Acta Pharmaceutica Sinica B 2026;16(1):169−197

Chinese Pharmaceutical Association
Institute of Materia Medica, Chinese Academy of Medical Sciences

Acta Pharmaceutica Sinica B

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REVIEW

Immunocyte reprogramming empowers live-cell drug delivery: Mechanistic insights, delivery strategies, and clinical perspectives

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Received 22 May 2025; received in revised form 6 August 2025; accepted 7 September 2025

KEY WORDS

Immune cells;
Reprogramming;
Tumor-targeted drug delivery;
Loading strategies;
Live-cell carriers;
Tumor microenvironment;
Programmable drug release;
Clinical translation

Abstract Conventional drug-delivery systems (DDSs) for oncology often face challenges such as insufficient tumor selectivity, rapid systemic clearance, limited penetration across stromal and immune barriers, and suboptimal biocompatibility. Live immune cell-based drug-delivery systems (LCDDSs) overcome these limitations by exploiting the innate tumor-homing capacity, high biocompatibility, and dynamic tumor microenvironment (TME) interactions intrinsic to leukocytes, facilitating precise targeting with minimal systemic toxicity. Furthermore, immune cells act as "mobile microprocessors", actively converting precursor payloads into therapeutically functional cargos at the tumor site and dynamically reshaping the TME. Nonetheless, the clinical translation of LCDDSs remains impeded by limited drug-loading capacities, premature payload degradation, potential impairment of immune-cell function, and insufficient persistence in immunosuppressive environments. To overcome these hurdles, immune cell reprogramming *via* genetic, metabolic, or epigenetic modifications emerges as a promising strategy. Such interventions improve cellular fitness, enhance tumor infiltration, augment payload transport efficiency, confer programmable release profiles, mitigate cellular exhaustion, and increase adaptability to

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Peer review under the responsibility of Chinese Pharmaceutical Association and Institute of Materia Medica, Chinese Academy of Medical Sciences.

https://doi.org/10.1016/j.apsb.2025.10.019

the hostile TME. This review systemically evaluates how immune cell reprogramming advances LCDDSs by examining mechanistic benefits, drug compatibility considerations, payload loading strategies, and design criteria essential for achieving clinical controllability, safety, and scalability. By integrating immune-cell engineering with cutting-edge drug delivery technologies, reprogrammed LCDDSs represent a versatile and powerful platform for next-generation precision oncology therapeutics.

1. Introduction

Live immune cell-based drug delivery systems (LCDDSs) are gaining traction in oncology because they combine intrinsic tumor-homing, responsiveness to inflammatory cues and deep-tissue penetration-properties largely absent from synthetic nanocarriers[1−4]. Macrophages, T lymphocytes, and natural killer (NK) cells can be loaded *ex vivo* with therapeutic payloads and subsequently act asself-propelled vectors that navigate physiological barriers, localize selectively within malignant lesions and release their cargo *in situ*, thereby enhancing antitumor efficacy while minimizing systemic toxicity[5].

Despite their promise, LCDDSs face four major hurdles. First, native immune cells rarely penetrate deeply or uniformly into the hypoxic, poorly vascularized tumor microenvironment[6]. Second, tumor-derived cytokines drive phenotypic drift and reduce cell viability, eroding anti-tumor activity [7]. Third, sustained exposure to the tumor microenvironment (TME)'s hypoxic, nutrient-deprived milieu induces metabolic exhaustion, shortening immune-cell persistence and efficacy[8]. Finally, cell-drug compatibility is suboptimal: many payloads load inefficiently, undergo lysosomal degradation or are released uncontrollably at the disease site[9]. Together, these shortcomings highlight the need for advanced engineering strategies that improve homing accuracy, preserve functional durability, and optimize intracellular drug trafficking.

Immune cell reprogramming offers a versatile solution to these limitations. Through genetic engineering, transcriptional modulation, metabolic rewriting and other synthetic-biology tools, macrophages, T cells and NK cells can be endowed with greater resistance to tumor-derived inhibitory signals, enhanced metabolic fitness and stronger effector programs inside the TME[10,11]. These modifications improve homing accuracy, extend cell survival under hypoxia and acidosis, and enable stimulus-responsive, programmable drug release[8,12]. Reprogrammed cells also display superior payload compatibility: optimized trafficking and vesicular shielding increase drug loading, prevent lysosomal degradation and ensure site-specific delivery[13]. Collectively, these advances convert immune cells from passive drug courier into actively adaptive delivery platforms that overcome the principal bottlenecks of conventional LCDDSs (Fig. 1).

Successful clinical translation of reprogrammed immune cell delivery systems demands a thorough understanding of several critical factors, including interactions between various classes of drugs (*e.g.*, small molecules, proteins, nucleic acids) and engineered immune cells[14], optimal loading strategies tailored for specific payloads (*e.g.*, intracellular, membrane-bound, or extracellular vesicle-mediated)[15]; and methods to ensure the safety, controllability, and manufacturability of these complex therapeutic platforms[9]. Addressing these considerations is pivotal for developing next-generation cell-based drug delivery platforms that meet the rigorous requirements for precision oncology.

This review provides a comprehensive analysis of immune cell reprogramming as a strategy to enhances the efficacy of live-cell drug delivery systems. Initially, we summarize how reprogramming immune cells overcomes intrinsic limitations associated with native immune carriers, offering mechanistic insights. Subsequently, we discuss drug compatibility, delivery modalities, and biosafety considerations specific to engineered immune cells. Finally, we evaluate the broader applicability across various cancer types, identify emerging trends, and highlight current translational challenges Our aim is to inform the rational design and development of advanced immune-cell-based therapeutics at the nexus of drug delivery, immunoengineering, and personalized medicine.

2. Challenges of current immune-cell-based drug-delivery systems

Live immune cells are increasingly being explored as intelligent carriers for targeted drug delivery due to their intrinsic tumor-homing capacity, antigen-specific immune recognition, and capacity to navigate complex biological barriers[16,17]. Among these cellular carriers, macrophages, T cells, and NK cells dynamically respond to tumor-derived signals, actively interact with the TME, and thus provide substantial advantages over synthetic nanocarriers[18]. Despite these promising benefits, several physiological and pathological challenges currently limit the therapeutic efficacy of immune cell-based delivery systems[19]. For instance, after systemic administration, immune cell carriers are often sequestered in off-target organs-particularly the lungs, liver, and spleen-owing to their hemodynamic distribution and clearance by the mononuclear phagocyte system[1]. Even when immune cells bypass these initial filter mechanisms, the heterogeneous vascularization and dense stromal matrices of tumors significantly impede intratumoral accumulation[20,21]. Furthermore, conditions within the TME, such as hypoxia, nutrient scarcity, and immunosuppressive cytokine signaling, severely compromise immune cell viability, effector function, and persistence, collectively diminishing their ability to achieve sustained payload delivery[22−24].

Cargo loading onto immune cells presents additional technical and biological constraints. A crucial requirement is achieving high loading efficiency without adversely affecting the health, function, or phenotype of the carrier cells[25]. Excess concentrations of chemotherapeutic agents or nanomaterials can induce cytotoxicity and premature apoptosis, whereas suboptimal loading results in insufficient payload delivery[26,27]. Following internalization, many therapeutic agents become entrapped within endolysosomal compartments, undergoing degradation and subsequently reducing

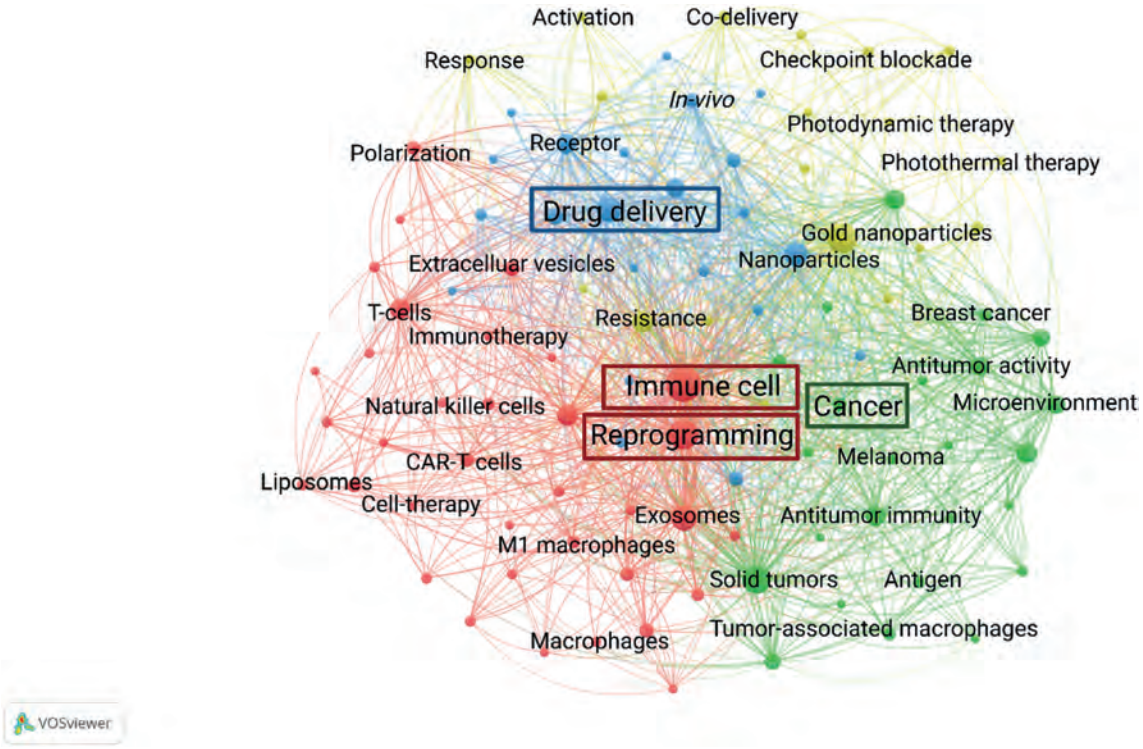

Figure 1 Term co-occurrence network of immune-cell reprogramming research generated with VOSviewer. The map depicts how immune-cell reprogramming concepts intersect with major themes in oncology and drug delivery. Nodes correspond to high frequency co-occurring terms in the literature, whereas edges denote their pairwise associations. Color coding delineates the principle thematic clusters. The Red cluster covers immune-cell reprogramming and related therapies, including chimeric antigen receptor T (CAR-T) cells, macrophages, exosomes, and other cell-based approaches. The Blue cluster highlights drug delivery platforms such as nanoparticles, extracellular vesicles, and liposomes. The Green cluster centers on tumor biology, including microenvironment modulation, antigen presentation, and immune responses. The Yellow cluster marks integrative concepts that link domains for example, co-delivery strategies, checkpoint blockade, and phototherapy.

their bioavailability at the tumor site[28]. Another critical issue is inadequate payload-release control; premature leakage can cause systemic toxicity, while delayed or insufficient discharge at the target location significantly reduces therapeutic efficacy[29].

To overcome these barriers, immune-cell reprogramming through genetic, metabolic, or epigenetic modulation has emerged as a highly promising strategy for improving live-cell drug delivery systems[30,31]. Each immune cell type offers distinct advantages: CAR-T cells exhibit prolonged persistence and precise antigen-directed targeting, chimeric antigen receptor natural killer (CAR-NK) cells provide rapid, non-major histocompatibility complex (MHC)-restricted cytotoxicity through combined CAR and native receptor activity, and macrophages effectively remodel stromal barriers, although they often require optimized chemotaxis for efficient tumor (Fig. 2)[32]. By employing reprogramming strategies, it is possible to enhance intracellular payload stability by mitigating endolysosomal degradation, prolong carrier-cell persistence, fine-tune cargo retention, and control intracellular trafficking. These adjustments minimize premature payload release while enabling stimulus-responsive, targeted discharge within tumors, collectively maximizing therapeutic efficacy.

3. Mechanistic advantages of immune cell reprogramming for *in vivo* drug delivery

Immune-cell reprogramming involves deliberate modulation of epigenetic and transcriptional pathways, enabling alterations in cell morphology, molecular networks, and effector functions[10,11]. By reorienting gene-expression patterns and signaling circuits in response to both intrinsic and extrinsic cues, immune cells can more precisely and effectively deliver therapeutic agents within challenging tumor environments[33]. Such classical pathway reprogramming improves carrier-cell survival, adaptability, and drug-conveyance capability, ultimately enhancing therapeutic outcomes.

