International Journal of Nanomedicine

Dovepress
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REVIEW

Advances in Nanotechnology for Lymphoma Treatment: Targeted Delivery, Immunomodulation, and TME-Responsive Therapy Strategies

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Abstract: Lymphoma is a heterogeneous malignant proliferative disease of lymphocytes, with characteristics of liquid tumor and solid tumor. With the emergence of targeted drugs, monoclonal antibodies, bispecific antibodies, antibody-drug conjugates, and CAR-T therapy, the treatment landscape for lymphoma has been transformed. However, these therapies also possess limitations such as short plasma circulation time, low bioavailability, the development of drug resistance, and dose-dependent toxicity. With the advancement of nanotechnology, nanotech-based targeted delivery systems enable tumor-specific targeting and reduce off-target toxicity. Nano-immunotherapeutic systems, such as nanobody-based CAR-T therapy and mRNA-LNP nanovaccines, address limitations like drug resistance and relapse caused by antigen escape, inducing long-term anti-tumor immunity. Furthermore, smart designs responsive to the tumor microenvironment (TME) can significantly enhance drug accumulation and release efficiency at the lesion site. Innovative nanotech-based therapies are progressively transitioning from the laboratory to the clinic. By designing targeted nanocarriers, nano-immunotherapies, and TME-responsive intelligent nanotherapeutic platforms, targeted delivery of anti-lymphoma drugs can be achieved, enhancing efficacy and reducing toxicity. Simultaneously, these platforms can integrate multiple therapeutic modalities (such as chemodynamic therapy, immunomodulation, and gene silencing) to achieve synergistic and enhanced anti-lymphoma effects, offering new paradigms for lymphoma treatment.

Keywords: lymphoma, nanotherapies, nanomedicines

Introduction

Lymphoma is an extremely heterogeneous malignant disease associated with uncontrolled growth of malignant lymphocytes (T-cells, B-cells, and natural killer (NK) cells), arising in lymph nodes or other extranodal lymphoid organs and presenting in a liquid state or as a solid mass in lymphatic immune system organs (lymph nodes and lymphoid organs). Lymphoma can be broadly divided into two lymphomas, namely Hodgkin lymphoma (HL) and Non-Hodgkin lymphoma (NHL). NHL represents 90% of all lymphomas, and it is the dominant component of mature lymphocyte tumors, with 85% to 90% of NHL cases arising from B cells, and the remaining from T and NK cells. Conversely, HL represents a B-lymphocyte tumor that develops from the germinal center, in which the presence of the Hodgkin Reed Sternberg (HRS) cell defines it.[1]

Traditional treatment methods for lymphoma include chemotherapy, radiotherapy, targeted therapy, and immunotherapy. Various immunotherapeutic approaches, including peptide-based cancer vaccines, monoclonal antibodies, and immune checkpoint inhibitors, have transformed the traditional cancer treatment paradigm. Although certain efficacy has been achieved, drug resistance, relapse, and systemic toxicity remain major clinical challenges. After circulating in

https://doi.org/10.2147/IJN.S587953
Received: 10 December 2025
Accepted: 27 February 2026
Published: 7 March 2026

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the body, nanocarriers often face difficulties in being efficiently taken up by tumor cells, exhibit insufficient deep penetration capability, and are prone to off-target effects. In addition, challenges posed by tumor immune evasion, drug resistance mechanisms, and the immunosuppressive tumor microenvironment (TME)—such as the inability to deliver therapeutic agents or immune cells to tumor sites—significantly diminish their antitumor efficacy. In recent years, treatment regimens based on the combination of immuno-targeted therapy and chemotherapy have achieved remarkable breakthroughs in the field of B-cell lymphoma. However, due to the numerous subtypes of lymphoma and its high heterogeneity, challenges such as drug resistance and side effects persist, particularly in drug-resistant relapsed/refractory B-cell lymphoma and T-cell lymphoma. Among relapsed and refractory patients in particular, approximately 90% eventually develop drug resistance, leading to an extremely poor survival prognosis.[2,3]

Nanoparticles, owing to their nanoscale dimensions (1–100 nm), excellent biocompatibility, high drug-loading capacity, as well as modifiability and smart responsive characteristics, are often utilized to construct TME-responsive smart delivery systems and immunotherapeutic systems, providing innovative solutions to overcome the bottlenecks in lymphoma treatment.[4]

The core advantages of nanomedicine in the lymphoma field are primarily reflected in the following aspects: Through functionalized surface modifications (such as antibodies, peptide ligands), nanocarriers can achieve tumor-specific targeting and reduce off-target toxicity. By employing biomimetic nanotechnology strategies, the biocompatibility of nanomedicines is improved, targeting is enhanced, drug accumulation at tumor sites is promoted, and clearance by the immune system is evaded, thereby achieving more efficient tumor therapy. Nanobody-based CAR-T therapy addresses issues of antigen escape and tumor heterogeneity, thereby countering drug resistance and relapse caused by antigen escape and overcoming the limitations of traditional CAR-T. The mRNA-LNP nanovaccines can not only enhance antigen stability and immunogenicity but also improve the efficiency of antigen delivery, inducing long-term anti-tumor immunity. Smart designs based on tumor microenvironment (TME) responsiveness (such as pH sensitivity, enzyme triggering, ultrasound/light-controlled drug release) can significantly enhance drug accumulation and release efficiency at the lesion site. Nanoplatforms can also integrate multiple therapeutic modalities (such as chemodynamic therapy, immunomodulation, gene silencing) to achieve synergistic and enhanced anti-lymphoma effects (Figure 1).[5,6]

Based on the aforementioned therapeutic strategies, we systematically reviews the cutting-edge advances in nanotechnology for lymphoma treatment in recent years, focusing on targeted delivery systems, immunomodulatory strategies, combination therapy innovations, and clinical translation challenges, aiming to provide theoretical references and directional guidance for the development of next-generation nanomedicines for lymphoma.

Targeted Nanodelivery System for the Treatment of Lymphoma

Biomimetic Nanodelivery Systems

For tumor therapy, ideal nanomedicines should possess characteristics such as prolonged drug circulation in the blood and targeted delivery to tumor tissues to achieve better antitumor efficacy. Therefore, functionally modified targeted drug delivery systems have gradually gained favor among researchers, as they enable safe, efficient, and economically controllable drug delivery. However, most nanoparticles, as foreign substances, are recognized and cleared by the body's immune system. Through surface modifications, nanoparticles can extend their circulation time in the blood and achieve specific targeting, thereby enhancing efficacy while reducing adverse effects. In recent years, leveraging nanobiomimetic strategies, nanoparticles prepared by mimicking cells or other biological components in nature have shown potential advantages in cancer treatment, such as improved biocompatibility, enhanced targeting, promoted drug accumulation at disease sites, and evasion of immune clearance.[6,7]

For instance, by coating nanoparticles with cell membranes enable targeted recognition and therapy of homologous cells. This strategy leverages specific adhesion molecules present on the cell membrane surface, allowing nanoparticles to specifically recognize and bind to homologous cells. Biomimetic nanoparticles covered with cell membrane can be classified according to their membrane origins, red blood cells, white blood cells, platelets, tumor cells, etc. Among these, nanoparticle-based drug delivery systems coated with macrophage cell membranes demonstrate unique value in targeted lymphoma therapy. Studies have shown that macrophage membrane coatings containing intact membrane

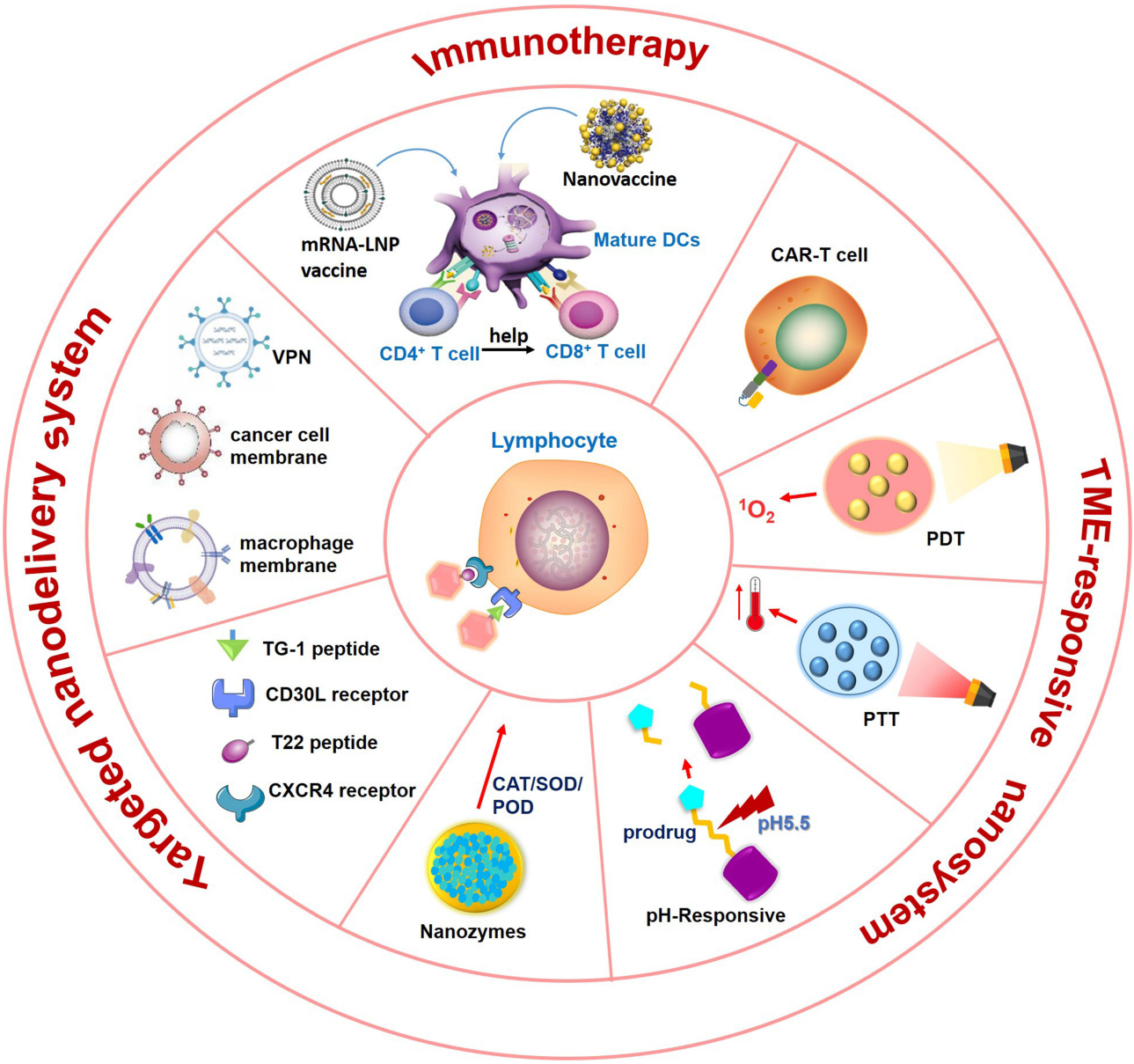

Figure 1 Novel therapies such as biomimetic nanodelivery systems, nanobody-based CAR-T, nanovaccines, mRNA-LNP vaccines, and tumor microenvironment (TME)-responsive nanodelivery systems have facilitated the efficient, low-dose targeted delivery of anti-lymphoma drugs, reducing toxicity while maintaining efficacy. These advancements also enable the combination and synergistic application of various anti-lymphoma nanotherapies, establishing a new therapeutic approach for lymphoma.

proteins preserve macrophage receptors and "self-markers" like CD47 for cell-cell interactions, thereby impeding immune cell recognition. This biomimetic strategy significantly enhances the accumulation of chemotherapeutic drugs in deep lymphoma tissues while remodeling the immunosuppressive microenvironment by polarizing macrophages toward a pro-inflammatory phenotype.[8] Wang et al coated obtained macrophage membranes onto liposomes loaded with vonoprazan, constructing a macrophage membrane-biomimetic nanodrug delivery system named MM-Lipid@Vpz for targeted delivery of vonoprazan against diffuse large B-cell lymphoma (DLBCL). Compared to Lipid@Vpz, the macrophage-modified MM-Lipid@Vpz significantly enhanced the delivery efficiency of vonoprazan to tumor tissues. By disrupting mitochondrial oxidative phosphorylation (OXPHOS) and altering mitochondrial morphology, while increasing intracellular reactive oxygen species (ROS) levels, MM-Lipid@Vpz markedly induced apoptosis in SU-DHL-8 cells. When combined with doxorubicin (Dox), MM-Lipid@Vpz demonstrated synergistic antitumor effects, further enhancing tumor suppression and potentially mitigating drug resistance. Similarly, in DLBCL model nude mice, MM-Lipid@Vpz

https://doi.org/10.2147/IJN.S587953

effectively targeted tumor tissues and inhibited tumor growth. When used in combination with Dox, the tumor suppression rate exceeded 70% compared to monotherapy, while also effectively reducing drug resistance and toxic side effects.[9]

Additionally, nanoparticles coated with tumor cell membranes, due to their homologous targeting ability, can enhance drug accumulation in tumor tissues and are currently being explored for applications in lymphoma treatment.[10] For example, Zhao et al designed a targeted nanodrug delivery system CCM@MSNs-ISOIM, which are formed by coating mesoporous silica nanoparticles (MSNs) with cell membranes from human DLBCL cells (OCI-LY10 tumor cells) (CCM) and load with traditional Chinese medicine ISOIM. Because the CCM vesicle was coated, this system was able to specifically bound to OCI-LY10 cells. The MSNs were pH sensitive so that CCM@MSNs-ISOIM could release ISOIM more effectively in the acidic TME. The in vitro studies have shown that CCM@MSNs-ISOIM can induce G2/M phase arrest, activate p53, and regulate the production of high-level ROS to finally induce the apoptosis of OCI-LY10 cells. In vivo studies further confirmed the active tumor-targeting capability and high drug delivery and release efficiency of CCM@MSNs-ISOIM. After intravenous administration, CCM@MSNs-ISOIM significantly inhibited tumor growth in OCI-LY10 tumor-bearing nude mice, showing superior anti-lymphoma effects compared to free ISOIM and MSNs@ISOIM.[11] Therefore, tumor cell membrane-modified nanocomposites, with their high targeting specificity and immune evasion advantages, offer a novel therapeutic option for lymphoma treatment. Although tumor cell membrane-coated nanoparticles have demonstrated advantages in targeted drug delivery, extreme caution must be exercised during their preparation process to ensure all intracellular components are thoroughly removed to eliminate any carcinogenic potential.

