REVIEW ARTICLES

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A Review of Recent Advances in Chimeric Antigen Receptor (CAR) T-Cell Therapy for Hepatocellular Carcinoma

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Hepatocellular carcinoma (HCC) is the most common form of primary liver cancer and poses a major global health burden. It remains a leading cause of cancer-related death worldwide, with persistently high incidence and mortality in regions affected by chronic viral hepatitis, cirrhosis, alcohol-related liver disease, and metabolic dysfunction-associated steatotic liver disease.

Although surgical resection, liver transplantation, locoregional therapies, molecular targeted agents, and immune checkpoint inhibitors have improved treatment options, outcomes for advanced HCC remain unsatisfactory. Chimeric antigen receptor (CAR) T-cell therapy is an adoptive cellular immunotherapy in which T lymphocytes are genetically engineered to recognize tumor-associated antigens and eliminate malignant cells. CAR-T-cell therapy has achieved major clinical success in hematologic malignancies, but its application in HCC is still developing because of tumor heterogeneity, antigen escape, limited T-cell trafficking, and an immunosuppressive tumor microenvironment. Recent studies have investigated several HCC-associated targets, including glypican-3 (GPC3), carcinoembryonic antigen (CEA), alpha-fetoprotein (AFP), CD133, epidermal growth factor receptor variant III (EGFRvIII), B7 homolog 3 (B7H3), mucin 1 (MUC1), natural killer group 2 member D ligand (NKG2DL), programmed death-ligand 1 (PD-L1)/c-Met, CD147, CD44, and epithelial cell adhesion molecule (EpCAM). This article provides a target-oriented synthesis of HCC-related CAR-T-cell therapy, summarizes registered clinical studies according to antigen target, CAR design, trial phase, administration route, and available outcomes, and discusses how CAR structural evolution may influence therapeutic development in HCC. This article aims to review recent advances in CAR-T-cell therapy for hepatocellular carcinoma.

Keywords: carcinoma, hepatocellular • receptors, chimeric antigen • T-lymphocytes • immunotherapy, adoptive • review

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Introduction

Hepatocellular carcinoma (HCC) is the predominant histologic subtype of primary liver cancer and represents a substantial global health burden [1-4]. Liver cancer remains among the leading causes of cancer-related death worldwide, and HCC accounts for most primary liver cancer cases [3-6]. The incidence and mortality of HCC remain high in regions with prevalent chronic hepatitis virus infection, cirrhosis, alcohol-related liver disease, and metabolic dysfunction-associated steatotic liver disease [4,7,8].

Curative-intent treatments for early-stage HCC include surgical resection, local ablation, and liver transplantation [9-11]. However, many patients are diagnosed at an advanced stage or have underlying chronic liver disease that limits curative treatment options [4,7,8,12]. Systemic treatment has evolved from sorafenib to several targeted agents and immune checkpoint inhibitor-based strategies, including regorafenib, lenvatinib, cabozantinib, ramucirumab, pembrolizumab, and nivolumab [13-25]. Despite these advances, durable responses remain limited in many patients with advanced HCC, supporting the need for new therapeutic approaches [20,23-25].

Chimeric antigen receptor (CAR) T-cell therapy is a form of adoptive cellular immunotherapy in which T cells are genetically modified to express synthetic receptors that recognize tumor-associated antigens independently of major histocompatibility complex (MHC) presentation [26,27]. CAR-T-cell therapy has produced substantial clinical responses in several hematologic malignancies, establishing a strong rationale for its exploration in solid tumors [28-31]. However, the translation of CAR-T-cell therapy into solid tumors has been constrained by antigen heterogeneity, inadequate T-cell trafficking and infiltration, physical stromal barriers, and immunosuppressive signals within the tumor microenvironment (TME) [32-35].

Several recent reviews have summarized CAR-T-cell therapy for HCC from broad translational and mechanistic perspectives [36,37]. Compared with these reviews, this article aims to review recent advances in CAR-T-cell therapy for hepatocellular carcinoma.