Conceptually, immune-cell reprogramming strategies can be classified into three complementary modalities: structural, functional, and metabolic. Structural reprogramming employs gene editing and membrane engineering techniques to modify cell-surface architecture, thus refining target recognition and enhancing specificity-for instance, through CAR installation and surface-protein modifications[34]. Functional reprogramming focuses on augmenting immune-cell cytotoxicity and immunostimulatory potential *via* cytokine priming, intracellular signaling adjustments, phenotypic polarization, or transient mRNA delivery. A notable example involves the transient expression of CAR or bispecific antibodies *via* mRNA delivery, which facilitates efficient antigen binding and precise activation of T-cell signaling to enhance target-specific cytotoxicity[35,36]. Metabolic reprogramming further optimizes immune-cell fitness and antitumor efficacy by redirecting metabolic fluxes such as glycolysis, oxidative phosphorylation, and fatty-acid metabolism[37]. Specifically, activation-induced metabolic shifts from oxidative phosphorylation to glycolysis enhance glucose flux through the pentose

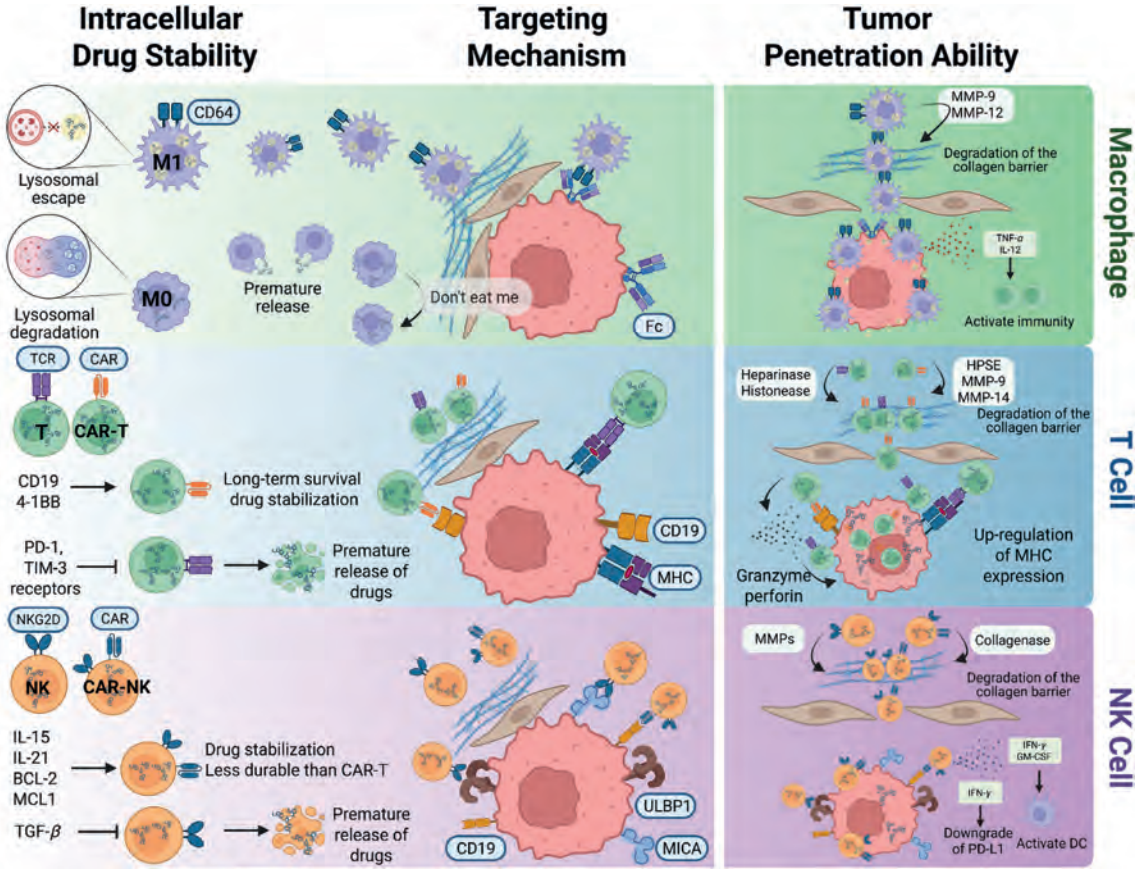

Figure 2 Schematic comparison of immune cell types as live carriers, summarizing relative strengths in drug stability, tumor targeting accuracy, and penetration through microenvironments.

phosphate pathway, promoting biosynthesis and redox balance, and thereby improving cellular resilience in nutrient-poor environments[38].

Collectively, these reprogramming modalities confer several tangible benefits for live-cell drug delivery systems. Enhanced structural features improve tumor-homing precision and antigen-specific accumulation, leading to higher local drug concentrations and improved penetration[39–41]. Functional and metabolically reprogrammed immune cells exhibit greater resilience in hypoxic, nutrient-deficient, and immunosuppressive TMEs, delaying exhaustion and extending the therapeutic window[8,42,43]. Additionally, reprogrammed cells demonstrate reinforced immunomodulatory capacity, facilitating more robust interactions with resident immune populations and overcoming local immunosuppression[44–47]. Finally, cellular carriers offer intrinsic biocompatibility and natural biodegradability, reducing the risk of immune rejection and long-term systemic accumulation compared to synthetic nanocarriers[48]. Together, structural, functional, and metabolic reprogramming strategies represent an integrated framework for designing advanced, next-generation live-cell therapeutic carriers (Fig. 3).

In addition to the previously described advantages of reprogrammed immune-cell drug delivery, another critical benefit lies in their distinctive ability to function as "mobile microprocessors". Unlike conventional carriers that merely transport therapeutic payloads, reprogrammed immune cells can actively process precursor cargos during transport. Through intracellular metabolic rewiring, epigenetic remodeling, and activation of signaling cascade, these engineered cells convert payloads into bioactive effectors, subsequently secreting them *in situ* to recalibrate their own functional state and reshape the surrounding immune microenvironment[49].

For example, antibody-decorated lipid nanoparticles carrying anti-CD3/CD28 fragments activate primary T cells while simultaneously delivering *CAR* mRNA, which is then translated intracellularly into CAR proteins[50]. Upon interaction with tumor-associated CD19, CAR engagement triggers a signaling cascade analogous to T-cell receptor (TCR) activation. This leads to rapid upregulation of activation markers (CD25, CD69, CD44), induction of cytotoxic molecules (granzyme B, perforin, soluble Fas ligand), and secretion of inflammatory cytokines such as interferon-gamma (IFNG) and tumor necrosis factor-alpha (TNFA). IFNG, *via* janus kinase-signal transducer and activator of transcription pathway, enhances tumor-cell MHC1 expression, improve immune recognition, while TNFA increases vascular permeability and chemokine gradients, recruiting additional immune cells. Importantly, the transient expression mediated by non-integrating mRNA ensures rapid CAR decay following T-cell division, thereby sustaining immediate antitumor effects and microenvironment remodeling while reducing the risk of persistent cytokine storms or long-term B-cell depletion.

Another illustrative scenario involves oxidized mannan−allergen conjugates that are internalized by peripheral monocytes *via* recognition by mannose receptor and dendritic cell-

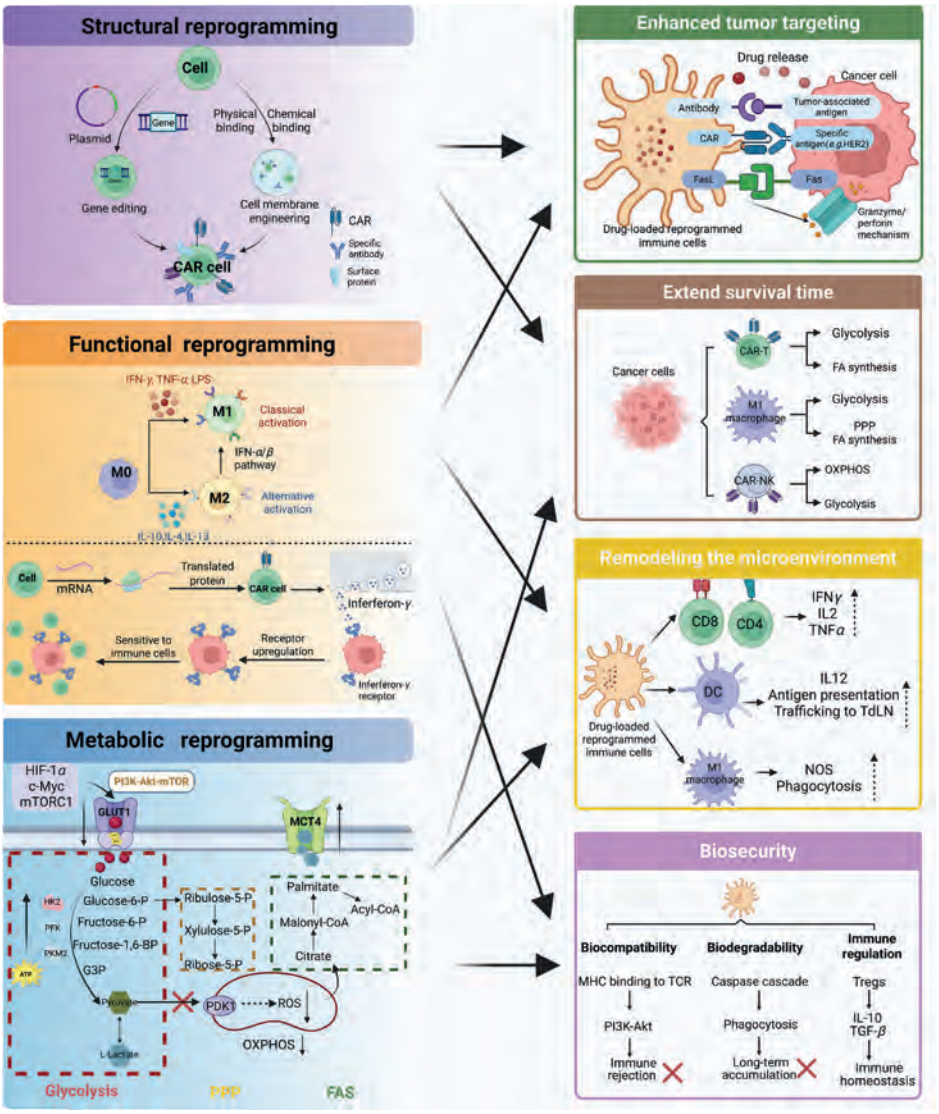

Figure 3 Schematic overview of structural, functional, and metabolic reprogramming that underpins the therapeutic advantages of immune cell-based drug delivery.

specific intercellular adhesion molecule-3-grabbing non-integrin. This uptake drives metabolic and epigenetic reprogramming, converting monocytes into tolerogenic dendritic cells characterized by secretion of immunosuppressive mediators such as interleukin-10 (IL10), programmed death-ligand 1 (PDCD1LG1), and suppressor of cytokine signaling 1/3. Upon migration to local inflammatory sites, these tolerogenic dendritic cells further engage forkhead box P3-positive regulatory T cells through MHC2−TCR interactions and maintain local immunosuppressive *via* continued cytokine release[51]. Thus, immune-cell reprogramming merges precision cargo delivery with intrinsic biological computation, significantly enhancing targeting specificity, prolonging therapeutic persistence within the tumor microenvironment, and enabling controlled payload processing and release. Collectively, these integrated functionalities address critical issues such as immune exhaustion, local immunosuppression, and payload bioavailability, thereby improving both efficacy and safety profiles of live-cell drug-delivery systems.

4. Applications of immune cell reprogramming for *in vivo* drug delivery

Immune-cell reprogramming has emerged as a robust strategy for converting live immune cells —and their derivatives, including cell-membrane− and exosome/extracellular vesicles (EV)-based carriers—into *in vivo* drug shuttles capable of functioning within the hostile TME[52]. By tuning cellular metabolism, surface-receptor repertoires, gene-expression programs and effector phenotypes, reprogramming equips these carriers to bypass immunosuppressive barriers, enhance tumor tropism and retain payloads with stimulus-responsive (on-demand) release. Complementary approaches-such as metabolic rewiring, cytokine priming, and genetic engineering (*e.g.*, transient or stable CAR insertion)-enable immune cells to act dually as therapeutic effectors and precision delivery vehicles[53−55], supporting targeted and durable transport of chemotherapeutics, photosensitizers, and immunomodulators[56−58]. This section therefore surveys

reprogramming modalities across immune-cell classes, outlines drug-loading compatibilities, and highlights the resulting therapeutic gains in oncology.

4.1. Macrophage reprogramming and drug delivery

Macrophages are integral components of host defense and tumor progression, characterized by phenotypic plasticity from pro-inflammatory, tumoricidal M1 to anti-inflammatory, tumor-promoting M2 macrophages[59]. Reprogramming tumor-associated macrophages toward an M1-like phenotype can enhance tumor antigen presentation, stimulate secretion of immunostimulatory cytokines, and potentiate the activation of cluster of differentiation (CD)8^+ T cells and NK cells, collectively augmenting antitumor immunity[60,61]. However, excessive or sustained M1 activation can produce high levels of pro-inflammatory mediators and elevate glycolysis-linked oxidative stress, generating reactive oxygen species (ROS) that jeopardize macrophage viability and functional persistence[62]. These adverse effects can be mitigated through rational drug loading—for instance, incorporating glucocorticoids to moderate inflammatory responses and antioxidants to counteract ROS-mediated cytotoxicity—thereby preserving effective antitumor functions while preserving cellular exhaustion[63].

Indeed, reprogrammed macrophages with strategic drug-loading demonstrate the feasibility of integrating targeted delivery with enhanced immune modulation within a single carrier. For example, M1 macrophages loaded with liposomal R848 and phospholipid-coupled DM4 (RDM) preferentially accumulate in lung metastases, responding to the TME by releasing their payload. This targeted delivery substantially increases $CD3^+CD8^+$ T-cell infiltration, achieving potent antimetastatic activity in the 4T1 breast cancer model[64]. Similarly, KTP-modified M1 macrophages loaded with Pexidartinib-containing zeolitic imidazolate framework-8 (ZIF-8) nanoparticles (P@ZIF-8) exhibit efficient tumor homing, effectively inhibit colony stimulating factor 1 receptor signaling, reduce myeloid-derived suppressor cells (MDSC) populations, and increase $CD4^+$ T-cell recruitment, thereby alleviating local immunosuppression[65]. These cases illustrate the synergistic potential of macrophage reprogramming to couple precise targeting and efficient payload delivery with intrinsic immune modulation.

In parallel, macrophage-derived carriers such as exosomes or EVs, and cell-membrane−coated nanoparticles naturally extend macrophage-based delivery by inheriting immunological characteristics from their parent cells[66,67]. M1 macrophage-derived exosomes (M1Exo) loaded with gemcitabine and deferasirox demonstrate improved drug retention and effectively overcome chemoresistance in pancreatic cancer models[68]. Similarly, engineered M1Exos delivering DNA damage repair inhibitors, catalase, and anti- PDCD1LG1 nanobodies serve as coordinated adjuvants for radiotherapy: catalase alleviates hypoxia to intensify radiolytic DNA damage; DNA damage repair inhibitors impair tumor-cell repair mechanisms; and programmed cell death protein 1 (PDCD1)/PDCD1LG1 blockade coupled with M1 polarization reprograms the immunosuppressive TME (Fig. 4)[69]. Additionally, nanoparticles encapsulated by M1-derived membranes exhibit enhanced stability and reduced systemic toxicity, making them promising platforms for tumor-specific drug delivery[17,70]. M1-membrane−coated poly(lactic-*co*-glycolic acid) (PLGA) nanoparticles co-encapsulating doxorubicin and catalase (CAT) achieve active tumor targeting, mitigate hypoxia, and enhance chemotherapeutic efficacy *in vivo*[71]. Nonetheless, significant translational challenges persist[72], including limited cellular payload capacity—high drug concentrations induce acute toxicity, while lower doses may prove ineffective[26]. Surface loading of drugs or drug-containing particles on macrophages can also interfere with critical signaling pathways, adhesion, and migration, potentially compromising trafficking and therapeutic efficacy[27,73]. Addressing these constraints through optimized reprogramming strategies and advanced formulation techniques will be essential for successful clinical translation.