Virus-like particles (VLPs) are hollow protein particles self-assembled from single or multiple viral structural proteins. They retain the natural conformation of viral antigens but contain no genetic material, rendering them non-infectious and non-pathogenic. Additionally, VLPs can also be protein nanoparticles with symmetrical structures formed through non-viral or synthetic methods, which are conjugated with tumor-specific antigens via genetic fusion or chemical/conjugate linkages. VLPs hold significant research value and application potential in vaccine development, targeted drug delivery, and bioengineering materials, and have emerged as versatile platforms for targeted drug delivery and tumor immunotherapy.[12] For example, Shukla et al developed a novel drug delivery platform based on the plant virus Potato Virus X (PVX) for loading the chemotherapeutic drug monomethyl auristatin (MMAE) to treat NHL. Potato Virus X (PVX) is a filamentous plant virus measuring 513 nm × 13 nm. After systemic injection in tumor-bearing mice, PVX demonstrated enhanced homing and penetration capabilities in solid tumors.[13,14] In load MMAE, PVX well delivered the drug to tumor tissues in Raji B cell tumor-bearing mice, inhibiting in vivo lymphoma growth and benefiting survival. PVX nanoparticles could be a hopeful drug delivery platform for B-cell malignancies.[15]

Inspired by the viral fusion mechanism mediated by spike protein-host receptor interaction, to overcome the restrictions of the traditional VLPs based on the thermal/pH-sensitivity and function ability of the protein shell and combine the advantages of therapeutic mRNAs and siRNA therapeutics, Dou et al have innovatively developed a biomimetic VLPs platform that consists of a lipid scaffold, siRNA encapsulation and a surface-anchored DbLYTAC-DNA aptamer-based design. Thus, by combining both siRNA-based gene silencing and DbLYTAC-based targeted drug degradation of the protein target this module functions in a synergic manner that enables not only the stabilization (due to the presence of more connected nanoparticles, meaning that even if one segment of the modular scaffold gets depolymerized, the nanoparticles would not disassemble) but also improved efficiency of carrying drugs to the desired target tissue with subsequently higher antitumor effects compared to the single pathways. It significantly inhibited tumor growth in mouse models with VLP mainly accumulated in the tumor region following intratumoral injection, without any obvious toxicity to and no harmful damage to main organs, revealing a favorable biosafety. This study achieves a multi-level precision strike against tumor cells through the synergistic “gene silencing + protein degradation” dual-modal strategy, while overcoming the limitations of protein-based viral mimics. It provides a novel option for the application of multifunctional biomimetic nanodrug delivery systems in cancer therapy (Figure 2).[16]

Therefore, the advantage of biomimetic nanodelivery systems over some exogenous nanoparticles lies in their ability to evade phagocytosis by the reticuloendothelial system while possessing homologous targeting capabilities. Moreover,

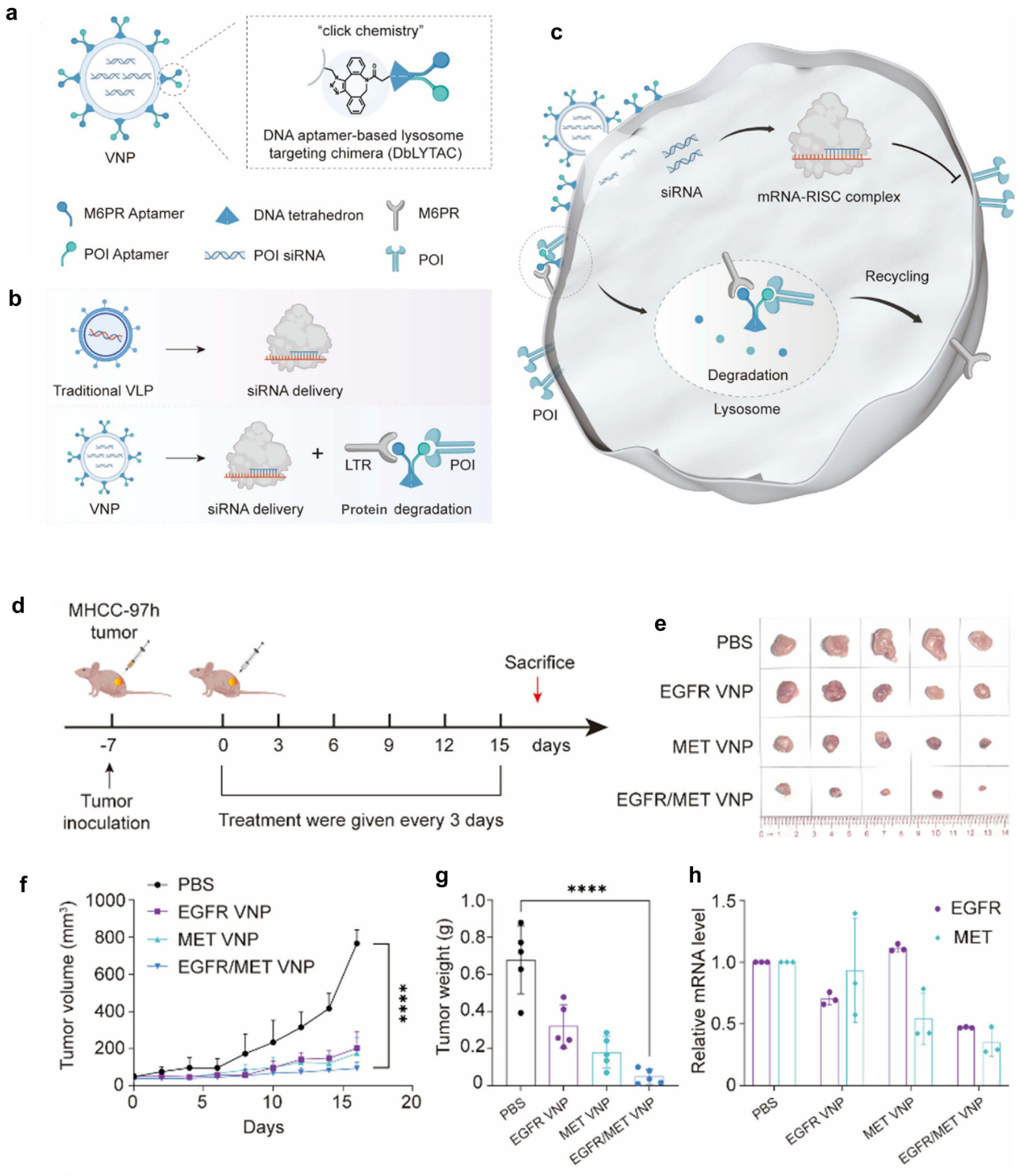

Figure 2 (**a**–**c**) Virus-like nanoparticle (VNP) design and schematic diagram of the protein degradation mechanism. (**a**) Schematic representation of the structural composition and covalent linkage of VNP. (**b**) Comparison of the capabilities of traditional VLP and VNP. (**c**) VNP undergoes membrane fusion to release siRNA, and DbLYTAC is loaded onto the cell membrane for lysosomal targeted degradation. (**d**–**h**) Antitumor effects of EGFR/MET VNP in vivo. (**d**) Schematic of the procedure for in vivo experimental studies. Including PBS (150 μL), EGFR VNP (equivalent to 0.2 mg/150 μL, MET VNP (equivalent to 0.2 mg/150 μL), EGFR/MET VNP (equivalent to 0.2 mg/150 μL). (**e**) Representative images depicting the size effects of xenograft tumors in each group after 16 days of treatment. (**f**) Changes in tumor volume were recorded every other day during the 16-day period of intratumoral injection therapy. The data represent the mean ± SD (n = 5). (**g**) Tumor weight of each group on Day 16 after the mice were sacrificed. The data represent the mean ± SD (n = 5). (**h**) The mRNA expression of MET and EGFR in tumor tissues after treatment in different groups. The data represent the mean ± SD (n = 3). Adapted with permission from,[16] copyright 2025, Wiley-Blackwell. ****p <0.0001.

https://doi.org/10.2147/IJN.S587953

biomimetic nanodelivery systems exhibit excellent biocompatibility and safety in vivo, with key features such as immune evasion and prolonged circulation, enabling more efficient tumor therapy.

Active Targeting Modifications for the Treatment of Lymphoma

To further enhance the efficacy of nanomedicines, enable drug-loaded nanoparticles to more efficiently target tumor tissues, and reduce toxic side effects on normal tissues and organs, researchers have attempted to attach specific targeting peptides to the surface of nanocarriers. By leveraging the interaction between ligands on the surface of nanomedicines and receptors on tumor cells, this approach increases the distribution of nanomedicines in tumor tissues and their uptake by tumor cells.

Researchers have discovered that nanoparticles modified with CD30L-specific targeting peptides can lead to a reduction in lymphoma cell viability by blocking the CD30/CD30L pathway. CD30 belongs to the tumor necrosis factor receptor superfamily and is upregulated in a variety of lymphoma cells. Highly expressed CD30 can influence the progression of lymphoma through multiple mechanisms, such as activating the NF-κB and MAPK/ERK signaling pathways, as well as affecting the TME, thereby promoting tumor cell proliferation and anti-apoptotic capacity. CD30L, a member of the tumor necrosis factor superfamily, is primarily expressed on activated T cells and other immune cells. Its binding to its receptor CD30 forms a signaling pathway that regulates the differentiation and proliferation of different T-cell subsets.[17,18] CD30-CD30L interaction acts via non-canonical NF-κB signaling which thereby increase the proliferation of lymphoma B-cell non-Hodgkin lymphoma (B-NHL) cell.[3] Shi et al screened the CD30L-specific binding peptide TG-1 (MHPNAGHGSLMR) using whole-cell phage display technology. This peptide forms 11 key interactions (including one salt bridge and three hydrogen bonds) with the Gln63–Asp234 region of CD30L. To enhance the peptide's stability and efficacy, they also constructed TG-1-functionalized gold nanoparticles (F-TG-1-AuNPs) and co-loaded them with doxorubicin (F-peptide-AuNPs + Dox). In both in vitro and in vivo experiments, F-peptide-AuNPs + Dox showed significant specificity against B-NHL and potent inhibition of lymphoma cell proliferation. This study highlights the potential of CD30L as a novel therapeutic target for B-NHL and demonstrates the promise of the CD30L-targeting peptide TG-1 in treating B-NHL.[3]

Furthermore, studies have found that CXCR4 is a crucial molecule in the development, progression, and development of drug resistance in lymphoma.[19,20] It is constitutively overexpressed in NHL cell lines and in approximately 50% of malignant B lymphocytes from patients with DLBCL.[21] Clinical data indicate that high CXCR4 expression is significantly associated with resistance to chemotherapy and rituximab (RTX), disease relapse, and poor prognosis. Targeting this critical molecule, researchers engineered a synthetic derivative, the T22 peptide ([Tyr5,12, Lys7]-polyphemusin II), from an alkaline peptide isolated from horseshoe crab hemocytes. Tyr5, Lys7, and Tyr12 mutations greatly increased its specificity for CXCR4.[22] Building on the selective binding properties of T22 toward CXCR4, Falgà et al have constructed a ligand protein-based nanocarrier T22-GFP-H6 for selective delivery of anti-CXCR4 molecular payloads to CXCR4+ lymphoma cells. In DLBCL models, T22-GFP-H6 was also specifically accumulated in organs and tissues infiltrated by lymphoma, including places such as bone marrow and lymph nodes where the EPR effect could be weak, with highly selective tumor uptake. And they then loaded this carrier with diphtheria toxin, building up the nanomedicine T22-DITOX-H6, which selectively eliminated lymphoma cells with negligible toxicity to hematopoietic stem cells and other normal tissues.[23] Further studies confirmed that T22-DITOX-H6 exhibits highly specific cytotoxicity against CXCR4+ DLBCL cells in the low nanomolar range. This effect is mediated through caspase-3 cleavage, PARP activation, and an increase in early/late apoptotic cells, thereby inducing significant anti-lymphoma activity.[24] Therefore, employing a nanodrug delivery system modified with the highly specific targeting peptide to treat refractory or recurrent lymphoma is an excellent strategy.

Nanotechnology-Enhanced Lymphoma Immunotherapy

Nanobody-Based CAR-T Cell Immunotherapy

Chimeric Antigen Receptor T-cell (CAR-T) therapy is an emerging cellular immunotherapy that involves genetically engineering T cells to express chimeric antigen receptors (CARs) on their surface. Depending on the differences in

intracellular domain structures, CARs have evolved from the first to the fifth generation. As an artificially designed transmembrane protein, the structure of CAR molecules has progressed to the fifth generation, which includes scFv, transmembrane domain, costimulatory molecules, CD3ζ, and cytokine receptor domains. This design endows cells with the ability to recognize and kill target cells independently of MHC. CAR-T therapy has shown remarkable efficacy in the treatment of hematological malignancies, particularly B-cell lymphomas, and is considered one of the most promising therapeutic modalities.[25,26] However, conventional CAR-T therapy still faces numerous challenges, including antigen escape-mediated relapse, treatment-related toxicities, severe adverse effects such as cytokine release syndrome, and lengthy manufacturing cycles. These limitations drive ongoing exploration of novel technological platforms to optimize CAR-T therapy. Identifying new antibodies and developing CAR-T cells based on them remains an urgent problem to be addressed.

Recent years have witnessed that nanobodies (Nbs) are essential elements in the design of CAR-T cells. Nbs are an antibody fragment generated from the heavy chain-only antibody variable domain (VHH) in camelids.[27] They were composed of four structural domains and three complementarity-determining domains (CDRs), CDR3 were longer than in ordinary antibodies, and this loop structure could make a protruding structure, thereby increasing the chance of antigens binding. The Nbs gene sequence shows high homology with the human VH gene family sequence, resulting in low immunogenicity of Nbs in humans. Additionally, the modular structure of Nbs facilitates the generation of bispecific or multispecific CARs, which can directly address the issues of antigen escape and tumor heterogeneity by simultaneously targeting multiple antigens. This novel structure has not only maintained the advantages of classical antibodies and eliminated shortcomings including time consuming development, poor stability and demanding storage environment, but also provides a new perspective for solving the limitations of classical CAR-T therapy. Currently, CAR-T therapy research primarily focuses on tumor-associated antigens as targets. These tumor-associated antigens are highly expressed in tumor cells but show low expression in normal cells. For example, CD7, CD19, and CD20 are among the widely used targets in lymphoma research[28] (Table 1).