CAR-T Immunotherapy

CAR-T-cell therapy uses genetically modified T lymphocytes to recognize tumor-associated antigens and mediate tumor cell killing [26,27]. Peripheral blood mononuclear cells (PBMCs) are commonly obtained through leukapheresis, followed by T-cell enrichment, activation, genetic transduction or transfection, ex vivo expansion, quality control, and reinfusion into the patient [26,27,38,39]. The single-chain variable fragment (scFv) within the extracellular domain mediates antigen recognition, whereas intracellular signaling domains activate T-cell cytotoxicity, proliferation, and cytokine release [27,40,41]. **Figure 1** illustrates the generation process, target recognition, and antitumor mechanisms of chimeric antigen receptor T-cell therapy in hepatocellular carcinoma (**Figure 1**).

Unlike conventional T-cell receptor (TCR)-mediated recognition, CAR-mediated antigen recognition does not require peptide presentation by MHC molecules [27]. This feature allows CAR-T cells to recognize surface antigens on tumor cells even when tumors downregulate MHC expression as an immune-evasion mechanism [27,42]. Nevertheless, the efficacy of CAR-T-cell therapy in solid tumors depends on target antigen specificity, antigen density, T-cell persistence, and the suppressive characteristics of the TME [32-35].

Structural Design and Evolution of CAR-T Cells

A CAR molecule generally contains an extracellular antigen-binding domain, a hinge or spacer region, a transmembrane domain, and intracellular signaling modules [40,41]. The extracellular antigen-binding domain is most commonly derived from an antibody scFv and determines target specificity [27,40]. The hinge and transmembrane domains affect receptor flexibility, stability, antigen accessibility, and cell-surface expression [40].

First-generation CARs contained CD3ζ or Fc receptor gamma chain signaling domains but lacked costimulatory domains, resulting in limited in vivo persistence and antitumor activity [41,43,44]. Second-generation CARs incorporated one costimulatory domain, such as CD28 or 4-1BB, thereby improving T-cell expansion, persistence, and cytotoxic function [44,45]. Third-generation CARs contain 2 or more costimulatory domains, such as CD28 combined with 4-1BB or OX40, to further enhance activation and survival signals [41,45,46].

Fourth-generation CAR-T cells, also known as T cells redirected for universal cytokine-mediated killing (TRUCKs), are engineered to secrete cytokines or immune-modulating molecules after antigen recognition [45,47]. Fifth-generation CAR-T-cell designs incorporate additional intracellular signaling modules or gene-editing strategies to improve safety, reduce rejection, and enhance antitumor activity [41,48]. These structural innovations provide the basis for optimizing CAR-T-cell therapy in HCC and other solid tumors [32,48,49]. **Figure 2** depicts the structural evolution of chimeric antigen receptor (CAR) T-cell constructs from the first to the fifth generation (**Figure 2**).

CAR-T-cell therapy has achieved clear clinical success in hematologic malignancies, with studies reporting high remission

