



Engineering immune cells with membrane-fusogenic liposomes: A new frontier in adoptive cell therapy

Qingguo Zhong¹, Yuxin Huang^{2,3}, Zhenhua Li⁴, Chunxiong Zheng^{5,*}, Yu Tao^{2,6}, Mingqiang Li^{2,6,7,*}

¹School of Medicine, Fuzhou University, Fuzhou 350108, Fujian, China.

²Laboratory of Biomaterials and Translational Medicine, Center for Nanomedicine, The Third Affiliated Hospital, Sun Yat-sen University, Guangzhou 510630, Guangdong, China.

³The First Affiliated Hospital, Guangzhou Medical University, Guangzhou 510120, Guangdong, China.

⁴The Tenth Affiliated Hospital, Southern Medical University, Dongguan 523059, Guangdong, China.

⁵School of Chemistry, South China Normal University, Guangzhou 510006, Guangdong, China.

⁶Cell-Gene Therapy Center, Institute for Frontier Interdisciplinary Research in Health Sciences and Technology, Sun Yat-sen University, Guangzhou 510080, Guangdong, China.

⁷Key Laboratory for Polymeric Composite and Functional Materials of the Ministry of Education, Sun Yat-sen University, Guangzhou 510275, Guangdong, China.

***Correspondence to:** Chunxiong Zheng, School of Chemistry, South China Normal University, Guangzhou 510006, Guangdong, China. E-mail: zhengchunxiong@m.scnu.edu.cn

Mingqiang Li, Laboratory of Biomaterials and Translational Medicine, Center for Nanomedicine, The Third Affiliated Hospital, Sun Yat-sen University, Guangzhou 510630, Guangdong, China; Cell-Gene Therapy Center, Institute for Frontier Interdisciplinary Research in Health Sciences and Technology, Sun Yat-sen University, Guangzhou 510080, Guangdong, China; Key Laboratory for Polymeric Composite and Functional Materials of the Ministry of Education, Sun Yat-sen University, Guangzhou 510275, Guangdong, China. E-mail: limq567@mail.sysu.edu.cn

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Abstract

Adoptive cell therapy continues to encounter diverse hurdles in treating solid tumors, including poor infiltration, an immunosuppressive microenvironment, and tumor immune evasion, necessitating the endowment of effector cells with multiple functionalities. However, conventional cell-engineering techniques, including genetic editing and chemical modification, usually modulate a single functional axis to yield a monofunctional effector cell that can overcome only one physiological barrier, leading to insufficient solid tumor suppression. Recently, membrane-fusogenic liposomes have emerged as a multiplex engineering tool capable of directly producing multifunctional effector cells to simultaneously surmount multiple challenges for effective antitumor efficacy. Through a fusion process, this liposome concurrently achieves immune cell surface functionalization and intracellular delivery of bioactive molecules, thereby endowing effector cells with multiple functionalities within a single step. This minireview summarizes recent advances in the use of fusogenic liposomes for immune cell engineering to boost their therapeutic efficacy against solid tumors. We discuss their design principles and representative applications, and analyze their technical advantages and current limitations. Looking forward, we propose that membrane-fusogenic liposomes hold potential to advance the development of multimodal engineered immune cells for next-generation cancer immunotherapies.

Keywords: Adoptive cell therapy, cell engineering, membrane fusion, liposome

1. Introduction

Adoptive cell therapy (ACT), involving a successive process that includes extracting immune effector cells from either a patient or a healthy donor, modifying those cells outside the body with diverse techniques, and infusing them back into the patient, has gained significant clinical importance against cancers^[1-4]. Unlike cancer immunotherapies that utilize the host's natural antitumor lymphocytes, ACT stands out by providing adequate cell supplies, tunable functionality, and sustained antitumor activity^[3,4]. One prominent form of ACT, known as chimeric antigen receptor (CAR) T cell therapy, has demonstrated a high rate of complete remission in individuals with B cell malignancies that are resistant, relapsed, or refractory to standard care, occasionally in combination with other treatment modalities^[5-7]. Owing to these striking successes, seven CAR T cell cancer therapies have received US Food and Drug Administration approval so far, all for hematological malignancies, and many promising trials of analogous strategies remain underway^[7,8]. Beyond CAR-T cells, other ACT platforms are also rapidly advancing. CAR-engineered natural killer (NK) cells offer a



