Health Innovation Reports 2025,1(3):66-78
DOI: 10.64048/hir.v1n2.007

Review Article

Targeting the Tumor Microenvironment with Gene-Engineered Immune Cells: Focus on CAR-Macrophages and CAR-NK Cells - A Review Article

Farzand F. Hamid [1, 2*]

Received: 12 Jun 2025 Revised: 10 September 2025 Accepted: 19 September July 2025 Published: 15 October 2025

Abstract

The TME is a culprit of immunosuppression and a significant hurdle to long-term immunotherapeutic success in solid tumors, which are often associated with a dense stroma, hypoxia, and immunosuppressive myeloid and lymphoid cells. Conventional CAR-T cells tend to fail in this scenario as they are subjected to restricted trafficking, functional exhaustion, and inhibitory cues. Innate immune effectors including macrophages and natural killer (NK) cells are natural resident solid tumor infiltrates with strong cytotoxic and phagocytic potential, and thus represent promising chassis for CAR engineering. CAR-macrophages (CAR-M) CAR-Ms can phagocytose tumor cells directly and modulate the TME towards inflammation and superior T cell priming, whereas CAR-NK cells have the advantage of combining antigen-specific targeting with innate recognition, ADCC, and outstanding safety profile. Here, we review recent preclinical and clinical progress in CAR-M and CAR-NK therapy, focusing on their potential to modulate the TME, discuss engineering approaches to resist TME-imposed challenges, and present new clinical trials. We conclude that CAR-M and CAR-NK platforms represent complementary strategies to turning "cold" tumors "hot", but that enhanced persistence, trafficking, and on-target, off-tumor safety are needed.

Keywords Cancer Therapies, Tumor Microenvironment, Gene-Engineered, Natural Killer (NK) Cells, Solid Tumor, Chimeric Antigen Receptor (CAR) Cells, Immune cells, Immunotherapy

✉ Farzand Farhad Hamid
farzand1995@gmail.com
farzand.farhadpd10@lfu.edu.krd

[1] General Directorate of Research Center, University of Salahaddin – Erbil, Kerkuk Street, Erbil, 44001, Iraq

[2] College of Pharmacy, Knowledge University, Erbil, Kerkuk Street, Erbil, 44001, Iraq

* General Directorate of Research Center, University of Salahaddin – Erbil, Kerkuk Street, Erbil, 44001, Iraq
farzand1995@gmail.com

Introduction

Immunotherapy, which aims to stimulate the immune system to eradicate cancer, has recently revolutionized cancer treatment and constitutes the fourth cornerstone of cancer therapy alongside surgery, radiation, and chemotherapy (Peng et al., 2024). Current cancer immunotherapy research encompasses a broad range of approaches, including antibodies, vaccines, cytokines, oncolytic viruses, bi-specific molecules, and cellular therapies (Ma et al., 2023). Among these, immune checkpoint inhibitors (ICIs) and adoptive cell therapy (ACT) have emerged as the most successful immunotherapy strategies for cancer treatment the clinical success of chimeric antigen receptor (CAR) T cell therapy in hematologic malignancies has galvanized the development of adoptive cellular immunotherapies (Amoozgar et al., 2025).

The TME consists of a diverse array of tumor cells, stromal cells, blood vessels and immune cells surrounded by a remodeled extracellular matrix (ECM) and influenced by hypoxia, nutrient deprivation and soluble factors. This environment promotes the growth of the tumor but also inhibits anti-tumor immunity by attracting myeloid-derived suppressor cells (MDSC), regulatory T cells (Tregs) and alternatively activated (M2-like) tumor-associated macrophages (TAMs) (Yu et al., 2025, He et al., 2025, Peng et al., 2025). Many solid tumors are thus 'immune-excluded' or 'cold,' exhibiting minimal infiltration by cytotoxic T or natural killer (NK) cells and resistance to checkpoint blockade (Balta et al., 2021). Treatment of B-cell malignancies has been revolutionized by adoptive cell therapy with CAR-T cells. Yet, its efficacy in solid tumors has been limited, hindered by poor trafficking, antigen heterogeneity, and TME-mediated exhaustion (Peng et al., 2024).

Innate immune cells, such as macrophages and NK cells, naturally traffic to solid tumors, can operate in hypoxic or metabolically challenged environments, and are less restricted by MHC. Such properties have led to the generation of CAR-M and CAR-NK platforms to specifically address TME challenge (Wang et al., 2022, Huang et al., 2024, Amoozgar et al., 2025). In this review I discuss how genetically engineered CAR-M and CAR-NK can recognize and modify the TME, focusing on the third-generation design and its early clinical translation from bench to bedside.

The Tumor Microenvironment as Barrier and Therapeutic Target

Anti-tumor immunity is regulated at virtually every stage of antigen generation and presentation to effector cell infiltration and the TME including anti-tumor immunity from antigenicity to effector cell function (Sarhan et al., 2022). Tumor progression is correlated with:

Myeloid skewing and MDSCs, can suppress both T- and NK-cell function by releasing arginase, nitric oxide, ROS and inhibitory cytokines (IL-10, TGF-β) (He et al., 2025).

TAM polarization, toward an M2-like, pro-angiogenic, pro-tumor phenotype that secretes VEGF, IL-10, and matrix-remodeling enzymes, while scavenging antigens without effective cross-presentation (Peng et al., 2025, Lu et al., 2024).

Physical and metabolic barriers, include dense ECM, abnormal vasculature, hypoxia, and accumulation of adenosine and lactate, all of which impair NK and T cells functions (Yu et al., 2025, de Visser and Joyce, 2023, Kuznetsova et al., 2025).

NK cells, in particular, display significant functional heterogeneity and exhaustion in the TME, with tumor-adapted NK subsets that can promote tumor progression or the accumulation of suppressive myeloid cells (Li et al., 2025, Galvez-Cancino et al., 2025).

Based on these learnings, there is increasing focus on reprogramming the TME itself by turning suppressive macrophage and myeloid compartments into pro-inflammatory partners, or by adding potent innate effector cells that are less susceptible to inhibitory signals (Lv et al., 2024). CAR-M and CAR-NK cells exemplify these strategies (Amoozgar et al., 2025). The (Figure 1) illustrate that barriers in the tumor microenvironment to CAR-T/Innate cell therapy.

