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Review Article

Nanotechnology-enhanced Chimeric Antigen Receptor-T Cell Therapy for Ovarian Cancer

Zhiwei Zheng[1], He Xu[1], Dandan Yang[1], Jing Yin[1], Kexin Si[1], Hao Ai[1,2] and Ying Liu[1,2*]

[1]*Liaoning Provincial Key Laboratory of Follicular Development and Reproductive Health, Jinzhou Medical University, Jinzhou, Liaoning, China;* [2]*Department of Gynaecology and Obstetrics, The Third Affiliated Hospital of Jinzhou Medical University, Jinzhou, Liaoning, China*

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Abstract

Chimeric antigen receptor (CAR)-T cell therapy faces significant challenges in treating solid tumors, including immune evasion, suppressive tumor microenvironments, and on-target/off-tumor toxicity, which limit its clinical efficacy. Although it has revolutionized treatment for hematological malignancies, these obstacles hinder its broader application in solid tumors. Nanotechnology offers innovative strategies to address these limitations through enhanced delivery, localization, and control. This review summarizes recent advances in nanotechnology-assisted CAR-T cell therapies for gynecologic cancers, with a particular focus on messenger RNA (mRNA)-based delivery systems, lipid nanoparticles, hydrogels, and external activation techniques such as photothermal and acoustogenetic modulation. The integration of nanotechnology, especially mRNA-based delivery systems, holds transformative potential for overcoming these barriers. mRNA enables transient, non-integrating expression of CARs, meaning the genetic modifications are temporary. This improves safety and allows flexible control over treatment intensity, while rational sequence optimization (e.g., codon usage, guanine-cytosine content, secondary structure) enhances mRNA stability and protein translation efficiency. Lipid nanoparticles, the leading delivery platform, can be engineered for cell-type specificity and tissue targeting through modulation of their components and surface functionalization. Recent innovations, including siloxane-modified lipid nanoparticles, injectable hydrogels, and photothermal or acoustogenetic activation strategies, enable precise spatiotemporal control of CAR-T cell function *in vivo*. In ovarian cancer, preclinical studies targeting nfP2X7 and employing multifunctional nanoparticles have demonstrated synergistic efficacy and tumor-specific delivery. This review highlights how nanotechnology platforms can be integrated with CAR-T cell therapies to enhance safety, precision, and therapeutic outcomes in ovarian cancer.

Introduction

Gynecologic malignancies, particularly ovarian cancer, pose significant clinical challenges due to their insidious onset, frequent recurrence, and limited responsiveness to conventional therapies.[1] These characteristics contribute to delayed diagnosis and poor long-term survival, making the development of novel, targeted therapies a clinical priority.[2] To address these limitations, nanotechnology-enhanced chimeric antigen receptor (CAR)-T cell therapy has emerged as a promising strategy. Among emerging treatment paradigms, CAR-T cell therapy has revolutionized hematologic cancer care,[3] but it faces substantial barriers in solid tumors, including immunosuppressive microenvironments,[4] inadequate T cell infiltration, and on-target/off-tumor toxicities.[5] Recent advances in messenger RNA (mRNA)-based delivery platforms, particularly using lipid nanoparticles (LNPs), have enabled transient and tunable CAR expression, offering potential for safer and more controllable therapy (Fig. 1). Integrating nanotechnology thus represents a transformative strategy to enhance CAR-T therapy efficacy, precision, and safety in solid tumors. In particular, mRNA-based delivery systems provide a non-viral, transient, and programmable platform for CAR expression,[6] while LNPs, tiny fat-like particles that protect mRNA and facilitate cellular entry, enable efficient intracellular delivery and organ-specific targeting.[7] Further innovations, including hydrogel scaffolds,[8] photothermal-responsive materials, and acoustogenetic modulation technologies, allow for localized, sustained, and externally controllable CAR-T cell activation. These interdisciplinary approaches not only expand the therapeutic window of CAR-T therapies but also en-

Keywords: Chimeric antigen receptor; CAR; CAR-T cell therapy; mRNA nano-delivery system; Lipid nanoparticle; Ovarian cancer; Hydrogel-based immunotherapy; Photothermal and acoustogenetic modulation.

***Correspondence to:** Ying Liu, Liaoning Provincial Key Laboratory of Follicular Development and Reproductive Health, Jinzhou Medical University, 2, Section 5, Heping Road, Linghe District, Jinzhou, Liaoning 121000, China. ORCID: https://orcid.org/0000-0002-4138-4974. Tel: +86-13897881924, E-mail: miraclepeking2010@163.com