favorable safety profile with reduced risks of cytokine release syndrome and graft-versus-host disease, although their limited *in vivo* persistence and large-scale expansion remain challenging^[9]. Likewise, chimeric antigen receptor macrophages (CAR-M) exploit the innate tumor infiltration and phagocytic capacity of myeloid cells, but are constrained by phenotypic plasticity and inefficient genetic modification^[10].

Despite its notable success in hematologic cancers, applying ACT to solid tumors has heretofore led to unsatisfactory clinical outcomes, revealing persistent obstacles that limit its effectiveness^[3,4,11-14]. These include physical barriers within tumor tissues that impede cell entry, an immunosuppressive tumor microenvironment (TME) that dampens the activity of transferred cells, and diverse immune evasion mechanisms employed by tumor cells^[3,4,12,15]. To address these issues, various engineering approaches, such as gene editing and chemical modification, have been explored to target intracellular or membrane-associated molecules, aiming to equip adoptive cells with enhanced functionalities^[12,16-19]. Nevertheless, these methods remain inadequate for improving solid tumor treatment. The main reason lies in their single-site engineering nature, which results in only one additional functionality per intervention, thereby overcoming just one physiological hurdle^[11]. Ideally, therapeutic adoptive cells should carry two or more functionalities simultaneously (such as improved tumor penetration, resistance to the suppressive TME, and augmented immune recognition), allowing them to tackle multiple barriers at once and achieve optimal therapeutic outcomes^[11]. Yet, constructing such multifunctional effector cells within a “single” engineering intervention, i.e., employing a one-step operative process without multi-technique integration, long-term treatment, or sequential and repeated handling, remains highly challenging owing to the distinct subcellular locations of the targets involved (Figure 1a)^[4,12,16-21]. Enhancing tumor recognition typically requires placing functional groups on the cell surface, whereas reducing cell exhaustion from the TME often demands interference with intracellular signaling pathways. Traditional chemical modification only enables rapid surface programming while generally cannot modulate intracellular targets. Genetic engineering can only modulate intracellular targets to alter cell-surface receptors, cytoplasmic pathways, or even secreted factors^[22]. Integrating multiple genetic modules into a single construct could combine both intracellular and surface modification in one operative process; however, this technique typically requires the combination of other cell engineering methods (viral, polymer, or electroporation techniques) with repeated transduction and is restricted by the sole type of engineered target^[23]. Combining different engineering techniques could flexibly produce multifunctional effector cells; however, such integration makes the procedure costly and complex, hampering clinical translation. Hence, there is an urgent need for a refined cell engineering platform that enables the simultaneous manipulation of multiple targets across different subcellular compartments in a single workflow, thereby advancing ACT against solid tumors.