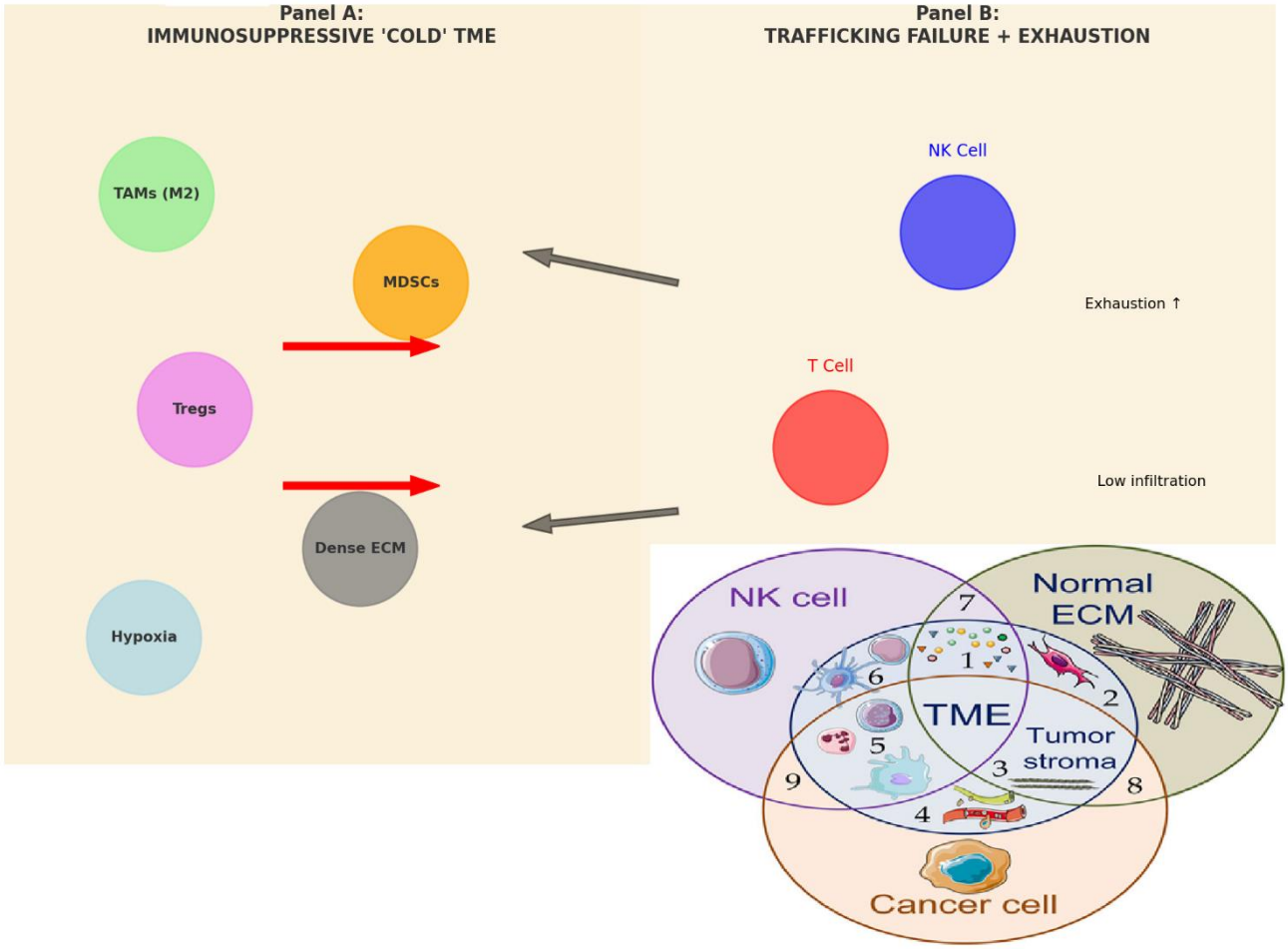

Figure 1: Schematic of the immunosuppressive TME and barriers to conventional CAR-T therapy. Panel A: Components of a "cold" TME (TAMs, MDSCs, Tregs, hypoxia, dense ECM). Panel B: Limited trafficking and exhaustion of T and NK cells in this setting and illustration of various components of the tumor microenvironment (TME) (1–6) and interactions between NK cells, cancer cells, and components of the extracellular matrix (ECM) (7–9).

CAR-Macrophages: Rewiring Myeloid Compartments in the TME

Design principles and engineering platforms, CAR-M constructs generally keep the canonical extracellular scFv that targets a tumor antigen (e.g. HER2, mesothelin), but utilize intracellular domains that are native to myeloid signaling (e.g., FcRγ, CD3ζ, CD28, or CD40) sometimes in combination with TLR (toll-like receptor) adaptors to amplify pro-inflammatory polarization (Wang et al., 2022, Huang et al., 2024). The gene transfer techniques are adenoviral vectors, lentiviral vectors, and now non-viral vectors like as mRNA/LNP platforms (Ning et al., 2024, Lv et al., 2024).

Mechanisms of TME remodeling, preclinical reports suggest that CAR-M perform a variety of TME-targeted actions other than killing tumor directly; antigen-dependent macrophage phagocytosis, of tumor cells with superior engulfment and killing capacity compared to naïve macrophages (Wang et al., 2022, Kuznetsova et al., 2025).

antigen-dependent macrophage phagocytosis, of tumor cells with superior engulfment and killing capacity compared to naïve macrophages (Wang et al., 2022, Kuznetsova et al., 2025).

Secretion of pro-inflammatory cytokines and chemokines, (TNF, IL-12, CXCL9/10), which attracts and stimulates $CD8^+$ T and NK cells (Pierini et al., 2025, Kuznetsova et al., 2025).

ECM degradation, through production of matrix metalloproteinases (MMPs) and other proteases facilitating immune cell infiltration (Kuznetsova et al., 2025, Lu et al., 2024).

Antigen presentation and cross-priming, as phagocytosed tumor antigens are processed and presented by CAR-M via MHC I/II to T cells, they have the potential to transform "cold" tumors into "hot" tumours with immune infiltration (Kuznetsova et al., 2025, Koppers et al., 2025).

Re-education of resident TAMs, a shifting in local

macrophage compartments toward an M1-like phenotype, associated with decreased immunosuppressive MDSCs (Peng et al., 2025, Pierini et al., 2025).

In immunocompetent hosts, HER2-directed CAR-M not only diminish tumor burden but also synergize with PD-1/PD-L1 blockade, boosting T-cell responses to an even greater extent (Pierini et al., 2025, Lv et al., 2024).

Preclinical and Early Clinical Experience, multiple preclinical models, ranging from breast and ovarian to pancreatic and brain tumors, demonstrate strong anti-tumor effects of CAR-M and show potent tumor infiltration as well as long term TME remodeling (Lu et al., 2024, Pierini et al., 2025, Lv et al., 2024).

The first-in-human, phase I trial of CT-0508, a HER2-targeted autologous CAR-M product, in patients with HER2-overexpressing advanced solid tumors was initiated (NCT04660929). Interim results demonstrate that CT-0508 can be successfully manufactured, demonstrates positive tumor-homing, and has a manageable safety profile associated with minimal cytokine release syndrome (CRS) and neurotoxicity (Abdou et al., 2024, Balta et al., 2021, Reiss et al., 2022, Reiss et al., 2025b). Early translational data suggest on-target CAR-M enrichment at tumor Site, increased local T-cell Infiltration, and Epitope Spreading (Reiss et al., 2025b, Abdou et al., 2024).

CAR-M formulations targeting mesothelin in ovarian cancer and other antigens in solid tumors have also been reported in small case series, with evidence of stable disease and acceptable toxicity (Li et al., 2024, Jing et al., 2025). Preclinical development of Lifespan-regulated CAR-M: Origin and differentiation of CAR-M targeting both longevity and TME remodeling from myeloid progenitors Lifespan-regulated CAR-M derived from myeloid progenitors have recently been shown to have enhanced persistence and TME remodeling in preclinical modeling, with potential to modulate in vivo longevity for improved safety (Abdou et al., 2024, Reiss et al., 2025a),

CAR-NK Cells: Leveraging Innate Cytotoxicity in Suppressive TMEs

NK cell biology in the TME, NK cell-mediated target cell lysis is regulated by a balance of activating and inhibitory receptor signals, does not require prior sensitization, and is mostly MHC independent (Galvez-Cancino et al., 2025). Yet, in solid tumors, NK cells are constantly subjected to binding their inhibitory receptors by ligands (such as HLA-E, PD-L1), to TGF-β, and to metabolic stress, promoting a state of dysfunction or pro-angiogenic phenotype (Li et al., 2025, de Visser and Joyce, 2023).