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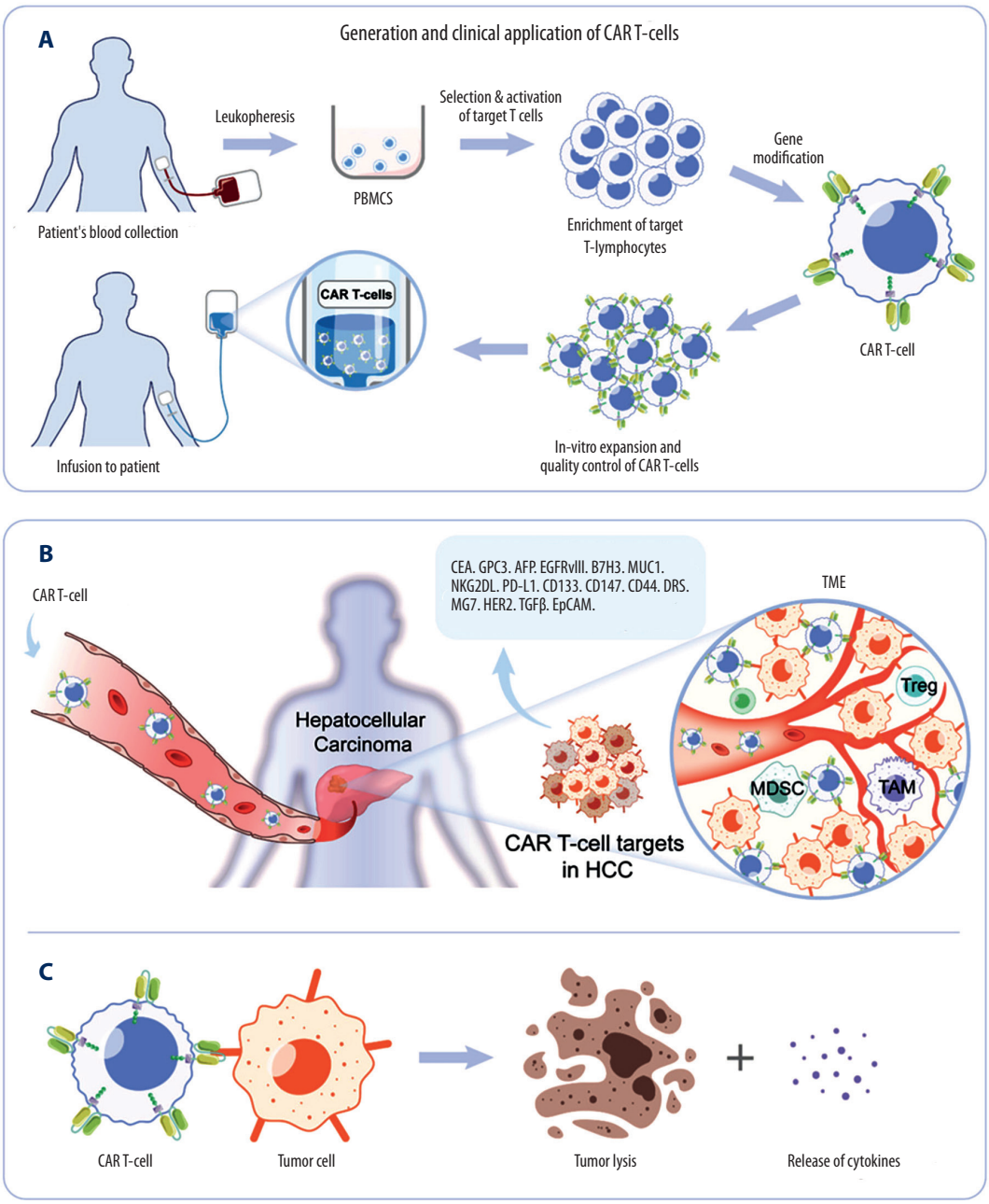

Figure 1. Generation process, target recognition, and antitumor mechanisms of chimeric antigen receptor T-cell therapy in hepatocellular carcinoma. Peripheral blood mononuclear cells (PBMCs) are collected from patients through leukapheresis. T lymphocytes are isolated, activated, genetically engineered to express chimeric antigen receptors (CARs), expanded ex vivo, and reinfused into patients after quality control. After infusion, CAR-T cells migrate to tumor sites and recognize hepatocellular carcinoma (HCC)-associated target antigens, including carcinoembryonic antigen (CEA), glypican-3 (GPC3), alpha-fetoprotein (AFP), epidermal growth factor receptor variant III (EGFRvIII), B7 homolog 3 (B7H3), mucin 1 (MUC1), natural killer group 2 member D ligand (NKG2DL), programmed death-ligand 1 (PD-L1), CD133, CD147, CD44, death receptor 5 (DR5), MG7, human epidermal growth factor receptor 2 (HER2), transforming growth factor beta (TGF-beta), and epithelial cell adhesion molecule (EpCAM). After antigen recognition through the single-chain variable fragment (scFv) domain, CAR-T cells become activated and induce tumor cell lysis through cytotoxic molecules and inflammatory cytokines. The figure was originally created by the authors using Adobe Illustrator and professional graphic design software and was not reproduced or adapted from previously published sources.