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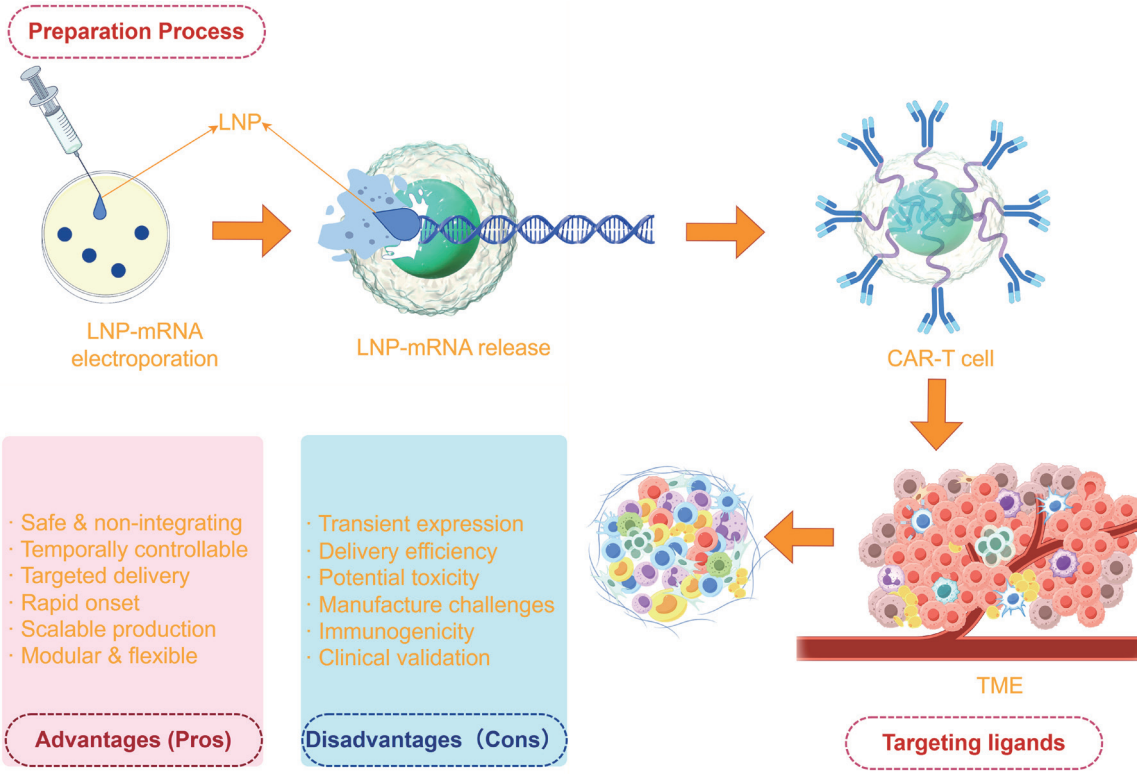

Fig. 1. Advantages and challenges of LNP–mRNA delivery systems for engineered cell therapy. Created with Figdraw. LNP-based mRNA delivery enables safe, transient, and controllable protein expression with rapid kinetics and scalable production. However, challenges include immunogenicity, manufacturing complexity, and limited clinical validation. Promising applications include CAR-T cell engineering and ligand-directed targeting within the tumor microenvironment (TME). CAR, chimeric antigen receptor; LNP, Lipid Nanoparticles; mRNA, messenger RNA.

able synergistic multimodal interventions. This review systematically examines recent advances in nanotechnology-assisted CAR-T engineering, focusing on mRNA delivery, carrier optimization, and biomaterial platforms, while highlighting promising preclinical applications in ovarian cancer. By elucidating the mechanistic basis and translational potential of these integrated strategies, we aim to chart a path toward next-generation, precision-targeted immunotherapies in ovarian cancer.

In addition to CAR-T therapy, other immunotherapeutic approaches have been explored in ovarian cancer. Immune checkpoint inhibitors targeting programmed death 1/ programmed death ligand 1 and cytotoxic T-lymphocyte-associated protein 4 have shown limited efficacy as monotherapy but may offer benefit when combined with chemotherapy or anti-angiogenic agents. Cancer vaccines based on whole tumor lysates or neoantigens are under investigation,[9] although few have advanced to late-phase trials. Tumor-infiltrating lymphocyte (TIL) therapy has shown promise in small clinical studies but remains logistically complex. For CAR-T therapy specifically, clinical data in ovarian cancer remain limited. A Phase I clinical trial (NCT02498912) evaluating MUC16-targeted CAR-T cells demonstrated safety and partial responses in patients with recurrent ovarian cancer. Integrating these approaches with mRNA-based CAR-T cell therapies holds substantial promise for enhancing antitumor efficacy. Checkpoint inhibitors can alleviate immunosuppressive signals that limit CAR-T cell function, while TIL therapies broaden the immune response repertoire, complementing CAR-T activity. This combinatorial strategy may overcome limitations such as T cell exhaustion and tumor heterogeneity, thereby promoting a more robust and durable immune attack on ovarian cancer cells. Furthermore, mRNA nano-delivery systems enable co-expression of immunomodulatory molecules (e.g., bispecific antibodies or cytokines), which can synergize with checkpoint blockade and TIL therapies to favorably modulate the tumor microenvironment.

This review is organized into several key sections: we first introduce the principles and advantages of mRNA-based CAR-T engineering; then explore structural optimization of mRNA and LNP carriers; followed by discussions on hydrogel-based delivery, photothermal, and acoustogenetic control strategies; and finally, we highlight preclinical applications in ovarian cancer and address translational challenges.

mRNA-based CAR-T technologies

Principles of mRNA therapy

mRNA is a single-stranded ribonucleic acid transcribed from DNA that carries the genetic information required for protein synthesis. Upon delivery into cells, mRNA is translated into functional proteins. The therapeutic potential of mRNA was first demonstrated in 1990, when Wolff and colleagues successfully achieved expression of *in vitro*-transcribed mRNA in mouse skeletal muscle cells, thereby establishing a foundation for mRNA-based therapies.[10] *In vivo*, mRNAs are synthesized through transcription mediated by RNA polymerases, generating precursor mRNAs that contain non-coding introns. These precursors undergo post-transcriptional