Nevertheless, NK cells maintain multiple benefits to be ideal CAR hosts including high innate cytotoxicity, no risk for graft-versus-host disease (GVHD), as well as reduced incidence of severe CRS and neurotoxicity when compared to CAR-T cells allowing for use of allogeneic “off-the-shelf” products (Peng et al., 2024, Yu and Ho, 2025, Amoozgar et al., 2025, Kumar Singh et al., 2025).

Engineering CAR-NK Cells for TME resistance, next-generation CAR-NK designs have indeed incorporated features that directly address TME-mediated suppression cytokine armoring, specifically with IL-15 or IL-15/IL-15Rα fusion, promotes persistence and proliferation in nutrient-poor TMEs (Balkhi et al., 2025, Amoozgar et al., 2025).

Disruption of checkpoint and inhibitory pathways, such as CISH deletion or the expression of dominant-negative TGF-β receptors, abrogates exhaustion and reestablishes cytotoxicity in tumors rich in TGF-β (Balkhi et al., 2025, Yu and Ho, 2025).

Engineering chemokine receptors, such as CXCR1/2, CXCR4, and CCR5, enhances trafficking to chemokine-rich tumor beds (Kuznetsova et al., 2025, Balkhi et al., 2025).

Bispecific, or NK-specific CARs, link recognition of tumor antigen to ligands for NKG2D and stress ligands, or Fc-binding domains, that yield both CAR-dependent and innate killing mechanisms (Amoozgar et al., 2025, Peng et al., 2024).

Indeed, such engineered CAR-NK cells in preclinical models show an improved infiltration into solid tumors, with intrinsic resistance to TGF-β and hypoxia, while having reduced exhaustion markers compared to conventional CAR-NK constructs (Balkhi et al., 2025, Look et al., 2025, Yu and Ho, 2025). Which presented in (Figure 2) the engineering designs and mechanisms of CAR-M and CAR-NK in the TME.

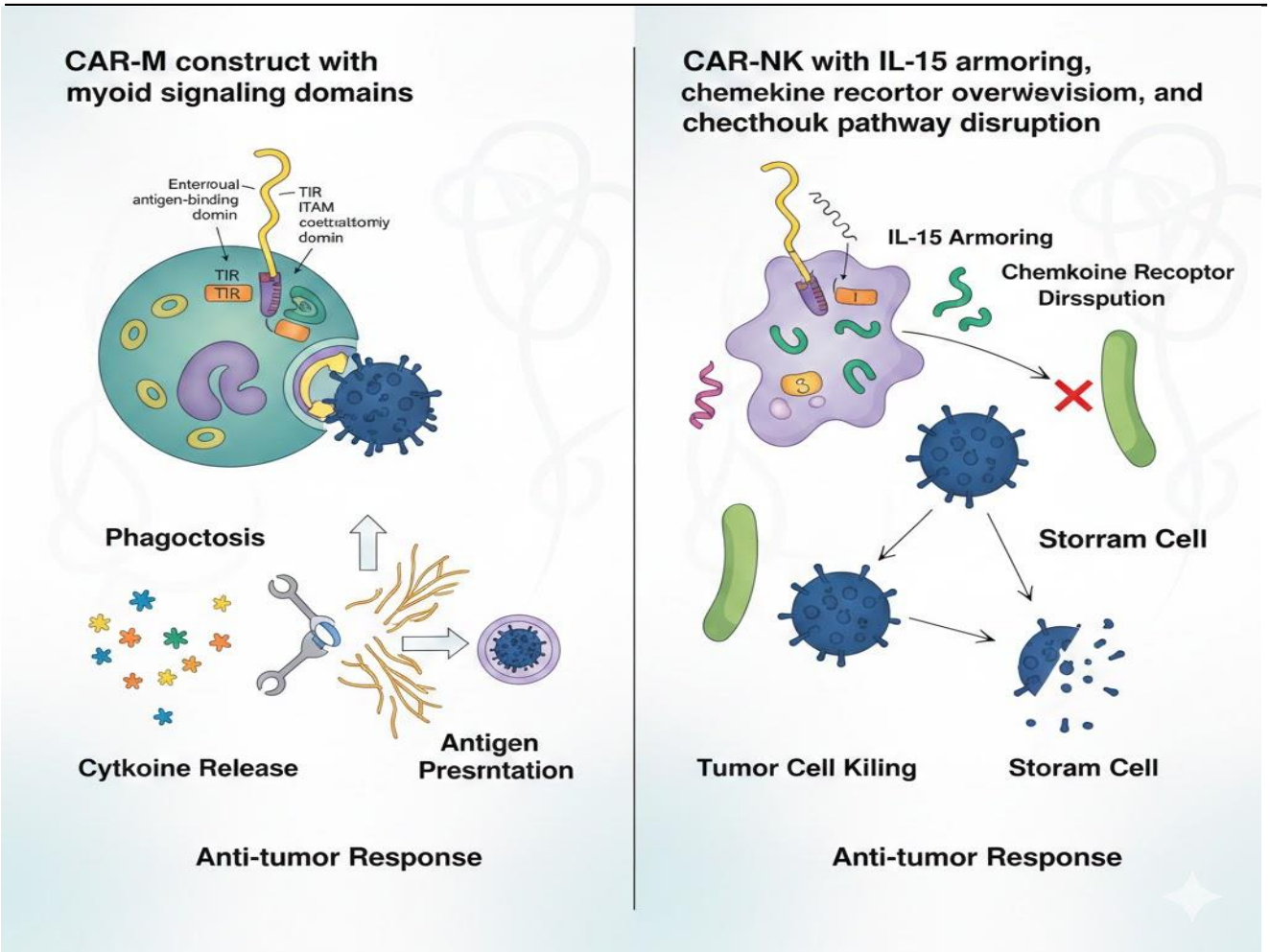

Figure 2: Engineering designs and mechanisms of CAR-M and CAR-NK in the TME. Left panel: CAR-M in the TME (CAR-M with myeloid signaling domains (CD3ζ/FcRγ, CD28/CD40), Phagocytosis of tumor cell, Cytokine/chemokine release (TNF, IL-12, CXCL9/10), ECM remodeling, Antigen presentation to $CD4^+$/$CD8^+$ T cells). Right Panel: CAR-NK in the TME (CAR-NK with IL-15 armoring, Chemokine receptor overexpression (CXCR1/2, CXCR4, CCR5), Checkpoint/TGF-β pathway disruption (e.g., TGF-βR DN, CISH KO), Killing of tumor and stromal/myeloid cells via perforin/granzymes and cytokines).

Clinical translation in solid tumors most clinical experience with CAR-NK cells is still focused on blood cancers, but several early-phase trials are now looking into solid tumors like glioma, gastric cancer, and hepatocellular carcinoma (Peng et al., 2024, Yu and Ho, 2025, Amoozgar et al., 2025). Preliminary data show a favorable safety profile, with a low rate of severe CRS, neurotoxicity, or graft-versus-host disease despite using allogeneic products (Kumar Singh et al., 2025, Amoozgar et al., 2025).

Evidence of tumor targeting and partial responses in some patients, although long-lasting complete remissions in solid tumors are still uncommon (Balkhi et al., 2025, Yu and Ho, 2025).

Recent reviews point out that the main challenges are persistence and suppression from the tumor microenvironment, not a lack of innate cytotoxicity. This emphasizes the need for better protective measures and smart combinations (Amoozgar et al., 2025, Balkhi et al., 2025).

CAR-M vs CAR-NK: Complementary Strategies for TME-Targeted Therapy

CAR-M and CAR-NK cells provide different but potentially complementary ways to reprogram the tumor microenvironment (TME). Cellular niche, CAR-M primarily operates within the myeloid compartment. It reverses immunosuppression, remodels the extracellular matrix (ECM), and coordinates adaptive responses. CAR-NK cells directly kill tumor cells and immunosuppressive stromal cells they also produce IFN-γ and chemokines, which recruit other immune effectors (Chettri et al., 2025, Lu et al., 2024, Kuznetsova et al., 2025, Kumar Singh et al., 2025).