4.2. T-cell reprogramming and drug delivery

Clustered regularly interspaced short palindromic repeats (CRISPR)-enabled T-cell reprogramming enhances live-cell drug delivery by improving metabolic fitness, persistence, trafficking and antigen-specific precision within the TME[74,75], yet major barriers persist-including dense stroma, inhibitory cytokines and checkpoint signalling, and the risk of immune-related toxicities with CAR-T therapy[76−78]. Integrating drug loading with reprogrammed T cells directly addresses these hurdles: cargos such as checkpoint blockers (*e.g*., anti- PDCD1LG1) or other immunomodulators can be deployed at the tumor site to relieve suppression and potentiate CAR-T activity[79]. T-cell−enabled delivery spans live CAR-T carriers and their derivatives-CAR-T exosomes and CAR-T−membrane−coated nanoparticles-which inherit the targeting repertoire of the parent cells[80−82]. Encapsulating chemotherapeutics (*e.g*., paclitaxel, PTX), within CAR-T membranes reduces off-target exposure and limits the cytotoxicity of free drug to normal tissues; for example, PTX-loaded CAR-T exosomes (CAR-Exos) outperform free PTX, particularly with aerosol administration for lung targeting, while endogenous granzyme B and perforin further augment efficacy and minimize systemic exposure[83]. As a representative biomimetic platform (Fig. 5), human epidermal growth factor receptor 2 (HER2)-directed CAR-T membranes can cloak drug-loaded PLGA nanoparticles, yielding vesicles that preferentially bind $HER2^+$ tumors, concentrate chemotherapeutic payloads and constrain off-target toxicity; analogous CAR-T membrane constructs carrying near-infrared dyes have shown enhanced hepatocellular-carcinoma targeting with minimal systemic toxicity[80].

4.3. NK cell reprogramming and drug delivery

NK cell reprogramming offers distinct advantages for antitumor therapy. Through CAR engineering, NK cells acquire antigen-specific recognition while retaining their innate, non-MHC-restricted cytotoxicity, which lowers the risk of off-target, TCR-dependent toxicities and provides a potentially safer alternative to T cells[84]. Nevertheless, immunosuppressive mechanisms in the TME—suppressive myeloid and regulatory populations, inhibitory cytokines, and checkpoint signaling— can still impair their function[85,86]. Incorporating drug loading into CAR-NK cells helps overcome these barriers by concentrating therapeutics at tumor sites and synergizing with immune effector programs, thereby improving efficacy and reducing systemic exposure. In addition to live CAR-NK carriers, NK-cell−derived exosomes and NK-cell−membrane−coated nanoparticles extend this delivery paradigm by inheriting the parent cell's targeting ligands and immune-evasion features.

As a representative example, CAR-NK cells loaded with biocompatible liposomal nanoparticles containing benzoporphyrin derivative exhibit markedly enhanced cytotoxicity upon laser

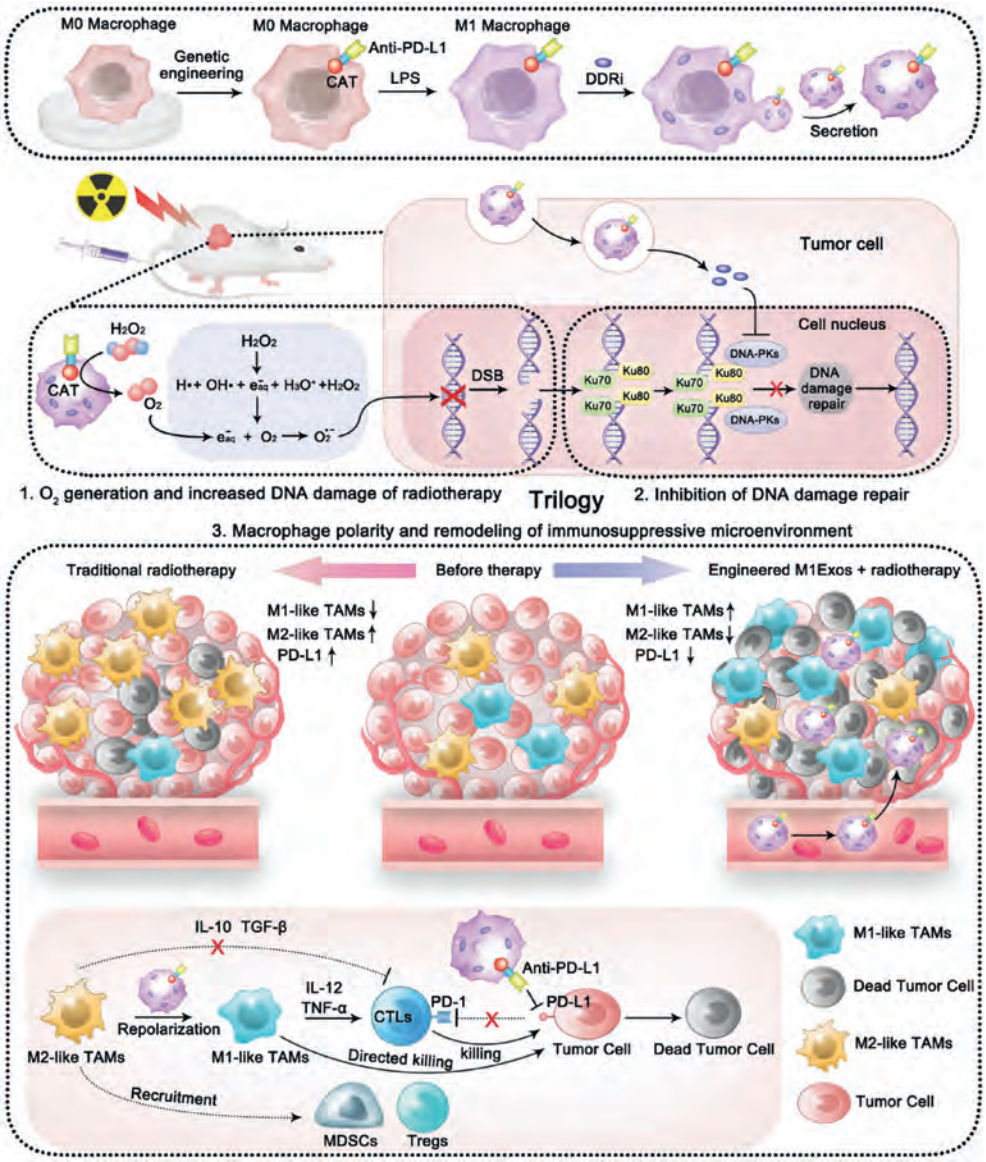

Figure 4 Reprogrammed M1exosome-mediated radiotherapy sensitization *via* a triple mechanism: oxygen generation, DNA repair inhibition, and immune microenvironment remodeling. Reproduced with permission from Ref. 69. Copyright © 2022, Xiaotu Ma et al., Wiley, Advanced Science.

irradiation, increasing tumor-cell death from ~30% to ~90% while minimizing systemic toxicity[87]. NK-cell derivatives also provide powerful delivery vehicles for hard-to-reach sites. CAR-NK-derived exosomes dual-modified with a T7 peptide (for transferrin receptor engagement on brain endothelium) and an anti-HER2 single-chain variable fragment efficiently traverse the blood–brain barrier and deliver PEG-TK-Ce6@RSL3 micelles, light activation boosts ROS generation, induces ferroptosis, and achieves potent killing of HER2-positive brain metastases[88].

4.4. DC reprogramming and drug delivery

Dendritic cells (DCs) are professional antigen-presenting cells that capture tumor debris or soluble antigens by phagocytosis/endocytosis and cross-present epitopes on MHC1 to prime T-cell responses[89]. In many tumors, however, cDC1 are scarce or functionally impaired, and the immunosuppressive milieu limits antigen presentation and T-cell activation, curtailing the efficacy of existing immunotherapies[90]. Reprogramming strategies that rewire metabolic, epigenetic, and signaling pathways can restore DC maturation and trafficking, overcome tolerogenic programming, and initiate systemic antitumor immunity.

A practical approach is to embed tumor-associated antigens, tumor cell lysates, or plasmid DNA in hyaluronic-acid or chitosan nano/hydrogel matrices that combine adjuvanticity with targeting. Following uptake, these carriers promote DC maturation and efficient cross-presentation, after which DCs migrate to draining lymph nodes, secrete interleukin-12 (IL12) and IFNG, and prime central- and effector-memory T cells to establish durable immune surveillance. Preloading neoantigens into reprogrammed DCs—and, where appropriate, into DC-derived formats such as exosomes or membrane-coated particles—enables a "cell-factory"

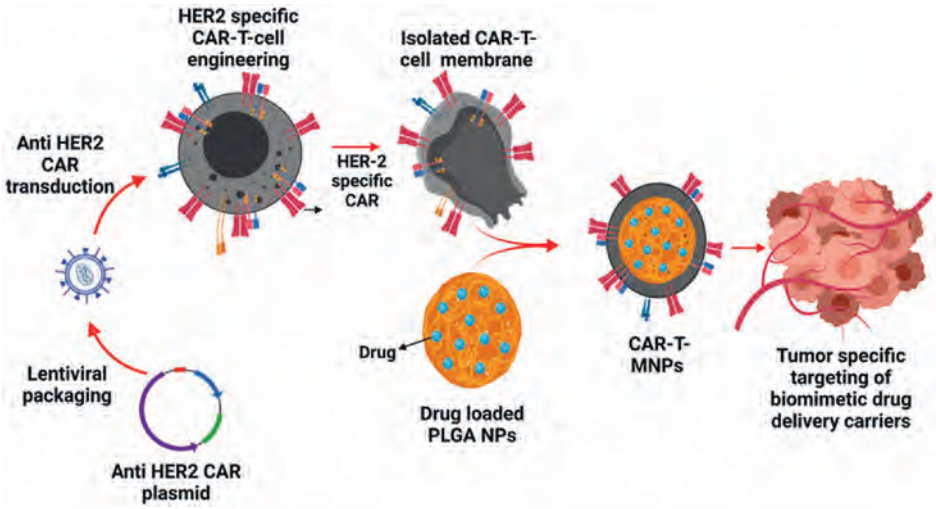

Figure 5 Biomimetic drug delivery *via* HER2-specific CAR-T cell membrane-coated PLGA nanoparticles for tumor-targeted therapy. Reproduced with permission from Ref. 80. Copyright © 2024, Serkan Yaman et al., Elsevier, Bioactive Materials.

mode of *in situ* antigen processing and delivery, simplifying *ex vivo* manipulation while enhancing *in vivo* efficacy and providing a scalable path toward individualized cancer vaccines[51].

4.5. Oncolytic virus-associated immune cell reprogramming and drug delivery

Oncolytic viruses (OVs) combined with immune cell reprogramming represent a promising strategy in cancer therapy, leveraging the unique strengths of each approach to overcome existing therapeutic limitations[91]. The combination offers enhanced tumor-specific targeting, improved local viral replication, and amplified anti-tumor immune responses[92]. However, challenges remain, including limited tumor penetration, premature viral degradation, systemic immune clearance, and insufficient therapeutic efficacy[93]. To address these issues, engineering OV-immune cell chimeras emerges as a vital solution, enabling precise tumor targeting, efficient viral delivery, and enhanced therapeutic performance[94].

Integrating OVs with reprogrammed immune cells significantly enhances payload delivery precision and therapeutic performance. Utilizing immune cells such as CAR-T cells, macrophages, or NK cells as virus carriers capitalizes on their inherent tumor-homing abilities, effectively directing viruses to tumor tissues and protecting them from host immune clearance during systemic circulation[95]. For instance, the ONCOTECH platform—combining T cells with oncolytic adenoviruses—demonstrates enhanced tumor-specific virus accumulation, reduced tumor PDCD1LG1 expression, and improved survival outcomes in melanoma and glioblastoma models[96]. Clinically, engineered OV-immune cell chimeras have exhibited superior therapeutic potential, with enhanced tumor infiltration and targeted virus release, ultimately generating durable antitumor immune responses even in solid tumors traditionally resistant to conventional therapies.

Moreover, using drug-loaded reprogrammed immune cells as OV carriers actively enhances the therapeutic function of the viruses themselves. OV-loaded CAR-T cells, for example, exhibit improved proliferation, sustained activation, and superior memory phenotypes, significantly amplifying the antitumor immune response. Dual-specific CAR-T cells preloaded with OVs such as vesicular stomatitis virus or reovirus have shown robust *in vivo* expansion, durable tumor control, and prolonged survival in preclinical melanoma and glioblastoma models[97].

4.6. Immune cell reprogramming serving as an intrinsic drug delivery platform

Immune-cell reprogramming offers a versatile toolkit for converting live immune cells—and their derivatives, such as cell-membrane—and exosome/EV-based carriers-into *in vivo* drug delivery. By tuning cellular metabolism, receptor repertoires, and gene-expression programs, reprogramming enhances tumor tropism, overcomes immunosuppression and increases payload retention with stimulus-responsive release. In macrophages, metabolic and signaling reprogramming (*e.g.*, M1-biased polarization and pathway tuning) augments antitumor activity and adaptability within the TME, enabling active carriage of chemotherapeutics and immunomodulators[98,99]. In T and NK cells, genetic engineering-particularly CAR installation *via* lentiviral or mRNA methods-improves tumor-specific recognition and persistence[100,101], allowing CAR-T and CAR-NK products to function both as cytotoxic effectors and as delivery platforms for cargos including chemotherapeutics, photosensitizers, nucleic acids, and checkpoint modulators[102]. Reprogrammed immune cells can also be paired with OVs to expand therapeutic breadth by enhancing targeted viral deposition, amplifying antitumor immunity and enabling additional payload delivery through synergistic virus—cell interactions. Carrier selection and the choice of reprogramming lever should be dictated by tumor biology, cargo class and delivery format (live cell, membrane-coated nanoparticle, or exosome/EV), together with administration route, mechanism of action, indication and stage of clinical translation, as summarized in Table 1[80,87,88,103-114].