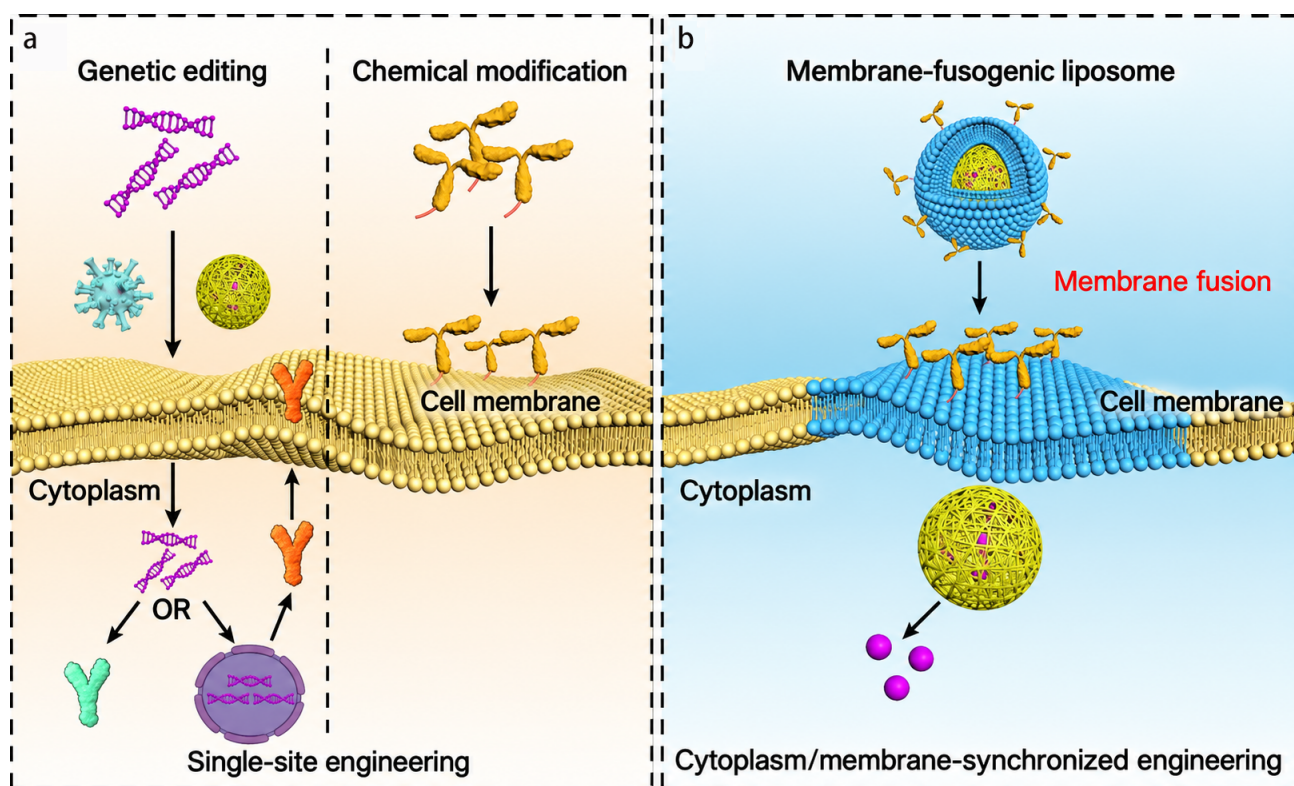


Figure 1. The schematic diagram comparing the traditional single-site engineering techniques (a) with membrane-fusogenic liposome (b) for cell engineering to boost ACT. Conventional genetic editing and chemical modification methods allow either intracellular target modulation or surface programming, respectively, endowing only a monofunctional module to adoptive cells in a single step. However, membrane-fusogenic liposomes can deliver payloads into the cytoplasm and anchor ligands onto cell membranes simultaneously via a one-step fusion process, thereby conferring cells with two or more functionalities in a single operation. ACT: adoptive cell therapy.

Recently, our team introduced an engineering approach based on membrane fusion that enables the simultaneous modulation of both intracellular and membrane-bound targets, allowing for the straightforward construction of multifunctional adoptive cells in a single step (Figure 1b)^[24–28]. This approach utilizes a core-shell nanoplateform known as the membrane-fusogenic liposome, which consists of a nanoscale core enclosed within a fusogenic lipid shell^[29]. Unlike any existing technique, this liposome modifies adoptive cells via a membrane fusion mechanism, with the lipid shell merging with the cell's plasma membrane while the core is concurrently released into the cytoplasm. Leveraging the high design flexibility and broad cargo-loading capability of this platform, we can readily encapsulate diverse therapeutic agents inside the core and attach a series of functional motifs onto the lipid shell^[26–29]. During the fusion event, these engineering components are simultaneously delivered to their respective destinations, surface-bound moieties to the cell membrane and cytosolic payloads to the interior, thereby endowing cells with two or more functionalities in a single operation. Furthermore, the core materials and lipid-conjugating methods can be tailored according to the physicochemical properties of a diverse array of engineered reagents, including small-molecule drugs^[30–32], genetic reagents (such as messenger RNA (mRNA), small interfering RNA (siRNA), and clustered regularly interspaced short palindromic repeats/associated proteins (CRISPR/Cas) systems)^[28,33,34], proteins, peptides, antibodies, and aptamers^[26,27,35], enabling multimodal functional integration. Importantly, the fusion is a biomimetic process mimicking natural membrane mixing events, making the liposomal engineering comparatively more cell-compatible than that of chemically driven approaches^[26–29]. This membrane-fusion strategy positions fusogenic liposomes as a rapid and multiplex platform for immune cell engineering, offering a promising route for *ex vivo* modification of immune cells to enhance therapeutic outcomes against solid tumors.