Trafficking and tissue residency, Macrophages naturally invade hypoxic tumor areas and perivascular niches. NK cells often gather at invasive fronts and perivascular regions their movement can improve with engineered chemokine receptors (Peng et al., 2025, Kuznetsova et al., 2025, Lu et al., 2024).

Safety considerations, Both CAR-M and CAR-NK show less risk of cytokine release syndrome (CRS) and neurotoxicity compared to CAR-T cells. However, long-lasting macrophage populations may lead to chronic inflammation or autoimmunity. On the other hand, short-lived NK products might need repeated doses or cytokine support (Reiss et al., 2025b, Wang et al., 2022, Gao et al., 2025, Amoozgar et al., 2025).

Manufacturing, CAR-NK cells are ideal for allogeneic, banked products. Presently, CAR-M is mostly produced using autologous methods, but it may shift towards using progenitor or induced pluripotent stem cell (iPSC)-derived allogeneic sources (Amoozgar et al., 2025, Ning et al., 2024, Koppers et al., 2025, Lv et al., 2024).

Head-to-head comparisons in glioma models show that CAR-T, CAR-NK, and CAR-M have different infiltration patterns and effector functions (Burger et al., 2023). However, all three significantly benefit from cytokine support, highlighting the key role of the TME in controlling effectiveness (Look et al., 2025, Koppers et al., 2025, de Visser and Joyce, 2023). In (Table 1) present a generalized, Comparative overview of CAR-M, CAR-NK, and CAR-T therapies in solid tumors (Peng et al., 2024, Look et al., 2025).

Table 1: Comparative overview of CAR-M, CAR-NK, and CAR-T therapies in solid tumors.

Feature	CAR-T (Chimeric Antigen Receptor T-cell)	CAR-NK (Chimeric Antigen Receptor Natural Killer cell)	CAR-M (Chimeric Antigen Receptor Macrophage)
Trafficking Patterns	**Limited Infiltration:** Poor migration into dense, **physical barriers** (Dense ECM). Infiltration often restricted to the tumor periphery in "cold" tumors.	**Improved Homing:** Innate tropism to many solid tumors, often via chemokine receptors. Better ability to traverse the dense TME than CAR-T.	**Excellent Infiltration:** Inherent ability of macrophages to **infiltrate dense and hypoxic tumor regions** (like solid tumor cores) to perform surveillance.
Primary Effector Functions	**Cytotoxicity** (Perforin/Granzyme release). Highly specific, potent, **MHC-independent** killing via CAR. T-cell proliferation (expansion).	**Cytotoxicity** (Perforin/Granzyme release). **MHC-independent** killing via CAR *and* activating receptors. Lower proliferation/persistence than CAR-T.	**Phagocytosis** (Engulfment and clearance). **Antigen Presentation** (Cross-priming T-cells). **TME Remodeling** (via enzyme/cytokine secretion).
Major TME Interactions	**High Exhaustion/Anergy:** Susceptible to TME immunosuppression (MDSCs, Tregs, inhibitory cytokines like TGF-β). Requires **"armoring"** to resist checkpoint inhibition (e.g., PD-1/PD-L1).	**Lower Susceptibility to Exhaustion:** Innate receptors are less affected by TME immunosuppression than T-cell receptors. MHC-independent killing is highly advantageous.	**TME Reprogramming:** Capable of clearing immunosuppressive cells (like TAMs) and remodeling the **Extracellular Matrix (ECM)**, converting a "cold" TME to "hot."
Manufacturing Model	Primarily **Autologous** (patient-derived). Manufacturing is complex, time-consuming, expensive, and leads to **product variability**. Allogeneic approaches exist but face GvHD risks (unless genetically modified).	Highly conducive to **Allogeneic** ("Off-the-shelf"). Sources include NK cell lines (e.g., NK-92), UCB-NK, or iPSC-derived cells, minimizing **GvHD** risk and allowing large-scale production.	Primarily **Autologous** (patient-derived, usually from monocytes) or **iPSC-derived**. Requires complex *ex vivo* culture and transduction/engineering protocols.
Main Toxicities	**High Risk: Cytokine Release Syndrome (CRS)** and **Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS)**, often severe ($\ge$ Grade 3). **On-target/Off-tumor** toxicity risk.	**Low Risk:** Significantly **lower incidence and severity of CRS and ICANS** due to reduced cytokine production and innate function. Virtually no risk of **GvHD**.	**Lower Risk:** Primarily associated with **on-target/off-tumor** effects. Potential for systemic inflammation, but initial data suggests low CRS/ICANS risk compared to CAR-T.

Current Clinical Maturity	**Most Mature:** FDA-approved for hematological malignancies, with numerous **Phase 1/2 trials** in solid tumors (despite limited success). Longest history of clinical data.	**Emerging:** Numerous ongoing **Phase 1/2 trials** across various solid tumors (e.g., Glioblastoma, Ovarian, Pancreatic). Rapidly expanding field due to safety and scalability.	**Nascent/Pre-Clinical:** Few active **Phase 1 trials** (e.g., NCT04660929 for HER2+ tumors). Highly promising but still at the **earliest stage** of clinical development.

The key differences safety, CAR-NK and CAR-M offer a significant safety advantage over CAR-T, with lower risk of severe CRS and ICANS. CAR-NK also inherently avoids Graft-versus-Host Disease (GvHD). TME penetration, CAR-M cells are inherently superior at trafficking and infiltrating dense, hypoxic tumor tissues, which is a major bottleneck for CAR-T cells in solid tumors. Mechanism, CAR-T relies primarily on cytotoxicity and proliferation CAR-M leverages phagocytosis and TME remodeling, creating a multi-faceted attack that can recruit the host's endogenous T-cells (adaptive immunity). Manufacturing, CAR-NK is the most amenable to "off-the-shelf" (allogeneic) manufacturing, offering lower cost and faster patient access compared to the autologous CAR-T model (Lu et al., 2024, Amoozgar et al., 2025, Lv et al., 2024).

Researchers are exploring combination strategies, CAR-M can defrost the TME and improve antigen presentation, this can happen before or alongside the use of CAR-NK or CAR-T cells for strong cytotoxic clearance. Preclinical studies that combine CAR-M with PD-1/PD-L1 blockade already support these multi-modality designs (Lv et al., 2024, Pierini et al., 2025, Doeppner et al., 2025).

Mechanism of action CAR-NK vs CAR–M, the CAR-NK cells primarily act through direct cytotoxicity, using perforin and granzymes to induce tumor cell apoptosis in contrast, CAR-macrophages (CAR-M) leverage their natural ability for phagocytosis, engulfing tumor cells and then presenting antigens to recruit a broader immune response to remodel the tumor microenvironment (TME) (Amoozgar et al., 2025, Morva et al., 2025, Maalej et al., 2023). The (Figure 3) explain Mechanism of action: CAR-NK vs. CAR–macrophages.

