Application and challenges of chimeric antigen receptor T cell therapy in the treatment of acute myeloid leukemia (Review)

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Abstract. Chimeric antigen receptor (CAR) T cell therapy is a rapidly evolving form of targeted immunotherapy that merges the antigen-recognition specificity of monoclonal antibodies with the potent cytotoxic function of T cells. While it has achieved remarkable clinical success in B cell hematologic malignancies, its application to acute myeloid leukemia (AML) remains limited by several key obstacles. These include the absence of AML-specific antigens, antigen escape, an immunosuppressive tumor microenvironment and pronounced intratumoral heterogeneity. Together, these challenges substantially hinder the efficacy and safety of CAR-T cell therapy in AML. The present review provides a comprehensive overview of current advancements in CAR-T cell therapy for AML, with particular emphasis on strategies to overcome existing barriers such as improved target antigen selection, CAR structural optimization and modulation of the tumor microenvironment. These insights aim to inform the development of next-generation CAR-T therapies with enhanced precision, persistence and therapeutic benefit in AML.

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Abbreviations: CAR, chimeric antigen receptor; AML, acute myeloid leukemia; OS, overall survival; R/R, relapsed/refractory; HSCT, hematopoietic stem cell transplantation; allo-HSCT, allogeneic hematopoietic stem cell transplantation; GVHD, graft-vs.-host disease; ADCs, antibody-drug conjugates; scFv, single-chain variable fragment; ALL, acute lymphoblastic leukemia; HSCs, hematopoietic stem cells; HSPCs, hematopoietic stem and progenitor cells; iCasp9, inducible caspase-9; CRS, cytokine release syndrome; CR, complete remission; DL4, dose level cohort; MRD, minimal residual disease; ICANS, immune effector cell-associated neurotoxicity syndrome; CLL-1, C-type lectin-like molecule-1; LSCs, leukemia stem cells; TME, tumor microenvironment; HLA, human leukocyte antigen; CNS, central nervous system; AI, artificial intelligence; UCAR-T, universal chimeric antigen receptor T cell; FLT3, FMS-like tyrosine kinase 3;ITD, internal tandem duplications; GO, gemtuzumab ozogamicin; CLEC12A, C-type lectin domain family 12 member A; NK, natural killer

Key words: chimeric antigen receptor T cells, acute myeloid leukemia, targeted therapy

Contents

1. Introduction

Acute myeloid leukemia (AML) is a clonal malignant proliferative disease originating from myeloid progenitor cells in the hematopoietic system. AML is characterized by a high relapse rate, with a 3- to 5-year overall survival (OS) rate of <30% (1). For patients with high-risk or relapsed/refractory (R/R) AML, allogeneic hematopoietic stem cell transplantation (allo-HSCT) remains the only potentially curative treatment option (2). However, its clinical application is often complicated by serious adverse events such as graft-vs.-host disease (GVHD) (3). With the growing understanding of the leukemia microenvironment and immune landscape, various immunotherapies including immune checkpoint inhibitors, antibody-drug conjugates (ADCs) and cellular therapies have entered clinical trials (3). Nevertheless, these approaches still face limitations such as resistance and disease relapse, highlighting the urgent need for novel therapeutic strategies.

Chimeric antigen receptors (CARs) are synthetic receptor molecules engineered through gene editing technologies. They endow effector T cells with the ability to specifically recognize target antigen epitopes, thereby

enhancing T lymphocyte recognition and activation toward tumor antigens (4). A CAR construct generally comprises four main components: i) An extracellular antigen recognition domain, typically composed of a single-chain variable fragment (scFv), which enables the specific targeting of tumor-associated antigens or tumor-specific antigens, conferring high selectivity to CAR-T cells; ii) a hinge or spacer region, which provides structural flexibility and connects to the scFv; iii) a transmembrane domain, often derived from molecules such as CD3ζ, CD4, CD8 or CD28, serving as a structural bridge between extracellular and intracellular regions; and iv) an intracellular signaling domain, primarily composed of CD3ζ, responsible for initiating T cell activation and downstream signaling cascades that are important for the cytotoxic function of CAR-T cells (5). To date, CAR-T cell therapy has achieved breakthrough success in treating B cell hematologic malignancies, such as acute lymphoblastic leukemia (ALL) (6). However, its application in AML remains notably limited due to various challenges.

The present review summarizes advances in CAR-T cell therapy for AML within a conceptual framework that separates fundamental biological barriers from technical and engineering limitations. From a biological perspective, AML poses unique challenges including the lack of leukemia-specific antigens, clonal heterogeneity, antigen escape, persistence of leukemia stem cells and a profoundly immunosuppressive tumor microenvironment (TME). From an engineering perspective, current CAR-T approaches are further constrained by limited *in vivo* persistence, treatment-related toxicities, insufficient functional control and manufacturing complexity. By integrating these two dimensions, the present review aims not only to summarize current progress, but also to highlight unresolved questions, areas of controversy and future directions for the rational development of next-generation AML CAR-T therapies.

2. Advancements in CAR-T cell therapy for AML

CD33. CD33, also known as sialic acid-binding immunoglobulin-like lectin 3, is a differentiation-associated antigen predominantly expressed on myeloid progenitor cells and broadly distributed across various stages of myeloid lineage development (7). In AML, CD33 is highly expressed on leukemic progenitor cells, whereas its expression on normal hematopoietic stem and progenitor cells (HSPCs) is relatively low (8). This differential expression profile renders CD33 a compelling target for AML-directed immunotherapy.