CD7 is a glycoprotein expressed on the surface of natural killer cells and T lymphocytes. It is frequently overexpressed in T-cell acute lymphoblastic leukemia and T-cell lymphoma, making it a potential immunotherapeutic target for T-cell malignancies. However, since CD7 is also expressed on CAR-T cells themselves, it leads to "fratricide"—where CAR-T cells attack each other—significantly reducing their persistence in vivo and antitumor activity. In a Phase I clinical trial (NCT04004637), researchers developed autologous CD7 VHH6-CAR T cells and infused them into patients with relapsed/refractory $CD7^+$ T-ALL/LBL. At the 3-month post-infusion assessment, the complete remission

Table 1 Preclinical Studies and Ongoing Clinical Trials of Nanobody-Based CAR T-Cell Therapies

Nanobody-Based CAR T	Antigen Target	Disease Type	Phase/Status	Trial ID	Outcome	References
CD7 VHH6-CAR T	CD7	T-ALL/LBL	Phase I	NCT04004637	High CR (~87.5%); mild CRS	[29]
dVHH NS7CAR-T	CD7	$CD7^+$ AML/T-ALL	Phase I	NCT04938115	High CR (~80%); mild CRS	[30]
HuH85 CAR-T	CD19	B-ALL	Cell model	——	Effectively inhibit the growth of tumor cells	[31]
CD20 VHH CAR-T	CD20	B-NHL	Cell model	——	Effectively inhibit the growth of tumor cells	[32,33]
CD19/CD20 Nb CAR-T	CD19/ CD20	PD-ALL	Cell model	——	Effectively inhibit the growth of tumor cells	[34]
CD20/CD3 BsNb CAR-T	CD20/ CD3	B-NHL	Cell model	——	Effectively inhibit the growth of tumor cells	[35]
]NbD4.13-H24 CAR	CD72	B-ALL/ B-NHL	Animal model	——	Remarkable anti-tumor effects (~80%) and persistent CD72 inhibitory action	[36,37]

https://doi.org/10.2147/IJN.S587953

(CR) was 87.5%; one leukemia patient achieved CR with minimal residual disease (MRD) negativity, and one lymphoma patient achieved CR lasting more than 12 months. The majority of patients (87.5%) experienced only grade 1–2 cytokine release syndrome (CRS), and no T-cell aplasia or any neurotoxicity was observed (Table 1).[29] In another Phase I clinical trial, researchers developed dVHH NS7CAR-T to treat patients with $CD7^+$ refractory/relapsed AML (NCT04938115). The results showed that at the 28-day post-infusion assessment, 70% of patients achieved CR, with 6 patients achieving MRD-negative CR, demonstrating the favorable efficacy of dVHH NS7CAR-T therapy. The majority of patients (80%) experienced only CRS, with no significant neurotoxicity (Table 1).[30] These findings offer new hope for survival to patients with T-cell lymphoma who have exhausted conventional treatment options.

CD19, as a hallmark target of B-cell tumors, has become a prominent focus in the treatment of hematological malignancies in recent years. It is widely expressed on the surface of various B-cell malignant tumor cells, with low levels also present on normal B cells and follicular dendritic cells, while it is absent in other tissues and blood cells. Moreover, studies have shown that B-cell depletion resulting from CAR-T therapy does not increase the risk of infection in patients, primarily because CD19 is not expressed on multipotent hematopoietic stem cells.[38,39] CD19 CAR-T cells, constructed using the variable region gene sequences of CD19-recognizing antibodies, can specifically eliminate B cells expressing CD19 antigens, thereby facilitating the clearance of tumor cells bearing CD19 antigens. For instance, Kozani et al screened a CD19-specific VHH, humanized it (named H85), and used CD8α as the spacer domain, along with 4–1BB and CD3ζ fragments as intracellular signaling domains, to construct a CD19-redirected CAR cassette. Primary T cells were transduced with a third-generation lentivirus to generate H85CAR-T cells and HuH85CAR-T cells. When HuH85 CAR-T cells were co-cultured with Ramos, Namalwa, and K562 cells, they effectively inhibited tumor cell growth (Table 1).[31] Therefore, CD19 is considered an ideal target for CAR-T therapy in B-cell tumors. CD19-targeting chimeric antigen receptor T cells have achieved success in treating B-ALL. CAR-T therapy based on the HuH85 Nbs holds promise for developing immunotherapies against CD19-related hematological malignancies. More importantly, the Nbs, which have been humanized by modifying the antigen-recognition domain of animal origin, represent a more rational immunotherapeutic strategy for addressing the risk of immunogenicity.

CD20 is also a transmembrane marker expressed during B-cell differentiation and is frequently overexpressed in B-cell malignancies.[40] Researchers immunized alpacas against CD20 using a DNA vaccine and generated CD20-specific nanobodies. CAR-T cells constructed based on CD20 VHH were applied in mouse xenograft models, demonstrating complete elimination of subcutaneous tumors and significantly prolonged survival in these models.[32,33] Therefore, CD20 VHH-based CAR-T cells are being extensively studied for the treatment of various types of B-cell-related malignancies, particularly in patients who do not respond to CD19-redirected CAR-T therapy.[41]

In response to drug resistance and relapse caused by antigen escape, researchers are developing combination therapy strategies that can simultaneously or sequentially target two or more antigens. For example, Wang et al integrated screened anti-human CD19 and CD20-specific Nbs sequences into lentiviral vectors containing other CAR components, successfully constructing bispecific CD19/CD20 Nb CAR-T cells through an optimized amplification system for T-cell transfection. These Nb CAR-T cells demonstrated strong recognition capabilities against Burkitt lymphoma cell lines Raji and Daudi, exhibited significant activation and expansion in vitro, induced lymphoma cell apoptosis within 24 hours, and achieved tumor cell clearance within 5 days. Moreover, when primary tumor cells from patients with acute lymphoblastic leukemia (PD-ALL) were used as targets, these Nb CAR-T cells specifically recognized and killed PD-ALL-derived tumor cells in vitro, with a cytotoxicity rate of approximately 60% (Figure 3, Table 1).[34] These bispecific CAR-T cells demonstrated effective killing of tumor cells expressing both antigens, show promising anti-tumor efficacy. Liu et al obtained anti-CD20 specific single-domain antibodies through enrichment and screening of a phage-display antibody library. Using genetic engineering methods, they further fused the anti-CD20 VHH gene with a validated anti-human CD3 VHH to construct a bispecific anti-CD20/CD3 BsNb (bispecific Nbs). Results demonstrated that this anti-CD20/CD3 BsNb could specifically bind to both the CD20 molecules on the surface of human lymphoma Raji cells and the CD3 molecules on T cells, significantly enhancing the killing of Raji cells. This indicates that the constructed anti-CD20/CD3 BsNb possesses strong anti-tumor effects, laying a foundation for further development of anti-tumor drugs and the clinical application of anti-CD20/CD3 BsNb (Table 1).[35]

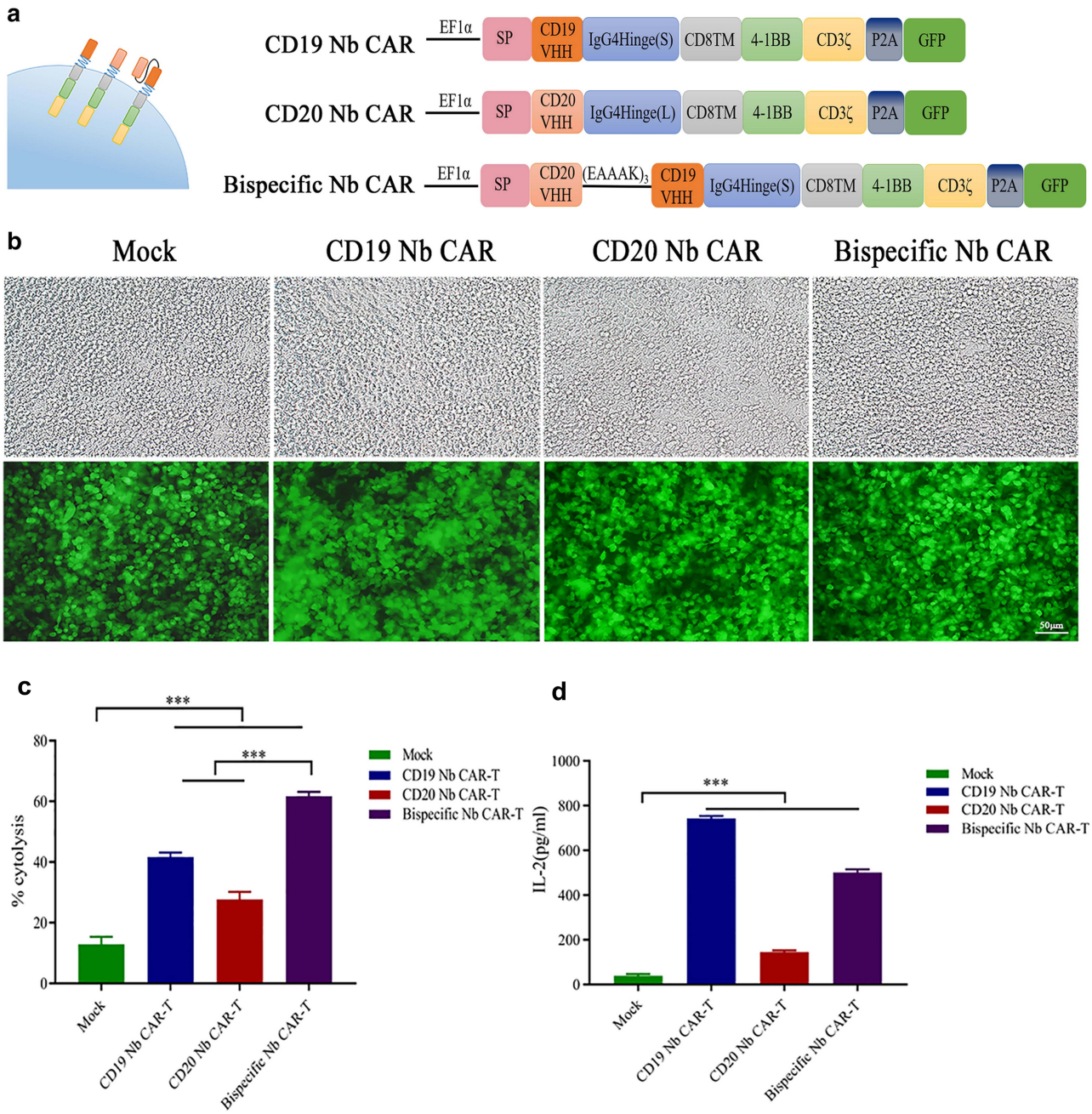

Figure 3 Nb CAR construction. (**a**) Schematic diagram of Nb CARs, including the CD8 signal peptide (SP), Nb, IgG4 hinge, CD8TM, 4–1BB, and CD3ζ domain. (**b**) Nb CARs expression on 293T cells. The 293T cells were transduced with control or different Nb CARs. (**c**) Nb CAR-T cell cytotoxicity to primary ALL tumor cells. Nb CAR-T cells were incubated with primary tumor cells, and LDH-based cytotoxicity assays were performed. (**d**) Cytokine production of Nb CAR-T cells to primary tumor cells. Nb CAR-T cells and primary tumor cells were coincubated overnight, and then, the expression of IL-2 was determined by ELISAs. Data were analyzed by one-way ANOVA. ***$p < 0.001$, ns, not significant ($p > 0.05$). Adapted with permission from,[34] copyright 2021, BioMed Central.

More recently, CD72 has emerged as a CAR-T cell therapy target that may have additional benefits to treat B-cell acute lymphoblastic leukemia (B-ALL). The expression of CD72 by B cells, and its oncogenic role in KMT2A/MLL1-rearranged B-ALL sub- type a leukemia, are tightly linked. Research has shown that B-ALL patients with KMT2A/MLL1 rearrangement (MLLr) exhibit the poorest prognosis, whether treated with standard chemotherapy or after CAR-T therapy.[42] However, CD72 expression is significantly higher than that of CD19 in MLLr B-ALL patients and is less prone to therapy-induced antigen loss, offering a novel target for nanobody-based CAR-T therapy.[43] Matthew A. Nix et al demonstrated by constructing CD72 (NbD4) CAR-T cells based on Nbs, which were capable of killing a highly tumor

https://doi.org/10.2147/IJN.S587953

killing capacity with decreased cytotoxicity and neurotoxicity than CD19-targeted therapy in vitro. Additionally, primary tumor model mice treated with CD72 (NbD4) CAR-T cells exhibited a robust response and undetectable leukemia burden, demonstrating efficacy comparable to CD19 CAR-T cells and a significantly increased survival rate compared to empty CAR-treated controls. Notably, CD72 (NbD4) CAR-T cells potently controlled the growth of CRISPRi CD19-knockout SEM tumor cells in vivo. More importantly, CD72 (NbD4) CAR-T therapy showed no or limited toxicity to normal tissues. This study provides a new therapeutic strategy for patients with MLLr B-ALL.[44]

Izgutdina et al utilized genetic engineering techniques to optimize the anti-CD72 nanobody (H24) and generated CAR-T cells via lentiviral transduction. This resulted in the development of affinity-matured CD72 nanobody-based NbD4.13 CAR-T cells and humanized affinity-matured NbD4.13-H24 CAR-T cells. The optimized CAR-T cells demonstrated significantly enhanced targeting of CD72 antigens on relapsed/refractory B-NHL cells. In an in vivo experiment with JeKo1-low, NbD4.13 CAR-T showed improved early tumor control than H24, but no survival benefit, while NbD4.13-H24 CAR-T showed a modest survival benefit ($p=0.0442$ by Log rank test). This approach utilizes high-affinity binders to enhance targeting of tumors with low CD72 expression, addressing the limitations of conventional CAR-T therapies. For non-Hodgkin lymphoma models with low CD72 expression, CAR-T cell therapy achieved tumor clearance rates exceeding 80%. Therefore, CD72 Nbs-based CAR-T therapy represents a promising alternative target for B-NHL patients who have relapsed after CD19 CAR-T therapy (Table 1).[36,42,43,45] Currently, research on CD72 Nbs-based CAR-T therapy is still in its early stages, but its specific expression pattern and low risk of antigen escape confer unique advantages in the treatment of hematological malignancies.[37] Currently, CD72 Nbs-based CAR-T therapy has also been extended to the treatment of B-NHL, particularly for patients who are unresponsive to or have relapsed after conventional therapies targeting CD19, CD22, etc.