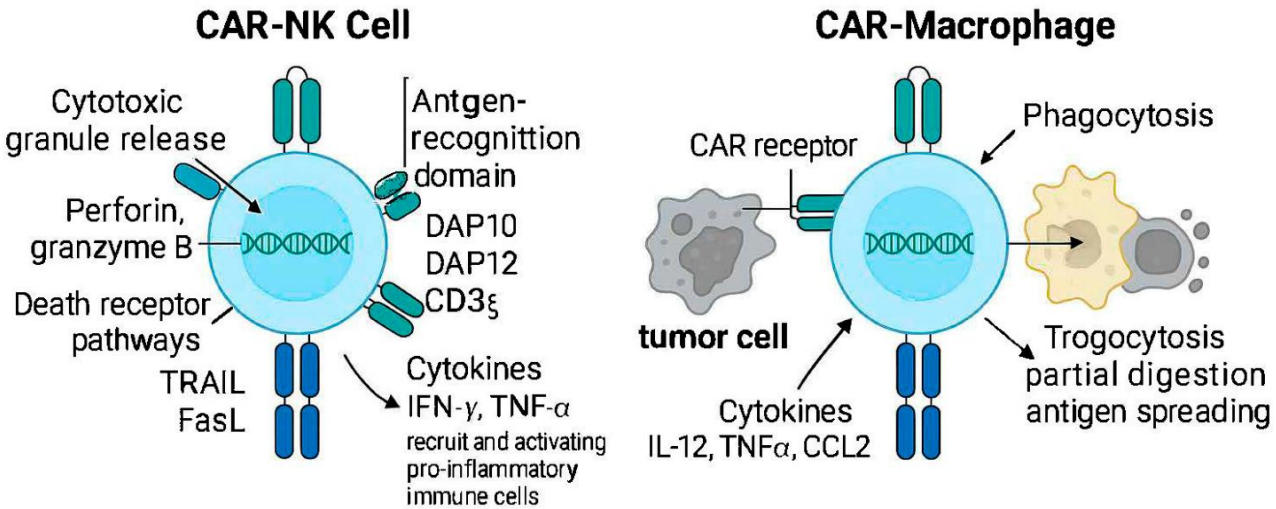

Figure 3: Mechanism of action: CAR-NK vs. CAR–macrophages. MHC-independent antigen recognition. Engineered CRA enables targeted tumor engagement. Distinct effector functions tailored to cell lineage (Amoozgar et al. 2025).

Clinical trials involving Chimeric Antigen Receptor Macrophage (CAR-M) and Chimeric Antigen Receptor Natural Killer (CAR-NK) products targeting the tumor microenvironment (TME) are currently in early phases, with a focus on treating solid tumors. These therapies are being explored for their inherent abilities to infiltrate solid tumors, remodel the TME, and potentially offer a safer, "off-the-shelf" alternative to CAR-T therapies (Morva et al., 2025, Pierini et al., 2025, Burger et al., 2023).

The TME targeting Strategies many trials incorporate engineering strategies to overcome the immunosuppressive TME (Kaiser et al., 2025), such as cytokine expression, engineering CAR-NK cells to secrete cytokines like IL-15 to enhance persistence and an inflammatory environment. Immune Checkpoint Blockade, Combining CAR-NK therapy with immune checkpoint inhibitors (e.g., anti-PD-1/PD-L1 antibodies) or engineering CARs that include PD-1 dominant-negative receptors to counteract TME suppression. Improved Homing, Modifying NK cells to express specific chemokine receptors (e.g., CXCR1) to

improve their infiltration into tumor sites. CAR-M Clinical Trials Research into CAR-M therapy is primarily in the preclinical and early clinical trial stages and CAR-NK Clinical Trials A greater number of CAR-NK clinical trials are underway compared to CAR-M trials, with many also targeting solid tumors (Balkhi et al., 2025, Chettri et al., 2025, Peng et al., 2024, Yu and Ho, 2025). In (Table 2) shows ongoing or completed clinical trials of CAR-M and CAR-NK products targeting the tumor microenvironment (TME), targeting the TME CT-0508 and related CAR-M products show direct TME reprogramming (Reiss et al., 2025b, Pierini et al., 2025). CAR-NK trials such as CAR2BRAIN (NCT03383978) and multi-armored platforms (NCT05410717) specifically include correlative TME biomarker programs and engineering features (checkpoint disruption, cytokine/chemokine armoring) designed to overcome immunosuppression (Amoozgar et al., 2025, Ning et al., 2024).

Table 2: Ongoing or completed clinical trials of CAR-M and CAR-NK products targeting the tumor microenvironment (TME).

Trial ID	Indication	Product (antigen; auto/allo; armoring / special features)	Route of administration	Key reported outcomes (safety, responses, TME biomarkers)
NCT04660929 (CT-0508)	HER2-overexpressing advanced / recurrent solid tumors (breast, gastric, etc.)	**CT-0508**: autologous anti-HER2 CAR-macrophages generated from peripheral blood monocytes; adenoviral CAR transfer; designed to adopt pro-inflammatory M1 phenotype (Reiss *et al.* 2025)	Intravenous infusion (dose-escalation), with cohorts including monotherapy and combination with pembrolizumab	Phase I: manufacturing feasible; treatment generally well tolerated with no dose-limiting toxicities; mainly grade 1–2 AEs and low-grade CRS. Early efficacy: mostly disease stabilization with occasional partial responses. Correlative studies show **TME remodeling** (↑ intratumoral $CD8^+$ T and NK cells, IFN-γ–related transcriptional signatures, evidence of antigen spreading).
NCT06562647 (SY001)	Mesothelin-positive ovarian cancer (early clinical experience in heavily pretreated patients)	**SY001**: autologous mesothelin-targeted CAR-macrophages (CAR introduced into PBMC-derived macrophages); no cytokine armoring reported (Li *et al.* 2024)	Intravenous infusion, evaluated alone and in combination with anti-PD-1 antibody	Small first-in-human series (2 patients so far): **good safety profile**, no high-grade CRS or neurotoxicity; signals of disease stabilization rather than deep responses. Immune monitoring focuses on **circulating cytokines and CAR copy number**; intratumoral TME biomarker data limited so far, though preclinical work suggests enhanced T and NK cell infiltration in $mesothelin^+$ models.
NA (investigator-initiated, China)	Recurrent ovarian cancer	Autologous mesothelin CAR-macrophages similar to SY001; PBMC-derived macrophages transduced with mesothelin-specific CAR; non-armored construct (Morva *et al.* 2025)	Intravenous; exploratory proof-of-concept	Early report on 2 patients: infusion **well tolerated**, with mainly low-grade cytokine elevations and no DLTs. Clinical benefit modest (disease control rather than major shrinkage). Authors highlight feasibility and suggest that **future intraperitoneal delivery** and