2. Engineering Immune Cells with Membrane-Fusogenic Liposomes for Adoptive Cell Therapy

Before cell engineering, the fusogenic liposome should be carefully designed. First, fusogenic lipid formulations need to be carefully selected. The most frequently used formulation typically combines a fusogenic phospholipid (e.g., 1,2-dimyristoyl-sn-glycero-3-phosphocholine (DMPC)), a cationic lipid (e.g., 1,2-dioleoyl-3-trimethylammonium-propane (DOTAP)), and a PEGylated lipid (e.g., 1,2-distearoyl-sn-glycero-3-phosphoethanolamine-N-methoxy(polyethylene glycol) (DSPE-PEG)) at defined molar ratios (e.g., 76.2/20/3.8) to balance fusion activity, colloidal stability, and cytocompatibility^[26]. Second, the cargoes of the core and shell should be allocated according to the corresponding subcellular locations of engineering targets. Small-molecule inhibitors, mRNA, and plasmids can be encapsulated within the core, whereas antibodies, peptides, or glycans are conjugated onto the lipid shell through covalent linkage^[26–29]. Moreover, *in vitro* engineering conditions are typically optimized, and fusion events should be verified by a series of related techniques, such as confocal laser scanning microscopy (CLSM), Förster resonance energy transfer assay, fusion probes, and cell-uptake inhibitors^[26]. For example, representative performance metrics from current studies include the completion of engineering within approximately 4 h, markedly shorter than the days-to-weeks timeline of viral transduction-based genetic engineering, accompanied by an approximately 2.7-fold enhancement of macrophage phagocytosis toward tumor cells after one-step fusion-based engineering^[26].

Using these membrane-fusogenic liposomes, we have engineered a range of immune cells and evaluated their antitumor activity in the context of enhanced ACT. Macrophages were the first cell type investigated in our studies involving membrane-fusogenic liposomes^[26]. In clinical practice, adoptive macrophage therapy faces two major obstacles: 1) tumor cells overexpress anti-phagocytic surface molecules that resist phagocytosis; and 2) cytokines present in the tumor microenvironment readily drive the repolarization of M1 macrophages toward a tumor-promoting M2 phenotype. To address these challenges, we developed an anti-phagocytosis-blocking repolarization-resistant membrane-fusogenic liposome (ARMFUL) (Figure 2a)^[26]. This system encapsulates the colony-stimulating factor 1 receptor (CSF1R) inhibitor BLZ945 within a poly(lactic-co-glycolic acid) (PLGA)-based polymeric core, while the fusogenic lipid shell is conjugated with an anti-CD47 antibody (aCD47). Upon membrane fusion, BLZ945 is released into the cytoplasm, and aCD47 is simultaneously inserted into the macrophage plasma membrane. The surface-anchored aCD47 enhances phagocytic capacity against tumor cells by blocking the anti-phagocytic signaling axis. Meanwhile, the cytosolic release of BLZ945 suppresses the CSF1R pathway, thereby preventing the repolarization of M1 macrophages into the M2 phenotype, even within the immunosuppressive tumor microenvironment. Macrophages engineered with this ARMFUL platform exhibited potent tumor inhibition and were able to activate adaptive T cell-mediated systemic immune responses, enabling control of both distant tumors and metastatic lesions.