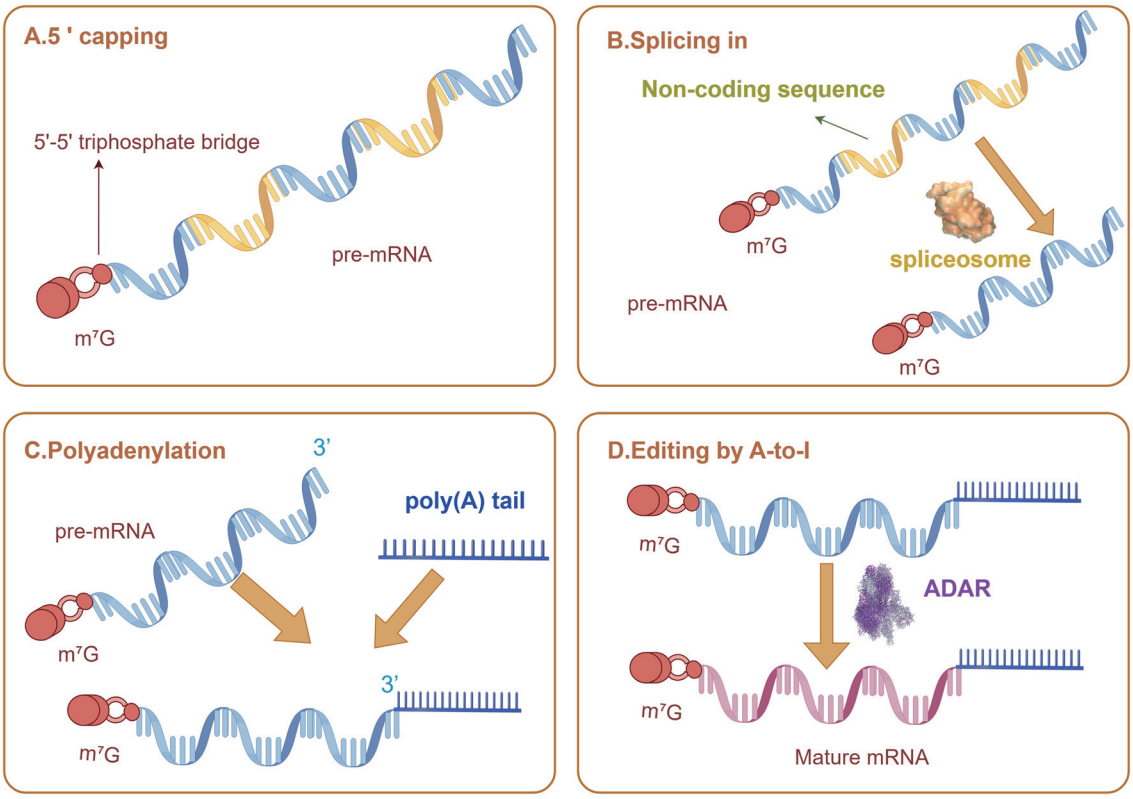

Fig. 2. Post-transcriptional processing of pre-mRNA. Created with Figdraw. This schematic shows, in sequence, the four key processing steps required to transform a eukaryotic pre-mRNA into mature mRNA. These steps ensure mRNA stability, efficient transport from the nucleus to the cytoplasm, and correct translation. ADAR, adenosine deaminase acting on RNA; mRNA, messenger RNA.

modifications, including 5′ capping, splicing, polyadenylation, and A-to-I editing, to form mature mRNAs suitable for translation into proteins (Fig. 2).[11]

Advantages of mRNA nano-delivery systems

Recent advances in mRNA synthesis, chemical modification, and delivery technologies have significantly accelerated the development of mRNA therapeutics.[12] The success of mRNA-based COVID-19 vaccines not only validated this platform clinically but also catalyzed interest in applying mRNA technologies to cancer immunotherapy, including CAR-T cell engineering.[13] Nano-delivery systems have emerged as promising non-viral vectors for delivering CAR-encoding mRNA into T cells or other immune cells, enabling efficient generation of functional CAR-T cells.[14] Compared with traditional viral vectors, mRNA nano-delivery platforms offer several distinct advantages that enhance their clinical potential.[15] These systems exhibit superior biosafety, as mRNA functions transiently in the cytoplasm without integrating into the host genome, thereby avoiding the risk of insertional mutagenesis. They also allow precise control over gene expression, with tunable dosing and administration frequency enabling fine temporal regulation.[16] Nanocarriers can be decorated with targeting molecules, such as antibodies, to deliver mRNA specifically to certain cell types, improving delivery precision and therapeutic selectivity.[17] Because mRNA does not require nuclear entry, translation in the cytoplasm is rapid and efficient, a process further enhanced by optimized sequences and chemical modifications.[18] In terms of production, mRNA and its carriers can be synthesized quickly and scaled efficiently in cell-free systems, in contrast to the limitations of cell-based viral vector manufacturing.[19] Additionally, mRNA nanocarriers can act as intrinsic immune adjuvants by stimulating innate immune responses, a property that can be tuned to synergize with adaptive immunity for antitumor effects.[20] Importantly, their modular and flexible design enables the incorporation of complex constructs such as bispecific antibodies,[21] cytokines,[22] and co-stimulatory molecules that are often difficult to deliver via viral vectors.[23] Collectively, these features position mRNA nano-delivery systems as a powerful platform for advancing next-generation CAR-T cell therapies.