Therefore, chimeric antigen receptor T cells derived from Nbs represent a significant advancement over traditional single-chain antibody fragment-based constructs. However, for therapeutic applications, the rapid clearance rate of Nbs from systemic circulation poses a notable limitation, necessitating strategies to prolong their duration of action. One approach to mitigate this issue involves converting these single-domain antibodies into bivalent and trivalent forms.[46,47] Furthermore, researchers have explored combining specific VHHs with other VHHs targeting various antigens and epitopes to enhance the circulation half-life of these constructs. This advancement is expected to promote the development of more effective therapeutic applications. Additionally, low immunogenicity remains a notable limitation that requires attention in CAR-T cell therapy. While humanizing VHH domains by grafting complementary-determining regions into human antibody frameworks generally reduces the risk of immunogenicity, it does not always completely eliminate this issue. Clinical observations have shown that certain fully humanized or native camelid VHHs may still induce the production of anti-drug antibodies in specific patients. This suggests that, in addition to sequence origin, factors such as low-level aggregation propensity or exposed C-terminal motifs can also influence immunogenicity.[28,48] More importantly, to make these therapeutics accessible to a broader population, they need to be more scalable and widely available on a global scale. In the future, combining nanobody-based CARs with allogeneic platforms, checkpoint inhibition, cytokine engineering, and AI-driven design holds the potential to significantly enhance their clinical efficacy.

Application of Nanovaccines in Lymphoma Immunotherapy

In addition to active and passive immunotherapy, active nanovaccines are thought to have potential for cancer prevention and treatment. Nanovaccine is defined as a cancer vaccine using nano-sized carriers to carry antigen(s) and adjuvant(s) for therapy/prevention of tumor. Particles below 1000 nm in size are considered nanoparticles. At this small scale, nanoparticles are advantageous because they would be able to concentrate in lymphoid organ such as lymph node and spleen. Furthermore, the nanoparticles are with the same size of pathogen; nanoparticles-based vaccine would be easily internalized by APCs. They can also selectively attack stimulatory and inhibitory factors of the “cancer-immunity cycle”, bring antigens and immune activators to target immune cells upon demand. In this mechanism, nanovaccines can directly stimulate and activate TAA-specific T cells, or help cross-present and capture TAAs by APCs to activate T cells, and these tumor-specific T cells induce an adaptive immune response; After stimulation, antigen-specific T cells can also kill tumor cell.[49] These vaccines must also overcome the immunosuppressive effects of the TME, ensure effective delivery to the tumor site, and avoid toxicity.

First, nanoparticles serve as carriers for tumor vaccines, providing a biomedical platform to enhance adaptive T-cell responses in tumor immunotherapy. Antigens can be conjugated to the surface of nanocarriers to increase their uptake by targeting specific immune cells, or encapsulated within nanocarriers to protect them from enzymatic degradation. Utilizing nanocarriers for vaccine delivery not only improves antigen stability and immunogenicity but also enhances antigen delivery efficiency and enables the induction of long-term anti-tumor immunity using the antigen itself as a carrier. For example, Dong et al developed a nanovaccine for co-delivery of antigens and adjuvants, which can be applied in tumor immunotherapy. This nanovaccine was constructed by electrostatically self-assembling the adjuvant (CpG) onto ovalbumin nanoparticles (ONPs). The ONPs not only served as antigens to induce innate and adaptive immunity but also acted as delivery carriers for CpG to enhance cellular uptake. The ONPs-CpG co-delivery system promoted dendritic cells (DCs) maturation, enhanced $CD8^+$ T cell activation and IFN-γ production, significantly improved immunogenicity, and strengthened anti-tumor activity. In a mouse lymphoma model, ONPs-CpG induced robust tumor-specific immunity and demonstrated significant anti-tumor immunotherapeutic effects.[50]

Furthermore, in addition to their ability to deliver antigens, nanoparticles also exhibit intrinsic adjuvant properties. In order to trigger effective cellular immune responses, vaccine adjuvants should stimulate augmentation of antigen cross-presentation by APCs, and especially DCs. Nanomaterial-based adjuvants have been proven to act as vaccine adjuvants when co-encapsulated with tumor antigens in the same nano-system, allowing efficient transport of antigens to the target organs, facilitating lysosomal escape of antigens and causing strong cellular immunity. Therefore, nanomaterial-based vaccine adjuvants exhibit novel advantages and broad application prospect in the betterment of the efficiency, persistence, and safety of the cancer vaccines. For example, Jia et al.We introduced arginine (R) and a fluorinated diphenylalanine peptide (DP) into supramolecular self- assembling peptides (SSAPs) to prepare the peptide adjuvant 4RDP (F5). This was then combined with the model antigen OVA to construct the 4RDP (F5)-OVA nanovaccine. 4RDP (F5) effectively elicits OVA antigen-specific $CD8^+$ T cell-mediated cellular immune responses, endowing the nanovaccine with strong antigen-binding affinity, efficient antigen delivery, and remarkable lysosomal escape capability. Consequently, the 4RDP (F5)-OVA nanovaccine induces robust cellular immunity in a prophylactic EG7-OVA lymphoma model expressing OVA, leading to long-term immune memory that protects against tumor challenge. Furthermore, in a therapeutic EG7-OVA lymphoma model, the combination of the 4RDP (F5)-OVA nanovaccine with anti-programmed cell death ligand-1 (anti-PD-L1) checkpoint blockade effectively triggers anti-tumor immune responses and suppresses tumor growth.[51]

Application of mRNA-LNP Vaccines in Lymphoma Immunotherapy

In the field of cancer treatment, mRNA vaccines stand out among various types of vaccines. Compared to traditional approaches, mRNA vaccines offer advantages such as high flexibility, good safety, and strong scalability, making them a transformative method in cancer immunotherapy. The fundamental principle of mRNA vaccines involves delivering mRNA that encodes specific antigens, tumor-associated antigens, or immunomodulatory factors into the body via specific delivery systems. Once inside, the mRNA expresses proteins, thereby stimulating a specific immune response. Unlike traditional vaccines (eg, peptide-based vaccines), mRNA vaccines can encode full-length tumor antigens, allowing APCs to carry out simultaneous or cross-presentation, potentially eliciting a broader T-cell response. More importantly, mRNA does not integrate into the host genome, significantly reducing the risk of genetic mutations. Additionally, mRNA production is relatively straightforward and can be scaled up for mass production.[52–54] However, challenges remain, including the poor stability of mRNA, susceptibility to degradation, and inefficient in vivo delivery. With advances in nanotechnology, particularly the emergence of nanocarriers such as lipid nanoparticles (LNPs), many of these challenges have been greatly alleviated. LNPs encapsulate mRNA within a structure composed of a phospholipid bilayer and cholesterol, effectively protecting it from degradation. Moreover, LNPs offer advantages such as low immunogenicity, tunability, and scalability in manufacturing. As exemplified by Zhang et al, a cationic LNPs constructed from the biodegradable polymer polycaprolactone-polyethylene glycol-polycaprolactone copolymer (PCL-PEG-PCL) and the cationic lipid 1,2-dioleoyl-3-trimethylammoniumpropane (DOTAP) was designed to co-deliver antigens and dual adjuvants specifically targeting DCs. Following prophylactic subcutaneous vaccination in mice, the levels of specific antibodies, memory T cells, and IFN-γ were significantly elevated, effectively preventing the development of T-cell

lymphoma and prolonging mouse survival. Moreover, the vaccine was able to directly treat mice with established T-cell lymphoma by inducing tumor infiltration of cytotoxic T lymphocytes (CTLs) and inhibiting the activity of regulatory T cells (Tregs) in the immune microenvironment. This overcame the immunosuppressive state of the tumor, ultimately leading to significant inhibition of tumor progression.[55] Therefore, mRNA-LNP nanovaccines represent a highly advanced and effective therapeutic platform in cancer immunotherapy, primarily serving as novel cancer vaccines and immune-activating tools that can complement other conventional therapies.

Furthermore, when developing mRNA vaccines suitable for clinical application, employing nucleotide chemical modification strategies can reduce immunogenicity without affecting the translation efficiency of the mRNA, thereby enhancing anti-tumor activity. For instance, Verbeke et al utilized DOTAP-LNPs to co-load antigen mRNA modified with pseudouridine (Ψ) and 5-methylcytosine (5meC) along with the invariant natural killer T cells (iNKT) ligand α-GC, constructing an mRNA Galsomes nanovaccine platform. This mRNA-LNP nanovaccine efficiently targets DCs, significantly enhances antigen mRNA expression levels, improves antigen presentation efficiency, and notably reduces the release of type I interferons. Compared to unmodified ovalbumin (OVA) mRNA vaccines, mRNA Galsomes demonstrated significantly stronger efficacy in tumor suppression, achieving up to 7-fold greater inhibition. In vivo experiments showed that after intravenous administration, low-dose α-GC synergized with mRNA to activate conventional T cells and iNKT cells, eliciting tumor-specific immune responses and significantly suppressing the growth of established E.G7-OVA lymphomas (Figure 4).[56] However, as an early representative of cationic lipids, DOTAP has been superseded by subsequently developed ionizable lipids due to its non-adjustable charge properties. Compared to traditional cationic lipids, ionizable lipids possess pH-responsive characteristics, which to some extent enhance their circulation half-life. These lipids carry a positive charge in acidic environments (such as inside the LNP or within endosomes, pH < 6.5), enabling tight binding with negatively charged mRNA while promoting nucleic acid release and endosomal escape. In contrast, under neutral conditions (eg, in the bloodstream, pH ≈ 7.4), they remain electrically neutral, reducing nonspecific interactions with plasma proteins. This enhances their stability and safety and improves delivery efficiency. Consequently, ionizable lipids, including DLin-MC3-DMA, SM-102, and C12-200, have become the core lipid components in modern novel mRNA-LNP vaccine systems.

Additionally, CAR mRNA-LNP therapy represents a cutting-edge strategy in cancer immunotherapy. It leverages LNPs to deliver in vitro transcribed CAR-mRNA into immune cells in vivo, enabling the efficient, in-situ generation of CAR-modified immune cells. This approach bypasses the complexities and potential risks associated with traditional ex vivo manufacturing. A core advantage of this technology lies in its use of a non-viral delivery system, addressing challenges inherent to conventional CAR therapies like CAR-T, such as high costs, lengthy manufacturing cycles, and potential carcinogenic risks associated with viral vectors. LNPs can safely and efficiently deliver the genetic instructions encoding the CAR directly to target immune cells within the body, effectively "programming" them in situ to become CAR cells with targeted killing capabilities. Qiaobing Xu et al developed two formulations, termed 9322-O16B LNPs and 76-O17Se LNPs, to deliver N1-methylpseudouridine (N1mψ)-modified CD19-targeting CAR mRNA to primary macrophages (CAR-Ms) and CD8+ T lymphocytes, respectively. Both types of CAR mRNA-engineered cells demonstrated a significant ability to eliminate B-cell lymphoma in vitro. Furthermore, this strategy proved more effective than using the liposomal transfection reagent Lipofectamine 2000 (LPF2K) or MC3 LNPs (an LNP formulation used for siRNA delivery). Xu et al successfully engineered both CAR-Ms and CAR T cells using LNPs to deliver CAR mRNA.[57]

Although LNP technology has demonstrated broad application prospects in mRNA cancer vaccines, it still faces challenges related to tissue targeting. To address the limitation of LNPs primarily targeting the liver, a novel LNP delivery platform called Selective Organ Targeting (SORT) LNPs has been developed. This breakthrough technology successfully overcomes the constraints of traditional LNP delivery, enabling precise targeting of specific organs. The SORT-LNP platform builds upon the conventional four-component LNP formulation (typically consisting of phospholipids, cholesterol, PEG-lipids, and ionizable lipids) by incorporating a fifth lipid component—the SORT molecule. This unique lipid composition design allows for the targeted delivery of CAR mRNA or gene editing systems to specific tissues. Compared to traditional LNPs, the SORT-LNP platform offers several advantages, including high selectivity and organ targeting, the ability to deliver various types of genetic medicines, and compatibility with multiple administration routes.[58] For example, Álvarez-Benedicto et al utilized spleen-targeting SORT-LNPs containing 10% 18:1 PA