5. Advantages of immune-cell reprogramming for enhanced drug-delivery efficacy

Conventional live-cell drug delivery has shown limited efficacy, whereas immune-cell reprogramming can optimize cargo loading

Table 1 Summary of reprogrammed immune-cell platforms, compatible cargo, delivery methods, mechanism of action, tumor indications, and clinical stage.

Reprogrammed Immune Cells	Reprogramming Strategy	Specific drugs	Drug type	Therapeutic advantages	Tumor type	Delivery method	Mechanism of action	Clinical stage	Ref.
M1 macrophages									
	Cytokine priming	Iron-glycol chitosan-polypyrrole nanoenzymes	Nanoformulations	Potentiates macrophage activation, synergistic therapy	Bladder cancer	Systemic injection	Enhance intrinsic immune response, multi-modal synergy	Preclinical	103
	Phenotypic polarization	Diselenide, tirapazamine	Chemosensitizers, chemotherapeutic	Activate innate immunity and remodel immunosuppressed TME	Triple negative breast cancer	NA	Ultrasound-activated ROS generation, M2→M1repolarization	Preclinical	104
	Membrane coating technology	Black phosphorus quantum dots, doxorubicin	Photosensitizer, chemotherapeutic	Induces ICD and augments antitumor immunity	Breast tumor, melanoma	Microneedle (MN) patch transdermal delivery	ICD-mediated potentiation of checkpoint blockade	Preclinical	105
	Membrane coating technology	Doxorubicin, indoximode, chlorin e6	Chemotherapeutic, metabolic modulator, photosensitizer	Enhance targeting and reverse immunosuppression	Breast tumor, melanoma	Intravenous	Enhance tumor targeting, Stimuli-responsive release	Preclinical	106
	Phenotypic polarization	Paclitaxel, baicalin	Chemotherapeutic, natural product	TAM re-education, phenotype shift	Breast cancer	Nanoparticle delivery	TME-responsive release, M2→M1 repolarization	Preclinical	107
CAR T									
	NA	Mesothelin	Tumor marker	Overcoming solid tumor barriers	Malignant pleural mesothelioma	Intrapleural drug administration	NA	Phase I	108
	Lentiviral transduction	IL-2	Cytokine	Overcoming solid tumor barriers	Pancreatic cancer	Hepatic artery infusion	Enhancing T-cell proliferation	Phase Ib	109
	Genetic engineering	NA	NA	Overcoming solid tumor barriers	Malignant pleural mesothelioma	Intrapleural infusion	Targeting the FAP protein	Phase I	110
	Lentiviral transduction	Adriamycin	Chemotherapeutic drugs	Reduced systemic toxicity, tumor-site delivery	Glioblastoma	Intravenous	Acidic-TME-triggered release from CAR-T −associated nanoparticles (NPs)	Preclinical	111
	CRISPR/Cas9-mediated editing	Interferon β	Cytokines	Antigen-specific delivery, improved persistence	Ovarian cancer	NA	Specific activation and clonal expansion	Preclinical	112
	NA	Fluorescein-TLR7 agonist coupler	Immunomodulatory drugs	Reverses exhaustion, shrinks resistant tumors	Solid tumor	NA	TLR7 activation restores effector function	Preclinical	113
	Lentiviral transduction	Cisplatin	Chemotherapeutic drugs	Prolonged circulation and specific accumulation	Non-small cell lung cancer	Intravenous	HER2-directed targeting *via* CAR-T −membrane-coated PLGA NPs, sustained release	Preclinical	80
	Membrane coating	Paclitaxel	Chemotherapeutic drugs	Avoids T cell depletion, promotes	Lung cancer	Intravenous	Lung-targeted accumulation,	Preclinical	114

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Table 1 (*continued*)

Reprogrammed Immune Cells	Reprogramming Strategy	Specific drugs	Drug type	Therapeutic advantages	Tumor type	Delivery method	Mechanism of action	Clinical stage	Ref.
	technology			immunogenic cell death			PDCD1LG1 blockade-potentiated ICD		
CAR-NK	Lentiviral transduction	Benzoporphyrin derivatives	Photosensitizers	Reduces off-target toxicity and enhances antitumor immunity	Lung cancer, Cervical	Intravenous	Real-time monitoring by microscope	Preclinical	87
	Lentiviral transduction	RSL3, transferrin receptor-binding peptide (T7)	Iron death inducers, biomolecules	Blood−brain barrier (BBB) penetration, potent killing of $HER2^+$ brain metastases	Breast cancer brain metastasis	Intravenous	T7-mediated BBB transit,light-/ROS-enhanced ferroptosis	Preclinical	88

and controlled release, thereby revitalizing live-cell delivery; conversely, advances in drug-delivery science-including improved loading chemistries and release kinetics-feed back to enhance the performance and durability of reprogrammed immune cells[115]. Centering on this bidirectional relationship, we consider how rational delivery regimens strengthen reprogrammed cells by improving metabolic fitness and stress adaption within the tumor micro-environment, thereby augmenting antitumor, anti-infective and anti-inflammatory functions while mitigating immune tolerance and immunesuppression[116]. Appropriately designed delivery strategies can also overcome therapeutic resistance, drive favorable phenotypic reprogramming and enable precision treatment with reduced off-target toxicity[117].

5.1. Augmenting the anti-tumor activity of immune cells

Drug delivery systems have emerged as powerful tools for augmenting the antitumor activity of immune cells by enhancing immune activation, cytokine secretion, and synergy with immune checkpoint inhibitors. For instance, chemotherapeutic agents can trigger immunogenic cell death, thereby activate myeloid cells and facilitating the presentation of tumor antigens to $CD8^+$ T cells. When coupled with checkpoint blockade, such as CD47 inhibitors, this strategy markedly boosts antitumor immune response. Furthermore, this combination fosters the formation of durable $CD8^+$ T-cell memory, crucial for preventing tumor recurrence even after treatment cessation, underscoring the long-term benefits of integrating drug delivery with immunotherapy[118].

Recent advancements exemplify this integrated approach's efficacy. PM@MC demonstrated significant therapeutic effects in a mouse model of 4T1 metastatic breast cancer, achieving 96.8% inhibition of primary tumor growth and 99.2% suppression of lung metastases, outcomes directly associated with drug-induced immune cell reprogramming[119]. Similarly, CD56 antibody-modified MnOX nano-enzymes, specifically binding to CAR-NK cells, significantly improved CAR-NK cell infiltration and antitumor functionality within a modified TME, thereby enhancing therapeutic outcomes at minimal doses in solid tumor mouse models[120]. Additionally, a novel CAR-derived exosome−drug conjugate (CAR-EDC), employing CAR-mediated endocytosis to covalently load SN-38 into Raji cells, markedly increased immune activation, T-cell migration, $CD8^+$ T-cell differentiation, and M1 macrophage polarization, resulting in substantial *in vivo* antitumor activity[121].

Epigenic modulation further exemplifies the potential of integrated delivery systems. High-throughput screening identified two class I histone deacetylase inhibitors, M344 and sildamoride, which significantly improved the antitumor efficacy of CAR-T cells by enhancing memory formation and reducing exhaustion both *in vitro* and *in vivo*[122]. Similarly, the targeted nano-delivery system HA-RES-BEX, which couples bexarotene (BEX) and resiquimod (RES) to hyaluronic acid (HA), increased the proportion of M1 macrophages in tumors, inhibited M2 macrophage-mediated immunosuppression, facilitating tumor cell phagocytosis, and enhanced $CD8^+$ T cells and $CD4^+$ T helper 1 cell−cell interactions, collectively strengthening adaptive antitumor immunity[123]. Additionally, sodium valproate, a drug capable of crossing the blood−brain barrier, elevated NKG2D ligand expression on glioblastoma cells *via* PI3K/Akt pathway activation, thereby improving tumor recognition and cytotoxicity of CAR-T cells[124]. These combined approaches highlight the immense

therapeutic potential and versatility of drug-delivery-enhanced immune cell therapies in cancer treatment.

5.2. *Promoting immune cell survival within the TME*

Drug delivery systems primarily enhance immune cell survival within the TME by modulating cellular metabolic pathways and reducing immunosuppressive influences. Specifically, drugs can improve immune cell adaptation to challenging microenvironmental conditions by promoting glycolysis or mitochondrial biosynthesis, thus enabling cells to thrive under hypoxic and nutrient-deficient conditions[125]. Furthermore, drugs can mitigate immune suppression and extend immune cell persistence by interfering with inhibitory signaling pathways, such as those mediated by immunosuppressive cytokines like interleukin 10 (IL10)[126].

One illustrative example involves encapsulating the toll-like receptor 7/8 agonist R848 and the selective indoleamine 2,3-dioxygenase 1 inhibitor (INCB024360) into C16-neuraminic acid-fused outer membrane vesicles produced by *Escherichia coli* (RILO). After endocytosis by M1 macrophages, these RILO complexes effectively remodel the immunosuppressive TME, supporting macrophage persistence and preserving their M1 phenotype. Additionally, by anchoring a glypican-3 (GPC3)-targeting peptide to their surface, these modified macrophages (RILO@MG) can specifically phagocytose GPC3-expressing tumor cells. This selective phagocytosis not only enhances direct tumor cell killing but also minimizes macrophage damage associated with non-specific phagocytic activity, indirectly extending macrophage viability. Furthermore, M1 macrophages loaded with RILO can induce repolarization of immunosuppressive M2 macrophages into pro-inflammatory M1 macrophages, amplifying the anti-tumor immune response[127].

IL10 exemplifies the context-dependent duality of immunosuppressive cytokines within the TME. While tumor or stromal cell-derived IL10 typically suppresses antitumor immunity by inhibiting dendritic cell maturation, impairing T-cell activation, and promoting regulatory T-cell function, engineered CAR-T cells secreting IL10 paradoxically exhibit enhanced persistence and reduced exhaustion. This engineered secretion of IL10 reshapes the TME, limiting immunosuppressive cell infiltration and activating antitumor myeloid cells, thereby fostering sustained antitumor responses[128]. Similarly, a cetuximab-based IL10 fusion protein (CmAb-IL10) significantly prolongs the half-life of IL10, extending its immunomodulatory impact on dendritic cells (DCs). By signaling through the IL10 receptor (IL10R) on DCs, CmAb-IL10 suppresses excessive IFNG production and reduces IFNG-dependent activation-induced cell death of antigen-specific $CD8^+$ T cells[129]. Consequently, this fusion protein enhances the survival, persistence, and effector functionality of $CD8^+$ T cells at tumor sites, thereby potentiating durable antitumor immunity.

5.3. *Optimizing drug delivery efficiency through drug loading*

A major challenge in drug delivery is the premature leakage of therapeutic payloads before reaching the target site, resulting in suboptimal delivery efficiency[130]. Immune cell reprogramming offers opportunities not only to improve drug compatibility and retention but also to enhance the precision of delivery through strategic cargo incorporation[131]. Conversely, drug loading itself can optimize immune cell function by stabilizing reprogrammed phenotypes and supporting sustained therapeutic action. The integration of rationally designed delivery systems—such as nanoparticles—into reprogrammed immune cells represents a synergistic approach that increases both delivery efficiency and therapeutic outcomes[132].

Encapsulating therapeutics in nanocarriers before immune-cell loading increases intracellular stability, prevents premature degradation and affords controlled release. One illustration is the multilayer, acoustically responsive M1/IR780@PLGA construct, in which the sonosensitizer IR780 is lodged in a PLGA core that is subsequently cloaked with M1-macrophage membranes, thereby minimizing dye leakage and achieving an encapsulation efficiency of 45.9%[133]. Structural optimization further yielded M1/PLGA@IR780/CAT particles that co-load CAT and IR780; by adjusting the membrane-to-core ratio (1:1, 1:2 and 1:3), encapsulation efficiencies rose to 84.9%, 98.0% and 96.0%, respectively, leading to synergistic enhancement of sonodynamic therapy and anti-PDCD1LG1 checkpoint blockade[134]. In a complementary approach[64], M1 macrophages were surface-decorated with a liposomal formulation containing the TLR7/8 agonist R848 and a fibroblast-activation-protein (FAP)—cleavable prodrug (RDM); R848 acted both as an immune adjuvant and as an autocrine stimulus that maintained the M1 phenotype, thereby preserving the cells, drug-carrying capacity and improving overall delivery performance.

5.4. *Enhancing tumor targeting capabilities of immune cells*

Drug loading can reinforce, rather than merely exploit, the tumor-homing properties of reprogrammed immune cells. Payload-induced modulation of signaling, metabolism and chemotactic pathways augments the infiltration, persistence and accumulation of M1-polarized macrophages or CAR-engineered lymphocytes within the TME[135,136]. For instance, M1 macrophages carrying sorafenib-loaded nanoparticles (M1/SLNPs) migrate more efficiently to hepatocellular-carcinoma lesions, where sorafenib both exerts cytotoxicity and stabilizes the macrophage's pro-inflammatory phenotype, enabling deeper penetration into otherwise suppressive regions[137]. Likewise, lenalidomide-loaded CAR-T cells show superior *in vivo* expansion and $CD3^+/CD8^+$ T-cell recruitment, prolonging their dwell time at disease sites[138]. Surface engineering further enhances targeting: PLGA nanoparticles cloaked with neutrophil membranes promote firm adhesion to tumour endothelium and improved intratumoral penetration, thereby extending the residence of the carried immune cells[139]. Collectively, these examples illustrate how rational payload selection and formulation can amplify the intrinsic tumour-seeking behavior of reprogrammed immune-cell carriers.

5.5. *Drug-induced reprogramming and immunomodulation*

Recent advances in drug delivery systems have introduced powerful strategies for modulating the phenotype and function of immune cells within the TME. Beyond serving as passive carriers, reprogrammed immune cells can undergo further enhancement through drug-induced immunomodulation[140]. Specific therapeutic agents—ranging from immunomodulators and chemotherapeutics to metabolic regulators—can reprogram immune cells *in situ* or *ex vivo*, thereby improving their functional resilience, cytokine secretion, and ability to withstand immunosuppressive signals within the TME[141,142].

These drug-induced modifications support immune cells not only in maintaining their therapeutic payload during circulation,

but also in reinforcing anti-tumor immune responses through cytokine release, enhanced antigen presentation, and improved TME penetration. For instance, certain agents can stimulate the secretion of chemokines that promote immune cell recruitment or induce a favorable shift in local immune cell populations from immunosuppressive to pro-inflammatory phenotypes[143]. As a result, the localized concentration of both the immune cells and their delivered drugs is significantly increased, leading to more potent and sustained therapeutic outcomes.