Structural design and synthesis of mRNA nano-delivery systems

mRNA nano-delivery systems typically consist of two key components: a core mRNA payload and an external nanocarrier shell.[24] Rational design of the mRNA sequence based on the target protein allows for enhanced expression of tumor-associated antigens in antigen-presenting cells or T cells, thereby boosting antitumor immune responses. Encapsulation of mRNA within carriers, such as LNPs, protects it from enzymatic degradation by RNases and facilitates targeted delivery to specific tissues or immune cell populations.[25] Both the engineering of the mRNA payload and the design of the nanocarrier vehicle are therefore crucial determinants of therapeutic efficacy.[26]

Structural optimization of mRNA

Therapeutic mRNAs are typically synthesized by *in vitro* transcription from a linearized DNA template.[27] A complete mRNA

Table 1. Comparison of mRNA nanocarriers and viral vectors for CAR expression (mRNA nanocarriers offer safer, non-integrating, and more controllable expression but face limitations in duration and *in vivo* persistence)

Feature	mRNA nanocarriers	Viral vectors	Feature
Genome integration risk	No integration	Possible insertional mutagenesis	Genome integration risk
Expression duration	Short (transient)	Long-lasting	Expression duration
Immunogenicity	Tunable	Higher risk	Immunogenicity
Manufacturing speed	Rapid, cell-free	Slower, cell-based	Manufacturing speed
Scalability	High (*in vitro* synthesis)	Limited by viral production systems	Scalability

CAR, chimeric antigen receptor; mRNA, messenger RNA.

transcript consists of five components: the 5′ cap, the 5′ untranslated region, the open reading frame, the 3′ untranslated region, and the 3′ poly(A) tail. The coding sequence (CDS) within the open reading frame encodes the antigen, antibody, or functional protein of interest.[28] Enhancing expression of exogenous proteins often involves optimizing the CDS region to improve translation efficiency and protein yield.[29]

Codon optimization is a widely used strategy that replaces rare codons with synonymous, frequently used codons to align with the host's tRNA abundance.[30] This improves mRNA stability and translation efficiency, particularly near the start codon, where optimal codon usage enhances ribosomal elongation and reduces the likelihood of translational stalling.[31] Higher guanine-cytosine content is associated with improved secondary structure stability and prolonged transcript half-life. For example, rare codons can hinder translation and even trigger mRNA degradation by slowing ribosome progression.[32]

The secondary structure of mRNA, defined by its folding free energy, plays a critical role in transcript stability and expression. mRNAs with more stable secondary structures (i.e., lower free energy) typically exhibit longer intracellular half-lives and higher protein output.[33]

Selection and engineering of nanocarriers

The efficiency of mRNA delivery is closely dependent on the properties of the nanocarrier system.[34] Lipid-based and polymer-based nanoparticles have emerged as the most promising platforms for delivering negatively charged, easily degradable mRNAs into the cytoplasm of immune cells.[35] These nanocarriers enhance mRNA stability, reduce cytotoxicity, and facilitate intracellular trafficking at relatively low manufacturing costs.[36]

Among these, LNPs are the most extensively studied and clinically validated.[37] They typically comprise four components: ionizable lipids, cholesterol, helper phospholipids, and polyethylene glycol (PEG)-lipids.[38] Ionizable lipids enable the particles to release their mRNA cargo once inside the cell by becoming positively charged in the acidic environment of endosomes. Cholesterol adds stability to the nanoparticle structure and assists with membrane fusion. Helper phospholipids support the particle's shape and facilitate interactions with cell surfaces. PEG-lipids form a protective outer layer that prevents rapid clearance by the immune system, allowing prolonged circulation. Ionizable lipids, positively charged at low pH, form electrostatic complexes with negatively charged mRNA molecules during formulation and facilitate endosomal escape following cellular uptake.[39] Cholesterol improves particle stability, promotes membrane fusion, and enhances cytoplasmic delivery.[40] Helper phospholipids stabilize the lipid bilayer and modulate phase behavior, while PEG-lipids enhance colloidal stability, reduce opsonization, and prolong circulation time.[41]

LNPs offer several advantages over viral vectors, including reduced immunogenicity, larger cargo capacity, and a lower risk of insertional mutagenesis.[42] Furthermore, their formulation can be tailored for organ-specific delivery.[43] For instance, increasing the proportion of cationic lipid (2,3-Dioleoyloxy-propyl)-trimethylammonium chloride (DOTAP) can shift LNP biodistribution toward pulmonary tissues,[44] while modifications to cholesterol structure can bias delivery toward hepatic T cells. Notably, a study identified heterocyclic lipopolyamines that not only improve mRNA transfection but also enhance innate immune activation via STING pathway signaling, further potentiating antitumor immunity.[45]

Surface modifications of LNPs with targeting ligands or by modulating PEG characteristics (e.g., PEG length, shedding kinetics, and protein corona composition) allow fine-tuned control of biodistribution and cellular uptake.[46] However, a balance must be struck: while longer PEG chains extend circulation time and reduce nonspecific serum interactions, they may hinder membrane fusion and impair endosomal escape.[47] Thus, careful optimization of both core and carrier components is essential to achieve robust, safe, and tissue-specific mRNA delivery (Table 1).

Progress in clinical application of mRNA-LNP for CAR-T cell therapy

The application of LNP-mediated mRNA delivery in CAR-T cell therapy has advanced rapidly in recent years, demonstrating both feasibility and therapeutic potential.[48] In 2020, a study demonstrated the use of LNPs to deliver CAR-encoding mRNA into primary human T cells *in vitro*, achieving efficient functional protein expression.[49] Ongoing clinical studies are typically conducted in early-phase (Phase I/II) formats, assessing the safety, persistence, and antitumor efficacy of mRNA-engineered CAR-T cells delivered via LNPs. These trials often employ short-lived mRNA constructs to minimize long-term risk, with repeated dosing strategies tested for sustained response. The strengths of mRNA-LNP systems include their non-integrating nature, rapid production, flexible design, and lower immunogenicity compared to viral vectors. Moreover, mRNA allows temporal control of CAR expression, which is beneficial for managing toxicity. However, limitations include the transient duration of expression, potential innate immune activation from RNA sensors, and the need for repeated administrations. The efficient delivery of mRNA to T cells *in vivo* remains an ongoing challenge (Table 2). This seminal work established LNPs as a viable non-viral platform for transient CAR expression, laying the foundation for mRNA-based CAR-T cell engineering. However, viral vectors, particularly lentiviral vectors, enable long-term, stable CAR expression, which is critical in many clinical protocols requiring durable antitumor activity, making them a well-established choice for hematologic malignancies.

