from the non-coding region of the genome (93, 95). As a result, there is a need for an ideal target antigen that is exclusively expressed on cancerous cells and restricted to normal tissues so as to maximize the specificity and minimize the off-tumor toxicity.

As such, using other therapeutic techniques like immune checkpoint antibodies, combinational treatments, tyrosine kinase inhibitors, and the medicines that are capable of elevating the expression of the intended antigen before CAR infusion may yield interesting results. Consequently, thorough preclinical and clinical evaluations are required to increase the success and safety of genetically engineered T-cells in susceptible patients. The methods of identifying multiple candidate antigens and managing the associated obstacles of CAR T-cells should also be assessed and prioritized.

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Conflict of interests

There is no conflict of interests to declare.

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