In summary, drug loading and delivery act synergistically with immune cell reprogramming to enhance the antitumor potential of live-cell-based therapies. From improving tumor homing and survival to reshaping the TME and promoting durable immune activation, this integrated strategy offers a robust platform for next-generation precision immunotherapy. Table 2[144–151] further details the diverse mechanisms by which specific drug delivery systems contribute to immune cell reprogramming and immunomodulation, highlighting their therapeutic relevance across various tumor types.

6. Drug-loading strategies for reprogrammed immune cells

Reprogrammed immune cells now serve as multifunctional platforms that combine intrinsic antitumor activity with highly precise drug delivery by exploiting their structural and functional plasticity[152]. Their plasma membranes present abundant chemical anchor points for surface conjugation, intracellular compartments permit controlled cargo encapsulation, and secreted extracellular vesicles—particularly exosomes—function as endogenous nanocarriers[153]. Together, these attributes provide spatiotemporal control over payload distribution and release within the TME. Drug-loading approaches can be grouped into three interconnected formats: whole-cell loading, vesicle-mediated delivery and cell membrane-derived nanocarriers (Fig. 6). Immune-cell reprogramming extends each format beyond the live cells themselves, integrating their derivatives—membranes and exosomes—into a unified therapeutic framework that maximises targeting accuracy and delivery efficiency.

6.1. Living cell drug loading

Immune cells can be directly utilized as drug carriers through surface or intracellular loading. Surface loading, or extracellular anchoring, includes both non-covalent interactions—such as receptor-ligand binding, host–guest inclusion, electrostatic and hydrophobic interactions—and covalent conjugation strategies that chemically modify the membrane without compromising cell viability. These approaches enable stable drug retention on the cell exterior while preserving immune functionality[154]. For intracellular delivery, drugs are introduced *via* cellular uptake pathways, which include various endocytic mechanisms such as phagocytosis, pinocytosis, receptor-mediated endocytosis, and direct membrane penetration[155]. These processes allow immune cells to internalize therapeutic agents either through the engulfment of larger particles (phagocytosis) or the uptake of extracellular fluid and solutes (pinocytosis). Receptor-mediated endocytosis enables selective internalization of specific molecules through receptor–ligand interactions, while direct membrane penetration involves the passive or active translocation of small molecules across the cell membrane without vesicle formation. Additionally, physical methods like electroporation or sonication can enhance drug delivery by temporarily disrupting the cell membrane, facilitating the entry of therapeutic agents[156].

6.1.1. Neutrophil delivery drug

Neutrophils have recently emerged as promising carriers for targeted drug delivery, particularly in oncology. Their inherent migratory capability toward infection sites and tumors, combined with their intrinsic ability to internalize and transport diverse therapeutic payloads—such as chemotherapeutics, immunomodulatory drugs, small interfering RNAs (siRNA), and nanoparticles-positions neutrophils as ideal drug carriers[157]. This targeted approach minimizes systemic toxicity and reduces off-target effects, as neutrophils selectively release therapeutic agents at tumor sites. Furthermore, neutrophils exhibit superior biocompatibility, mitigating immunogenic risks, and possess the unique ability to traverse physiological barriers, including the blood–brain barrier, making them particularly advantageous for treating central nervous system cancers[158]. Upon reprogramming, neutrophil attributes such as chemotaxis toward tumor-derived chemokine gradients and interactions mediated by adhesion molecules can be significantly enhanced, further expanding their utility. In addition to drug delivery, reprogrammed neutrophils can actively release cytokines, reactive oxygen species (ROS), and pro-inflammatory factors within the TME, thereby augmenting local anti-tumor immunity. Collectively, these qualities render neutrophils a compelling platform for combined therapeutic delivery and immune modulation.

A representative example of neutrophil-based delivery is the use of CAR-engineered neutrophils loaded with tirapazamine-encapsulated rough silica dioxide nanoparticles, which have demonstrated substantial therapeutic efficacy in glioblastoma models (Fig. 7). These CAR-neutrophils effectively navigate physiological barriers and synergistically combine chemotherapy and immunotherapy upon tumor infiltration. Silica dioxide nanoparticles provide robust cellular protection during systemic circulation, ensuring precise payload release within the tumor, thus significantly enhancing drug retention and overall therapeutic outcomes[158].

Neutrophils also facilitate drug transport through surface-loading mechanisms. Surface-modified neutrophils can directly bind drugs such as clozapine, procainamide, and vesnarinone, thereby enhancing their therapeutic potential, particularly for anti-infective purposes, by facilitating the specific modification of target proteins[159]. This dual strategy—combining intracellular encapsulation and extracellular surface binding—maximizes the therapeutic versatility of neutrophils, underscoring their value as multifunctional vehicles in precision medicine and drug delivery.

6.1.2. Other immune cell delivery drugs

Immune cells, such as macrophages, T-cells and NK-cells, possess inherent characteristics like tumor infiltration and tumor tropism, making them ideal candidates for DDS[160]. Immune cells can be equipped with drugs through two main strategies: extracellular drug loading and intracellular drug loading. For extracellular loading, non-covalent interactions such as receptor–ligand binding, electrostatic, or hydrophobic interactions can anchor drugs onto the cell surface. For instance, adriamycin liposomes can be anchored to macrophages using a biotin-affinity system, creating a macrophage-liposome platform. This approach leverages the tumor chemotaxis of macrophages to achieve active targeting, improving drug penetration in tumor tissues, activating anti-tumor immunity, and offering low toxicity and high biocompatibility[161]. Similarly, maleimide liposomes can covalently bind to T cell

Table 2 Drug delivery strategies for immune cell modulation: platforms, mechanisms, and immunotherapeutic outcomes.

Delivery Platform	Delivered drug/agent	Target immune cells	Release mechanism	Mechanism of immune modulation	Immunological outcome	Experimental models	Ref.
Protein nanogels (NG)	IL15 superagonist complex (IL15Sa)	T Cells	Responsive release based on TCR activation	Rapid expansion of cytotoxic T cells	Rapid amplification and enhancement of anti-tumor activity	Mice and cells	144
Dendritic macromolecules	Carboxy-terminal phenylalanine (Phe)-modified dendritic polymer	T Cells and their subpopulations	Enhanced cellular uptake in weak acidic environments	Reduction of immunosuppressive cells and enhancement of pro-inflammatory immune responses	Enhance cancer immunotherapy	Cells	145
Multifunctional mesoporous silica nanoparticles	R848 (toll-like receptor 7/8 agonist)	Antigen-presenting cells (APC), DC, T cells	pH-responsive release targeted delivery to lysosomes	Promotes T cell proliferation *via* APC activation	Promote the activation and proliferation of immune cells, causing enhanced immune response	Mice and cells	146
Self-assembling nanoparticles vaccines	TLR-7/8 agonist, chimpanzee adenovirus (ChAdOx1)	Conventional dendritic cell type 1 (cDC1), CD8 T cells	IFN signaling	Induces robust $CD8^+$ response and cytokine secretion	Elicits high intensity CD8 T cell response and regulates tumor microenvironment	Mice and cells	147
Mesoporous silica nanoparticles	Stattic, small molecule inhibitor	T Lymphocytes	NA	Inhibition of STAT3 signaling pathway enhances T cell infiltration and immune remodeling	Regulates the tumor microenvironment and increases immune cell proliferation and infiltration	Mice and cells	148
Temperature sensitive lipid gels	Photosensitizer, anti-PDCD1LG1 antibody and exosome inhibitor	DC and T cells	Thermally triggered release	Enhancement of immune infiltration and reduction of immunosuppression	Enhances immune cell infiltration to remodel immunosuppressive TME and increase T cell activity	Mice and cells	149
Nanoparticles	Tellurium	Macrophages, dendritic cells, CD8 T cells	Dual camouflaged delivery platform with near-infrared laser irradiation to induce photothermal therapy	Matures APCs and reprograms TME	Promote immune cell maturation and reprogramming to remodel the immunosuppressive tumor microenvironment	Mice	150
Yeast beta-glucan	Adriamycin	Macrophages, dendritic cells	Self-assembly method to form chiral nanocarriers to induce cytokines	Triggers cytokine release and DC maturation	Activation of enhanced immunity	Cells	151

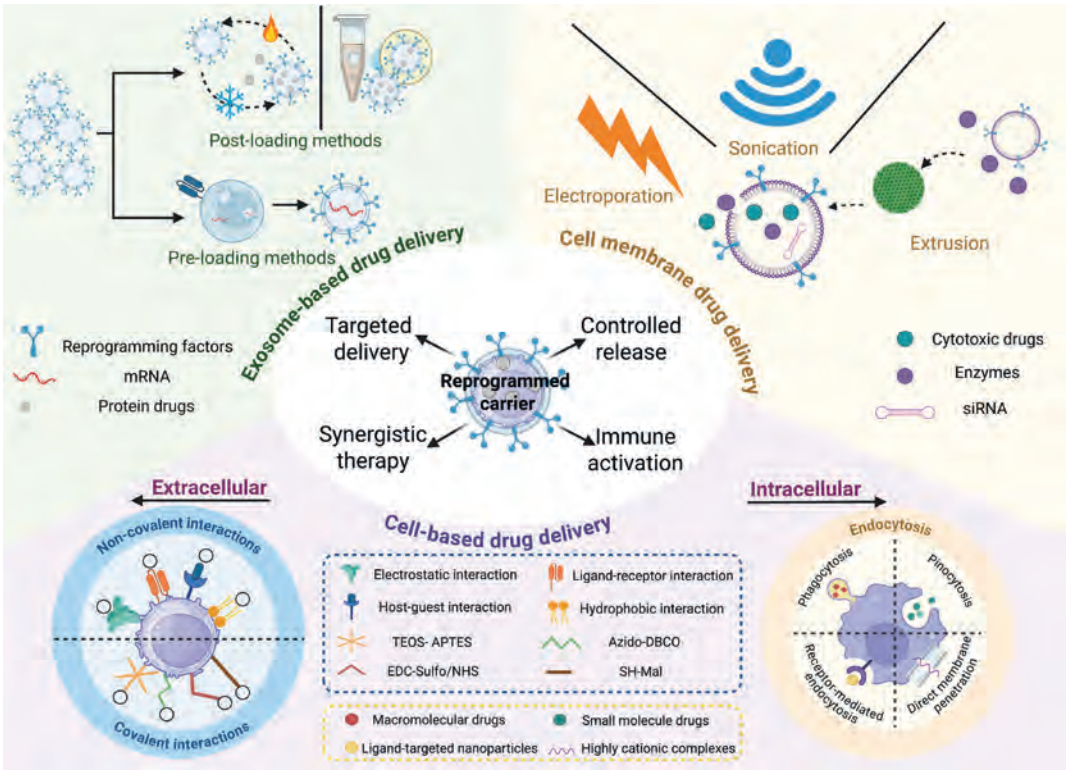

Figure 6 Engineering strategies for drug-loaded immune cell carriers: from whole cells to derivatives.

surface proteins like CD45 *via* free thiols. Upon antigen recognition, this binding facilitates the delivery of drug-loaded nanoparticles directly to the immunological synapse, enhancing TCR signaling and T cell function in the tumor microenvironment while minimizing systemic exposure[162]. For intracellular drug loading, drugs are internalized by immune cells *via* endocytosis. A prominent example of this strategy is the use of pHLip liposomes, which are first incorporated into NK cell membranes to form NKpH. These liposomes are endocytosed by NK cells *via* electrostatic−hydrophobic interactions. Once the liposomes are anchored at the tumor surface, they promote ROS release, damage the NK cell membrane, and open the tumor vascular barrier, facilitating the release of siRNA and photodynamic agents. This combination enables gene silencing and photodynamic killing, enhancing the therapeutic effect in tumor cells[163].

6.2. *Living cell-derived exosome- and extracellular vesicle-mediated drug delivery*

Living cell-derived exosomes and extracellular vesicles (EVs) derived from reprogrammed immune cells possess native targeting capabilities and immunomodulatory potential, making them highly attractive for drug delivery. There are two main approaches to incorporating cargo into exosomes: pre-loading and post-loading[164]. In the pre-loading strategy, therapeutic agents are introduced into the parent immune cells either through passive co-incubation or *via* genetic modification. These cells naturally secrete exosomes that encapsulate the desired cargo, enabling continuous, non-disruptive production of drug-loaded vesicles. For example, lipopolysaccharide (LPS)/IFNG-induced polarized M1 macrophages were co-incubated with adriamycin to create cell membrane vesicles, which exhibited pH-sensitive release, allowing for a synergistic chemo-immunotherapy effect in CT26 colon cancer and 4T1 breast cancer models[165]. This method not only enhances the efficacy of chemotherapy but also improves immune cell targeting within the TME. On the other hand, post-loading involves directly introducing drugs into isolated exosomes through passive diffusion or active methods such as electroporation and sonication. This approach offers flexibility in the drug type and dosage, but requires careful control to maintain vesicle integrity[166]. For instance, chemiluminescent substrates and photosensitizers were loaded into extracellular vesicles *via* ROS-induced membrane rupture, while the immunotherapeutic agent cytosine-phosphate-guanine (CpG) was loaded *via* electroporation. This method enables immunotherapy, photodynamic therapy (PDT), and chemotherapy to work synergistically in preclinical models[167]. Another example involves shikonin, IR820, and metformin, which were loaded into extracellular vesicles *via* freeze−thaw cycles to remodel the tumor-associated macrophage (TAM) phenotype, improving the effectiveness of therapies in 4T1 mammary tumor and B16F10 melanoma models[168]. Regardless of the method, living cell-derived exosome-based carriers can navigate biological barriers, extend systemic circulation time, and deliver their payloads in a targeted and biocompatible manner, especially when derived from functionally enhanced immune cells.