				combination with checkpoint blockade may better exploit TME remodeling (macrophage infiltration and antigen presentation).
NCT03383978 (CAR2BRAIN)	Recurrent HER2$^+$ glioblastoma	**NK-92/5.28.z**: HER2-specific CAR-NK-92 cell line (allogeneic, irradiated); second-generation CAR (CD28–CD3ζ); no exogenous cytokine armoring (Burger *et al.* 2023)	Local intracranial administration: injection into the wall of the resection cavity during relapse surgery, followed by repeated intralesional doses via an implanted reservoir	Phase I dose-escalation: **acceptable safety**, with no systemic CRS or GvHD; main AEs are procedure-related or local neurological events. Early efficacy: some patients show delayed progression compared with historical controls. Correlative analyses (NanoString, flow cytometry) indicate **TME modulation**, with increased cytotoxic gene signatures (IFNG, CD3E, CD4) and higher leukocyte / T-cell scores in tumors after therapy.
NCT04319757 (ACE1702-001)	Advanced or metastatic HER2-expressing solid tumors (breast, gastric, etc.)	**ACE1702**: off-the-shelf, allogeneic **oNK** product (expanded NK cells expressing anti-HER2 CAR); exploits endogenous NK killing plus CAR-mediated recognition; no IL-15 armoring in first-generation product (Li *et al.* 2024)	Intravenous infusion in repeated cycles	Ongoing Phase I: preliminary reports from company and reviews describe **favorable safety**, with no dose-limiting CRS, neurotoxicity or GvHD and evidence of disease stabilization in some patients. Detailed TME biomarker readouts are not yet widely reported; current focus is on safety, pharmacokinetics, and peripheral immune activation.
NCT02839954 (anti-MUC1 CAR-NK-92)	MUC1$^+$ relapsed/refractory solid tumors (NSCLC, pancreatic, ovarian, colorectal, breast, etc.)	**MUC1-CAR-NK-92**: allogeneic NK-92 cell line with MUC1-targeting CAR containing CD28 and 4-1BB costimulatory domains and a truncated PD-1 peptide (designed to **partially block PD-1/PD-L1** signaling) (Maalej *et al.* 2023)	Intravenous infusion (multiple cycles)	Completed Phase I: treatment **well tolerated**; in an early cohort of 13 patients, majority achieved **stable disease**, with one progression and no severe CRS or neurotoxicity. The trial primarily reports clinical and peripheral immune outcomes; intratumoral TME biomarker analyses are limited, but the PD-1-truncated design directly targets checkpoint pathways within the TME.
NCT03940820	Advanced solid tumors expressing ROBO1 (e.g. pancreatic, hepatobiliary,	**ROBO1 CAR-NK**: allogeneic NK cells transduced with ROBO1-specific CAR; early-generation product without	Intravenous; Phase I/II dose-escalation and expansion cohorts	Trial is **ongoing**; primary endpoints are safety and determination of the maximum tolerated / recommended phase II dose. Published summaries to date

	colorectal malignancies)	explicit cytokine armoring; aimed at broad ROBO1⁺ solid tumors (Wang *et al.* 2022)		do not yet provide detailed efficacy or TME biomarker results, but the design includes correlative analyses of immune cell subsets and soluble factors in blood and (where available) tumor biopsies.
NCT05410717	Stage IV ovarian, refractory testis and recurrent endometrial cancers	Multi-target **CAR-NK** platform recognizing Claudin-6, GPC3, mesothelin or AXL; allogeneic NK cells engineered to **secrete IL-7/CCL19 and/or scFvs against PD-1, CTLA-4 or LAG-3**, providing both cytokine and checkpoint armoring (Doeppner *et al.* 2025)	Intravenous (with possible intraperitoneal delivery in some cohorts, depending on protocol)	Early-phase, exploratory study: designed to assess **safety, pharmacokinetics, and preliminary antitumor activity** across multiple gynecologic and germ-cell solid tumors. Correlative plans include intensive **TME and systemic biomarker profiling**, evaluating how IL-7/CCL19 and checkpoint-blocking scFvs shape intratumoral T- and NK-cell infiltration and exhaustion markers; full outcome data not yet available.
NCT03692637	MSLN⁺ recurrent or refractory solid tumors (with emphasis on ovarian cancer)	**Anti-mesothelin CAR-NK** (peripheral blood–derived NK cells expressing MSLN-CAR); allogeneic; designed to exploit NK homing to peritoneal metastases in ovarian cancer (Maalej *et al.* 2023)	Intravenous, with repeat dosing	Ongoing early-phase trial; preclinical data show strong **anti-mesothelin CAR-NK activity** in ovarian and other mesothelin⁺ models with improved survival. Clinical results so far focus on safety and feasibility; detailed response rates and TME biomarker analyses (e.g. changes in ascites tumor cell burden and immune infiltrates) are anticipated but not yet fully reported.

Challenges, Safety Concerns, and Future Directions

The main obstacles for CAR-M and CAR-NK therapies that target TME are selection of Antigens and Their Diversity, Tumor-associated antigens like HER2, mesothelin, and GD2 are significantly overexpressed, but not absolutely tumor-specific, hence the risk of on-target off-tumor effects, especially in macrophages that are widely distributed (Lu et al., 2024, Li et al., 2024, Jing et al., 2025). Complexities are added by multiplex or logic-gated CARs (e.g. AND-gate, SynNotch) that may enhance specificity (Peng et al., 2024, Amoozgar et al., 2025).

Cell lifespan and phenotypic control, excessively long-lived CAR-M might lead to continuous inflammation, fibrosis, or autoimmunity, while short-lived CAR-NK might not provide enough strength. Lifespan-controlled CAR-M and apoptosis-inducible switches are in the process of being created as a remedy for this (Chettri et al., 2025, Lv et al., 2024).

Resistance and Plasticity Mediated by TME tumors can recruit new suppressive myeloid subsets, up-regulate alternative checkpoint ligands, or regulate cytokine and metabolic networks as means of adapting (Yu et al., 2025, He et al., 2025, Galvez-Cancino et al., 2025). The use of dynamic monitoring to track TME composition along with single-cell transcriptomics in ongoing trials will play a crucial role in the refinement of engineering strategies (Abdou et al., 2024, Look et al., 2025, de Visser and Joyce, 2023).

Route of Administration and Distribution, the routes of administration (IV, intratumoral, or regional like intrapleural, intraperitoneal, intra-arterial) may have a

differential effect on the interaction of CAR-M/NK with the TME and also the location of such interactions, especially in sanctuary sites such as the brain where the blood-brain barrier is a limiting factor for access (Koppers et al., 2025, Kaiser et al., 2025).

Rational combinations, it is conceptually appealing to combine CAR-M and CAR-NK with checkpoint blockade, oncolytic virus, radiation therapy, or targeted myeloid-directed agents (like CSF1R inhibitors, MDSC-targeting strategies) and also supported by preclinical studies showing synergy. However, this may lead to increased toxicity and higher costs (Pierini et al., 2025, He et al., 2025, Sarhan et al., 2022).

The future directions include in vivo programming methods such as the delivery of CAR constructs to target endogenous macrophages or NK cells using LNP, the development of synthetic cytokine circuits that are able to detect and react to the cues in the local TME and, ultimately, the integration with spatial omics to better understand individual patient TME-targeted cell therapy designs are all to be considered as future directions.

Conclusion

This review conclusion it looks like gene-edited immune cell therapies could be a great way to attack and change the area around a tumor. CAR-macrophages use the way myeloid cells naturally go to tumors and adapt to turn off the defenses around the tumor so T-cells can come in and fight. CAR-NK cells are really good at killing cells and seem safe to use as ready-made treatments. Early tests of CAR-M (like CT-0508) show that it's possible and does something in patients with solid tumors who have already had a lot of treatment. There are many CAR-NK tests happening now to find ways to get around the tumor's defenses.

Even though there are still some big problems to solve like making sure the treatment targets the right thing, lasts long enough, and can keep up with how the tumor changes CAR-M and CAR-NK treatments each have good things going for them, so it makes sense to keep working on them. It is worth developing them on their own, or with each other, or even with the immune treatments we already have. In the future, these CAR-based strategies might be key in turning tumors that don't respond to treatment into ones we can actually cure.

Statements and Declarations

Author Contributions Farzand F. Hamid: Conceptualization; supervision: data curation; formal analysis; investigation; methodology; resources; software; validation; visualization; writing original draft; writing review and editing.

Acknowledgements I thanks to my family and friends who had a role in this paper.

Data Availability Statement All prove and evidence provided to improve this review paper are available online and can be accessed from the appropriate reference in the reference list.

Ethics Statement Not required.

Transparency Statement The author, Farzand Farhad Hamid, asserts that this manuscript provides an honest, accurate, and transparent account of the reported study. I confirm that no significant aspects of the study have been omitted and that any deviations from the original study plan, including registration if applicable, have been properly explained.