Similarly, we applied membrane-fusogenic liposomes to engineer NK cells, equipping them with two complementary functions in a single engineering step to counter immune resistance mechanisms such as inhibitory ligands and immunosuppressive cytokines (Figure 2b)^[27]. Specifically, galunisertib (GST) was loaded in the liposomal core and subsequently delivered into the cytoplasm to inhibit transforming growth factor β (TGF- β) signaling through the fusion process, while phenylboronic acid (PBA) was anchored on the liposomal surface and presented on the cell membranes to mask sialic acids. As a result, these bifunctional NK cells were able to retain their activating receptors and cytotoxic activity even in a TGF- β -rich environment, while also displaying enhanced binding and killing toward sialic acid-expressing tumor cells. Across multiple human tumor models, adoptively transferred engineered NK cells demonstrated potent therapeutic efficacy and were further able to stimulate host T cell responses, leading to synergistic tumor elimination.

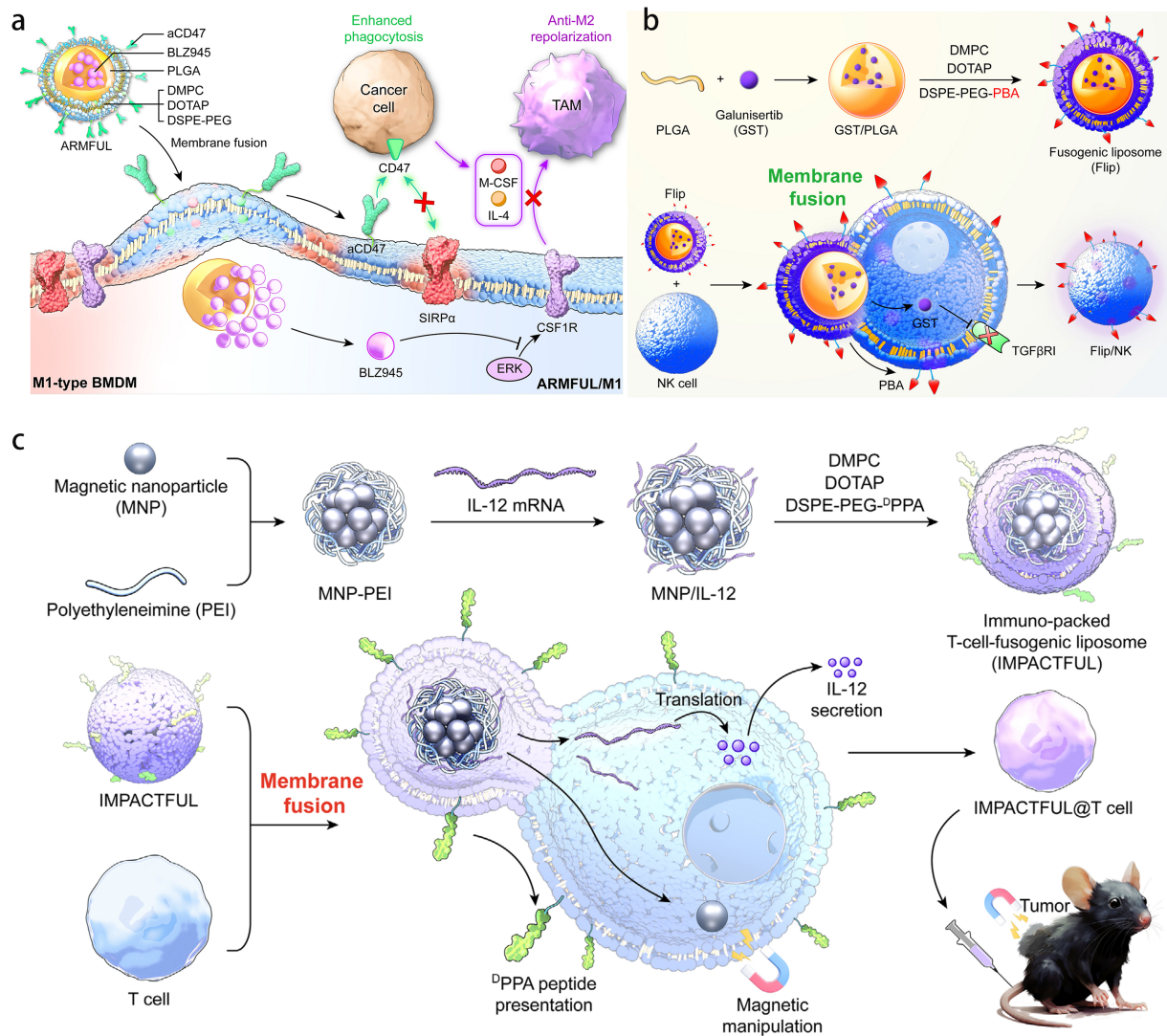


Figure 2. Examples of membrane-fusogenic liposome engineering immune cells for enhanced ACT against solid tumors. (a) Schematic illustration of anti-phagocytosis-blocking repolarization-resistant membrane-fusogenic liposome endowing M1-type BMDM with enhanced phagocytosis and resistance to M2 repolarization. Reproduced from reference^[26]. CC BY 4.0; (b) Schematic illustration of fusogenic-liposome-equipped NK cells with two complementary functions to address immune resistance mechanisms, including inhibitory ligands and immunosuppressive cytokines. Reproduced with permission from reference^[27]. Copyright © 2026 Elsevier; (c) Schematic illustration of immuno-packed T-cell-fusogenic liposome-engineered multifunctional T cells capable of infiltrating tumors, overcoming tumor immune tolerance, and modulating the immunosuppressive tumor microenvironment. Reproduced with permission from reference^[28]. Copyright © 2026 Wiley. ARMFUL: anti-phagocytosis-blocking repolarization-resistant membrane-fusogenic liposome; CSF1R: colony-stimulating factor 1 receptor; PLGA: poly(lactic-co-glycolic acid); aCD47: anti-CD47; DMPC: 1,2-dimyristoyl-sn-glycero-3-phosphocholine; DSPE-PEG: 1,2-distearoyl-sn-glycero-3-phosphoethanolamine-N-methoxy(polyethylene glycol); M-CSF: macrophage colony-stimulating factor; IL-4: interleukin-4; BMDM: bone marrow-derived macrophage; SIRPα: signal regulatory protein alpha; ERK: extracellular signal-regulated kinase; TAM: tumor-associated macrophage; PBA: phenylboronic acid; TGFβRI: transforming growth factor beta receptor inhibitor; NK: natural killer; IL-12: interleukin-12; mRNA: messenger RNA; GST: galunisertib; MNP-PEI: polyethyleneimine-coated magnetic nanoparticles.

Subsequently, T cells were remodeled with an immuno-packed T-cell-fusogenic liposome (IMPACTFUL) for three complementary functions capable of effectively infiltrating tumors, overcoming tumor immune tolerance, and reshaping the immunosuppressive TME (Figure 2c)^[28]. In this system, the ⁰PPA peptide is attached to the fusogenic lipid shell, while both polyethyleneimine-coated magnetic nanoparticles (MNP-PEI) and interleukin-12 (IL-12) mRNA (collectively referred to as MNP/IL-12) are encapsulated within the liposomal lumen. Upon membrane fusion, a single step accomplishes two tasks: ⁰PPA peptides are anchored onto the T-cell surface, and MNP/IL-12 is delivered into the cytoplasm. After reinfusion, the magnetic nanoparticles guide the engineered T cells toward tumors more efficiently under an external magnetic field. The engineered T cells secrete IL-12 in an autocrine manner, which in turn reverses the immunosuppressive tumor microenvironment. Meanwhile, the surface-anchored ⁰PPA counteracts tumor immune tolerance by blocking the PD-L1 checkpoint. Overall, IMPACTFUL offers a distinct advantage by rapidly conferring multiple functions onto T cells through membrane fusion, thereby addressing the key challenges associated with solid tumor therapy.