6.3. *Living cell-derived membrane-based drug loading*

Living cell-derived membrane coating technology leverages the natural antigenic and homing properties of immune cells by fusing their membranes with synthetic nanoparticle cores to create biomimetic delivery systems. These hybrid systems preserve the surface proteins and recognition functions of the original immune cells while gaining the structural advantages of nanoparticles, such

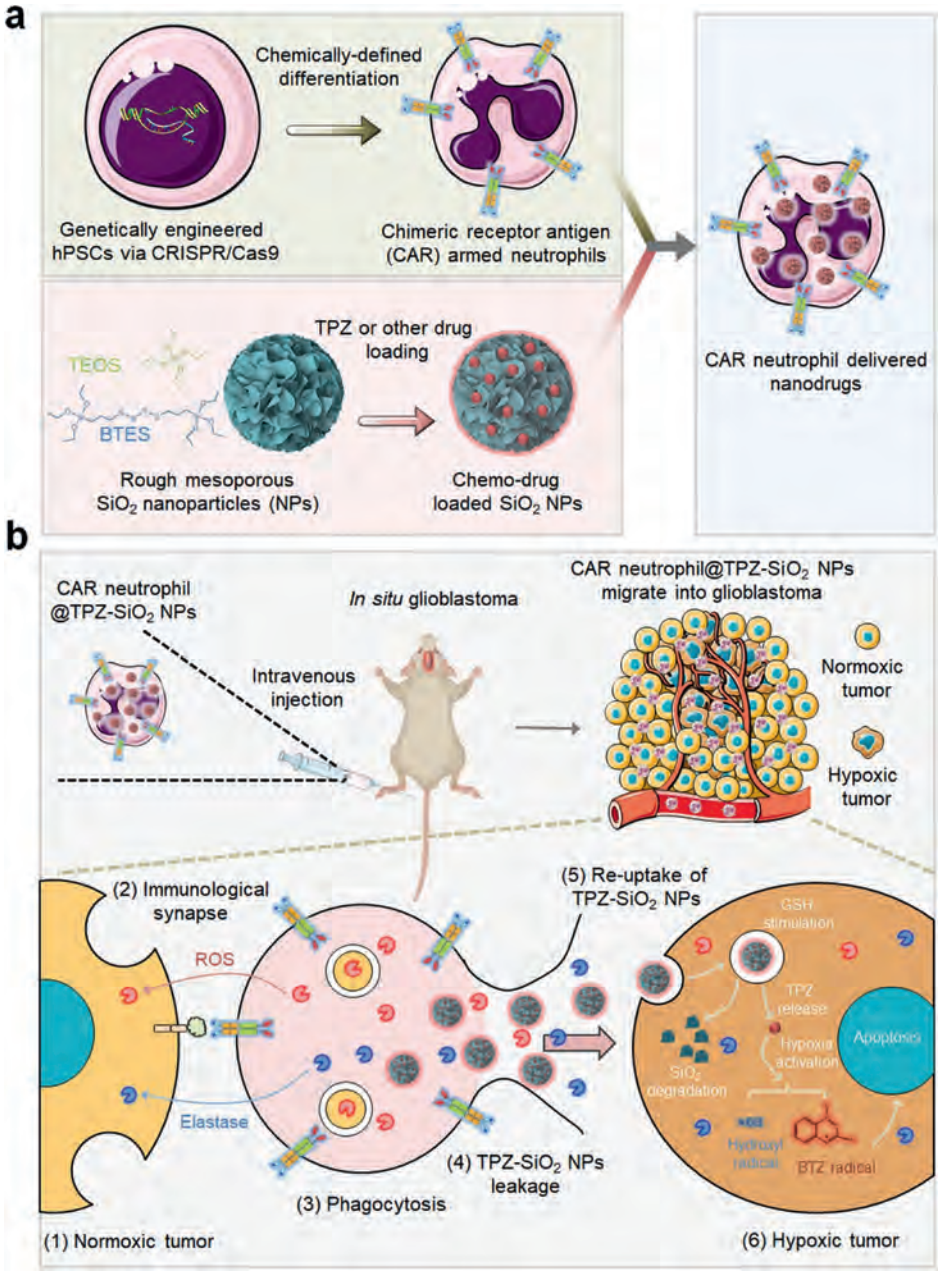

Figure 7 CAR-neutrophil-mediated delivery of TPZ-loaded mesoporous silica nanoparticles for targeted glioblastoma therapy and tumor microenvironment modulation. Reproduced with permission from Ref. 158. Copyright © 2023, Yun Chang et al., Nature Communications.

as controlled drug release and enhanced pharmacokinetics. Several engineering approaches have been developed for membrane-nanoparticle fusion[169]. One widely used method is coextrusion, which involves physically extruding membrane vesicles with nanoparticles to form stable core−shell architectures[170]. Cannabidiol was loaded into macrophage membrane vesicles *via* co-extrusion, combined with ultrasound assistance. This approach leveraged the inflammatory chemotaxis properties of macrophage membranes and ultrasound-induced BBB opening, enabling efficient drug enrichment in brain inflammatory regions. Consequently, it demonstrated significant therapeutic efficacy in a murine model of post-traumatic stress disorder[171]. Alternatively, sonication can promote membrane fusion *via* ultrasonic agitation, though it requires parameter optimization to prevent protein denaturation[172]. In one example, ultrasonication was used to create T lymphocyte−macrophage hybrid membrane-coated siIRF1@ZIF-8 nanoparticles (siIRF1@ZIF@HM NPs) for targeted myocarditis therapy. The hybrid membrane coating enabled precise delivery of siIRF1 to inflammatory myocardial sites, effectively silencing the *IRF1* gene and suppressing macrophage pyroptosis[173]. In membrane-templated polymerization, the immune cell membrane serves as a scaffold to polymerize nanoparticle cores *in situ*, allowing precise control over particle size and rigidity[174]. This method has been applied to develop nanoparticles that were coated with NK cell membranes to enhance their ability to infiltrate tumors and provide efficient drug delivery. This process allows for high stability and improved targeting within the tumor microenvironment. Finally, microfluidic

electroporation further enables scalable and tunable assembly of membrane-coated nanoparticles through electric field-driven vesicle fusion[172]. This approach has been employed to coat exosome-based carriers with NK cell membranes, which significantly enhanced the carriers' drug delivery capabilities and tumor-targeting ability.

The success of reprogrammed immune-cell therapies depends not only on precise cellular engineering but also on efficient drug-loading strategies. Whole-cell loading, vesicle-mediated delivery, and membrane-cloaked nanocarriers each offer distinct advantages and are suited to different cancer-therapy scenarios. These strategies enable immune cells to carry larger drug payloads, protect the cargo from degradation, and achieve site-specific release, thereby amplifying both immune and cytotoxic responses. Table 3[158,165,167,168,175−183] summarizes representative reprogrammed immune cells, their drug-loading methods, and the mechanistic advantages these strategies offer for tumor-targeted therapies.

7. Controllability and safety considerations for reprogrammed immune-cell drug-delivery systems

Reprogrammed Immune-cell carriers provide precise tumor targeting and enhanced therapeutic efficacy. However, their clinical translation is still limited by concerns regarding controllability and biosafety[184]. The complex interactions between therapeutic immune cells, their payloads, and the TME demand the development of strategies that ensure condition-specific activity, minimize systemic toxicity, and prevent off-target immune responses.

Given their innate ability to home to tumors and adapt to hostile microenvironments, reprogrammed immune cells serve as ideal candidates for constructing TME-responsive delivery systems. Their inherent plasticity allows for integration with smart materials that can respond to specific TME cues—such as acidic pH, elevated ROS, hypoxia, self-destruct switch and tumor-associated enzymes.

7.1. *pH-sensitive release*

Leveraging the weak acidity of the tumor microenvironment, pH-sensitive drug delivery systems are designed with "molecular switches" that activate upon entry into the acidic tumor areas, enabling precise spatiotemporal drug release[185]. By coupling therapeutic agents such as photosensitizers, metal ions, or prodrugs with acidic linker arms (*e.g.*, stilbene bonds or citraconic anhydride), these systems can be rapidly "unlocked" within the tumor, amplifying their therapeutic effects *via* PDT, ferroptosis, or immune pathways, while significantly reducing toxicity to normal tissues.

For instance, SR780Fe, an amphiphilic photosensitizer, exhibits a pH-responsive PDT effect upon excitation at 808 nm and has been integrated into reprogrammed immune cell delivery systems for targeted photodynamic therapy. In the acidic TME, SR780Fe undergoes pH-triggered degradation, releasing Fe^{3+} and SR780, transitioning SR780 from the "off" state to the "on" state. Upon 808 nm near-infrared irradiation, SR780 generates ROS, inducing tumor ablation and immunogenic cell death *in situ*[186]. This process also activates the cGAS−STING pathway in cancer cells, resulting in increased lipid peroxidation and disruption of cell membrane structure and function.

Similarly, nickel-arsenic oxide nanocomplexes, encapsulated by M1 macrophage membranes, utilize pH-sensitive arsenic release in acidic tumor sites[187]. The degradation products, dopamine and MM, work together to promote tumor immunity and modulate the TAM response, repolarizing them to the M1 phenotype. In this approach, the nickel-arsenic oxide core dissociates in an acidic environment and releases arsenic, which kills tumor cells.

7.2. *Enzyme response release*

The level and type of expression of tumor-specific enzymes, such as matrix metalloproteinases, cathepsins, and FAP, in tumors significantly differ from those in normal tissues, making it possible to design DDS with targeted and controlled release based on the properties of these overexpressed enzymes[188]. Tumor-associated fibroblasts are highly enriched in metastatic foci, providing an opportunity to target these regions with enzyme-responsive DDS[189]. By embedding specific protease substrate sequences (*e.g.*, FAP substrate sequences) on the surface of drug carriers or immune cells, an enzyme-responsive system is created that remains stable in the bloodstream and normal tissues. Upon reaching the tumor site, the overexpressed enzyme catalyzes the drug release, triggering a local burst release of the therapeutic agent.

For instance, spatially engineered M1 macrophages co-loaded with liposomal R848 and FAP-responsive RDM exploit the overexpression of FAP in metastatic lung cancer[64]. The FAP protease catalyzes the localized release of the drug, producing a killing effect directly at the metastatic site. This immune cell-based system demonstrates a promising approach for tumor-selective activation *via* TME responsiveness, offering the potential for highly localized drug release with minimized off-target effects. Additionally, co-loading reprogrammed immune cells with immune checkpoint regulators such as PDCD1 or CTLA-4 modulators can help balance immune activity within the TME. Surface modification with FAP-sensitive molecules has been shown to attenuate PDCD1LG1 expression in tumor tissues, mitigating hyperinflammation while sustaining anti-tumor immunity[190].

7.3. *Self-destruct switch-induced and logic-gated drug release*

To prevent immune overactivation or uncontrolled proliferation of therapeutic cells, suicide gene circuits, immune checkpoint modulators, and logic-gated drug delivery systems are integrated into drug delivery platforms, enhancing the controllability and safety of treatments. Suicide switches, such as inducible caspase-9 and herpes simplex virus thymidine kinase (HSV-TK), provide external control over cell viability, allowing targeted elimination of immune cells when necessary[191].HSV-TK is the most widely tested suicide gene in humans and can regulate sustained or transient drug release by initiating an apoptotic cascade within the cell[191].

For example, constructs like RapaCasp9-G or RapaCasp9-A, activated by rapamycin, enable conditional dimerization and trigger apoptosis in CAR-T cells by activating the caspase 9 catalytic domain, minimizing off-target toxicity or cytokine storms and improving therapeutic safety[192]. Similarly, anti-CD19 CAR-T cells co-expressing HSV-TK have shown self-elimination in response to immunogenic pressure, further enhancing safety[193].

In addition, logic-gated drug delivery systems ensure drug activation only when multiple tumor-specific conditions are met, offering precise spatial and temporal control over drug release. For instance, nanocomplexes targeting M2-like TAMs can deliver CpG oligonucleotides and baicalin simultaneously. These dual-functional agents repolarize M2 macrophages into an M1-like phenotype, enhancing antigen presentation and cytokine release

Table 3 Classification of drug-loading strategies for reprogrammed immune cells: carriers, techniques, and therapeutic applications.

Reprogrammed immune cells	Reprogramming strategy	Type of substance delivered	Specific substance delivered	Drug loading type	Loading method	Drug release mechanism	Therapeutic objective	Tumor model type	Research stage	Ref.
M1 Macrophage										
	LPS/IFNG-induced polarization	Anthracycline antitumor drugs	Adriamycin	Cell membrane vesicle	Co-incubation methods	pH sensitive release	Synergistic chemo-immunotherapy	CT26 colon cancer and 4T1 breast cancer mice	Preclinical	165
	LPS/IFNG-induced polarization	Molecular Probes	BN-O	Cell membrane	Ultrasonication and co-extrusion methods	Photothermal trigger	Tumor imaging enables precise diagnosis and treatment	4T1 Holoblastoma mouse	Preclinical	175
	Exosome engineering	Chemiluminescent substrate, photosensitizer, chemotherapeutic drug precursor	Bis[2,4,5-trichloro-6-(pentyloxycarbonyl) phenyl]oxalate, chloro e6, prodrug alloxan	Extracellular vesicle	Post-loading method	Membrane rupture induced by unilinear oxygen species	Immunotherapy, PDT and chemotherapy for synergistic effects	NA	Preclinical	167
	Exosome engineering	Chemotherapeutic agent, photosensitizer, immunomodulator	Shikonin, IR820, metformin	Extracellular vesicle	Post-loading method	NA	Remodeling the TAM phenotype	4T1 mammary tumor and B16F10 melanoma	Preclinical	168
	NA	Photosensitizer, siRNA, nitric oxide donor	Pyropoxypenta-a (PPA), anti-PDCD1LG1 siRNA, poly-L-arginine (Arg9)	Cell membrane vesicle	Post-loading method	NA	Synergistic photodynamic immunotherapy	Hypoxic pancreatic tumor	Preclinical	176
	NA	Photosensitizer	TP-IS1	Cell	Non-covalent interactions	ROS-triggered release	Synergistic photodynamic immunotherapy	NA	Preclinical	177
	Gene reprogramming	Plasmid DNA (coding IL12)	Plasmid DNA IL12	NA	NA	DNA release	Macrophage M2 → M1 repolarization	HeLa cells	Preclinical	178
CAR neutrophils	CRISPR/Cas9-mediated editing	Bioreductant antitumor agents, alkylating agent antitumor agents	Tirapazamine, Temozolomide	Cell	Non-covalent interactions	Environmental response release	Reduction of off-target effects	Glioblastoma *in situ* xenograft mice	Preclinical	158
DC	Lentiviral transduction	Living cells(DC)	Ad-CCL21-DC	Cell	NA	Continuous secretion of CCL21 chemokine	Recruitment of $CD8^+$ T cells infiltrating tumors	Non-small cell lung cancer patients	Phase I	179
CAR-T										
	CRISPR/Cas9-mediated editing	Endogenous RNA	RN7SL1	Cell	Non-covalent interactions	NA	Enhancement of the immune response	NOD scid gamma mice	Preclinical	180
	Lentiviral transduction	A2a Adenosine receptor-specific small molecule	SCH-58261	Cell	Covalent conjugation	Environmental response release	Improving solid tumor treatment	NOD scid gamma mice	Preclinical	181

(*continued on next page*)

Table 3 (*continued*)

Reprogrammed immune cells	Reprogramming strategy	Type of substance delivered	Specific substance delivered	Drug loading type	Loading method	Drug release mechanism	Therapeutic objective	Tumor model type	Research stage	Ref.
		antagonists								
	Lentiviral transduction	Imaging agents	Near infrared dye IR780	Cell membrane	Extrusion method	Photothermal triggered release	Targeted therapy	NA	Preclinical	182
NK	Transfection	CIR mRNA (express CD19)	Anti-CD19 CIR mRNA	NA	Electroporation	Natural mRNA degradation	Targeted therapy for hematological malignancies and solid tumors	Non-obese diabetic/severe combined immunodeficient mice	Preclinical	183

(*e.g.*, IL12, IFNG, TNFA). The logic-gated architecture ensures staged activation, reshaping the TME while minimizing unintended systemic effects[194].