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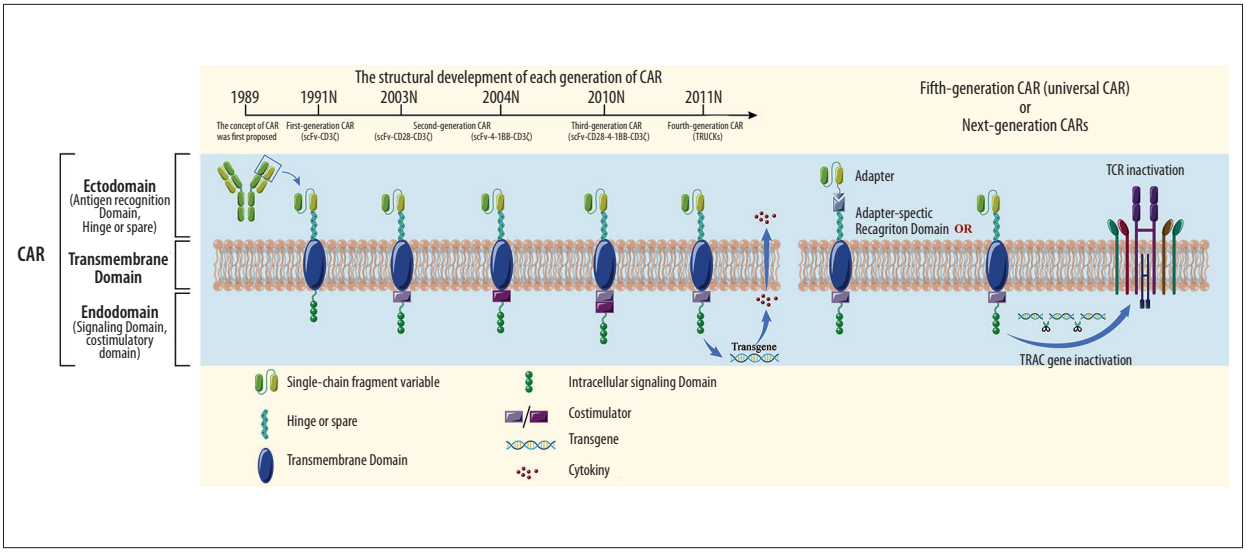

Figure 2. Structural evolution of chimeric antigen receptor T-cell constructs from first- to fifth-generation CARs. The first-generation chimeric antigen receptor (CAR) contains an extracellular antigen-binding domain, a transmembrane domain, and an intracellular CD3ζ signaling domain without costimulatory signaling. Second-generation CARs incorporate one costimulatory domain, such as CD28 or 4-1BB, to enhance T-cell activation and persistence. Third-generation CARs contain 2 or more tandem costimulatory domains to further improve antitumor activity. Fourth-generation CAR-T cells, also termed T cells redirected for universal cytokine-mediated killing (TRUCKs), are engineered to secrete cytokines following activation to modulate the tumor microenvironment (TME). Fifth-generation CAR-T cells incorporate additional intracellular signaling modifications and gene-editing strategies to improve antitumor efficacy and reduce immune rejection. The figure was originally created by the authors using Adobe Illustrator and professional graphic design software and was not reproduced or adapted from previously published sources.

rates in refractory B-cell malignancies [28-31]. In contrast, the development of CAR-T-cell therapy for solid tumors has been more difficult because tumor-associated antigens are often heterogeneously expressed and may also be present at low levels in normal tissues [32,42,50].

Successful CAR-T-cell therapy for solid tumors requires identification of targets that are highly expressed in tumor cells but limited in essential normal tissues [33,42,50]. Additional barriers include inadequate homing of CAR-T cells to tumor sites, limited penetration into dense tumor tissue, metabolic stress, checkpoint-mediated exhaustion, and suppression by regulatory T cells, myeloid-derived suppressor cells, tumor-associated macrophages, and cytokines such as transforming growth factor beta (TGF-beta) [32-35].

Several strategies have been investigated to improve CAR-T-cell activity in solid tumors, including regional infusion, dual-target CAR design, armored CAR-T cells, checkpoint blockade combinations, cytokine engineering, and modification of the TME [32-35,49]. These approaches are particularly relevant to HCC, which develops in a tolerogenic liver environment and frequently coexists with chronic inflammation and cirrhosis [4,7,8].