Beyond immune cells, this one-step fusion strategy has also been explored in other cell types for related applications, illustrating its versatility. For example, Yu's team engineered platelets by conjugating the proinflammatory cytokine interleukin-15 (IL-15) onto platelet membranes while encapsulating doxorubicin (DOX) within the cytoplasm; exploiting the innate ability of platelets to target metastatic lesions and postoperative bleeding sites, these dual-engineered platelets synergistically suppressed metastatic progression and postsurgical recurrence in murine melanoma models^[36]. Similarly, this strategy has been extended to engineer tumor cells to amplify the efficacy of ACT: a membrane-fusogenic liposome simultaneously delivered a sialyltransferase inhibitor [peracetylated 3-fluoro-N-acetylneuraminic acid (PFNAc)] into the cytoplasm and anchored NK-activating Lewis X (LeX) trisaccharide onto the tumor cell surface in a single fusion step, reprogramming the tumor surface from an immune-resistant to an immune-susceptible state and thereby potentiating adoptive NK cell therapy against solid tumors^[29].

Collectively, our established membrane-fusogenic liposomes have served as a potent platform for efficient cell engineering in macrophages, T cells, and NK cells for enhanced ACT against solid tumors (Table 1). Moreover, this engineering concept has also been extended to other cell types for different biomedical applications^[35,37-39]. Our ongoing investigations are extending this approach to other cell types, including dendritic cells (DCs), regulatory T cells (Tregs), neutrophils, and even highly promising stem cells.

Table 1. Summary of membrane-fusogenic liposomes for adoptive cell therapy against solid tumors and related applications.

Cell type	Lipid components	Drugs in the core	Therapeutics on the shell	Functionalities	Ref.
Macrophages	DMPC/DOTAP/DSPE-PEG	CSF1R inhibitor BLZ945	Anti-CD47	1) Enhancing phagocytic capacity of macrophages against tumor cells; 2) Blocking M1-to-M2 macrophage polarization.	[26]
NK cells	DMPC/DOTAP/DSPE-PEG	TGF- β receptor inhibitor GST	PBA	1) Reversing immunosuppressive microenvironment; 2) Shielding sialic acid.	[27]
T cells	DMPC/DOTAP/DSPE-PEG	IL-12 mRNA	^D PPA peptides	1) Enhancing tumor targeting; 2) Reversing immunosuppressive microenvironment; 3) Overcoming immune tolerance.	[28]
Platelets	DOPC/DPPC/DOTAP/DSPE-PEG	DOX	IL-15	1) Releasing chemotherapeutic drug to induce ICD; 2) Activating T cells and NK cells and increasing memory CD8 ⁺ T cells.	[36]
Tumor cells	DMPC/DOTAP/DSPE-PEG	Sialyltransferase inhibitor PFNAc	LeX	1) Downregulating NK-inhibitory sialic acid expression on tumor surfaces; 2) Presenting NK-activating LeX on tumor surfaces.	[29]

NK: natural killer; DMPC: 1,2-dimyristoyl-sn-glycero-3-phosphocholine; DOTAP: 1,2-dioleoyl-3-trimethylammonium-propane; DSPE-PEG: 1,2-distearoyl-sn-glycero-3-phosphoethanolamine-N-methoxy(polyethylene glycol); DOPC: 1,2-dioleoyl-sn-glycero-3-phosphocholine; DPPC: 1,2-dipalmitoyl-sn-glycero-3-phosphorylcholine; CSF1R: colony-stimulating factor 1 receptor; IL-12: interleukin-12; mRNA: messenger RNA; TGF- β : transforming growth factor β ; GST: galunisertib; PBA: phenylboronic acid; DOX: doxorubicin; IL-15: interleukin-15; ICD: immunogenic cell death; PFNAc: peracetylated 3-fluoro-N-acetylneuraminic acid; LeX: Lewis X.