Among CD33-targeted strategies, ADCs have achieved notable clinical progress. In 2017, the U.S. Food and Drug Administration approved gemtuzumab ozogamicin (GO) for the treatment of $CD33^+$ AML, marking the first approved ADC for AML and representing a major milestone in precision medicine for hematologic malignancies (9). The clinical success of GO has verified the potential of CD33 as an effective therapeutic target and has also promoted the development of subsequent cell-based immunotherapies, including CAR-T cell therapy.

As CD33-directed CAR-T cells advance into clinical evaluation, a primary research objective is to enhance antileukemic efficacy while minimizing on-target, off-tumor toxicity. To improve therapeutic safety, researchers have developed CD33-targeted CAR-engineered natural killer (NK) cells, which have shown potent cytotoxicity against AML cells both *in vitro* and *in vivo*, with limited cytotoxic effects on normal HSPCs in phase I trials (10). In parallel, 'controllable CAR systems' have emerged as a promising safety-enhancing strategy. By integrating inducible safety switches such as inducible caspase-9 (iCasp9) into the CAR construct, these systems enable the selective elimination of CAR-T cells upon administration of small-molecule dimerizers such as AP1903, thereby mitigating prolonged myelosuppression and reducing the risk of severe adverse events (11).

CD33-targeted CAR-T therapy has now entered multiple phase I/II clinical trials. In the dose-escalation clinical trial, NCT03971799, conducted in adolescents and young adults with R/R AML, cytokine release syndrome (CRS), an acute systemic inflammatory toxicity caused by CAR-T-cell activation and cytokine release, occurred in 68% of patients, with grade ≥3 CRS reported in 21% (12). This highlights that, despite promising antileukemic activity, CD33-directed CAR-T therapy in AML may be associated with substantial treatment-related immune toxicity. However, cross-trial comparison of toxicity rates should be approached with caution due to differences in study population, dose level and trial design as these may substantially affect the observed safety profile. Despite these toxicities, promising efficacy was observed: In the highest dose level cohort, 40% of patients achieved complete remission (CR) with minimal residual disease (MRD) negativity (12) (Table I). To further improve the safety profile, the use of donor-derived CD33 CAR-T cells (such as VCAR33) in the post-hematopoietic stem cell transplantation (HSCT) setting has been explored. In a phase I/II trial, 41.7% (5/12) of patients achieved bone marrow CR, with four attaining MRD negativity. Additionally, patients with central nervous system (CNS) leukemia also showed MRD clearance following CAR-T infusion. The treatment was generally well tolerated, with most patients experiencing only grade 1-2 CRS and no cases of immune effector cell-associated neurotoxicity syndrome (ICANS). Some patients developed transient hepatic dysfunction and infections, which were manageable with supportive care. As of June 2024, six patients had either undergone a second HSCT or remained in remission following CD33 CAR-T therapy (13).

C-type lectin domain family 12 member A (CLEC12A). CLEC12A, also known as C-type lectin-like molecule-1 (CLL-1), is a type II transmembrane glycoprotein that is highly expressed on leukemia precursor cells and leukemia stem cells (LSCs) of AML, while its expression is extremely low on normal HSPCs, making it a potential target for AML treatment (14). This differential expression of CLL-1 confers high specificity for targeted therapy and reduces the risk of off-target effects. Moreover, the expression of CLL-1 remains relatively stable during disease progression, suggesting it has value in the application of MRD monitoring and has potential as a reliable prognostic biomarker (15). CLL-1 is still present in AML subtypes with low or absent expression of CD33/CD34 (16), which expands the treatment coverage and overcomes the limitations associated with traditional single antigen targets. Multicenter clinical

Table I. Contextual summary of representative single-target CAR-T strategies in acute myeloid leukemia.

Target	Expression characteristics	Therapeutic advantages	Major challenges	Efficacy index (CR Rate)	Toxic reactions (≥grade 3)	(Refs.)
CD33	Highly expressed in AML progenitor cells, low expression in normal hematopoietic cells	Validated as an ADC target; CAR-NK reduces myeloid toxicity	Off-target toxicity; CRS (21% ≥grade 3)	40% in DL4 cohort	CRS (21%), bone marrow suppression	(8,10,12,13)
CD123	Highly expressed in AML blasts and LSCs, low expression in normal HSCs	High specificity; suitable for MRD monitoring	Targeting normal monocytes, requiring optimization of iCasp9	≤81.8%	Monocytopenia (15%)	(24,26,28-30)
CLL-1	Expressed in 80% of adult AML cases and the majority of pediatric AML cases, not expressed in normal HSCs	Strong specificity; suitable for MRD monitoring	Delayed monocyte recovery (28% of patients)	>50% in pediatric cohort	No dose-limiting toxicity	(14,16-18)
CD7	Ectopically expressed in 20-35% of AML cases, commonin high-risk subtypes	Gene editing relieves fratricide; suitable for specific subtypes	Fratricide; immunosuppression	Not disclosed	No severe ICANS reported	(19,21,22)
FLT3	Mutated (ITD/TKD) in >50% of AML cases, regulating cell proliferation and differentiation	Strong mutation-driven property; suitable for combination targeted therapy				(30,31)