7.4. Design for controllability and safety of drug release

In the tumor microenvironment, various drug release mechanisms—such as pH-sensitive, enzyme-responsive, and self-destructive switch-induced release—offer precise control over drug activation, ensuring spatial and temporal accuracy in therapeutic delivery. pH-sensitive release exploits the acidity of the tumor site to trigger the breakdown of linkers, such as germanium bonds or citraconic anhydride, enabling the rapid release of photosensitizers or metal ions, which induces immunogenic cell death and triggers an iron death cascade[186]. Enzyme-responsive systems use tumor-associated fibroblasts—expressed FAPs to cleave drugs from stable carriers, delivering a localized, high-concentration shock, while also enabling sustained drug release to maintain macrophage polarization[190]. Self-destructive switches, such as inducible caspase-9 or HSV-TK, can be activated remotely by rapamycin or ganciclovir, leading to apoptosis in therapeutic cells and providing a final pulse of drug release when necessary, ensuring control over immune overactivation and cell proliferation[191]. These mechanisms complement each other by using burst release to initiate the first attack and immune activation, sustained release to consolidate the therapeutic effect and reduce recurrence, and self-destructive switches to provide an essential safety measure to balance drug efficacy and toxicity. Together, they enable dynamic synergy in tumor killing, TME remodeling, and patient safety, presenting a robust platform for the future of precision immunotherapy.

8. Cross-cancer potential of immune-cell-reprogramming drug-delivery systems

Tumor heterogeneity, both intertumoral (across distinct cancer types) and intratumoral (within t individual tumors and their subtypes), presents considerable obstacles to the effectiveness of conventional therapies, including immunotherapeutic strategies[195]. Variability in antigen expression, immune cell infiltration, stromal density, and cytokine profiles contribute to inconsistent therapeutic responses among different patients and even within separate regions of the same tumor[196]. To address this complexity, reprogrammed immune cells provide a robust and versatile strategy, capitalizing on their instinct functional plasticity. Immune cell-reprogramming-based drug delivery systems, characterized by modularity and multifunctionality, can effectively adapt to tumor heterogeneity. Specifically engineered to identify distinct antigens, respond to particular microenvironmental cues, and deliver therapeutic payloads contextually, these cells exhibit high adaptability. As illustrated conceptually in Fig. 8, drug-loaded macrophages, CAR-T cells, and CAR-NK cells can be strategically tailored and deployed across various cancers, aligning therapeutic cargoes with tumor-specific signaling pathways and immune phenotypes. These strategies aim to inhibit tumor cell proliferation, promote immune activation, regulate immune escape, and influence the tumor microenvironment by modulating specific signaling pathways, thereby enhancing treatment efficacy. By regulating these mechanisms, it is possible to more effectively target tumor heterogeneity, enhance immune responses, inhibit tumor growth, and potentially

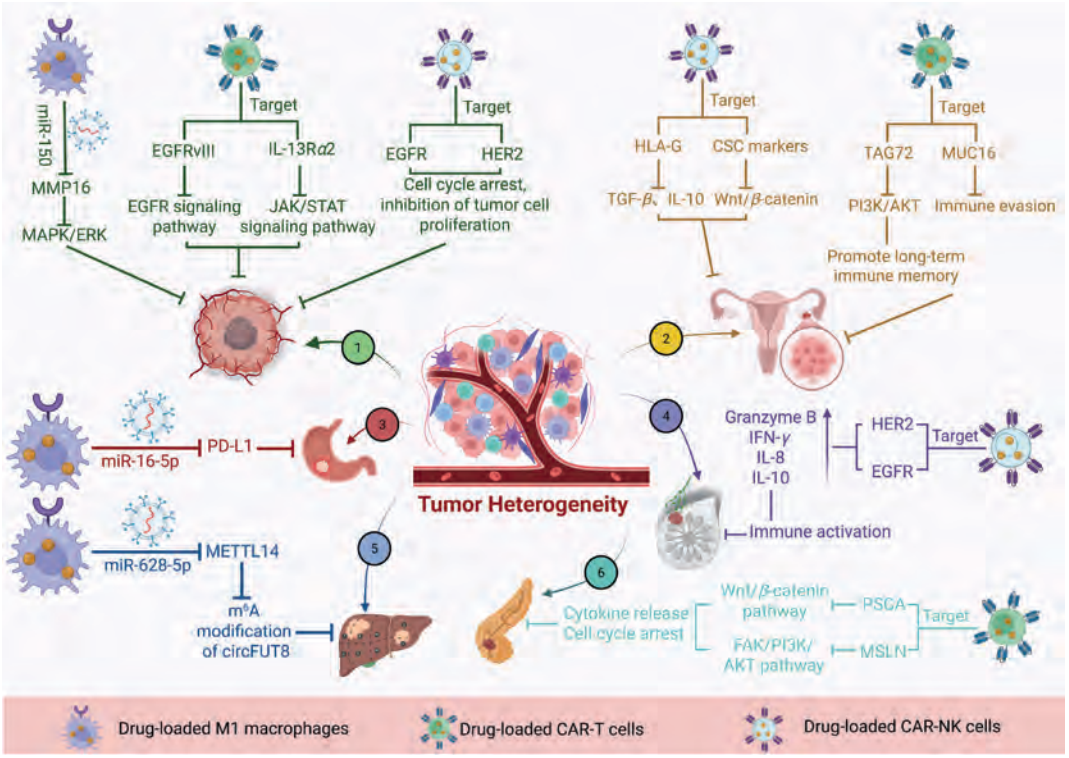

Figure 8 Reprogrammed immune cell-based strategies to overcome tumor heterogeneity in multiple cancer types (1: Glioma, 2: Ovarian Cancer, 3: Gastric Cancer, 4: Breast Cancer, 5: Hepatocellular Carcinoma, 6: Pancreatic Carcinoma).

promote the formation of long-term immune memory, providing diverse strategies for cancer treatment.

8.1. Tailored drug delivery strategies for solid and non-solid tumors

Solid and hematological malignancies present fundamentally different obstacles to immune-cell trafficking and drug delivery: pancreatic cancer and glioblastoma, for example, are shielded by dense stroma, aberrant vasculature and hypoxia, whereas leukemias and multiple myeloma lack such physical barriers yet display pervasive immune evasion and systemic dissemination[197,198]. Even within one histological category, molecular subtypes vary widely in immunological architecture-HER2-positive, triple-negative and luminal breast cancers differ in infiltrating-lymphocyte density and antigen repertoire[199,200], while hepatocellular-carcinoma subsets show disparate PDCD1LG1 expression and T-cell exclusion profiles[201], These inter-and intra-tumoral variations demand tailored reprogramming and loading protocols for macrophage carriers or CAR-engineered lymphocytes to achieved efficient payload delivery[202]. Consequently, combinatorial strategies are emerging: bispecific CAR-T cells counter antigen escape, STING- or TLR-agonist payloads remodel suppressive niches, and tumor-microenvironment-responsive materials—such as fibroblast-activation-protein-cleavable prodrugs or pH-sensitive vesicles-add an additional layer of spatial precision[203,204].

8.2. Tailored reprogramming strategies for immune hot and cold tumors

Immunologically "cold" tumors—such as microsatellite-stable colorectal and prostate cancers—exhibit sparse effector T cell infiltration and a suppressive cytokine milieu dominated by TGF-β and IL10[205]; in this context, reprogramming focuses on activating innate immunity and remodeling the TME to permit adaptive-cell entry. Macrophage carriers delivering TLR agonists or chemokines can initiate inflammatory cascades, mature dendritic cells and recruit T cells into otherwise excluded lesions[206], and the emerging paradigm of adoptive immune-cell-induced *in situ* vaccination extends this effect: CAR-T cells engineered to secrete immunostimulatory RNAs (*e.g.*, RN7SL1) activate endogenous dendritic cells, enhance antigen cross-presentation and mobilize endogenous T-cell clones against non-CAR antigens, thereby converting "cold" tumors into "hot" ones by broadening antigenic breadth and inflaming the TME[180]. By contrast, "hot" tumors—such as melanoma and select lung-cancer subtypes—already harbor robust immune infiltrates; here, the therapeutic priority shifts to sustaining cytotoxic function and preventing exhaustion, for which drug-loaded CAR-T or CAR-NK cells equipped with cytokine-secretion modules or checkpoint-blockade elements can amplify effector activity and maintain T-cell persistence[207].

9. Future development trends and challenges

Reprogrammed immune cell−based drug delivery systems have shown transformative potential in cancer therapy by integrating precise tumor targeting with immune modulation. However, as these systems advance toward clinical translation, a range of opportunities and challenges emerge at the intersection of immunology, bioengineering, and systems biology[208]. The complexity of tumor immune heterogeneity, inter-individual variability in therapeutic responses, and the evolving understanding of immune-tumor−microbiome interactions demand a forward-looking framework for optimizing these delivery platforms. By

embracing multidimensional insights—from metabolic reprogramming and spatial immunoprofiling to personalized medicine and AI-guided system design—future research can further elevate the therapeutic precision, adaptability, and safety of immune cell–based drug delivery strategies.

9.1. Synergistic optimization of drug delivery systems via immune–microbiome interactions

Emerging evidence has established the gut microbiome as a critical modulator of tumor immunity and therapeutic response[209–211]. Dysbiosis, epithelial barrier dysfunction, and microbial translocation contribute not only to carcinogenesis but also to treatment resistance in multiple malignancies, including pancreatic ductal adenocarcinoma, hepatocellular carcinoma, and gastrointestinal tumors[212,213]. In pancreatic ductal adenocarcinoma, microbial dysregulation promotes innate and adaptive immunosuppression *via* TLR signaling pathways, leading to the accumulation of myeloid-derived suppressor cells and the polarization of TAMs toward an immunosuppressive phenotype. Gut microbiota depletion reverses these effects by enhancing $CD8^+$ cytotoxic T lymphocyte infiltration, promoting M1-like macrophage activation, and increasing T helper 1 cell-type $CD4^+$ responses[213]. Notably, this shift correlates with elevated PDCD1 expression and enhanced efficacy of immune checkpoint blockade therapies. These findings suggest that microbiome-targeted strategies could synergize with reprogrammed immune cell-based delivery systems to remodel the tumor microenvironment and potentiate drug responsiveness.

Furthermore, the therapeutic efficacy of DC-based immunotherapies in melanoma has been linked to host microbiome composition and serum metabolites[214]. For example, beneficial microbial taxa such as Fusobacterium pullorum and bile acid—modulating microbiota positively correlate with treatment outcomes. Recent studies show that microbiota-derived cyclic dinucleotides (*e.g.*, c-di-AMP), acting as STING agonists, can induce intratumoral IFN1 production, promote monocyte-to-DC reprogramming, and facilitate NK–DC cross-talk[215]. These effects were further enhanced by enhanced activation of the STING pathway, resulting in improved immune stimulation[216].

9.2. Integration of immune cell reprogramming with personalized medicine

Given the inter-individual heterogeneity in tumor genetics, immune contexture, and metabolic landscapes, universal therapeutic strategies often fall short. Immune cell reprogramming—through transcriptional, metabolic, and epigenetic modification—represents a flexible platform that can be adapted to patient-specific tumor features, aligning with the goals of precision medicine[217,218].Personalized T-cell immunotherapies, particularly CAR-T and TCR-engineered cells, have demonstrated clinical success in hematologic malignancies and are rapidly advancing into solid tumor applications[219]. Beyond gene-editing approaches, the combination of immune cell reprogramming with personalized antigen delivery systems further enhances therapeutic outcomes. For instance, the CpG/cGAMP-loaded hybrid liposomal vaccine (C/G-HL-Man), derived from autologous tumor cell membranes and functionalized with mannose ligands, targets dendritic cells for antigen cross-presentation. This approach induces robust cytotoxic T lymphocyte responses, significantly inhibits tumor recurrence, and prolongs survival in murine postoperative cancer models[220]. Importantly, when combined with metabolic modulators such as peroxisome proliferator–activated receptor alpha agonists, this vaccine platform also facilitates T-cell metabolic reprogramming, thereby enhancing cellular persistence and effector function.

9.3. Intelligent patient stratification based on tumor immune profiling

Achieving precision in immune cell reprogramming-based drug delivery requires an intelligent patient selection framework rooted in tumor immune profiling. Tumor immune characteristics—including the extent and composition of immune cell infiltration, expression of immune checkpoint markers, and transcriptional signatures of immune regulation—offer predictive insights into patient responsiveness[221]. Evaluating these features enables stratification of patients who are most likely to benefit from reprogrammed immune cell therapies, while minimizing off-target effects and immune-related adverse events.

For instance, tumor burden has been inversely correlated with immunotherapy efficacy, as larger tumors are typically associated with heightened immunosuppressive signaling. Biomarkers such as increased frequencies of myeloid-derived suppressor cells, regulatory T cells, and elevated PDCD1LG1 expression levels have been linked to poor immune response[221]. Quantifying these markers can guide clinicians in assessing immune responsiveness and predicting outcomes of reprogramming-based interventions.