3. Conclusions and Future Perspectives

In summary, membrane-fusogenic liposomes offer a fast, multiplex, and complementary approach for the *ex vivo* engineering of immune cells, enabling the simultaneous addition of surface functions and delivery of bioactive agents into the cytoplasm in a single fusion step. This one-step process allows for the straightforward generation of multifunctional effector cells. Proof-of-concept studies have shown that this strategy can substantially improve the performance of ACT against solid tumors. As a robust cell-engineering platform, fusogenic liposomes stand out for several key attributes: (i) they concurrently remodel both intra- and extracellular targets; (ii) they accommodate a wide range of therapeutic payloads with high flexibility; (iii) their biomimetic fusion mechanism is generally well tolerated by engineered cells, although compatibility is formulation dependent and requires empirical verification; and (iv) based on their physicochemical properties, they are broadly applicable to various immune cell types.

Nevertheless, several technical hurdles remain to be resolved. These include balancing fusion efficiency with cell selectivity, preserving the correct membrane orientation and bioactivity of functionalized molecules, minimizing potential adverse effects on cell viability and immune function, and establishing scalable, standardized manufacturing processes with rigorous quality control. Specifically, three issues deserve particular attention: (a) the potential immunogenicity and cumulative toxicity of repeated lipid fusion events on cell viability and function, especially for formulations containing cationic lipids; (b) the risk of off-target fusion with non-target cells during *ex vivo* processing, which necessitates defined cell-isolation, washing, and release-testing steps; and (c) batch-to-batch reproducibility and Good Manufacturing Practice (GMP)-compatible manufacturing feasibility, including control of lipid composition, endotoxin limits, and standardized release assays for fusion efficiency and residual free liposomes, which are critical for clinical translation but have so far been discussed only in passing. Looking ahead, future efforts should focus on developing controllable or stimulus-responsive fusion systems, such as those triggered by light, heat, enzymes, or pH, to enable spatiotemporally precise cell engineering^[34,40–42]. Examples include pH-responsive charge-reversal liposomes and stiffness-gated fusion for selective targeting^[41,42]. Integrating membrane fusion with other modalities, including gene editing, metabolic reprogramming, or nanomedicine loading, holds great promise for creating engineered immune cells that function simultaneously as living therapeutics and drug delivery vehicles. Expanding the toolbox of functional molecules, such as membrane-anchored immune checkpoint antibodies, decoy receptors, or synthetic signaling modules, as exemplified by synthetic Notch receptors, will further broaden the clinical applicability of this platform^[43]. On the translational front, both autologous cell modification followed by reinfusion and the engineering of allogeneic “off-the-shelf” immune cells warrant systematic investigation. Because all described work remains preclinical, progression toward first-in-human application will require the investigational new drug (IND)-enabling studies, such as safety pharmacology, biodistribution and toxicity assessment of the engineered cell products, potency assays, and comparability testing across manufacturing batches, and careful regulatory attention to quality control and safety profiles for such combination products. Meanwhile, recent advances in *in vivo* cell engineering, such as lipid nanoparticle-mediated generation of CAR-T cells directly *in vivo*^[44], offer a transformative alternative that bypasses *ex vivo* manufacturing altogether. Compared with such *in vivo* modulation strategies, *ex vivo* ACT with fusogenic liposomes affords tighter control over cell dose, phenotype, and quality before reinfusion, but remains limited by manufacturing complexity, cost, and turnaround time; the two routes are therefore likely to be complementary in future clinical practice. Collectively, membrane-fusogenic liposomes are well positioned to complement traditional engineering approaches and accelerate the development of next-generation adoptive immune cell therapies.

Declarations

Authors contribution

Zhong Q: Conceptualization, investigation, writing-original draft.

Huang Y, Li Z, Tao Y: Writing-review & editing.

Zheng C: Conceptualization, writing-review & editing.

Li M: Conceptualization, funding acquisition, supervision, writing-review & editing.

Conflicts of interest

The authors declare no conflicts of interest.

Ethical approval

Not applicable.

Consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data and materials

Not applicable.

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