The efficacy and toxicity data summarized in the present table are derived from different studies with heterogeneous trial designs, patient populations, age groups, disease status, dose levels and endpoint definitions. Therefore, these results are intended to provide contextual information only and should not be interpreted as direct head-to-head comparisons across CAR-T targets. AML, acute myeloid leukemia; ADC, antibody-drug conjugates; CAR-T, chimeric antigen receptor T cell; CAR-NK, chimeric antigen receptor-engineered natural killer; CLL-1, C-type lectin-like molecule-1; CR, complete remission; CRS, cytokine release syndrome; DL4, dose level cohort; FLT3, FMS-like tyrosine kinase 3; HSCs, hematopoietic stem cells; HSPCs, hematopoietic stem and progenitor cells; ICANS, immune effector cell-associated neurotoxicity syndrome; iCasp9, inducible caspase-9; ITD, internal tandem duplications; LSCs, leukemia stem cells; MRD, measurable residual disease; TKD, tyrosine kinase domain.

Table II. Contextual summary of representative clinical trials of targeted CAR-T therapies in AML.

Trial no.	Target	Sample size	Patient population	Key findings	Toxicity management strategies
NCT03971799	CD33	30	R/R AML (adolescents)	40% CR rate in DL4 cohort; 68% patients experienced CRS	No safety switch used
ChiCTR1900027684	CLEC12A	42	Adult R/R AML	81.8% CR rate; no dose-limiting toxicity	Not mentioned
NCT04219163	CLEC12A	28	Pediatric R/R AML	>50% CR rate; delayed monocyte recovery	Supportive care
NCT04581390	CD7	15	$CD7^+$ R/R AML	Gene-edited CAR-T reduced fratricide	CRISPR-mediated knockout of CD7/TCR
NCT04601529	CD123	20	$FLT3^+$ AML	iCasp9 safety switch reduces toxicity	Inducible caspase-9 system

The trials listed in the present table differ in phase, sample size, patient characteristics, disease setting, target selection, dose-escalation design and response assessment criteria. Accordingly, the reported CR rates and toxicity profiles should be interpreted cautiously within the context of each individual study and should not be regarded as evidence of comparative superiority among different CAR-T strategies. AML, acute myeloid leukemia; CAR-T, chimeric antigen receptor T cell; CR, complete remission; CLEC12A, C-type lectin domain family 12 member A; CRS, cytokine release syndrome; FLT3, FMS-like tyrosine kinase 3; iCasp9, inducible caspase-9; R/R, relapsed/refractory; TCR, T cell receptor.

trials have suggested that the CLL-1 targeted CAR-T cell therapy can achieve encouraging therapeutic effects. In a clinical trial of pediatric patients with R/R AML, the CR rate was >50%, and the safety profile appeared favorable. Specifically, all patients developed only grade 1-2 cytokine release syndrome (CRS) and no lethal events were reported (17).

The preliminary results of early clinical trials (NCT04219163 and ChiCTR1900027684) further corroborate the efficacy and safety of the CLL-1 targeted CAR-T therapy in pediatric and adult patients with AML, with the highest CR rate reaching 81.8%, and only 5% of patients experienced ≥3 grade CRS (17,18) (Table II). Nevertheless, these findings should be interpreted within the context of the individual study settings, as differences in patient population, disease status and trial design may limit direct comparison with other CAR-T studies.

CD7. CD7 is a transmembrane glycoprotein belonging to the immunoglobulin superfamily, primarily expressed on T cells and NK cells. In AML, 20-35% of patients display ectopic expression of CD7, particularly among those with cytogenetically high-risk subtypes (19), $CD7^+$ AML is frequently associated with resistance to chemotherapy, increased disease aggressiveness and worse clinical outcomes (20). Therefore, despite its relatively limited expression prevalence, CD7 represents a compelling therapeutic target for selected AML subgroups.

CD7-targeted CAR-T cells have demonstrated potent, antigen-specific cytotoxicity against $CD7^+$ AML cells in preclinical studies (21). However, two major challenges hinder their clinical translation: i) Fratricide: Since CAR-T cells inherently express CD7, they may attack each other during *ex vivo* expansion, compromising their viability and persistence; and ii) off-target toxicity: The ubiquitous expression of CD7 on normal T cells and NK cells increases the risk of profound immunosuppression and related complications (22).

To address these limitations, CRISPR/Cas9 gene-editing technology has been applied to eliminate the expression of CD7, T cell receptor and human leukocyte antigen (HLA) class II molecules, thereby generating 'universal' CD7 CAR-T cells. These engineered cells exhibit enhanced proliferative capacity, prolonged functional persistence and reduced immunotoxicity (23). In addition, a study has explored the transient use of tyrosine kinase inhibitors, such as ibrutinib and dasatinib, to reversibly suppress CAR signaling. This pharmacological approach mitigates fratricide during cell manufacturing while preserving the cytolytic function of CAR-T cells (22). In animal models, this strategy has yielded durable antileukemic responses, and early-phase clinical trials are currently underway (22).

Collectively, CD7-directed CAR-T cell therapy offers a promising treatment modality for patients with $CD7^+$ AML. Continued advancements in gene editing and pharmacologic modulation are expected to further enhance the safety and therapeutic efficacy of this approach.

CD123. CD123, the α subunit of the IL-3 receptor α, is highly expressed on leukemic blasts and LSCs in AML, while its expression is either absent or minimal in normal hematopoietic stem cells (HSCs). Several therapeutic approaches targeting CD123, such as bispecific antibodies and ADCs, are currently in clinical development (24). As early as 2002, Testa *et al* (25) conducted a systematic analysis of CD123 expression in AML and reported that ~45% of cases exhibited high levels of CD123. This upregulation was associated with increased blast proliferation, elevated white blood cell

counts and hypersensitivity to IL-3 signaling, all of which were associated with worse prognosis. These observations have since been consistently validated in subsequent studies (26,27).