Table 2. Summarizes the key strengths and limitations of using mRNA nanocarriers for CAR-T cell engineering

Aspect	Pros	Cons
Safety	No risk of genomic integration; reduced long-term adverse effects	Requires repeated administration due to transient expression
Manufacturing	Scalable, cell-free, rapid production	Sensitive to RNase degradation; cold-chain dependent
Design flexibility	Easily programmable, allows for rapid modification of CAR sequences	Sequence needs optimization to avoid innate immune activation
Regulatory potential	Lower regulatory complexity compared to viral vectors	Novel delivery systems face approval uncertainties
Control over expression	Temporal control allows better toxicity management	Short expression window may limit persistence and efficacy

CAR, chimeric antigen receptor; mRNA, messenger RNA.

As interest in mRNA-LNP therapeutics surged, researchers focused on optimizing the delivery system to address key challenges such as formulation complexity, manufacturing scalability, and transfection efficiency.[50] Formulation modifications have been shown to dramatically influence T-cell transfection efficiency. Among various formulations tested, the B10 LNP emerged as a promising candidate for CAR-mRNA delivery, offering enhanced efficiency and potential for clinical translation.[51]

In 2024, a team achieved a milestone in targeted delivery by enabling simultaneous organ- and cell-type-specific mRNA delivery. Utilizing advanced targeting moieties, they demonstrated precise mRNA delivery across multiple tissues, expanding the therapeutic versatility of LNP-based platforms.[52]

Concurrently, another group developed an acid-sensitive linker, "azido-acetal," to design rapidly degradable LNPs.[53] These carriers consisted of PEGylated lipids conjugated to azido-acetal moieties, enabling hydrolysis within the acidic environment of endosomes. In both *in vitro* and *in vivo* models, rapidly degradable-LNPs significantly outperformed conventional LNPs, delivering mRNA to the liver, lung, spleen, and brain, as well as to hematopoietic stem/progenitor cells. This work highlights the potential of modulating degradation rates as a strategy to tune intracellular delivery kinetics and enhance therapeutic efficacy.

mRNA delivery offers unique advantages in the CAR-T context by enabling transient, non-integrating expression of chimeric receptors. This allows more controlled dosing, reduced toxicity, and iterative design adjustments without permanent genomic modification. Such flexibility is particularly important in solid tumor contexts where antigen specificity and safety are major concerns. The ability to rapidly reprogram T cells via mRNA also accelerates preclinical testing and patient-specific customization. Looking ahead, next-generation mRNA platforms may incorporate multiplexed antigen targeting, RNA switches for conditional activation, or self-amplifying RNA systems for prolonged expression. Emerging technologies, such as *in vivo* CAR-T generation, where LNPs directly deliver CAR-encoding mRNA into circulating T cells, and AI-guided optimization of codon usage and RNA secondary structures, may dramatically enhance the precision and efficacy of CAR-T therapy. These advances could fundamentally shift the paradigm from ex vivo cell engineering to rapid, on-demand immunotherapy.

Optimization strategies for next-generation mRNA nanocarriers

One emerging strategy for LNP optimization involves the incorporation of silicone-based materials. In October 2024, a group introduced a new class of silicone-modified lipid nanoparticles (SiLNPs) by integrating siloxane amines with alkylated tail groups, including epoxides, esters, and amides.[54] Systematic structure–activity relationship studies revealed that parameters such as the number of cyclic siloxane units, tail length, substitution pattern, and lipid morphology significantly influence cellular uptake and endosomal escape (Fig. 3).

These modified SiLNPs demonstrated enhanced organ-specific delivery, achieving selective mRNA transfection in tissues such as the lung, liver, and spleen. The study confirmed that rational design of siloxane-modified lipids can modulate the biodistribution and target specificity of LNPs, paving the way for precision-targeted mRNA therapeutics.

Developmental maturity of mRNA-based CAR-T technologies

While significant progress has been made in the engineering and delivery of mRNA-based CAR-T therapies, it is important to delineate the maturity levels of different approaches to inform clinical translation efforts. Most nanocarrier platforms, including LNPs optimized for CAR mRNA delivery, have demonstrated robust efficacy in preclinical animal models but remain in early development stages, focusing on optimization of stability, targeting, and safety profiles. For example, hydrogel-based delivery systems and acoustogenetic or photothermal control strategies are largely experimental and currently confined to preclinical validation.

Conversely, certain mRNA CAR-T modalities leveraging clinically validated LNP platforms have progressed into early-phase clinical trials, particularly for hematologic malignancies and select solid tumors, marking critical milestones toward clinical adoption. Moreover, the recent successful application of mRNA technology in COVID-19 vaccines provides a translational framework and regulatory precedent that supports expedited clinical evaluation of mRNA CAR-T products. However, combination immunotherapy strategies integrating checkpoint inhibitors or TILs with mRNA CAR-Ts are still predominantly under investigation in preclinical settings.