Moreover, recent advancements in high-throughput functional genomics and spatially resolved transcriptomics have revealed the spatial heterogeneity of immune landscapes. The physical proximity of effector $CD8^+$ T cells to tumor cells, the phenotypic state of TAMs, and the architecture of the immunological synapse all contribute to treatment efficacy. Such spatial immune profiling provides a high-resolution view of immune–tumor interactions and supports the customization of cell-based drug delivery strategies[222]. For example, designing reprogrammed macrophage systems that selectively target M2-like TAMs within specific niches can enhance reprogramming efficiency and therapeutic selectivity.

9.4. AI-assisted design and optimization of immune cell reprogramming-based drug delivery systems

Artificial intelligence (AI) is revolutionizing the design and optimization of immune cell-based drug delivery platforms by offering predictive, data-driven solutions for complex biological systems[223]. Through machine learning and deep learning algorithms, AI can analyze multidimensional data encompassing drug physicochemical properties, carrier formulations, and host biological variables[224]. This enables the prediction of drug behavior across biological scales, including release kinetics, cellular uptake, biodistribution, and immune cell interaction profiles.

One major application of AI is in optimizing extracellular vesicle (EV)-based delivery derived from reprogrammed immune cells. Precise control over EV-cell interactions—such as selective targeting, uptake efficiency, and endosomal escape—can be achieved using AI-guided models[225]. Furthermore, in the context of gene reprogramming, AI algorithms assist in optimizing CRISPR-Cas9 design by predicting on-target efficacy and minimizing off-target genomic alterations. The integration of AI into guide RNA design not only enhances genome editing precision but also supports the scalability of cell reprogramming protocols for therapeutic applications[226].

AI-driven image analysis tools, such as cell painting platforms, offer novel opportunities for evaluating the polarization states of macrophages and other immune cells[227]. These tools use deep neural networks to extract morphological and phenotypic features beyond the binary M1/M2 classification. By integrating morphological profiling with compound screening, researchers can rapidly identify small-molecule modulators of immune cell function, enabling high-throughput discovery of synergistic drug candidates for use in reprogrammed immune cell systems.

9.5. Role of liquid biopsy in monitoring drug delivery and feedback-controlled dosing

Liquid biopsy, a non-invasive diagnostic technique based on the analysis of circulating biomarkers (*e.g.*, exosomes, circulating tumor DNA, cytokines), holds significant promise in enhancing the controllability and precision of reprogrammed immune cell-based drug delivery systems[228]. In these systems, reprogrammed immune cells such as CAR-T cells or M1 macrophages serve not only as therapeutic effectors but also as dynamic drug carriers. However, their *in vivo* behavior—such as biodistribution, drug release kinetics, and functional persistence—remains difficult to track in real time using conventional imaging techniques.

By detecting circulating exosomes or cytokines derived specifically from reprogrammed immune cells, liquid biopsy can serve as a real-time monitoring tool to evaluate whether therapeutic cells are successfully homing to tumor sites, releasing payloads, and eliciting immune activation[229]. For example, exosomal RNA markers or cell-specific surface proteins (*e.g.*, CD63 from CAR-T-derived exosomes) can reflect drug release events, while cytokine panels (*e.g.*, IL12, TNFA, or IFNG) may provide surrogate indicators of therapeutic activity and immune engagement[230]. Additionally, temporal changes in tumor-derived circulating markers can be used to indirectly infer therapeutic efficacy or emerging drug resistance.

Moreover, integrating liquid biopsy into a closed-loop dosing system allows for dynamic adjustment of drug administration. Real-time feedback—such as rising levels of tumor markers, increased cytokine toxicity, or early signs of relapse—can be used to modify dosing frequency, reprogramming strength, or immune cell subtype selection, thereby improving safety and treatment personalization[231]. Liquid biopsy can also help identify patients at high risk for immune-related adverse events by detecting early immunopathological signals, thus providing a safety checkpoint for immune cell-based therapies.

Importantly, liquid biopsy offers a valuable platform for stratifying patients prior to treatment[232]. By profiling the immune landscape (*e.g.*, PDCD1LG1 expression, tumor mutational burden, exosomal miRNA), it is possible to predict a patient's responsiveness to reprogrammed immune-cell therapies and select appropriate payloads or delivery strategies accordingly.

10. Challenges in clinical translation and industrialization of engineered immune cell-based drug delivery systems

Engineered immune cell-based drug delivery systems face significant challenges in clinical translation and industrialization despite promising preclinical results. A primary challenge lies in the complexity of cell processing: immune cells must be isolated, expanded, reprogrammed, and loaded with therapeutic agents *ex vivo* before administration. This process is time-sensitive and technically demanding, particularly for short-lived cells that experience declining viability post-isolation. Cellular integrity and function may be compromised during expansion/manipulation, and some cells exhibit functional plasticity, displaying both pro- and anti-inflammatory phenotypes. This variability necessitates rigorous quality control for phenotypic consistency and therapeutic reliability[154]. Moreover, reprogramming efficiency presents another critical hurdle, as only a fraction of cells typically undergo successful reprogramming due to intrinsic cellular heterogeneity and patient-specific variability. The underlying mechanisms—such as transcriptional regulation, epigenetic remodeling, metabolic rewiring-remain incompletely understood, hindering rational design and reproducibility of *in vivo* fate engineering[233]. Technological limitations like labor-intensive high-throughput screening and functional validation also impede progress[234]. Additionally, drug loading introduces further complexity[235]: extracellular surface-loading strategies can impede migration/proliferation through nonspecific adsorption or poorly defined covalent attachment sites. Immune cells carrying cytotoxic payloads are vulnerable to premature drug leakage and degradation, diminishing efficacy and potentially impairing cell viability and motility[236]. These challenges highlight the urgent need for enhanced loading technologies and robust nanocarriers to ensure payload stability during *in vitro* manipulation and systemic circulation. An emerging approach involves genetically engineering immune cells to locally produce immunomodulatory cytokines/chemokines within the TME[237], enabling them to act as *in situ* bioreactors that reshape the TME and enhance tumor targeting. This strategy could immune suppression, promote infiltration, and boost efficacy in "cold" tumors.

From an industrial perspective, scalability, standardization, and regulatory compliance present substantial challenges. The entire process—from cell sourcing and genetic modification to drug loading/formulation—requires strict process validation/quality assurance for clinical-grade standards[238]. Achieving high-yield, reproducible manufacturing with consistent quality is difficult given biological variability. Additionally, cryopreservation, storage, and transportation add logistical/economic burdens due to strict temperature requirements[239]. Economic constraints further hinder commercialization, as CAR-based therapies require substantial upfront investment in infrastructure, quality control, and patient monitoring[234]. Unlike small-molecule drugs, cell therapies cannot easily benefit from economies of scale, and expansion into new indications often necessitates distinct trials and additional capital. Consequently, despite broad preclinical potential, transforming these therapies into widely accessible clinical solutions remains a formidable challenge.

Expanding on these challenges, recent clinical advances illustrate how engineered immune cell products are overcoming translational barriers. In a Phase I trial for relapsed/refractory lymphoma, the armored CAR-T product huCART19-IL18—featuring CD19-targeting single-chain variable fragment with CD28/CD3ζ domains, along with interleukin-18 (IL-18) secretion—achieved an 81% objective response rate (52% complete response) with a 9.6-month median duration of response in CD19 CAR-T refractory patients, utilizing a streamlined 3-day manufacturing process[240]. Similarly, a Phase II trial of HER2-targeting bispecific antibody-armed T cells (HER2 BATs) in metastatic HER2-negative breast cancer extended the median progression-free survival beyond conventional benchmarks (2−4 months post-first-line failure) by inducing endogenous adaptive and innate immunity[241]. Furthermore, a Phase I study of

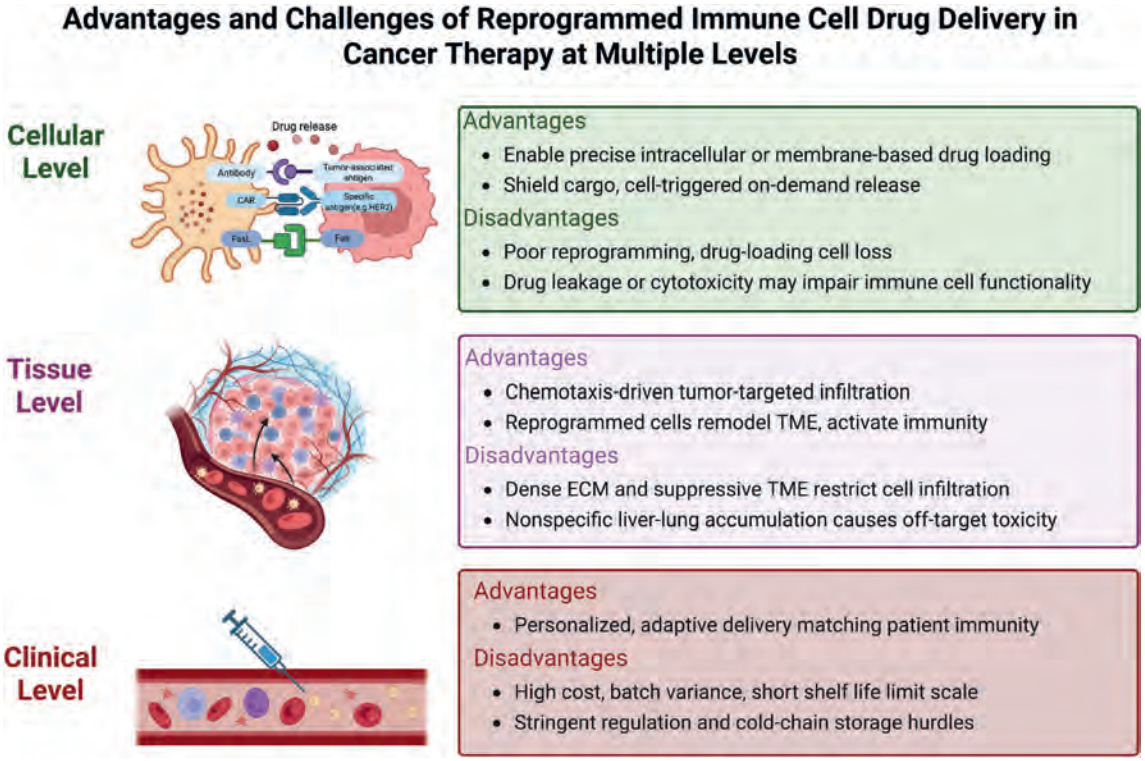

Figure 9 Advantages and challenges of reprogrammed immune cells as multifunctional drug carriers in cancer therapy across cellular, tissue, and clinical levels.

engineered anti-MUC1 CAR-T cells, incorporating IL12 secretion and armored modifications, eradicated metastatic seminal vesicle cancer without significant toxicity, while eliciting positive serum cytokine responses[242]. In addition, the engineered exosome-based therapeutic ExoIL12, developed by Codiak Biosciences, has shown promising potential as a drug delivery system, demonstrating the ability to deliver IL12 directly to the tumor site[243]. These examples demonstrate the feasibility and advantages of utilizing engineered immune cells as localized immunomodulatory "factories" for drug delivery, which not only overcome the suppression of the tumor microenvironment but also effectively address resistance to conventional therapies, thereby enhancing the precision of drug delivery and therapeutic efficacy.

To accelerate clinical adoption, future efforts must focus on optimizing production workflows, improving drug-carrier compatibility, clarifying the mechanisms of immune cell reprogramming, and developing cost-effective, standardized manufacturing platforms. Fig. 9 summarizes the core advantages and limitations of reprogrammed immune cell-based drug delivery systems, emphasizing their challenges and potential across cellular, tissue, and clinical levels.

11. Conclusions

The development of reprogrammed immune cell-based drug delivery systems has opened new frontiers in cancer immunotherapy by integrating cell fate engineering with precise therapeutic payload transport. These systems offer distinct advantages such as tumor-specific targeting, sustained cytotoxic activity, and improved resistance to the immunosuppressive TME. In particular, reprogrammed immune cells demonstrate enhanced functional plasticity, including increased secretion of bioactive cytokines, higher glucose metabolism, and mitochondrial biogenesis—all of which contribute to prolonged survival and antitumor efficacy. Beyond whole-cell approaches, cell-derived components such as exosomes and membrane-coated nanoparticles further extend the utility of reprogrammed immune cells as delivery platforms. These derivatives leverage the parent cells' targeting properties to improve drug retention and release precision while minimizing systemic toxicity. Moreover, a synergistic interaction exists between drug delivery and immune cell function: reprogramming improves cellular drug-carrying capacity, while appropriate drugs can also promote or sustain immune reprogramming, further reinforcing therapeutic responses.

Despite these advancements, clinical translation remains limited. Major challenges include difficulties in harvesting and expanding immune cells at scale, variability in reprogramming efficiency due to inter-patient heterogeneity, and the lack of standardized, scalable manufacturing protocols. Additionally, cell-derived delivery systems may fail to fully recapitulate the dynamic biological behaviors of live immune cells, leading to suboptimal drug release profiles. Critical gaps also persist in understanding their *in vivo* biodistribution, systemic immune interactions, and long-term safety. Nonetheless, with ongoing progress in synthetic biology, nanotechnology, and artificial intelligence—assisted drug system design, these barriers are gradually being addressed. In the future, immune cell reprogramming-based delivery systems are poised to become a cornerstone of personalized oncology, offering a robust, adaptable, and precision-guided platform for treating a wide range of cancers.

Acknowledgements

This research was funded by the National Natural Science Foundation of China (No. 82374050).

Author contributions

Zheng Sun, Jun Ge, and Hui Fu collect data and screen articles. Ziqiu Chen, Chengcheng Zhao, Xiuyan Li and Yujiao Sun are responsible for framing the article. Zheng Sun, Jun Ge, and Hui Fu analyzed the data and wrote the main manuscript. Zhonggao Gao, Yunfei Li and Yingpeng Li were responsible for the design of comments and the revision of the manuscript. All authors have contributed to the article and approved the submitted version.

Conflicts of interest

The authors declare no conflicts of interest.

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