Clinically, CD123 has proven useful for risk stratification and prognostic assessment in AML. In pediatric cohorts, CD123 expression was stratified into quartiles, and patients in the highest-expression quartile (Q4) were notably enriched for adverse genetic alterations, including FMS-like tyrosine kinase 3 (FLT3)-internal tandem duplications (ITD) and lysine methyltransferase 2A rearrangements (26). By contrast, favorable genetic markers such as t(8;21), inv (16) and CCAAT enhancer binding protein α mutations were more frequently observed in the low-expression group. Patients with high CD123 expression demonstrated markedly shorter OS and event-free survival, establishing CD123 as an independent biomarker of worse prognosis (26). To address the on-target/off-tumor toxicity associated with CD123-targeted CAR-T therapy, several research groups have incorporated safety switches into CAR constructs. These include inducible systems such as iCasp9 and CD20, which can be externally activated in response to severe treatment-related toxicity (28,29). Activation of these switches enables rapid and selective elimination of CAR-T cells, thereby minimizing non-specific damage to normal tissues and improving the overall safety profile of the therapy.

FLT3. FLT3 is a glycosylated protein belonging to the class III receptor tyrosine kinase family. It is predominantly expressed on HSCs and myeloid progenitors, where it plays a key role in regulating cell survival, proliferation and differentiation. FLT3 mutations are detected in >50% of patients with AML (30). These mutations are primarily categorized into two major types: ITDs within the juxtamembrane domain, accounting for ~25% of cases, and point mutations in the tyrosine kinase domain, which occurs in 6-8% of patients (31); the current standard of care for FLT3-mutated AML involves induction chemotherapy in combination with midostaurin, followed by allo-HSCT (31). A recent clinical study demonstrated that gilteritinib, when administered in conjunction with allo-HSCT, can notably extend relapse-free survival in patients with FLT3-ITD$^+$ AML (32). Additionally, quizartinib has shown promise as a post-transplant maintenance therapy, sustaining FLT3 inhibition to reduce MRD and prevent relapse (33). While the majority of research to date has focused on FLT3-ITD$^+$ AML, the therapeutic potential of FLT3 targeting in patients that are FLT3-ITD$^-$ remains largely unexplored. Further prospective studies are needed to elucidate the role of FLT3 in non-canonical signaling pathways and to assess its broader applicability as an immunotherapeutic target in diverse AML subtypes.

The clinical outcomes summarized in Tables I and II are derived from heterogeneous studies and are not directly comparable. Differences in trial phase, sample size, patient age, disease status, target antigen selection, dose-escalation design and response criteria may substantially influence the reported CR rates and toxicity profiles. Therefore, these tables are intended to provide a contextual overview of the current clinical landscape rather than to indicate the superiority of one CAR-T target over another.

3. Target specificity and persistence of CAR-T therapy in AML

The barriers limiting CAR-T therapy in AML can be broadly categorized into two dimensions. The first comprises fundamental biological barriers intrinsic to AML, such as antigen overlap with normal hematopoietic cells, clonal and phenotypic heterogeneity, antigen escape, leukemia stem cell persistence and suppressive bone marrow microenvironment. The second involves technical and engineering limitations of CAR-T therapy itself, including suboptimal CAR construct design, inadequate persistence, restricted controllability, treatment-related toxicities and manufacturing constraints. Although these categories are analytically distinct, they are biologically interconnected and together shape the limited efficacy of CAR-T therapy in AML (5).

Despite the success of CAR-T cell therapy in B cell malignancies (6), its application in AML remains limited by the unique biological characteristics of this disease. AML is highly heterogeneous, with leukemic cells exhibiting substantial immunophenotypic variability across different patients, disease stages and clonal subtypes. Compared with CD19, a highly specific and consistently expressed antigen in B-ALL, AML lacks a universally reliable, leukemia-specific target antigen (34,35). Frequently explored targets in AML, such as CD33 and CD123, are abundantly expressed on AML blasts (36); however, they are also present at varying levels on normal HSPCs (37). This overlap contributes to notable on-target/off-tumor toxicity. For instance, CAR-T therapies targeting CD33 or CD123 have been associated with hematologic toxicities, including myelosuppression, cytopenias and prolonged marrow suppression, which may result in serious hematologic complications (38). In addition to target specificity challenges, CAR-T cells in patients with AML often display suboptimal *in vivo* expansion and worse persistence, leading to transient therapeutic responses and high relapse rates, reported to range from 60 to 80%. Enhancing the specificity and durability of CAR-T cells in AML thus remains a key objective in ongoing translational research.