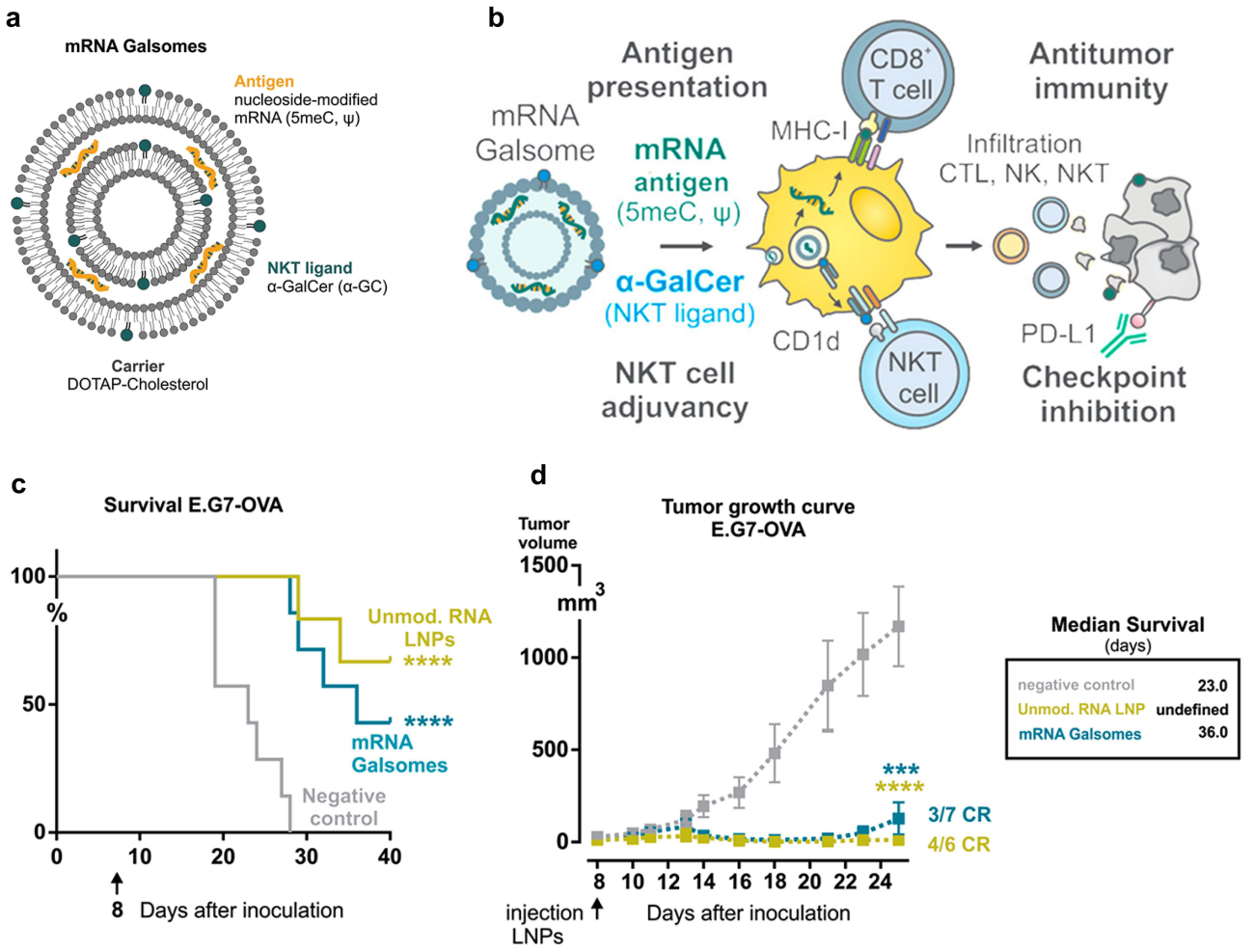

Figure 4 (a-b) mRNA Galsomes promote the delivery of α-GC to DCs without affecting mRNA transfection. (**a**) Schematic representation of a nanoparticle consisting of DOTAP–cholesterol LNPs, nucleoside-modified mRNA (5meC, ψ), and the NKT ligand α-GC. (**b**) Schematic diagram of the mechanism of OVA mRNA Galsomes in treating lymphoma. (**c** and **d**) Therapeutic vaccination with OVA mRNA Galsomes or nanoparticles containing unmodified OVA mRNA in an E.G7-OVA lymphoma model. Mice were subcutaneously inoculated with E.G7-OVA cells (3×10^5 cells). E.G7-OVA-bearing mice were vaccinated on day 8 when tumors were clearly visible. Graphs show Kaplan–Meier survival curves in the E.G7-OVA model and the respective tumor growth curves (**d**) as a function of time for an untreated control group (negative control) and for mice treated with OVA mRNA Galsomes or nanoparticles containing unmodified OVA mRNA (n = 7–8). Statistical analysis on the survival curves (**c**) was performed using a log-rank (Mantel–Cox) test. In (**d**), tumor volumes measured at day 25 were compared by a one-way ANOVA followed by Tukey's post hoc test. Asterisks indicate statistical significance compared to the untreated group (***, $p < 0.001$; ****, $p < 0.0001$). Adapted with permission from,[56] copyright 2019, American Chemical Society.

(phosphatidic acid) to deliver CD19-targeted CAR mRNA and validated the efficacy of SORT-LNP-mediated in situ CAR T-cell therapy. The results showed that this modification successfully reprogrammed the organ tropism of LNPs from the liver to the spleen, without relying on active targeting ligands like antibodies. In reporter mouse models, approximately 7% of total T cells, 5.8% of CD8+ T cells, and 5.5% of CD4+ T cells in the spleen were successfully transfected after two injections, demonstrating effective targeting of key immune cells. In a B-cell lymphoma mouse model, intravenous injection of spleen-targeting SORT-LNPs loaded with CD19-targeted CAR mRNA, along with co-stimulatory molecules (41BB or CD28) and CD3ζ signaling domains (CAR19-41BBz mRNA LNP), inhibited tumor growth, increased tumor-infiltrating lymphocytes, and significantly extended overall survival. However, while this strategy achieved successful transfection, its efficiency (approximately 7%) still has substantial room for improvement, which is crucial for achieving potent therapeutic outcomes.[59] Overall, these results offer a promising alternative method for CAR cell production, with potential therapeutic applications for hematologic malignancies in the preclinical stage. In the future, further optimization of CAR cells based on the mRNA-LNP technology platform remains possible.

https://doi.org/10.2147/IJN.S587953

Tumor Microenvironment-Responsive Nanosystem Therapeutic Strategy

Precision drug release systems play a crucial role in tumor therapy, particularly for delivering drugs to specific sites in the body, which requires suitable drug delivery carriers to enhance therapeutic outcomes. In recent years, smart responsive nanocarriers have been developed as a novel drug delivery strategy, enabling selective drug accumulation in diseased tissues, reducing the side effects of therapeutic agents, and improving the efficacy of chemotherapy. In particular, significant progress has been made in the research of TME-responsive smart nanodrug carriers, offering new avenues for innovative cancer treatment.[60]

The TME plays a key regulatory role in the occurrence, development, and metastasis of tumors. The TME is characterized by unique physiological features, including high reducing potential, elevated levels of ROS, low pH, hypoxia, high enzyme activity, and immunosuppression. These features not only drive malignant tumor progression but also provide targets for cancer therapy. In recent years, smart nanodelivery systems designed based on these characteristics—capable of responding to or modulating the TME—have shown great promise in controlled drug release, immune activation, and multimodal synergistic therapy.[61,62] Stimuli-responsive nanodrug delivery systems offer targeted specificity, controlled release, and the ability to cross biological barriers, thereby enabling more precise drug delivery to tumors, enhancing antitumor efficacy, and reducing toxicity to non-targeted (normal) tissues. Leveraging the properties of the TME, researchers have recently proposed various therapeutic strategies targeting the TME. These include the use of TME-responsive materials for controlled drug release, activation of host antitumor immune responses by modulating the immunosuppressive state, and synergistic tumor cell killing through physical approaches such as phototherapy and hyperthermia. The core of these strategies lies in constructing therapeutic systems capable of recognizing, responding to, and regulating the TME, enabling precise and intelligent anticancer interventions through the sensing of specific biochemical signals in the TME and the active modulation of the immunosuppressive state. In addition to utilizing nanomaterials capable of undergoing Fenton reactions, it is also possible to introduce specific functional molecules (such as photosensitizers (PS), enzyme-responsive substrates, gas donors, and immunomodulatory factors) that respond to external stimuli (eg, light, magnetic fields) or specific internal signals within the TME (eg, pH, redox state, enzyme activity). This enables the modulation of the immunosuppressive TME, achieving controlled drug release and TME remodeling.[63] For example, the photothermal conversion properties of noble metal materials and carbon-based materials enable spatiotemporally controllable photothermal therapy for cancer. The PS such as indocyanine green and porphyrins, along with their related assemblies, can achieve highly effective photodynamic therapy through the generation of highly toxic free radicals. Nanozymes can promote the generation of substances like hydroxyl radicals (·OH) and superoxide anion radicals ($\cdot O_2^-$) or facilitate the consumption of substances such as glucose and glutathione, thereby enabling TME-responsive cancer therapy. Designing nanocarriers with an "on-off" function offers distinct advantages in both therapy and diagnosis. They allow for personalized monitoring of drug administration at the tumor site, potentially leading to more precise and versatile drug delivery strategies that further enhance the efficacy of cancer treatment.

GSH-Responsive Nanodelivery System

The glutathione (GSH) is a tripeptide small molecule rich in sulfhydryl groups (-SH), with high concentrations in cancer cells, particularly in the cytoplasm, and is thus commonly used as an endogenous stimulating factor in responsive drug delivery systems. Therefore, intelligent responsive prodrug nano-assemblies designed based on the high GSH concentration in the TME can enable selective and rapid drug release at the target site, providing more options for precise tumor therapy. For instance, disulfide bonds have been demonstrated to undergo rapid cleavage in response to overexpressed GSH in tumor cells, thereby triggering redox-based prodrug release. As evidenced by Zhong et al, a redox-responsive and self-assembling nanomedicine system, GSP NPs, was synthesized via esterification and acylation using hydrophilic gemcitabine, amphiphilic mPEG2k-OH, and the disulfide-containing 3,3'-dithiodipropionic acid (DTDP). In normal tissues, the hyperbranched polymer prodrug formed through self-assembly cannot embed into DNA, ensuring the drug remains "inactive." However, under the high GSH conditions of the TME, the abundant disulfide bonds in the highly branched structure rapidly cleave, "activating" the prodrug and enabling precise, on-demand release of gemcitabine. This restores its chemical and spatial structure and environment, allowing it to regain the opportunity to bind with DNA,

thereby significantly inducing apoptosis in BCL in vitro. Concurrently, in a A20 tumor xenograft mouse model, GSP NPs effectively suppressed tumor growth and showed little systemic toxicity.[64]

The advantage of GSH-responsive systems lies in their well-defined responsive mechanism and relatively simple design. However, this strategy also has notable limitations. For instance, GSH levels vary significantly across different tumor types and among individuals, affecting the universality of the treatment. Moreover, high GSH levels themselves are central to the antioxidant defense of tumors, and simply depleting GSH may not be sufficient to completely disrupt the redox balance. Combining GSH responsiveness with other stimuli (such as pH or H_2O_2) or co-administering GSH synthesis inhibitors (eg, buthionine sulfoximine) may enhance therapeutic efficacy.

pH-Responsive Nanosystem

Design and develop pH-responsive nanodelivery systems by incorporating protonatable or acid-labile chemical bonds, coating with pH-sensitive "shells," and other methods. These systems are designed to degrade or dissolve within the acidic TME, leveraging the pH difference between tumor and normal tissues to achieve intelligent, stimuli-responsive drug release. For example, a pH sensitive controlled drug release system was designed by Zhou et al on the basis of mesoporous silica nanoparticles (MSNs). They loaded Dox into mesopores of MSNs (DMSNs), and then conjugated rituximab to DMSNs as a targeting ligand for the drug delivery system. This drug delivery system of great selectivity can home onto the lymphoma cells overexpressing CD20 without premature drug release at physiological pH but undergoing effective pH-responsive intracellular drug release under weak acidic environments. The in vitro tests confirmed that RDMSNs could selectively adhere onto lymphoma B cells surface via specific binding to CD20 antigen and being internalized in CD20-positive Raji cells. In slightly acidic intracellular microenvironment, the encapsulated Dox was released by pH stimulation efficiently, followed by the apoptosis of Raji cell. What's more, in vivo studies showed that RDMSNs could serve as an efficient vehicle to deliver Dox into lymphoma B cells, thus inducing apoptosis to inhibit the tumor growth in vivo with few toxic side effect. This nanoplatform with targeting and pH-sensitive control holds potential for improving therapeutic outcomes and reducing side effects in B-cell lymphoma treatment.[65] As described by Hira et al, a pH-sensitive ABA-type double hydrophilic amphiphilic polyethylene glycol-*b*-aliphatic polyketal-*b*-polyethylene glycol block copolymer was synthesized using alkyne-azide click reactions. Dox was then loaded into the copolymer micelles to construct the PEG-*b*-PK-*b*-PEG-DOX nanosystem. This nanosystem exhibited pH-sensitive drug release under the pH of 6.4, had significant antitumor activity against Dalton's lymphoma (DL) and Raji tumor cells, exhibited significant inhibition of tumor growth, and induced apoptosis.[66] Cai et al devised pH-sensitive magnetic nanoparticles, ADM-As_2O_3-MNPs, that are assembled with adriamycin (ADM) and arsenious acid (As_2O_3) through dimercaptosuccinic acid (DMSA), a kind of linker. With this design, the tumor cells can be selectively eliminated by the rapid ADM release in the acidic conditions (eg, TME) mediated by Fe^{2+} instead of reduction in weak or neutral conditions. The ADM-As_2O_3-Fe_3O_4 NPs can improve the accumulation and efficiency of the anticancer drugs through up-regulating expression of Bax, caspase-3 mRNA and protein and down-regulating expression of Bcl-2. Our in vitro studies revealed that the ADM-As_2O_3-Fe_3O_4 NPs increased the apoptosis of Raji lymphoma cells to a much more significant degree than the single-drug treatment. Among all tested mice, in Raji lymphoma immunodeficient nude mouse model, the nanocapsules showed the best killing ability against tumor cells with obvious therapeutic benefits.[67]

Besides, researchers also try to use the dual pH-responsive carriers simultaneously for drug and gene therapy co-delivery to realize synergistic treatment of cancer. Li et al synthesized DNA nanomicelles (DNMs) by rolling circle amplification (RCA) on amphiphilic primer–polylactic acid (PLA) micelles, co-loading Dox and anaplastic lymphoma kinase (ALK)-specific siRNA. Here, the RCA reaction was carried out on the surface of PLA micelles, the ssDNA concatemers of multiple tandem repeats were formed, that assisted the periodic assembly of a large number of pH-responsive DNA probes and facilitated the effective intercalation with Dox. As the pH of the TME changes, simultaneous release of both the anticancer drug Dox and ALK-specific siRNA is triggered. Since siRNA-mediated silencing of ALK gene expression increases the chemosensitivity of anaplastic large cell lymphoma (ALCL) cells, the therapeutic efficacy of Dox/siRNA/DNMs against ALCL is significantly superior to chemotherapy alone, markedly enhancing apoptosis in ALCL K299 cells. In vivo, this approach effectively inhibits tumor growth without apparent toxicity, offering a potential strategy for achieving precise control over drug release within the TME and synergistic gene therapy for cancer (Figure 5).[68]