CAR-T Therapy for Hepatocellular Carcinoma

HCC is characterized by molecular heterogeneity, vascular invasion, high recurrence risk, and an immunologically complex microenvironment [4,7,8,20]. Immune checkpoint inhibitors and antiangiogenic combinations have changed the systemic treatment landscape for advanced HCC, but resistance and limited durable responses remain major challenges [15,16,20,23-25]. CAR-T-cell therapy provides a target-directed approach that may complement existing systemic and locoregional therapies [27,32,42,50].

According to registered clinical studies and published reports, multiple CAR-T-cell strategies for HCC have focused on antigens such as GPC3, CEA, CD133, AFP, EGFRvIII, B7H3, MUC1, NKG2DL, PD-L1/c-Met, CD147, CD44, DR5, MG7, human epidermal growth factor receptor 2 (HER2), TGF-beta, and EpCAM [49,51-88]. The current evidence remains dominated by early-phase trials and preclinical studies, and large randomized trials are still lacking [54,55,61,64,80].

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HCC-Associated CAR-T Targets

CEA

Carcinoembryonic antigen (CEA), also known as CEACAM5, is a tumor-associated antigen expressed in several epithelial malignancies [51]. Anti-CEA CAR-T-cell approaches have been explored using hepatic artery infusion to enhance regional delivery to liver lesions [52]. In a phase Ib study of intraarterial CAR-T-cell therapy combined with selective internal radiation therapy for CEA-positive liver metastases, the approach was feasible and did not produce severe cytokine release syndrome or neurotoxicity [52].

GPC3

Glypican-3 (GPC3) is a glycosylphosphatidylinositol-anchored heparan sulfate proteoglycan that is overexpressed in many HCC tissues and is associated with tumor progression [53]. GPC3 is one of the most widely investigated targets for CAR-T-cell therapy in HCC [54,55,89,90]. In early-phase clinical studies, GPC3-targeted CAR-T cells demonstrated acceptable safety and preliminary antitumor activity in selected patients with advanced GPC3-positive HCC [54]. Fourth-generation GPC3-targeted CAR-T-cell strategies secreting interleukin 7 (IL-7) and C-C motif chemokine ligand 19 (CCL19) have also been explored to enhance immune cell recruitment and antitumor activity [55].

CD133

CD133 is a transmembrane glycoprotein expressed in cancer stem-like cells and has been associated with aggressive tumor biology and poor prognosis in HCC [56-60]. CD133-directed CAR-T-cell therapy has been evaluated in patients with advanced malignancies and HCC [61,64]. In a single-arm phase II trial of CD133-directed CAR-T cells in advanced HCC, partial response and stable disease were observed in a subset of patients, with median overall survival and progression-free survival suggesting preliminary clinical activity [64].

AFP

Alpha-fetoprotein (AFP) is a classical biomarker of HCC and has been investigated as a target for T-cell-based immunotherapy [65]. Because AFP is an intracellular and secreted antigen, AFP-targeted CAR-T-cell strategies rely on recognition of AFP-derived peptide-major histocompatibility complex complexes rather than direct surface antigen binding [65]. Preclinical findings support the feasibility of AFP-MHC complex targeting, although further clinical evidence is needed [65].

EGFRvIII

Epidermal growth factor receptor variant III (EGFRvIII) is a tumor-specific mutant form of epidermal growth factor receptor that has been detected in several malignancies, including HCC [66-68]. EGFRvIII-specific CAR-T cells produced using the piggyBac transposon system inhibited HCC cell growth in vitro and in vivo, supporting EGFRvIII as a potential HCC CAR-T target [69].

B7H3

B7 homolog 3 (B7H3) is a member of the B7 immunoglobulin superfamily and is overexpressed in several solid tumors [70]. Tandem CAR-T cells targeting CD70 and B7H3 showed potent preclinical activity against multiple solid tumors, suggesting a potential strategy for tumors with heterogeneous antigen expression [70]. Clinical translation of B7H3-targeted CAR-T cells in HCC remains under investigation.

MUC1 and NKG2DL

Mucin 1 (MUC1) is a transmembrane glycoprotein involved in tumor progression and immune regulation [71,72]. MUC1 expression has been observed in HCC models, and MUC1-targeted CAR-T-cell approaches have shown antitumor activity in experimental HCC systems [73]. Natural killer group 2 member D ligand (NKG2DL) is another target of interest because NKG2D ligands are frequently induced by cellular stress and malignant transformation [74,75]. NKG2D-based CAR-T cells have eradicated NKG2DL-positive HCC cells in preclinical models [77].