4. Immunosuppressive TME

The TME of AML is a major obstacle to the efficacy of CAR-T cell therapy. This immunosuppressive microenvironment is characterized by the presence of various inhibitory cells, molecules and metabolic limitations, which work together to weaken the antileukemic efficacy of CAR-T cells and lead to treatment resistance and failure (39). As illustrated in Fig. 1, AML-associated immunosuppression involves both extrinsic inhibitory signals from the TME, such as suppressive myeloid cells, regulatory T cells, tumor-associated macrophages and inhibitory cytokines, and intrinsic functional consequences in CAR-T cells, including progressive exhaustion marked by reduced cytokine production and increased checkpoint expression. A thorough understanding of these complex inhibitory mechanisms is important for developing more effective CAR-T cell strategies (40). Importantly, recent clinical evidence has reinforced the central role of the AML microenvironment in determining CAR-T treatment outcomes. In a landmark study, Bhagwat *et al* (41) provided the first in-human

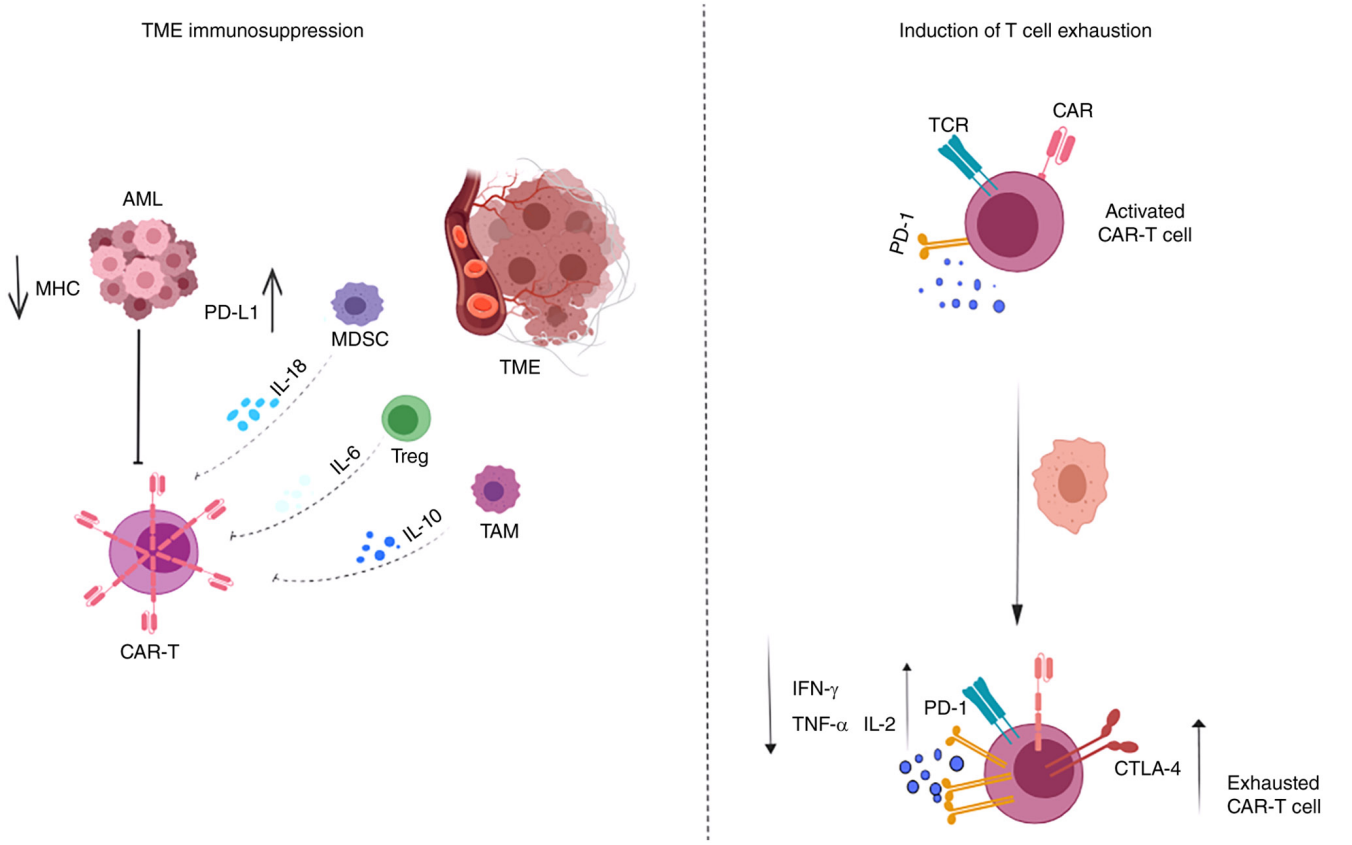

Figure 1. CAR-T cell dysfunction in AML. The AML microenvironment suppresses CAR-T cells through PD-L1 expression, MHC downregulation and immunosuppressive cytokines such as IL-6 and IL-10, and chronic stimulation induces exhaustion via PD-1 and CTLA-4 upregulation. CAR-T, chimeric antigen receptor T cell; AML, acute myeloid leukemia; MHC, major histocompatibility complex; PD-L1, programmed death-ligand 1; MDSC, myeloid-derived suppressor cells; TME, tumor microenvironment; TAM, tumor-associated macrophage; TCR, T cell receptor; Treg, regulatory T cell; CTLA-4, cytotoxic T-lymphocyte associated protein 4.

demonstration that cytokines released from AML-associated myeloid cells such as granulocyte-macrophage colony stimulating factor, IL-3 and FLT3-L activate JAK/STAT-dependent pro-survival signaling and induce exhaustion-related transcriptional programs in leukemic blasts. These microenvironment-driven alterations directly impair CAR-T cell expansion and accelerate functional exhaustion, highlighting that resistance in AML arises not solely from antigenic factors but predominantly from TME-mediated immunologic and transcriptional reprogramming. This concept is further summarized in Fig. 1, which associates TME-derived suppressive signaling to the transition from activated CAR-T cells to an exhausted functional state.