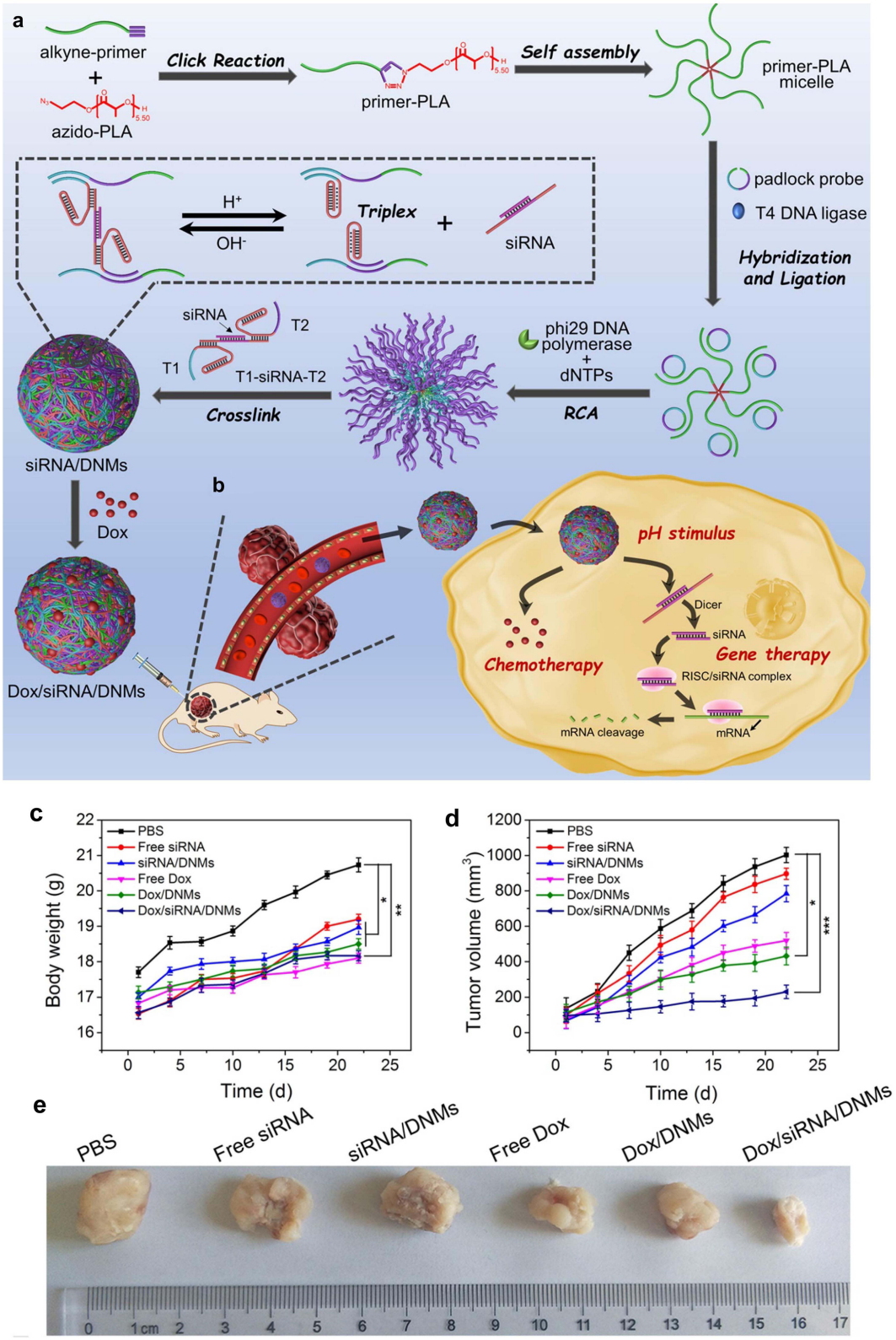

Figure 5 (**a** and **b**) Schematic of pH-responsive DNMs co-loaded with anticancer drug Dox and ALK-specific siRNA for synergetic chemo-gene therapy of ALCL. (**a**) Construction and (**b**) delivery of Dox/siRNA/DNMs to K299 cells for synergetic chemo-gene therapy. (**c**–**e**) In vivo therapeutic study. (**c**) Bodyweight changes of mice in different groups during therapy. (**d**) Tumor volume changes of different groups during therapy. Error bars indicate SD (n = 3). (**e**) Photographs of tumors dissected from the K299 tumor-bearing mice at the therapeutic terminal. Adapted with permission from,[68] copyright 2020, Ivyspring International Publisher. *p < 0.05, **p < 0.01, and ***p < 0.001.

pH-responsiveness is one of the most mature and widely applied TME-responsive strategies. However, its limitation lies in the relatively shallow pH gradient (normal tissue pH 7.4, tumor pH 6.5–6.9), which results in a narrow selectivity window and may lead to premature drug leakage in the bloodstream or normal tissues. Moreover, pH-responsive systems primarily achieve "release after accumulation" in tumor tissues but offer limited control over processes such as lysosomal escape following cellular internalization. The precision and specificity of pH responsiveness can be enhanced by combining it with other response mechanisms.

Photoresponsive Nanotherapy for Lymphoma Treatment

Unlike traditional chemotherapy and cellular therapies, photothermal therapy (PTT) and photodynamic therapy (PDT) represent emerging approaches in tumor diagnosis and treatment. These modalities are based on light energy and leverage the differential sensitivity of tumor cells versus normal cells to heat and ROS, enabling efficient local tumor ablation while minimizing damage to normal tissues. They hold promising application prospects. PDT primarily relies on PS to generate ROS, such as singlet oxygen ($^1O_2$) and superoxide anion (O_2^-), under specific wavelength light irradiation, thereby inducing oxidative stress.[69,70] PTT, on the other hand, utilizes photothermal conversion agents (eg, gold nanoparticles or carbon-based materials) to generate localized hyperthermia (>42°C) under NIR irradiation, leading to protein denaturation and membrane disruption.[71] As cancer therapeutic strategies, PDT and PTT not only exert local antitumor effects by directly inducing tumor cell death (eg, apoptosis, necrosis, or autophagy) but also significantly activate the host immune system, inducing systemic antitumor immune responses. This immune effect primarily stems from immunogenic cell death (ICD) triggered during the treatment process. These signals transform "cold" tumors (immunosuppressive) into "hot" tumors (immunoactive), promoting the infiltration and activation of DCs, CTLs, and NK cells. Both can disrupt the immunosuppressive balance of the TME and enhance the efficacy of immunotherapy.[72,73]

PDT has low toxicity risks and relies on three key elements: a photosensitizer (PS), light of an appropriate wavelength, and dissolved oxygen. PS such as porphyrin compounds and molecular oxygen in cells and tissues are non-toxic by themselves; their cytotoxic effects are triggered only when the photosensitizer is activated by a specific wavelength of laser. By modulating the distribution of the photosensitizer and controlling the light source, malignant tumors can be selectively destroyed while sparing normal tissues and organs. However, its main limitation is insufficient penetration depth, restricting its application to early-stage localized cutaneous lymphoma. Nevertheless, combining PDT with immunotherapy strategies can significantly enhance antitumor efficacy.[74,75] For instance, Blaudszun et al loaded the clinically applied porphyrin-based PS Temoporfin into cytotoxic T cells (OT-1 cells), enhancing the therapeutic efficacy against lymphoma by combining PDT with adoptive T-cell immunotherapy (ACT). The stimulus-sensitive PS remains in a non-toxic state in the absence of light to prevent premature damage to T cells. However, upon visible light irradiation, PS-OT-1 cells efficiently generate large amounts of ROS, inducing significant cytotoxicity. In an EG7-OVA tumor-bearing mouse lymphoma model, intravenously injected PS-OT-1 cells accumulated within the targeted tumor tissue due to the tumor-homing effect of T cells. Meanwhile, when the tumor tissue was locally exposed to visible light, intravenously administered PS-OT-1 cells significantly suppressed tumor growth compared to non-loaded OT-1 cells. The study confirmed that the combination of PDT and ACT, via PS-loaded cytotoxic T lymphocytes, provides a novel approach for effective cancer immunotherapy.[76]

The therapeutic efficacy of PTT depends on the type and concentration of light-absorbing agents, irradiation parameters, and the thermal sensitivity of tumor tissues. Tumor cells are more susceptible to hyperthermia due to their high metabolic rates and reduced thermotolerance. The localized thermal effect of PTT ensures targeted treatment, generating high temperatures exclusively within the irradiated area and minimizing damage to surrounding normal tissues. Additionally, PTT can promote the release of tumor antigens through heat-induced immunogenic cell death, thereby activating antitumor immune responses and further enhancing therapeutic outcomes.[77,78] For example, Kang et al prepared photothermal organic nanoparticles (PO NPs) using a novel NIR-absorbing organic polymer PTA (PYIT-OD) with excellent optical properties and photostability, for mild photothermal therapy (MPTT). Unlike conventional chemotherapy, MPTT (42°C–45°C) significantly reduces systemic side effects and minimizes damage to normal tissues through a mechanism that disrupts the targeted cell cycle. This characteristic makes MPTT a promising strategy for the precise treatment of lymphoma. Meanwhile, they synergized the senescence-inducing drug Abemaciclib with PYIT-OD

nanoparticles to induce cell cycle arrest and accelerate tumor cell senescence. Both in vitro and in vivo experimental results demonstrated that the combination of PO NPs and the anti-aging drug abemaciclib significantly enhanced the anti-tumor effect, effectively reduced damage to normal tissues at physiological temperatures, and exhibited no systemic toxicity or side effects. Therefore, this strategy, combined with cellular senescence, holds great potential for anti-tumor therapy and offers a promising approach for the treatment of DLBCL.[79]

During the process of tumor elimination, single PTT or PDT has certain limitations. For instance, the heat shock response of cells can reduce the efficacy of PTT, and the hypoxic conditions in the TME can significantly impair the ability of PDT to generate ROS. However, combining PTT and PDT can leverage the advantages of each treatment method while overcoming their limitations, thereby synergistically enhancing the killing effect on tumor cells. For example, Nan et al embedded a novel PS (1-oxo-1H-benzoo[de]anthracene-2,3-dicarbonitrile-triphenylamine (OBADC-TPA)) into an amphiphilic polymer (DSPE-PEG2K-NHS) and further functionalized it with a sialic acid (SA) derivative (9-NH2-SA), synthesizing OBADC-TPA-based multifunctional nanoparticles (NPs-SA). NPs-SA utilize a small coplanar structure and strong electron-withdrawing acceptor groups to promote intramolecular charge transfer, endowing them with efficient photothermal conversion capability and ROS generation under NIR-II irradiation. Meanwhile, the modification with SA enhances targeting toward lymphoma. In a Raji tumor-bearing nude mouse model, NPs-SA combined with 808 nm laser irradiation demonstrated significantly enhanced tumor inhibition. These results indicate that NPs-SA possess great potential for NIR-II fluorescence imaging-guided combined PTT/PDT therapy (Figure 6).[80]

Sonodynamic Therapy

Ultrasound (US) is an established tool in medical imaging and therapy, and its unique properties offer a promising alternative for cancer treatment. Unlike light, ultrasound can enter deeper into the human tissues, overcoming the limits of phototherapy. Sonodynamic therapy (SDT) is an emerging methods which are based on a combination of ultrasound and sonosensitizing drugs. It can act as an attractive and controllable exogenous stimulus to penetrate human tissues noninvasively, precisely focusing on the target region, by generating heat and mechanical vibrations to trigger drug release from nanocarriers. Taking advantage of the cavitation effect of US, SDT could facilitate cancer cell membrane permeability so that therapeutic agents could be targeted delivered and activated, and add acoustically responsive nanomaterial to SDT to promote controllable drug release and activation, thereby minimize injury to normal tissues.[81,82] For instance, Wang et al design the UiO-66-type metal-organic framework (MOF) as the basis for CRUPPA19 particles. These particles internalized a copper complex of m6A-mRNA demethylase inhibitor and surface-displayed with mPEG-PO_3 and ant-CD19 antibodies, achieving dual-targeted precise delivery and these particles preferentially collected in B-cell lymphoma (BCL) tissues to target lymphoma cells of bone marrow; ultrasound irradiation excited CRUPPA19 to induce ROS triggering tumor cell apoptosis. However, concurrently, it induced autophagy to be released of the copper ions and emodin, respectively causing “cuproptosis” and inhibition of PD-L1 transcription, a cascade effect of these together inducing a synergistic immunogenic cell death (ICD), and subsequently activating the response of $CD8^+$ T cells to induce an anti-lymphoma immunity response. It has been proved that this therapy can not only kill the primary and metastatic lymphoma but also eliminate lymphoma cells in bone marrow, and can serve as a novel therapeutic approach to BCL (Figure 7).[83]

Besides, the synergistic action of SDT with the conventional therapy, including chemotherapy, PTT, PDT or immunotherapy could be promising to achieve more effective tumor ablation by overcoming the tumor treatment resistance. Thus, design of the multifunctional nanoparticles that can be stimulated with US for targeted drug delivery and therapy activation is a new step of cancer-targeted therapy. For example, by combining the outstanding physical and chemical properties of black phosphorus nanosheets (BPNSs), Zhu et al proposed a fluorescence and thermal imaging-guided photo/sono-dynamic synergistic therapy platform named BPNSs@PEG-SS-IR780/RGD, which is a multifunctional therapeutic platform consisting of BPNSs, heptamethine cyanine dye IR780 and targeting molecule RGD. BPNSs not only serve as carriers but also function as photothermal and sonodynamic sensitizers; NH_2-PEG-RGD acts as a targeting peptide to facilitate active targeting of tumor regions; and the disulfide bond in IR780 enables the release of IR780 in the TME. Consequently, BPNSs@PEG-SS-IR780/RGD exhibits outstanding photothermal conversion efficiency, highly effective ROS generation, as well as excellent biocompatibility, tumor-targeting capability, and TME responsiveness. In vitro and in vivo experiments