Hydrogel platforms for localized CAR-T cell delivery

Hydrogels have emerged as a promising biomaterial-based platform for the localized and sustained delivery of CAR-T cells, offering an innovative alternative to systemic administration.[55] Among these, polymeric nanoparticle hydrogels are particularly attractive due to their self-assembling and injectable properties.[56] These hydrogels can be formulated under mild, cell-compatible conditions without requiring modification of the therapeutic cargo, enabling

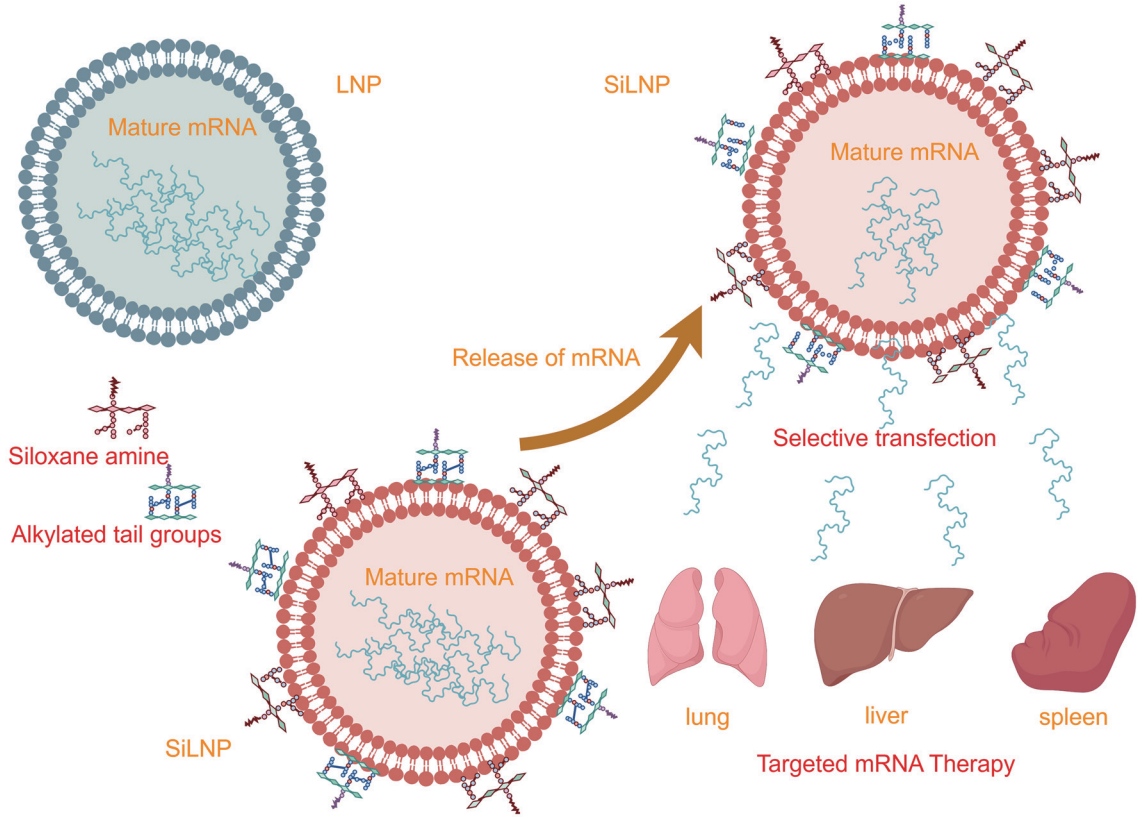

Fig. 3. Schematic representation of a silicon-based lipid nanoparticle (SiLNP)-Based mRNA-targeted delivery System. Created with Figdraw. This schematic compares the mechanism and effect of mRNA delivery between conventional lipid nanoparticles (LNP, left) and silicone-modified lipid nanoparticles (SiLNP, middle and lower panels). mRNA, messenger RNA.

the direct encapsulation of CAR-T cells and immunomodulatory agents such as cytokines.[57] Upon administration, they form a transient inflammatory niche that promotes the expansion, activation, and persistence of CAR-T cells at the tumor site, significantly enhancing antitumor efficacy.[58] This niche is characterized by the local release of cytokines such as interleukin (IL)-2, IL-15, and granulocyte-macrophage colony-stimulating factor, which activate JAK/STAT and PI3K/AKT pathways to enhance CAR-T cell proliferation and survival. The temporary pro-inflammatory environment mimics natural immune activation without causing systemic toxicity.

In a notable example, one group developed an injectable Gelatin Methacryloyl-based hydrogel system termed i-GMD for local CAR-T cell delivery.[59] This photo-crosslinkable hydrogel retains excellent solubility prior to injection and rapidly forms a three-dimensional scaffold upon UV irradiation. The resulting matrix provides a supportive microenvironment that preserves CAR-T cell viability and proliferation within the immunosuppressive tumor microenvironment. Notably, this system allows for non-invasive, localized delivery of CAR-T cells, enabling their prolonged retention and gradual release at the tumor site without the need for surgical intervention.

Moreover, the hydrogel matrix can be co-loaded with various therapeutic agents, including cytokines, monoclonal antibodies, immune checkpoint inhibitors, and small-molecule drugs, to further modulate the immune response and synergistically enhance antitumor activity. This multifunctional capability positions hydrogel-based platforms as a highly versatile strategy for the next generation of localized, programmable CAR-T cell therapies.

Photothermal therapy (PTT) synergy with CAR-T cells

The integration of PTT with CAR-T cell therapy presents a powerful strategy to overcome the limitations of immunotherapy against solid tumors.[60] PTT leverages exogenous energy sources, such as near-infrared (NIR) light, to generate localized hyperthermia via photothermal agents, enhancing both direct tumor ablation and immune activation.