The formation of an oxygen-depleted microenvironment is a direct consequence of the rapid proliferation of cancer cells and insufficient angiogenesis. This oxygen deficiency not only directly impairs the metabolic activities and survival of CAR-T cells, but also further exacerbates the inhibition of CAR-T cells by inducing adaptive responses of cancer cells (42,43). Under hypoxic conditions, hypoxia-inducible factor-1 plays a central role in cancer cells, mediating their adaptation to the hypoxic environment, for instance, by promoting angiogenesis and regulating the expression of cancer stem cell markers to enhance survival (44). The TME reshapes its metabolic mechanisms and transcriptome profile through the hypoxic response, leading to challenges such as nutrient competition and accumulation of metabolic waste for CAR-T cells, thereby damaging their proliferation, persistence and effector functions (39), Furthermore, the 2025 consensus guidance by Naik *et al* (40) reinforces these observations by systematically outlining how TME-derived cytokines, suppressive myeloid populations and metabolic deprivation converge to blunt CAR-T cell activity in AML. This guideline emphasizes the clinical necessity of incorporating TME-targeted interventions such as JAK/STAT blockade, myeloid-directed therapies or metabolic reprogramming into future CAR-T design to overcome microenvironment-driven resistance. Therefore, a deep understanding and targeting of hypoxia and its related metabolic pathways are important for overcoming metabolic limitations in the TME and enhancing the efficacy of CAR-T cells. As summarized in Fig. 2, these barriers have driven the development of multiple optimization strategies, including precision genome editing, checkpoint modulation, enhancement of T cell fitness and combinatorial engineering approaches, which are discussed in later sections of the present review.

5. Toxicities and adverse effects

CAR-T cell therapy is associated with notable toxicities that limit its broader application in AML. CRS is the most common and potentially life-threatening adverse event, arising from extensive T cell activation and the subsequent