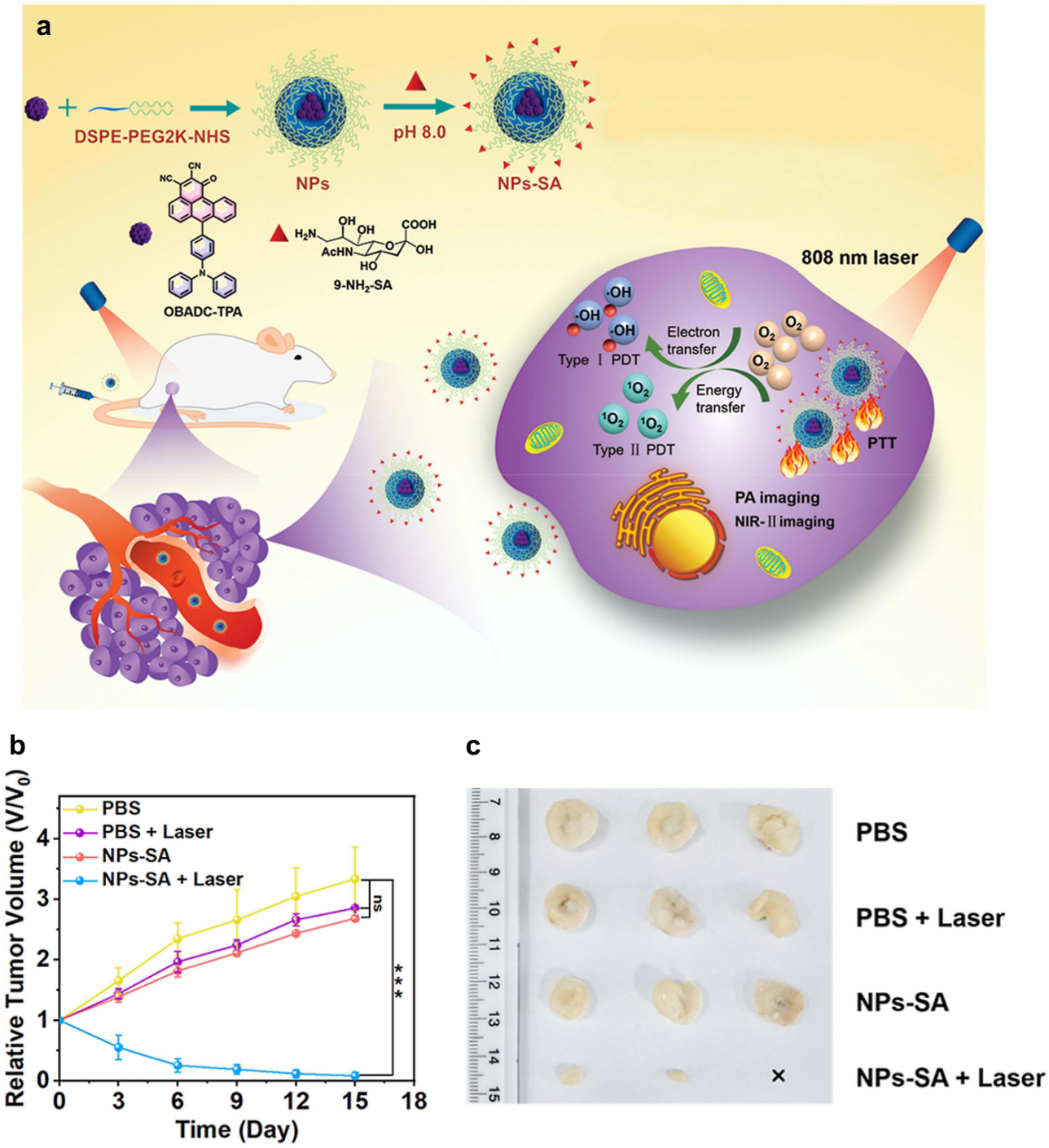

Figure 6 (**a**) Schematic Illustration of the Fabrication of NPs-SA for Lymphoma PA/NIR-II Fluorescence Imaging-Guided Combination PDT/PTT. In Vivo combination therapy. (**b**) Calculation of the relative tumor volumes. Data are presented as mean values ± SD (n = 4). ns = not significant, ***p < 0.001. (**c**) Photographs of tumors from the mice after different treatments. Adapted with permission from,[80] copyright 2025, American Chemical Society.

demonstrated that BPNSs@PEG-SS-IR780/RGD can more effectively kill tumor cells and inhibit tumor cell proliferation through photo/sono-dynamic synergistic therapy.[84] Wang et al encapsulated superparamagnetic iron oxide nanoparticles (SPIONs) and celastrol (CST) in poly(lactic-co-glycolic acid) (PLGA), followed by modification with a CD20 monoclonal antibody, to construct an US/PTT/chemotherapy multifunctional nano-platform (TscNPs) for the synergistic treatment of BCL. Here, the nano-platform consists of monoclonal antibodies aimed at the CD20 antigen in BCL cells, to precisely deliver drug to the tumor site. The encapsulated SPIONs also give the magnetic resonance (MR) imaging ability and the

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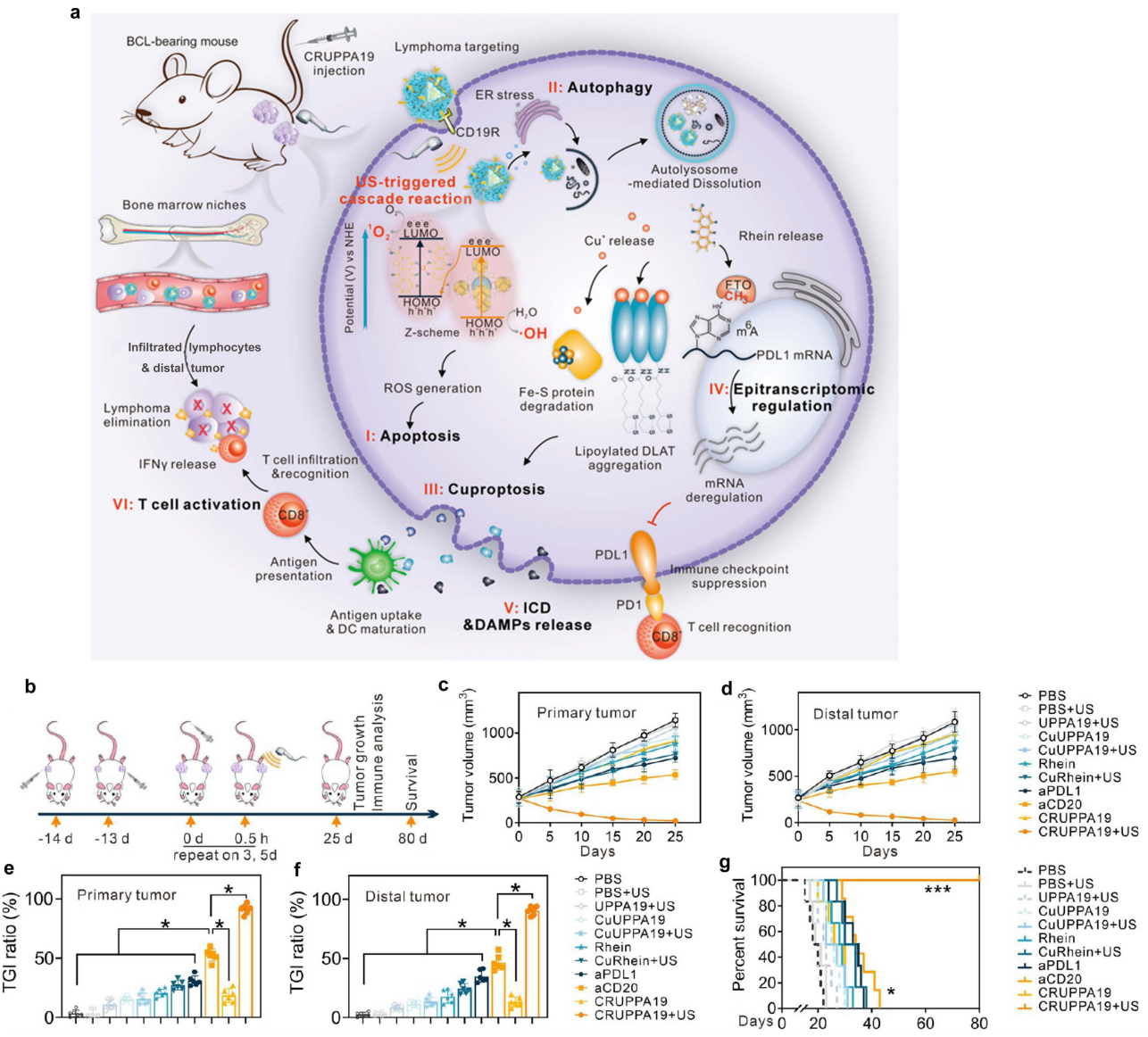

Figure 7 (**a**) MOF-Based Sono-Immuno/Epigenetic Therapy Platform for B-Cell Lymphoma via Cascade Induction of Apoptosis, Autophagy, Global mRNA Methylation, and Cuproptosis. (b-g) Sono-immunotherapeutic effect of CRUPPA19 in lymphoma mouse model. (**b**) Diagram illustrating the A20 bilateral tumor model establishment and the schedule of CRUPPA19-mediated sono-immunotherapy. Growth curves of (**c**) primary and (**d**) distant tumors in the indicated groups. TGI ratio of (**e**) primary and (**f**) distant tumors in the indicated groups. (**g**) Kaplan–Meier curves showing the overall survival probability of the differentially treated A20-bearing mice for 80 days. Adapted with permission from,[83] copyright 2025, American Chemical Society. *$p < 0.05$, ***$p < 0.001$.

photothermal conversion in order to ablate tumor by thermal means. Under NIR laser irradiation, the generated heat by TscNPs will make optical droplet vaporization (ODV) of perfluoropentane (PFP) and convert it into the microbubbles. It can improve the US imaging and release celastrol (CST) from nano-platform in a synergistic PTT/chemotherapy treatment effect, meanwhile. In tumor-bearing nude mice, TscNPs had a good accumulation to the tumor area, the combination treatment of TscNPs and NIR laser irradiation had an inhibition ratio of about 96.57% tumors compared with PTT or chemotherapy treatment.[85] Overall, these results show that multifunctional therapeutic nano-platforms responsive to a US stimulation are a promising new strategy towards treatment of lymphoma.

Nanozyme for Lymphoma Treatment

Nanozymes are artificial nanomaterials that mimic the activity of natural enzymes with the function of enabling to bypass some limitations of natural enzymes. Specifically, nanozymes mimic the function of redox-active enzymes, including

catalase (CAT), peroxidase (POD), superoxide dismutase (SOD), and oxidase (OXD), and may potentially manipulate the TME.[86,87] For tumor therapy, mostly nanozymes working in tumor therapy serve as redox enzymes, due to that, tumor proliferation induces redox dysregulation in the TME, characterized by high levels of H_2O_2, hypoxia, and low pH. These circumstances cause the accumulation of many cell growth factors, chemokines, and hydrolytic enzymes in the TME, and these molecules initiate inflammation inducing rapid proliferation of the tumor cells. The accumulated tumor factors thus confer resistance to radiation and chemotherapeutic treatment. TME redox levels could be manipulated with nanozymes and inhibit tumor development.[88–90] Nanozymes can also utilize its OXD and POD activities to catalyze the chemical conversion of H_2O_2 into poisonous ROS (ie, hydroxyl radicals (•OH), superoxide anions (O_2^-), and singlet oxygen ($^1O_2$), inducing ROS–mediated oxidative stresses to eliminate tumor cells. Or nanozyme' CAT can utilize the chemical conversion of H_2O_2 in the TME into O_2 catalyzed by nanozymes to overcome the tumor hypoxia and then indirectly cause tumor cell death, which will promote anticancer catalytic therapy. Especially, due to synergy between nanozyme and other tumor treatment modes such as responsive enzyme-like functions, including photo-thermal and magnet effect. Thus, not only is ROS produced to increase the treatment effect but also decrease the treatment side effect, then surpass the deficiency of traditional methods and greatly bring advances to clinical applications. Thus, nanozyme can catalyze in situ activation of therapeutic agents, such as Yan et al prepared an injectable Fe_3O_4@DMSA@Pt@PLGA-PEG-PLGA hydrogel system to treat DLBCL by incorporating magnetothermal therapy (MHT), chemodynamic therapy (CDT) and immunomodulation. The Fe_3O_4@DMSA@Pt nano-particles have superparamagnetism, and kill tumor cells directly based on ablation under hyperthermia induced by MHT. As the addition of Pt not only further stimulate POD-like reaction of Fe_3O_4@DMSA to catalyze the generation of ROS, but also improve the catalytic reaction microenvironment, increasing the damage of intracellular redox homeostasis. Fe_3O_4@DMSA@Pt@PLGA-PEG-PLGA creates magnetothermal effect and chemo-dynamic effect to provide coordination to bring DCs maturation and activate T cells synergistically. It also triggers damage associated molecular patterns (DAMPs) signaling, promotes ICD, increases cytotoxicity and eventually triggers apoptosis of lymphoma cells (Figure 8).[91]

Additionally, hydrolase nanozymes can mimic natural hydrolases and participate in the hydrolysis of biomolecules, demonstrating unique advantages in cancer treatment.[92] Research indicates that nanozymes with phosphatase-like activity exhibit promise for clinical application in the treatment of lymphoma. For instance, Nguyen et al developed a drug-free polypyrrole-polyethyleneimine nanozyme (PPY-PEI NZ) with phosphatase activity, which responds to the TME of BCL for precise cancer immunotherapy. Through its phosphatase activity, PPY-PEI NZ induces dephosphorylation and inactivation of AKT (Ser 473 and Thr 308) and ERK (Thr202/Tyr204) in BCL. This is followed by GSK-3β-mediated Mcl-1 destabilization and loss of mitochondrial transmembrane potential (MTP), ultimately leading to apoptosis of lymphoma cells. In a subcutaneous xenograft model, PPY-PEI NZs effectively and sustainably inhibited the growth of BCL-driven nodules, while demonstrating no cytotoxicity in wild-type mice, confirming both the antitumor efficacy and safety profile. These findings validate PPY-PEI with phosphatase activity as a potential anticancer agent against BCL.[93]

Current Status of Clinical Translation

Current clinical treatment for malignant lymphoma primarily includes surgery, combination chemotherapy, and hematopoietic stem cell transplantation. The first-line treatment for most non-Hodgkin lymphomas is comprehensive therapy based on the R-CHOP regimen, ie, rituximab combined with cyclophosphamide, doxorubicin, vincristine, and prednisone. Although this regimen yields a high complete remission rate, it often leads to severe toxic side effects. Moreover, due to the high heterogeneity of lymphoma, a considerable number of patients still experience relapse or drug resistance.[94,95] Nanotechnology has brought revolutionary changes to the lymphoma treatment paradigm, evolving from a simple drug delivery tool into a programmable immunomodulatory hub and multimodal therapeutic platform. As nanotechnology-based CAR-T, mRNA LNP vaccines, and other nanotech-driven innovative therapies transition from the laboratory to clinical practice, nanomedicine has demonstrated irreplaceable value in improving drug targeting, reversing the immunosuppressive microenvironment, and overcoming drug resistance. Lymphoma treatment has fully transitioned from traditional chemotherapy into the era of targeted therapy and immunotherapy. The clinical translation of