One team developed a biodegradable polydopamine-coated chromium-based nanosystem with strong photothermal conversion capacity.[61] Upon targeted NIR laser irradiation, the system induces localized hyperthermia, effectively ablating solid tumor cells through the PTT mechanism. In a preclinical mouse model, NIR irradiation raised tumor temperature by approximately 10°C within 5 m, leading to 70% tumor cell death and a significant reduction in tumor volume after treatment. Beyond direct cytotoxicity, this approach also triggers systemic immune activation, as evidenced by elevated serum levels of key cytokines, including IL-2, interferon-gamma, and tumor necrosis factor-alpha, which collectively enhance CAR-T therapy antitumor immunity. Furthermore, localized hyperthermia induced by NIR irradiation upregulates the expression of chemokines such as CXCL9 and CXCL10, and adhesion molecules like ICAM-1 and VCAM-1 within the tumor microenvironment. These factors facilitate T cell trafficking

and infiltration, increasing CAR-T cell accumulation at the tumor site and improving therapeutic outcomes.

Complementing this thermal strategy, one team pioneered an acoustogenetic approach that utilizes magnetic resonance imaging-guided focused ultrasound to spatially control engineered CAR-T cell activation *in vivo*.[62] By allowing gene expression to be turned "on" only within the targeted tumor region, this technique minimizes off-target toxicity and reduces immune-related adverse effects in healthy tissues. By transducing acoustic signals into genetic responses, this method enables precise, non-invasive activation of T cells within defined anatomical regions, thereby minimizing off-target effects and enabling the targeting of antigens that may otherwise be expressed in healthy tissues.

Further advancing this field, one group engineered temperature-responsive gene switches that enable photothermal control of CAR-T cell activity *in situ*.[63] In this system, synthetic switches activate transgene expression under mild hyperthermic conditions (40–42°C), induced by gold nanorod-mediated photothermal heating. *In vitro*, transient heating (15–30 m) resulted in up to a 60-fold increase in transgene expression without impairing T cell viability, migration, or cytotoxic function. In murine models, this approach enabled localized expression of IL-15 superagonists or bispecific T cell engagers targeting NKG2D ligands, enhancing antitumor efficacy while mitigating systemic adverse effects. Notably, this photothermal control strategy also showed potential in overcoming antigen escape in metastatic tumor settings.

Together, these advances underscore the potential of integrating photothermal or acoustic modulation with genetic engineering to spatially and temporally regulate CAR-T cell functions, offering a new dimension of precision in cancer immunotherapy.

Application of CAR-T and nanoparticle technologies in ovarian cancer

Ovarian cancer remains one of the most lethal gynecologic malignancies, largely due to its asymptomatic progression and high recurrence rate after standard therapy.[64] Emerging strategies based on CAR-T cell therapy and nanomedicine are being actively explored to address these challenges.[65]

One promising CAR-T target is non-functional P2X7 (nfP2X7),[66] an aberrantly expressed variant of the P2X7 receptor found on the surface of various malignant cells, including ovarian cancer cells. Owing to its restricted expression in normal tissues, nfP2X7 has attracted attention as a selective target for adoptive immunotherapy. Researchers successfully constructed nfP2X7-specific CAR-T cells and demonstrated potent cytotoxic activity against ovarian cancer cells across multiple platforms, including monolayer cell culture, 3D spheroid models, and *in vivo* mouse models. These findings highlight the therapeutic potential of nfP2X7-directed CAR-T cells in overcoming the immunosuppressive ovarian tumor microenvironment.

In addition to cellular therapies, nanoparticle-based drug delivery systems are making significant advances in ovarian cancer treatment.[67] A study developed a tumor-penetrating nanoparticle platform for the co-delivery of adavosertib (a Wee1 G2 checkpoint kinase) and olaparib (a poly ADP-ribose polymerase inhibitor).[68] The tumor-penetrating nanoparticle-adavosertib-olaparib formulation effectively targets ovarian tumor tissue, enhances intratumoral drug accumulation, and improves therapeutic efficacy while minimizing systemic toxicity. This co-delivery strategy exemplifies the power of nanomedicine to achieve synergistic combination therapy within a single platform.

Further expanding the diagnostic and therapeutic integration of nanotechnology, one group engineered a multifunctional nanocarrier by coordinating cotton phenol and a cisplatin derivative with Fe^{3+} ions, followed by hyaluronic acid coating to target CD44-overexpressing ovarian cancer cells.[69] The resulting HA@PFG nanoparticles exhibited high tumor specificity, deep tissue penetration, redox-sensitive drug release, and excellent imaging contrast both *in vitro* and *in vivo*. Mechanistically, the therapeutic efficacy is driven by the synergistic effects of cisplatin-mediated DNA damage, Fe^{3+}-induced ferroptosis, and oxidative stress. These nanoparticles exemplify the therapeutic potential of nanocarriers that simultaneously diagnose and treat ovarian cancer.

Together, these preclinical advances underscore the promise of both CAR-T and nanoparticle-based strategies in ovarian cancer therapy. Their ability to selectively target tumor cells, modulate the tumor microenvironment, and reduce systemic toxicity offers a compelling path forward for personalized and precision treatment in this challenging malignancy.

While the clinical experience with CAR-T therapy in ovarian cancer is still maturing compared to hematologic malignancies, early-phase trials have provided critical insights into target feasibility, safety, and prevailing challenges, such as the immunosuppressive tumor microenvironment. As summarized in Table 3.[66] Key Clinical Trials of CAR-T and mRNA-CAR-T Platforms in Ovarian Cancer: Targets, Outcomes, and Translational Potentialkey trials targeting antigens like MUC16 (NCT02498912) and mesothelin (NCT01583686) have demonstrated preliminary evidence of anti-tumor activity and manageable safety profiles. However, the limited persistence and potency of CAR-T cells in solid tumors highlight the need for innovative approaches. This is where the mRNA-CAR-T platform holds significant translational promise. Its transient nature allows for safer targeting of antigens with potential on-target/off-tumor concerns (e.g., MUC16, mesothelin), enabling rapid dose-finding and toxicity management. Furthermore, the flexibility of mRNA-LNP systems facilitates the co-delivery of immunomodulatory cargoes, positioning this platform as a powerful tool to overcome the immunosuppressive barriers identified in earlier trials, such as those targeting folate receptor alpha (NCT03615313). The promising preclinical data targeting nfP2X7 using mRNA-LNPs further underscore the platform's potential for rapid clinical translation in ovarian cancer.