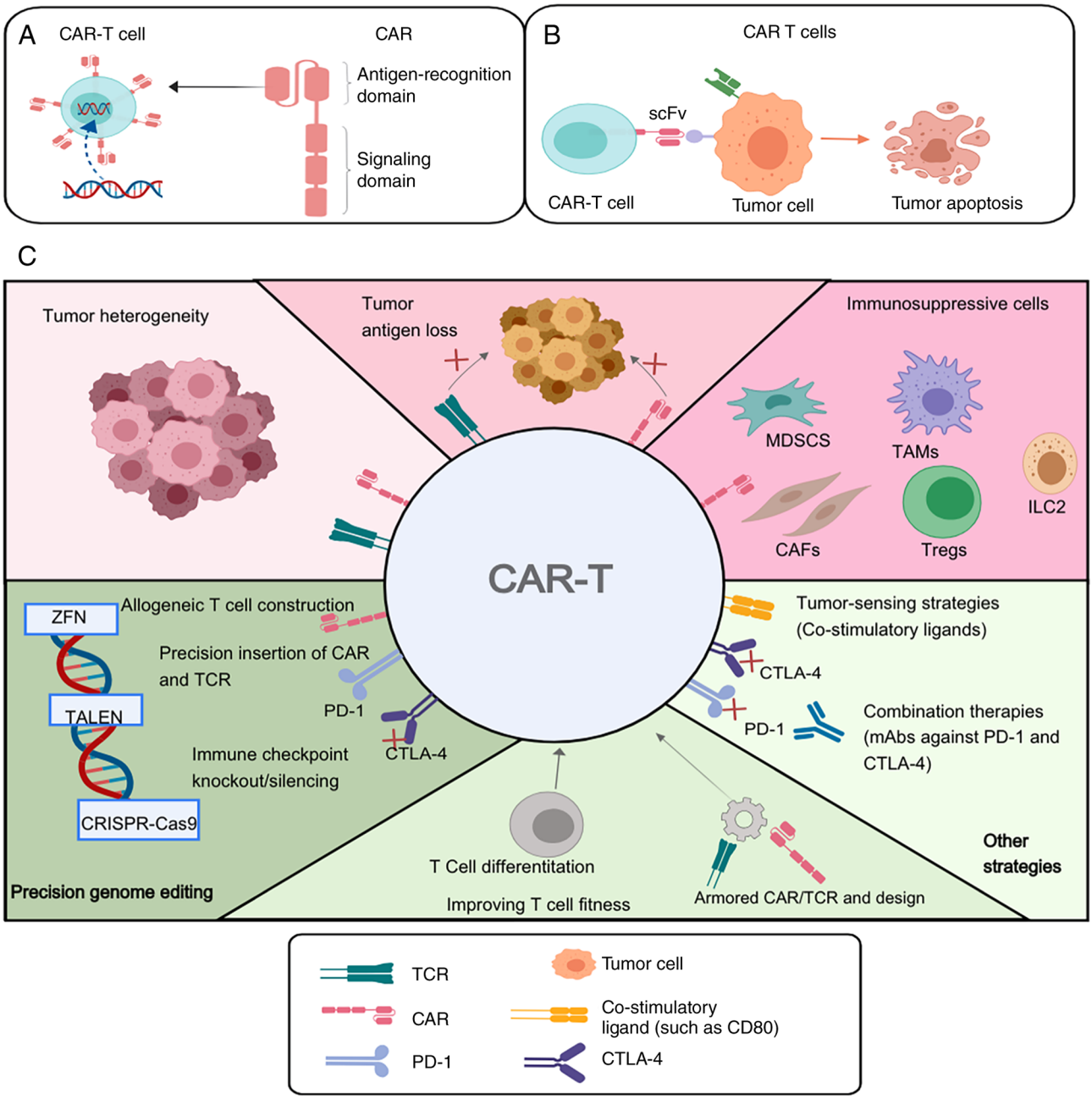

Figure 2. Limitations and optimization strategies of CAR-T therapy in AML. (A) Schematic illustration of the basic structure of a CAR, including the antigen-recognition domain and signalling domains. (B) Schematic illustration of CAR-T-cell recognition of tumor cells and the induction of tumor apoptosis. (C) Major biological and technical barriers affecting CAR-T therapy in AML and representative strategies to overcome them, including tumor heterogeneity, immunosuppressive cells, precision genome editing, improving T cell fitness and other combinatorial engineering approaches. CAR, chimeric antigen receptor; CAR-T, chimeric antigen receptor T cell; CTLA-4; cytotoxic T-lymphocyte associated protein 4; MDSC, myeloid-derived suppressor cells; CAFs, cancer-associated fibroblasts; Treg, regulatory T cell; PD-1, programmed death-ligand 1; TCR, T cell receptor; ZFN, zinc-finger nuclease; scFv, single-chain variable fragment; mAbs, monoclonal antibodies.

release of pro-inflammatory cytokines. Clinical manifestations of CRS range from mild symptoms such as fever and fatigue to severe conditions including shock and multi-organ failure (45). Another notable complication is ICANS, which frequently occurs following CRS and is considered to result from blood-brain barrier disruption and increased expression of vascular activation markers such as angiopoietin-2 (24). Currently, tocilizumab effectively mitigates CRS but exhibits limited penetration of the CNS, rendering it less effective for treating ICANS. Corticosteroids are commonly employed to manage neurotoxicity; however, their immunosuppressive effects may impair CAR-T cell expansion and antitumor activity, posing a clinical challenge in balancing therapeutic efficacy and toxicity management (46).

6. Opportunities and challenges of CAR-T cell therapy in the treatment of AML

Novel target strategies. Dual-targeted CAR-T cell therapies have emerged as promising strategies to overcome the

limitations of single-antigen targeting in AML. For instance, Ma *et al* (47) developed Loop33 x 123 CAR-T cells, a bispecific CAR-T design incorporating tandem antigen-recognition domains that enables simultaneous targeting of the two myeloid antigens CD33 and CD123. This dual targeting effectively eliminates both AML blasts and LSCs. *In vitro* assays demonstrated that Loop33 x 123 CAR-T cells exhibited superior cytotoxicity compared with single-target CAR-T cells, while an *in vivo* study showed notable prolongation of survival in murine models without evident toxicity (48).

Similarly, dual-target CAR-T cells targeting CD123 and CLL-1, designed either via a bicistronic vector or tandem scFv architecture, have been developed to achieve precise recognition and elimination of diverse AML subtypes. A study reported that CD123/CLL-1 dual-targeted CAR-T therapy exerted robust antileukemic effects in animal models and reduced the likelihood of antigen escape (49). Furthermore, comparative analyses of two tandem CAR constructs (CD123/CLL-1 vs. CLL-1/CD123) revealed that dual-targeted CAR-T cells possessed enhanced tumor-killing efficacy and improved resistance to antigen escape relative to single-target counterparts (50). Beyond these, other dual-target CAR designs such as CD33/CLL-1 are also under investigation, further broadening the immunotherapeutic target landscape in AML.

While these findings highlight the potential of dual-target strategies, their translational relevance in AML remains uncertain because the available evidence is still largely preclinical. Expanding antigen coverage may help reduce immune escape, but it may also increase the risk of hematopoietic toxicity when target expression overlaps with normal cells. In addition, greater structural complexity may introduce further challenges for signaling coordination, persistence and manufacturing consistency (5). Whether these theoretical advantages can be translated into a clinically meaningful improvement in efficacy without compromising safety will require validation in future clinical studies.

CAR-T cell optimization strategies. Beyond target selection, Fig. 2 highlights the importance of engineering strategies to improve T cell fitness, controllability and resistance to immunosuppressive cues in AML CAR-T therapy.

Universal chimeric antigen receptor T cell (UCAR-T) technology. Conventional CAR-T therapy relies on autologous T cells harvested from patients with hematologic malignancies, which entails challenges such as prolonged manufacturing times, high costs and considerable product heterogeneity (51). UCAR-T cells, derived from healthy donors and genetically engineered via CRISPR/Cas9 or TALEN technologies to disrupt T cell receptor and HLA genes, represent 'off-the-shelf' universal CAR-T products designed to minimize the risk of GVHD. Recent preclinical studies have demonstrated that optimized UCAR-T cells exhibit a defined memory phenotype and dose-dependent antitumor efficacy, along with favorable safety profiles in xenograft models (52).

UCAR-T is attractive because it may simplify production and reduce delays associated with autologous manufacturing. However, its broader clinical application is still constrained by several unresolved issues, including alloreactivity, host immune rejection, limited persistence after infusion and the need for robust large-scale manufacturing. Gene editing may help address some of these barriers, but it also raises additional concerns regarding genomic stability and regulatory oversight (53,54). Therefore, the clinical value of UCAR-T will depend on whether these products can achieve reproducible safety and durable efficacy in patients.