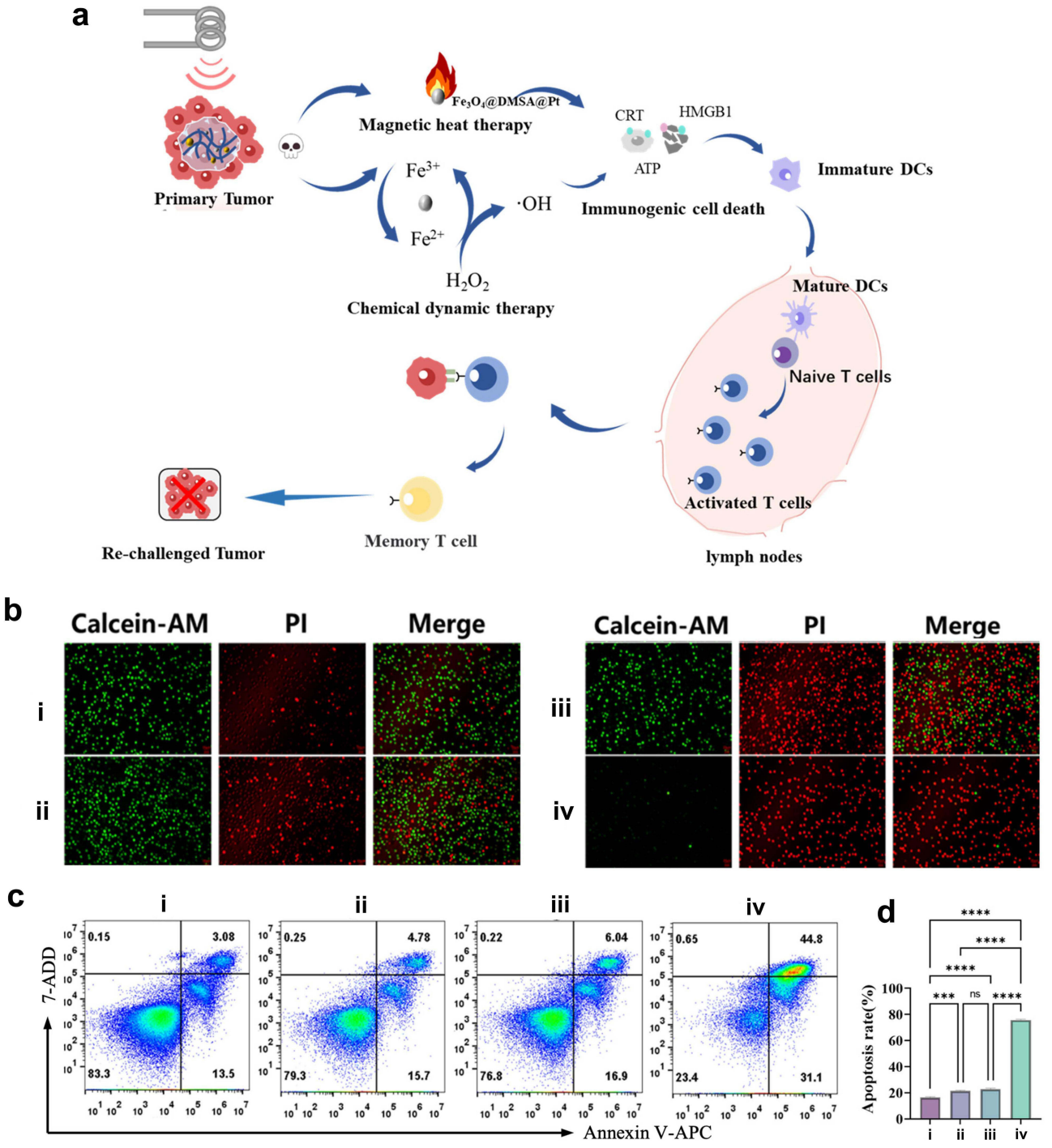

Figure 8 (**a**) Schematic diagram depicting the synergistic mechanisms of magnetic heat therapy, chemical dynamic therapy, and immunogenic cell death activation within the injectable hydrogel system for antitumor treatment. (**b**) Fluorescence images of live (Calcein-AM) and dead (PI) A20 cells in different treatment groups and merged images. (**c**) Flow-cytometry analysis of A20 cell apoptosis in different treatment groups using Annexin V-APC/7-AAD staining. Pseudocolour plots build upon scatter plots by adding heat-map like colors. The shades of these colors show the cell density. Warmer tones like red denote regions with high cell density. Cooler tones such as blue or lighter colors represent regions with low cell density, indicating fewer cells. (**d**) Quantification of apoptosis rates of A20 cells in different treatment groups. Group i (untreated A20 cells), Group ii (A20* + Comhydrogel at 37°C for chemodynamic therapy [CDT] alone), Group iii (A20* + Com-hydrogel heated to 42°C by AMF, integrating magnetothermal therapy [MHT] and CDT), and Group iv (A20* + Com-hydrogel heated to 50°C by AMF, combining MHT and CDT). Bars means ± S.D. *** $p < 0.001$, **** $p < 0.0001$, ns: not significant. n = 3. Adapted with permission from,[91] copyright 2025, MDPI.

various nanotechnology-based innovative therapies is profoundly reshaping the treatment landscape, while simultaneously facing numerous challenges.

For instance, although liposomes exhibit good biocompatibility, their stability is often insufficient, and they are readily recognized and cleared by the mononuclear phagocyte system, resulting in poor targeting efficiency. Gold nanoparticles, despite their excellent photothermal conversion capability, still pose certain risks in clinical application. In terms of targeting, the precision of current nanodrug delivery systems is generally low. While targeting can be enhanced through antibody or ligand modification, this approach is costly, operationally complex, and subject to variability in antibody reactivity among patients. Stability represents another major challenge. During circulation in the bloodstream, nanodrug delivery systems are susceptible to adsorption and degradation by plasma proteins, leading to uneven or premature drug release. To address these bottlenecks, researchers are exploring a range of solutions, such as developing novel degradable materials, optimizing nanoparticle surface modification techniques, and improving targeting accuracy. Surface modification of nanocarriers with ligands—including multivalent antibodies, peptides, or small molecule inhibitors—enables more specific recognition of highly expressed receptors on tumor cells. Simultaneously, investigating new targeting ligands and their modification strategies is critical for overcoming tumor heterogeneity and achieving deep tissue penetration. More importantly, the use of nanoparticles with immune reprogramming capabilities allows for targeted modulation of multiple key components within the TME, thereby reversing the immunosuppressive state and activating antitumor immune responses.[96] Furthermore, the adoption of biomimetic cell membrane coating strategies not only endows nanocarriers with superior immune evasion capabilities and long-circulating properties but also leverages natural proteins on the membrane surface to achieve active targeting and homologous targeting, significantly enhancing their enrichment efficiency in tumor tissues. In recent years, emerging smart responsive nanocarriers have enabled controlled drug release based on changes in pH, temperature, or enzyme levels within the TME; meanwhile, remote-controlled regulation technologies—such as magnetic field response, ultrasound response, and NIR response—render therapy more precise and controllable. Future development trends will involve the engineering of nanocarriers through techniques such as gene editing and immune engineering, while integrating advanced technologies like artificial intelligence and big data for drug design and optimization, thereby facilitating the formulation and implementation of personalized treatment regimens. Integrated therapeutic systems combining intelligent nanocarriers with immunotherapy are poised to dominate the clinical market. Additionally, the adoption of biomimetic cell membrane coating strategies not only endows nanocarriers with superior immune evasion capabilities and long-circulating properties but also leverages natural proteins on the membrane surface to achieve active targeting and homologous targeting, significantly enhancing their enrichment efficiency in tumor tissues. In recent years, emerging smart responsive nanocarriers have enabled controlled drug release based on changes in pH, temperature, or enzyme levels within the TME; meanwhile, remote-controlled regulation technologies—such as magnetic field response, ultrasound response, and near-infrared light response—render therapy more precise and controllable. Future development trends will involve the engineering of nanocarriers through techniques such as gene editing and immune engineering, while integrating advanced technologies like artificial intelligence and big data for drug design and optimization, thereby facilitating the formulation and implementation of personalized treatment regimens. Integrated therapeutic systems combining intelligent nanocarriers with immunotherapy are poised to dominate the clinical market. Here, we analyze the advantages and disadvantages of various therapeutic strategies for lymphoma (Table 2).

In cancer research, cell lines and mouse models have long served as essential tools for studying tumor biology and evaluating therapeutic efficacy. However, these models exhibit notable limitations, particularly in recapitulating the complex heterogeneity of tumors. Traditional cell line models are typically cultured in two-dimensional environments and fail to replicate the three-dimensional growth patterns and behaviors of tumor cells. Cell lines also lack the complex TME, including vasculature, immune cells, and extracellular matrix—factors that play critical roles in tumor progression and treatment response. Mouse models are often generated using single tumor cell clones, making it difficult to accurately reflect the heterogeneity of human tumors. More importantly, significant genetic, physiological, and metabolic differences between mice and humans may compromise the clinical relevance of experimental findings. Consequently, there is an urgent need to develop organoids and organ-on-a-chip platforms that reconstruct lymphoma-specific microenvironment models, thereby enhancing the predictive accuracy of in vitro

Table 2 Comparison of the Advantages and Disadvantages of Various Therapeutic Strategies for Lymphoma

Therapeutic Strategies	Advantages	Disadvantages	Applicability
Biomimetic nanodelivery systems	By modifying targeting peptides that bind to CD30L and CXCR4, precise recognition of lymphoma cells is achieved, enhancing therapeutic efficacy. Coated with a biomimetic cell membrane, it exhibits excellent biocompatibility and safety, along with key functions such as immune evasion and prolonged circulation, enabling more effective tumor treatment.	The preparation process of biomimetic coatings is complex, quality control standards are difficult to unify, and large-scale production faces challenges; the efficacy is poor for lymphoma subtypes with high heterogeneity.	Applicability for B-cell lymphomas.
Nanobody-based CAR-T cell immunotherapy	The sequence is closer to that of human origin, resulting in lower immunogenicity; it can be easily linked to form bi-/multi-specific CARs to simultaneously target multiple antigens, thereby overcoming tumor immune evasion and tumor heterogeneity.	It may occur T cell exhaustion to affect long-term immune response; it may trigger cytokine release syndrome (CRS).	Applicability for various types of lymphoma, including refractory/ relapsed lymphomas such as T-lymphoblastic lymphoma.
Nanovaccines	Can precise targeting and subtype-specific design; effectively activates immune response; overcomes the tumor immunosuppressive microenvironment.	Difficulty in the identification and selection of tumor antigens; challenges in balancing the safety and performance of carrier materials, as well as maintaining delivery efficiency; manufacturing processes and clinical translation are challenging.	Can possible develop intelligent or personalized cancer vaccines.
mRNA-LNP vaccines	Efficiently delivers mRNA encoding tumor antigens to antigen-presenting cells to initiate subsequent immune responses; possesses strong immune activation capability; carries no risk of genomic integration; allows for rapid production and is scalable.	Tends to accumulate in the liver; presence of an immunosuppressive microenvironment in lymphoma.	Can develop intelligent responsive delivery systems to enhance localized immune responses and combine them with therapies such as immune checkpoint inhibitors.
GSH-responsive nanodelivery system	The response mechanism is clear and the design is relatively simple; by formulating chemotherapeutic drugs into GSH-responsive prodrugs and encapsulating them in nanocarriers, the pharmacokinetic properties of the parent drug can be significantly improved.	Material safety and biocompatibility need improvement; heterogeneity in GSH levels may render some cells insensitive to GSH-responsive systems, leading to treatment failure; complex processes make scale-up production difficult and costly.	Enables multimodal synergistic enhancement by combining chemotherapy, photodynamic therapy, chemodynamic therapy, and other approaches.
pH-responsive nanodelivery system	Precisely identifies and kills lymphoma cells with minimal impact on normal cells; offers highly controllable drug release; significantly enhances efficacy while reducing toxicity.	There is a risk of off-target effects; it may be cleared by the immune system or undergo premature degradation, affecting delivery efficiency.	Can integrate multiple functions, such as dual pH-responsive capabilities to achieve sequential drug release.

(*Continued*)

Table 2 (Continued).

Therapeutic Strategies	Advantages	Disadvantages	Applicability
Photodynamic therapy	Minimally invasive and precise, with minimal damage to surrounding healthy tissue and low systemic toxicity; enables targeted activation; allows for repeated treatments.	Limited tissue penetration depth; the response to PDT varies across different lymphoma subtypes and among patients with the same subtype.	Can combined with immunotherapy and other approaches to form multi-modal therapy, thereby enhancing therapeutic efficacy.
Photothermal therapy	Minimally invasive and precise; can remodel the tumor microenvironment and activate antitumor immune responses.	Limited tissue penetration depth; issues related to the batch-to-batch stability of nanomaterials, long-term toxicity, and large-scale production.	Can be combined with other treatment modalities (such as chemotherapy, immunotherapy) to achieve synergistic effects.
Sonodynamic therapy	Non-invasive/minimally invasive, high tissue penetration depth; low systemic toxicity; strong tumor cell killing ability; allows for repeated treatments.	Insufficient targeting; poor water solubility of some sonosensitizers, making them prone to aggregation; reduced therapeutic precision for deep-seated lesions.	Combined with immune checkpoint inhibitors and CAR-T cell therapy to achieve synergistic effects.
Nanozyme	Flexible design of catalytic activity allows for the development of nanozymes with specific enzyme-like activities tailored to the characteristics of the tumor microenvironment; exhibits tumor microenvironment responsiveness and targeting capabilities.	Potential biosafety concerns; has off-target effects.	Can combined with immunotherapy to achieve synergistic effects.

and in vivo correlations and advancing lymphoma diagnosis and treatment. For instance, researchers have developed patient-derived lymphoma organoid (PDLO) models to evaluate and target the tumor immune microenvironment in follicular lymphoma, providing robust support for precision medicine in this context.[97] In addition, although traditional cell line-derived xenograft (CDX) models are widely used, standard immunodeficient mice (eg, NSG) lack the key humanized cytokines required to support the growth of human lymphoma cells, rendering intraperitoneal or subcutaneous transplantation models inadequate for faithfully recapitulating systemic dissemination characteristics. Future drug screening models for lymphoma may adopt the patient-derived xenograft (PDX) model as a validation platform, as it preserves the original histological, molecular, and genetic features and heterogeneity of tumors while offering superior predictive value for clinical efficacy, thereby providing a more authentic simulation of the human TME.[98–100] For example, using NOD/ShiltJGpt as the genetic background with knockout of the Prkdc and IL2RG genes, a mouse PDX model can be established, resulting in functional defects in T cells, B cells, and NK cells, and exhibiting greater pathological similarity to clinical presentations. The anti-lymphoma nanomedicines and their delivery systems can gradually develop towards the clinical translation in lymphoma diagnosis and treatment.

Conclusion

In summary, from a single drug delivery platform to a programmable immune regulation centre to a multimodal therapeutic platform, nanotechnology has been transformed the treatment of lymphoma. The development of nanotechnology, innovative therapies including nanobody-based CAR-T, nanovaccines, biomimetic nanodelivery systems, and intelligence TME-responsive nanodelivery systems, has gradually transitioned from the laboratory stage to clinical application. These advancements open routes to providing the targeted drug delivery anti-lymphoma drugs that are

more effective and less toxic. Moreover, combined use of multiple anti-lymphoma nanotherapies presents new perspectives of anti-lymphoma treatments.

Funding

There is no funding to report.

Disclosure

The authors declare that they have no competing financial interests.

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