Despite the promising potential, this review has several limitations. Most of the evidence presented is derived from preclinical models, and limited clinical data are currently available to validate these strategies in human subjects. Additionally, the scalability and reproducibility of complex nanomaterial systems, such as SiLNPs or hydrogel-CAR-T formulations, remain to be fully resolved. Regulatory approval pathways for combination nanomedicine and cellular therapies are also underdeveloped, introducing uncertainty for clinical translation. From an ethical and regulatory perspective, the clinical translation of mRNA nanotechnology-based CAR-T therapies must navigate complex frameworks. The U.S. Food and Drug Administration (FDA) classifies products combining drugs, biologics, and devices, such as mRNA nano-delivery systems with CAR-T cells, as combination products, requiring coordinated review under specific regulations (21 CFR Part 3). Developers must comply with FDA guidance on manufacturing controls, nanoparticle characterization, and safety monitoring to address potential risks unique to nanomaterials, including biodistribution and long-term toxicity. Additionally, the FDA increasingly emphasizes nanoparticle tracking technologies (e.g., radiolabeling, fluorescence tagging) to monitor *in vivo* fate and ensure patient safety in clinical

Table 3. Key clinical trials of CAR-T and mRNA-CAR-T platforms in ovarian cancer: targets, outcomes, and translational potential

Trial identifier	Target antigen	Platform / Vector	Phase	Key clinical outcomes	Safety profile	mRNA-CAR-T platform potential assessment
NCT02498912	MUC16 (CA-125)	Viral vector	I	Partial responses observed in patients with recurrent ovarian cancer	Manageable cytokine release syndrome (CRS)	↑High Potential: Transient expression is ideal for managing potential on-target/off-tumor toxicity
NCT01583686	Mesothelin	Viral vector	I/II	Disease stabilization; CAR-T cell persistence observed in some patients	Acceptable safety, with one case of severe CRS	↑High Potential: Allows for safer "dose-titration" exploration of targets expressed in normal tissues.
NCT03615313	Folate receptor alpha (FRα)	Viral vector	I	Limited antitumor activity; highlighted immunosuppressive icroenvironmentas a barrier.	Well-tolerated.	↑High Potential: Suitable for combinatorial designs with immunomodulators to overcome suppression.
Preclinical (Bandara *et al*., 2023[66])	nfP2X7	mRNA-LNP (Preclinical)	N/A	Potent cytotoxic activity in vitro and in vivo.	Good specificity in preclinical models	↑Very High Potential:Ideal for rapid clinical translation of this promising target with minimized risk

↑ denotes an advantage or high potential. CAR, chimeric antigen receptor; LNP, lipid nanoparticle; mRNA, messenger RNA.

trials. Ethical considerations include informed consent detailing novel delivery platforms and post-treatment surveillance to manage unforeseen adverse effects. Such regulatory specificity provides practical pathways but demands rigorous documentation and collaboration with regulatory bodies to facilitate safe and effective clinical deployment. Finally, while this review focuses on ovarian cancer, broader tumor-specific factors and interpatient variability may impact generalizability. Future clinical studies are essential to confirm the translational potential of these nanotechnology-assisted CAR-T therapies.

Challenges and limitations

Despite promising preclinical outcomes, several critical challenges remain for translating nanotechnology-integrated CAR-T therapies into clinical practice. First, the large-scale, reproducible manufacturing of LNP formulations is technically complex, requiring tight control over particle size, charge, and encapsulation efficiency. Second, immune responses to nanoparticle components, particularly PEGylated lipids, can lead to accelerated blood clearance or allergic reactions, complicating repeated dosing strategies. Third, the regulatory landscape for combination products involving both advanced biologics and nanomedicine is still evolving, posing uncertainties in approval timelines and pathways. Finally, the high cost of CAR-T manufacturing and nanoparticle synthesis raises questions about scalability and access, especially in resource-limited settings. Addressing these issues will be critical for ensuring the safe, effective, and equitable application of these cutting-edge therapies.

Conclusions

The convergence of nanotechnology and CAR-T therapy offers unprecedented opportunities to overcome the intrinsic limitations of solid tumor immunotherapy, particularly in gynecologic malignancies such as ovarian cancer. Advances in mRNA-based nonviral delivery systems have demonstrated substantial improvements in safety, controllability, and scalability, while innovations in nanocarrier composition and surface functionalization allow for cell-specific, organ-targeted delivery. Biomaterial platforms such as hydrogels enable localized and sustained CAR-T cell release, and external activation strategies, including photothermal and acoustogenetic modulation, provide precise spatiotemporal control over T cell function. Despite encouraging preclinical evidence, key challenges remain, including optimizing *in vivo* delivery efficiency, minimizing immunogenicity, and navigating complex regulatory pathways for clinical translation. Continued interdisciplinary collaboration among immunologists, materials scientists, and clinicians will be essential to transform these technologies into safe, effective, and accessible treatments. Collectively, these emerging strategies represent a promising blueprint for the next generation of precision-engineered immunotherapies in ovarian cancer.

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Conflict of interest

The authors declare that they have no competing interests.

Author contributions

Study conception (ZZ, HA), data curation (ZZ), writing and editing (HX, DY, JY, KS), editing of the manuscript, study supervision (HA), writing of the manuscript, subject investigation, and literature review (YL). All authors have read and approved the manuscript.

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