Logic-gated CAR-T technology. Logic-gated CAR-T cells regulate T cell activation and cytotoxicity by integrating multiple cellular signals, enabling precise discrimination between malignant and normal cells. Key design strategies include: i) OR gate CARs, which recognize multiple antigens simultaneously and are thus referred to as multi-antigen CARs (55); ii) gate CARs, which require co-expression of two target antigens (such as CD19 and CD22) to become fully activated (56); and iii) NOT gate CARs, which detect markers expressed on healthy cells (such as CD34) and trigger inhibitory signaling pathways to protect normal tissues and reduce off-tumor toxicity (55).

These designs are conceptually attractive as they offer a more selective way to distinguish leukemic cells from normal tissues. Their clinical application, however, may be more complicated than their design principle suggests. Because logic-gated systems depend on coordinated multi-signal responses, their activity may vary with antigen density, dynamic target expression and the surrounding leukemic microenvironment. Greater circuit complexity may also complicate vector construction, manufacturing workflows and quality control (57,58). Whether this added precision is sufficient to justify the increased complexity remains an important translational question.

Clinical translation, standardized manufacturing and artificial intelligence (AI). The clinical translation of CAR-T therapy is advancing rapidly in parallel with technological innovations that integrate manufacturing processes with AI. Leading pharmaceutical companies including Gilead, Novartis, Johnson & Johnson and Bristol-Myers Squibb have successfully reduced CAR-T cell manufacturing timelines from >30 days to ~14 days, with ongoing efforts aimed at achieving a 7-day production cycle. This acceleration is primarily driven by the adoption of automated, good manufacturing practice-compliant platforms and streamlined, rapid quality control procedures (51). For instance, fully automated, closed-loop manufacturing systems such as CliniMACS Prodigy, coupled with expedited 24-h production workflows, have demonstrated feasibility in preclinical and early clinical settings while preserving key naïve and memory T cell subsets essential for therapeutic efficacy (59). Concurrently, AI has emerged as a transformative tool in CAR-T development across multiple domains: i) CAR design and target recognition optimization, where machine learning algorithms predict antigen affinity, structural stability and intracellular signaling activation to inform the engineering of enhanced CAR constructs; ii) intelligent manufacturing process control, leveraging digital twin models and reinforcement learning to enable real-time monitoring and regulation of bioreactor parameters, thereby improving process stability and product yield; and iii) quantitative prediction of

therapeutic efficacy and toxicity through the integration of multi-omics, imaging and clinical datasets, providing robust support for dose optimization and personalized treatment strategies.

Collectively, these innovations herald the emergence of a 'digital pharmaceutical' paradigm in CAR-T therapy, offering promising avenues to enhance safety, manufacturing efficiency and patient accessibility. From an engineering perspective, these optimization strategies have substantially expanded the design space of AML CAR-T therapy, however, technical sophistication does not necessarily guarantee clinical feasibility. For dual-target CARs, universal CAR-T platforms and logic-gated systems alike, the central translational challenge is whether theoretical advantages can be converted into reproducible clinical benefit without introducing excessive toxicity, manufacturing complexity or regulatory barriers. Addressing these issues will be essential for translating next-generation CAR-T strategies into meaningful and durable clinical benefit.

7. Conclusions and future perspectives

Despite substantial progress, the central challenge of AML CAR-T therapy remains unresolved: Whether therapeutic failure is driven primarily by insufficient target specificity or by microenvironment-induced functional suppression. In practice, these mechanisms are likely intertwined. The absence of truly leukemia-restricted antigens increases the risk of on-target/off-tumor toxicity, whereas the AML microenvironment simultaneously limits CAR-T expansion, persistence and cytotoxicity. This suggests that further improvements in target selection alone may be insufficient unless they are accompanied by strategies that restore T cell fitness within the leukemic niche.

Another area of ongoing debate is whether increasingly sophisticated engineering solutions such as dual-target CARs, logic-gated circuits, universal CAR-T platforms and safety-switch systems will translate into meaningful clinical benefit in AML. Although these approaches are highly promising, the majority of supporting evidence remains preclinical and their true feasibility, scalability and safety in patients are still uncertain. Thus, the future of AML CAR-T therapy will likely depend not on any single innovation, but on the rational integration of biologically informed target selection, engineering optimization and microenvironment-directed combination strategies.

To fully realize the therapeutic potential of CAR-T cell therapy in AML, several key barriers must be overcome: i) Identification of highly specific and immune escape-resistant antigens to minimize on-target/off-tumor effects; ii) structural optimization of CARs to improve their *in vivo* persistence, proliferative capacity and functional control; and iii) integration of combination strategies that modulate the TME such as targeting immunosuppressive cellular components and incorporating immune checkpoint blockade, to restore effective antileukemic immune responses. With continued advances in molecular biology, gene-editing technologies and systems immunology, CAR-T therapy is expected to evolve from a novel experimental intervention into a mainstream therapeutic modality for AML. Sustained efforts in translational and clinical research will be essential for overcoming current barriers and establishing CAR-T cell therapy as a cornerstone of AML treatment.

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JZ was responsible for manuscript preparation and figure creation. YC provided guidance on the overall approach and contributed to the manuscript revisions. FW, DS and ZH conducted the literature review. All authors have read and approved the final version of the manuscript. Data authentication is not applicable.

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Competing interests

The authors declare that they have no competing interests.

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