PD-L1/c-Met, CD147, CD44, and Other Targets

Programmed death-ligand 1 (PD-L1) contributes to immune evasion by interacting with programmed death 1 (PD-1) on T cells [78]. Dual-targeting strategies involving PD-L1 and c-Met have been explored as a way to combine tumor targeting with checkpoint-related mechanisms [79]. CD147 is highly expressed in HCC and is associated with invasion, metastasis, and poor prognosis [80-82]. Anti-CD147 CAR-T cells demonstrated antitumor efficacy against HCC in preclinical studies, and inducible CD147-targeted CAR-T designs have been developed to improve controllability [80,86]. CD44 is a cancer stem cell-associated marker, and CD44-targeted CAR-T cells suppressed HCC growth in experimental models [87,88]. Additional targets, including death receptor 5 (DR5), MG7, HER2, TGF-beta, and EpCAM, are being explored in registered studies and preclinical reports [49].

Clinical Studies of CAR-T Therapy in HCC

Most clinical studies of CAR-T-cell therapy for HCC are early-phase trials designed to evaluate safety, feasibility, dose

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Table 1. Relevant clinical studies.

Target	Intervention and reference	Phase	Main findings	Status	NCT number	CAR design	First posted	Route
CEA	Anti-CEA CAR-T cells [52]	Phase 1	No results posted	Completed	NCT01373047	2nd generation	2011	Hepatic artery infusion
CEA	Anti-CEA CAR-T cells [52]	Phase 1	No results posted	Recruiting	NCT05240950	Unknown	2022	Intravenous infusion
CEA	CEA CAR-T cells [52]	Phase 1/2	No results posted	Recruiting	NCT04348643	Unknown	2020	Intravenous injection
CEA	Anti-CEA CAR-T cells plus SIR-Spheres [52]	Phase 1	No results posted	Completed	NCT02416466	Unknown	2015	Hepatic artery infusion
CEA	Anti-CEA CAR-T cells [52]	Phase 1	CEA and CA19-9 levels normalized for 2-3 months	Completed	NCT02850536	CD28/CD3ζ	2016	Hepatic artery infusion
GPC3	Y035 [54]	Phase 1	3-year, 1-year, and 6-month OS rates were 10.5%, 42.0%, and 50.3%	Completed	NCT02395250	Humanized anti-GPC3 CAR	2015	Intravenous injection
GPC3	CT011 [54]	Not applicable	Tumor progression-free survival > 36 months	Active, not recruiting	NCT03302403	Unknown	2017	Intravenous injection
GPC3	4G-CAR-GPC3 T cells [54]	Phase 1	ORR 16.7%; DCR 50%; median PFS 4.2 months	Completed	NCT03980288	4th generation	2019	Intravenous injection
GPC3	CAR(hYP7)-T [54]	Phase 1	No results posted	Recruiting	NCT05003895	Unknown	2021	Injection
GPC3	Anti-GPC3 CAR-T cells [54]	Early Phase 1	No results posted	Recruiting	NCT04951141	Unknown	2021	Intratumoral injection
GPC3	TC-CAR031 [54]	Phase 1	No results posted	Recruiting	NCT05155189	Unknown	2021	Intravenous infusion
GPC3	GPC3-CAR-T cells [54]	Phase 1	No results posted	Suspended	NCT04506983	Unknown	2020	Intravenous infusion
GPC3	Anti-GPC3 CAR-T [54]	Phase 1/2	No results posted	Unknown	NCT03084380	2nd generation, 4-1BB/CD3ζ	2017	Intravenous or catheter injection
GPC3	Ori-C101 [54]	Phase 1/2	No results posted	Recruiting	NCT05652920	Unknown	2022	Hepatic arterial infusion

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Table 1 continued. Relevant clinical studies.