References

ABDOU, Y., MORTIMER, J., POHLMANN, P., JOHNSON, M., MAZIARZ, R., SPECHT, J. M., DEES, C., UENO, N., YUAN, Y. & ANGELOS, M. Translational insights from a phase 1, first-in-human (FIH) clinical trial of the anti-HER2 CAR macrophage CT-0508 in participants with HER2 positive metastatic breast cancer and other HER2 overexpressing solid tumors. Cancer Research, 2024. AMER ASSOC CANCER RESEARCH 615 CHESTNUT ST, 17TH FLOOR, PHILADELPHIA, PA. https://doi.org/10.1158/1538-7445.SABCS23-PO2-04-08.

AMOOZGAR, B., BANGOLO, A., MANSOUR, C., ELIAS, D., MOHAMED, A., THOR, D. C., EHSANULLAH, S. U., TRAN, H. H.-V., AGUILAR, I. K. & WEISSMAN, S. 2025. Engineering Innate Immunity: Recent Advances and Future Directions for CAR-NK and CAR–Macrophage Therapies in Solid Tumors. Cancers, 17, 2397. https://doi.org/10.3390/cancers17142397.

BALKHI, S., ZUCCOLOTTO, G., DI SPIRITO, A., ROSATO, A. & MORTARA, L. 2025. CAR-NK cell therapy: promise and challenges in solid tumors. Front Immunol, 16, 1574742. https://doi.org/10.3389/fimmu.2025.1574742.

BALTA, E., WABNITZ, G. H. & SAMSTAG, Y. 2021. Hijacked Immune Cells in the Tumor Microenvironment: Molecular Mechanisms of Immunosuppression and Cues to Improve T Cell-Based Immunotherapy of Solid Tumors. International Journal of Molecular Sciences, 22, 5736. https://doi.org/10.3390/ijms22115736.

BURGER, M. C., FORSTER, M. T., ROMANSKI, A., STRAßHEIMER, F., MACAS, J., ZEINER, P. S., STEIDL, E., HERKT, S., WEBER, K. J., SCHUPP, J., LUN, J. H., STRECKER, M. I., WLOTZKA, K., CAKMAK, P., OPITZ, C., GEORGE, R., MILDENBERGER, I. C., NOWAKOWSKA, P., ZHANG, C., RÖDER, J., MÜLLER, E., IHRIG, K., LANGEN, K. J., RIEGER, M. A., HERRMANN, E., BONIG, H., HARTER, P. N., REISS, Y., HATTINGEN, E., RÖDEL, F., PLATE, K. H., TONN, T., SENFT, C., STEINBACH, J. P. & WELS, W. S. 2023. Intracranial injection of natural killer cells engineered with a HER2-targeted chimeric antigen receptor in patients with recurrent glioblastoma. Neuro Oncol, 25, 2058-2071. https://doi.org/10.1093/neuonc/noad087.

CHETTRI, D., SATAPATHY, B. P., YADAV, R., UTTAM, V., JAIN, A. & PRAKASH, H. 2025. CAR-macrophages: tailoring cancer immunotherapy. Frontiers in Immunology, Volume 15 – 2024. https://doi.org/10.3389/fimmu.2024.1532833.

DE VISSER, K. E. & JOYCE, J. A. 2023. The evolving tumor microenvironment: From cancer initiation to metastatic outgrowth. Cancer Cell, 41, 374-403. https://doi.org/10.1016/j.ccell.2023.02.016.

DOEPPNER, C. A., BINDER, A. K., BREMM, F., FEUCHTER, N., DÖRRIE, J. & SCHAFT, N. 2025. Rendering NK Cells Antigen-Specific for the Therapy of Solid Tumours. International Journal of Molecular Sciences, 26, 6290. https://doi.org/10.3390/ijms26136290.

GALVEZ-CANCINO, F., ARMERO, M., WITHERS, D. R., MOLERO-GLEZ, P., MELERO, A., PALENCIA, B. & MELERO, I. 2025. The Dark Side of NK Cells in Cancer Immunotherapy. Cancer Discovery, 15, 1777-1779. https://doi.org/10.1158/2159-8290.CD-25-1042.

GAO, C., HONG, F., DONG, Y., FU, Y., MA, Y., SUN, X., ZHANG, J., CHEN, J. & HUANG, Z. 2025. Lifespan-Regulated CAR-Macrophages from Myeloid Progenitors for Enhanced Colorectal Cancer Therapy. Advanced Science, 12, e17677. https://doi.org/10.1002/advs.202417677.

HE, S., ZHENG, L. & QI, C. 2025. Myeloid-derived suppressor cells (MDSCs) in the tumor microenvironment and their targeting in cancer therapy. Molecular Cancer, 24, 5. https://doi.org/10.1186/s12943-024-02208-3.

HUANG, T., BEI, C., HU, Z. & LI, Y. 2024. CAR-macrophage: Breaking new ground in cellular immunotherapy. Frontiers in Cell and Developmental Biology, Volume 12 – 2024. https://doi.org/10.3389/fcell.2024.1464218.

JING, J., CHEN, Y., CHI, E., LI, S., HE, Y., WANG, B., SHEN, H., FAN, L., WANG, J., SHANGGUAN, T., GE, X., JIANG, Y., CHEN, Y. & XU, C. 2025. New power in cancer immunotherapy: the rise of chimeric antigen receptor macrophage (CAR-M). Journal of Translational Medicine, 23, 1182. https://doi.org/10.1186/s12967-025-07115-9.

KAISER, Y., GARRIS, C. S., MARINARI, E., KIM, H. S., OH, J., PEDARD, M., HALABI, E. A., CHOI, M., PARVANIAN, S., KOHLER, R., MIGLIORINI, D. & WEISSLEDER, R. 2025. Targeting immunosuppressive myeloid cells via implant-mediated slow release of small molecules to prevent glioblastoma recurrence. Nature Biomedical Engineering. https://doi.org/10.1038/s41551-025-01533-2..

KOPPERS, M. J. A., MONNIKHOF, M., MEELDIJK, J., KOORMAN, T. & BOVENSCHEN, N. 2025. Chimeric antigen receptor-macrophages: Emerging next-generation cell therapy for brain cancer. Neuro-Oncology Advances, 7. https://doi.org/10.1093/noajnl/vdaf059.

KUMAR SINGH, V., AWASTHI, S. & SHARMA, S. 2025. Natural killer cell-based Immunotherapy for Solid tumors: A Comprehensive Review Iran J Blood Cancer. 2025 June 30; 17 (2): 83-98. Iran J Blood Cancer, 17, 83-98. http://dx.doi.org/doi:0000-0002-7556-2505.

KUZNETSOVA, A. V., GLUKHOVA, X. A., BELETSKY, I. P. & IVANOV, A. A. 2025. NK cell activity in the tumor microenvironment. Frontiers in Cell and Developmental Biology, Volume 13 – 2025. https://doi.org/10.3389/fcell.2025.1609479.

LI, X., WANG, X., WANG, H., ZUO, D., XU, J., FENG, Y., XUE, D., ZHANG, L., LIN, L. & ZHANG, J. 2024. A clinical study of autologous chimeric antigen receptor macrophage targeting mesothelin shows safety in ovarian cancer therapy. Journal of Hematology & Oncology, 17, 116. https://doi.org/10.1186/s13045-024-01635-5.

LI, Y., GAO, Y., WANG, L. & SI, J. 2025. NK cell adaptation in the tumor microenvironment: Insights for NK cell-based immunotherapy. Cytokine & Growth Factor Reviews, 86, 181-198. https://doi.org/10.1016/j.cytogfr.2025.10.003.