Target	Intervention and reference	Phase	Main findings	Status	NCT number	CAR design	First posted	Route
GPC3/ TGF-beta	GPC3 and/ or TGF-beta targeting CAR-T cells [49,55]	Phase 1	Tumors were completely eliminated within one month in one patient	Recruiting	NCT03198546	3rd/4th generation	2017	Systemic or local infusion
CD133	CART-133 [61,64]	Phase 1/2	ORR 7%; SD 64%; median OS 12 months; median PFS 6.8 months	Completed	NCT02541370	CD137/CD3ζ	2015	Injection
AFP	ET1402L1-CAR-T cells [65]	Phase 1	No results posted	Terminated	NCT03349255	CD28/CD3ζ	2017	Intrahepatic artery catheter or intravenous infusion
EGFRvIII/DR5/ NY-ESO-1	CAR-T cells [49,69]	Phase 1/2	No results posted	Unknown	NCT03941626	Unknown	2019	Injection
B7H3	fhB7H3.CAR-Ts [70]	Phase 1/2	No results posted	Recruiting	NCT05323201	Unknown	2022	Transhepatic arterial infusion
MUC1	Anti-MUC1 CAR-T cells [73]	Phase 1/2	No results posted	Unknown	NCT02587689	Unknown	2015	Injection
MUC1/HER2/ GPC3/EGFR/ B7H3	CAR-TILs [49,73]	Phase 1	No results posted	Unknown	NCT04842812	Unknown	2021	Injection
NKG2D	KD-025 CAR-T cells [77]	Phase 1	No results posted	Unknown	NCT04550663	Unknown	2020	Injection
NKG2D	NKR-2 cells [77]	Phase 1	No results posted	Unknown	NCT03370198	Unknown	2017	Hepatic transarterial administration
NKG2D	NKR-2 cells [77]	Phase 1	No results posted	Unknown	NCT03310008	Unknown	2017	Injection
NKG2D	NKG2D CAR-T cells [77]	Early Phase 1	No results posted	Recruiting	NCT05248048	Unknown	2022	Hepatic artery transfusion
PD-L1/c-Met	c-Met/PD-L1 CAR-T cells [79]	Early Phase 1	No results posted	Unknown	NCT03672305	Unknown	2018	Intravenous drip
PD-L1	HerinCAR-PD1 cells [49]	Phase 1/2	No results posted	Unknown	NCT02862028	Unknown	2016	Intratumoral injection
CD147	CD147-CAR-T [80,86]	Phase 1	No results posted	Unknown	NCT03993743	Unknown	2019	Hepatic artery infusion
MG7	MG7-CAR-T cells [49]	Phase 1/2	No results posted	Unknown	NCT02862704	2nd generation, 4-1BB/CD3ζ	2016	Intratumoral injection

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Table 1 continued. Relevant clinical studies.

Target	Intervention and reference	Phase	Main findings	Status	NCT number	CAR design	First posted	Route
EpCAM	EpCAM-targeted CAR-T cells [49]	Phase 1/2	No results posted	Unknown	NCT03013712	2nd generation, CD28/CD3ζ	2017	Vascular interventional or endoscopic administration
EpCAM	EpCAM-targeted CAR-T cells [49]	Not applicable	No results posted	Unknown	NCT02729493	Unknown	2016	Injection
IM83	IM83 CAR-T cells [49]	Phase 1	No results posted	Recruiting	NCT05123209	Unknown	2021	Injection
OX40	CpG-ODN [49]	Phase 1	No results posted	Recruiting	NCT04952272	Unknown	2021	Intratumoral injection

Abbreviations: AFP, alpha-fetoprotein; B7H3, B7 homolog 3; CAR, chimeric antigen receptor; CEA, carcinoembryonic antigen; DCR, disease control rate; DR5, death receptor 5; EGFRvIII, epidermal growth factor receptor variant III; EpCAM, epithelial cell adhesion molecule; GPC3, glypican-3; HCC, hepatocellular carcinoma; HER2, human epidermal growth factor receptor 2; MUC1, mucin 1; NKG2D, natural killer group 2 member D; NY-ESO-1, New York esophageal squamous cell carcinoma 1; ORR, overall response rate; OS, overall survival; PD-L1, programmed death-ligand 1; PFS, progression-free survival; SD, stable disease; TGF-beta, transforming growth factor beta. Table note: References in square brackets indicate sources cited in the main reference list. The NCT number is retained as the clinical trial registration identifier. Trial information was summarized from registered clinical studies and the corresponding cited literature, with the final search conducted on March 27, 2023.

escalation, route of administration, and preliminary efficacy [36,54,55,61,64,91]. GPC3 remains the most clinically advanced HCC-related CAR-T target, with published phase I data supporting tolerability and early signs of activity [54,55]. CD133-directed CAR-T-cell therapy has also been evaluated in advanced HCC, with disease stabilization observed in some patients [61,64].

Regional delivery strategies, including hepatic artery infusion, transcatheter arterial infusion, and intratumoral injection, have been used in several trials to increase local exposure and reduce systemic toxicity [51,64]. However, the available clinical evidence remains limited by small sample sizes, heterogeneous trial designs, variable target expression, and incomplete reporting of long-term outcomes [54,55,61,64]. **Table 1** summarizes registered clinical studies of CAR-T-cell therapy targeting HCC-related antigens.

Safety, Toxicity, and Barriers to Clinical Translation

CAR-T-cell therapy can be associated with cytokine release syndrome (CRS), immune effector cell-associated neurotoxicity syndrome, cytopenias, and on-target/off-tumor toxicity [92,93]. In solid tumors, safety concerns are amplified when target antigens are also expressed in normal tissues [32,42,50]. Careful target selection and controllable CAR designs are therefore important for improving the therapeutic index in HCC [80,86].

The TME is a major barrier to CAR-T-cell efficacy in HCC [32-35]. Physical barriers, hypoxia, metabolic stress, immune checkpoint signaling, TGF-beta-mediated suppression, regulatory T cells, myeloid-derived suppressor cells, and tumor-associated macrophages can impair CAR-T-cell trafficking, activation, and persistence [32-35,94]. Antigen heterogeneity and antigen loss can further reduce response durability [49].

Potential solutions include dual- or multi-target CAR constructs, cytokine-armored CAR-T cells, checkpoint-resistant CAR-T cells, hypoxia-responsive designs, regional infusion, and combination therapy with immune checkpoint inhibitors, antiangiogenic agents, targeted therapies, or locoregional treatments [32-35,49,55,89,90,94].

Future Directions

Future development of CAR-T-cell therapy for HCC should prioritize accurate target selection, standardized antigen-expression assessment, and rational trial design. Biomarker-driven enrollment may help identify patients most likely to benefit from target-specific CAR-T-cell therapy [53,54,64,80]. Multi-antigen strategies may reduce antigen escape, whereas inducible or switchable CAR systems may improve safety and controllability [49,80,86].

Combination strategies are also likely to be important. CAR-T-cell therapy may be combined with immune checkpoint inhibitors to

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counteract T-cell exhaustion, with antiangiogenic agents to improve tumor perfusion and immune infiltration, or with locoregional therapies to enhance antigen release and local immune activation [20,23-25,32-35]. Regional delivery may further improve the balance between efficacy and toxicity in liver tumors [52,64].

Long-term clinical translation will require larger multicenter trials, harmonized toxicity reporting, standardized response assessment, and extended follow-up for delayed adverse events and durability of response [54,55,64,93]. Manufacturing optimization and cost reduction will also be essential for broader clinical application.

Conclusions

CAR-T-cell therapy is an emerging immunotherapeutic strategy for HCC. Recent advances in CAR design, target identification, and early clinical translation have expanded the therapeutic potential of CAR-T cells in this disease. GPC3, CD133, AFP, EGFRvIII, NKG2DL, CD147, and EpCAM are among the most actively investigated HCC-related targets. However, tumor heterogeneity, antigen escape, limited tumor infiltration, and the immunosuppressive TME remain major barriers. Future research should focus on safer CAR engineering, multi-target strategies, rational combination therapies, and well-designed clinical trials to clarify the clinical role of CAR-T-cell therapy in HCC1.

Data Availability

All data supporting the findings of this review are available within the manuscript and its cited sources.

Declaration of Figures' Authenticity

All figures submitted have been created by the authors who confirm that the images are original with no duplication and have not been previously published in whole or in part.

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