LOOK, T., SANKOWSKI, R., BOUZEREAU, M., FAZIO, S., SUN, M., BUCK, A., BINDER, N., MASTALL, M., PRISCO, F., SEEHUSEN, F., FREI, J., WYSS, C., SNIJDER, B., NOMBELA ARRIETA, C., WELLER, M., PASCOLO, S. & WEISS, T. 2025. CAR T cells, CAR NK cells, and CAR macrophages exhibit distinct traits in glioma models but are similarly enhanced when combined with cytokines. Cell Reports Medicine, 6. https://doi.org/10.1016/j.xcrm.2025.101931.

LU, J., MA, Y., LI, Q., XU, Y., XUE, Y. & XU, S. 2024. CAR Macrophages: a promising novel immunotherapy for solid tumors and beyond. Biomarker Research, 12, 86. https://doi.org/10.1186/s40364-024-00637-2.

LV, R., GUO, Y., LIU, W., DONG, G., LIU, X., LI, C., REN, Y., ZHANG, Z., NEO, S.-Y. & MAO, W. 2024. Revolutionizing cancer treatment: the emerging potential and potential challenges of in vivo self-processed CAR cell therapy. Theranostics, 14, 7424. https://doi.org/10.7150/thno.101941.

MA, R., LI, Z., CHIOCCA, E. A., CALIGIURI, M. A. & YU, J. 2023. The emerging field of oncolytic virus-based cancer immunotherapy. Trends Cancer, 9, 122-139. https://doi.org/10.1016/j.trecan.2022.10.003.

MAALEJ, K. M., MERHI, M., INCHAKALODY, V. P., MESTIRI, S., ALAM, M., MACCALLI, C., CHERIF, H., UDDIN, S., STEINHOFF, M., MARINCOLA, F. M. & DERMIME, S. 2023. CAR-cell therapy in the era of solid tumor treatment: current challenges and emerging therapeutic advances. Molecular Cancer, 22, 20. https://doi.org/10.1186/s12943-023-01723-z.

MORVA, A., ARROYO, A. B., ANDREEVA, L., TAPIA-ABELLÁN, A. & LUENGO-GIL, G. 2025. Unleashing the power of CAR-M therapy in solid tumors: a comprehensive review. Frontiers in Immunology, Volume 16 – 2025. https://doi.org/10.3389/fimmu.2025.1615760.

NING, P., DU, F., WANG, H., GONG, X., XIA, Y., ZHANG, X., DENG, H., ZHANG, R. & WANG, Z. 2024. Genetically engineered macrophages as living cell drug carriers for targeted cancer therapy. Journal of Controlled Release, 367, 697-707. https://doi.org/10.1016/j.jconrel.2024.02.003.

PENG, L., SFERRUZZA, G., YANG, L., ZHOU, L. & CHEN, S. 2024. CAR-T and CAR-NK as cellular cancer immunotherapy for solid tumors. Cellular & Molecular Immunology, 21, 1089-1108. https://doi.org/10.1038/s41423-024-01207-0.

PENG, M., ZHU, Y., HU, Y., WEN, J. & HUANG, W. 2025. Advances in the regulation of macrophage polarization by the tumor microenvironment. Discover Oncology, 16, 1487. https://doi.org/10.1007/s12672-025-03258-9.

PIERINI, S., GABBASOV, R., OLIVEIRA-NUNES, M. C., QURESHI, R., WORTH, A., HUANG, S., NAGAR, K., GRIFFIN, C., LIAN, L., YASHIRO-OHTANI, Y., ROSS, K., SLOAS, C., BALL, M., SCHOTT, B., SONAWANE, P., CORNELL, L., BLUMENTHAL, D., CHHUM, S., MINUTOLO, N., CICCAGLIONE, K., SHAW, L., ZENTNER, I., LEVITSKY, H., SHESTOVA, O., GILL, S., VARGHESE, B., CUSHING, D., CEERAZ DELONG, S., ABRAMSON, S., CONDAMINE, T. & KLICHINSKY, M. 2025. Chimeric antigen receptor macrophages (CAR-M) sensitize HER2+ solid tumors to PD1 blockade in pre-clinical models. Nature

Communications, 16, 706. https://doi.org/10.1038/s41467-025-57496-0.

REISS, K., YUAN, Y., UENO, N., JOHNSON, M., CLAIRE DEES, E., ANGELOS, M., CHAO, J., GILL, S., SHESTOVA, O., SERODY, J., PRICEMAN, S., RONCZKA, A., QURESHI, R., SONAWANE, P., CUSHING, D., BARTON, D., KLICHINSKY, M., CONDAMINE, T., SWABY, R. & ABDOU, Y. 2022. 634 A phase 1, first-in-human (FIH) clinical trial of the anti-HER2 CAR macrophage CT-0508 in participants with HER2 overexpressing solid tumors. Journal for Immunotherapy of Cancer, 10. https://doi.org/10.1136/jitc-2022-SITC2022.0634.

REISS, K. A., ANGELOS, M. G., DEES, E. C., YUAN, Y., UENO, N. T., POHLMANN, P. R., JOHNSON, M. L., CHAO, J., SHESTOVA, O. & SERODY, J. S. 2025a. CAR-macrophage therapy for HER2-overexpressing advanced solid tumors: a phase 1 trial. Nature medicine, 1-12. https://doi.org/10.1038/s41591-025-03495-z.

REISS, K. A., ANGELOS, M. G., DEES, E. C., YUAN, Y., UENO, N. T., POHLMANN, P. R., JOHNSON, M. L., CHAO, J., SHESTOVA, O., SERODY, J. S., SCHMIERER, M., KREMP, M., BALL, M., QURESHI, R., SCHOTT, B. H., SONAWANE, P., DELONG, S. C., CHRISTIANO, M., SWABY, R. F., ABRAMSON, S., LOCKE, K., BARTON, D., KENNEDY, E., GILL, S., CUSHING, D., KLICHINSKY, M., CONDAMINE, T. & ABDOU, Y. 2025b. CAR-macrophage therapy for HER2-overexpressing advanced solid tumors: a phase 1 trial. Nat Med, 31, 1171-1182. https://doi.org/10.1038/s41591-025-03495-z.

SARHAN, D., EISINGER, S., HE, F., BERGSLAND, M., PELICANO, C., DRIESCHER, C., WESTBERG, K., BENITEZ, I. I., HAMOUD, R., PALANO, G., LI, S., CARANNANTE, V., MUHR, J., ÖNFELT, B., SCHLISIO, S., RAVETCH, J. V., HEUCHEL, R., LÖHR, M. J. & KARLSSON, M. C. I. 2022. Targeting myeloid suppressive cells revives cytotoxic anti-tumor responses in pancreatic cancer. iScience, 25. https://doi.org/10.2139/ssrn.4047254.

WANG, S., YANG, Y., MA, P., ZHA, Y., ZHANG, J., LEI, A. & LI, N. 2022. CAR-macrophage: An extensive immune enhancer to fight cancer. EBioMedicine, 76, 103873 https://doi.org/10.1016/j.ebiom.2022.103873.

YU, J., KONG, X. & FENG, Y. 2025. Tumor microenvironment-driven resistance to immunotherapy in non-small cell lung cancer: strategies for Cold-to-Hot tumor transformation. Cancer Drug Resist, 8, 21. https://doi.org/10.20517/cdr.2025.14.

YU, Y. & HO, M. 2025. CAR NK cell therapy for solid tumors: potential and challenges. Antibody Therapeutics, 8, 275-289. https://doi.org/10.1093/abt/tbaf019.