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REVIEW

Innovative Strategies of Nanocapsules for Maximizing Efficacy in Tumor Immunotherapy

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Abstract: This review explores nanocapsules as a versatile platform to overcome the limitations of drug resistance inherent in conventional cancer therapy and immunotherapy. These nanosystems are capable of enhancing drug delivery, facilitating immune activation and modulating the tumor microenvironment. The review systematically classifies nanocapsules into distinct categories, including bacterial carriers, protein frameworks, lipids, metals, inorganic non-metals and polymers. Key findings demonstrate that nanocapsules possess the capacities for targeted delivery, stimuli-responsive release and synergistic combination with chemotherapy, radiotherapy, as well as photodynamic/photothermal therapy. However, several hurdles remain for their clinical translation, namely insufficient clinical trials and challenges in production scalability. In addition, the review discusses the impacts of different physical properties of nanocapsules and the underlying mechanisms of drug resistance. By uniquely integrating the classification of nanocapsules with corresponding therapeutic strategies, this review provides valuable insights for improving the efficacy of tumor immunotherapy.

Keywords: cancer immunotherapy, nanocapsules, drug delivery, tumor microenvironment, combined therapy

Introduction

Cancer remains a pressing global health concern with profound clinical and societal consequences. As of 2022, global data reported approximately 20 million new cases and 9.7 million deaths, with lifetime risk estimates indicating that one in five individuals may develop cancer, and roughly one in nine men and one in twelve women may die from it.[1] The burden of cancer varies considerably by region, gender, and age, with low- and middle-income nations confronting daunting barriers to prevention and treatment.[2,3]

Conventional therapies, including surgery, chemotherapy, and radiotherapy, are routinely employed but often fall short in terms of safety and tumor specificity.[4,5] These treatments frequently produce substantial side effects and exhibit limited discrimination between malignant and healthy cells, imposing heavy physical and psychological burdens on patients.[6,7] For instance, fatigue and pain are common adverse outcomes resulting from collateral damage to normal tissues during chemotherapy and radiotherapy.[8] Additionally, many malignancies are detected only in advanced stages, when the efficacy of standard interventions is diminished and the prognosis remains poor.[9,10]

Immunotherapy has become a promising alternative with notable advantages, particularly in terms of targeting precision and a more favorable side-effect profile.[11–14] This modality enables the selective recognition of tumor-specific antigens, allowing the immune system to effectively attack cancer cells while sparing healthy tissues.[15–17] Compared with traditional modalities, immunotherapy is generally associated with a lower incidence of adverse effects, which tend to be manageable.[18] For example, although immune checkpoint inhibitors may elicit autoimmune reactions,

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they can typically be controlled through appropriate clinical interventions.[19] Several studies have suggested that immunotherapies may offer improved safety in both systemic and localized toxicities relative to older treatments.[20] Nevertheless, high treatment costs and complexity of the underlying mechanisms present ongoing challenges. Therefore, immunotherapy is often administered alongside conventional treatments to enhance therapeutic benefits via multimodal strategies.[21]

Despite these advancements, immune resistance continues to limit treatment efficacy.[22–25] At present, clinical immunotherapy still faces three major challenges: low antigen delivery efficiency and insufficient immune activation; the immunosuppressive barrier of the tumor microenvironment (TME); and the dilemma of off-target toxicity and systemic immune-related adverse reactions. In response to these clinical difficulties, emerging nanotechnology has shown potential in these aspects. In particular, nanocapsules offer unique advantages in this context. Nanocapsules are sub-micron (10–1000 nm) vesicular drug-delivery systems with a well-defined shell–core structure, typically consisting of a polymeric or lipidic shell that encapsulates a liquid or solid active-pharmaceutical core. Engineered to enable targeted delivery, controlled release, and protection of the therapeutic agent from degradation, nanocapsules are extensively employed in oncology, vaccine delivery, gene therapy and related biomedical fields.[26]

To tackle inefficient antigen delivery and inadequate immune activation, nanocapsule-mediated strategies serve as effective optimization approaches. Encapsulation of antigens and adjuvants in polymeric or liposomal nanocarriers prevents in vivo degradation, prolongs circulation time, and enhances bioavailability. Surface modification with ligands (eg, mannose, specific antibodies) enables precise targeting of dendritic cell (DC) pattern recognition receptors, promoting cellular uptake and antigen presentation to boost immune activation. For instance, protein nanocapsules (NCs) developed by the Qizhen Zheng team efficiently deliver ovalbumin to pulmonary antigen-presenting cells (APCs) via vitronectin-enriched protein corona-mediated endocytosis, overcoming the key limitation of poor tissue targeting in traditional protein therapies.[27] Furthermore, nanocapsule-enabled co-delivery of antigens and adjuvants increases DC-driven proliferation of antigen-specific $CD4^+$ and $CD8^+$ T cells by severalfold, exerting superadditive effects with adjuvants to reduce tumor immune escape.[28]

Nanocapsules can disrupt the immunosuppressive tumor microenvironment (TME) through local modulation and microenvironment remodeling. Targeted delivery of immune checkpoint inhibitors (eg, PD-1 antibodies), IDO1 inhibitors, and metabolic modulators to tumor sites relieves immunosuppression while minimizing systemic toxicity.[29,30] In addition, encapsulation of lactate oxidase reduces intratumoral lactate levels to suppress regulatory T cell proliferation, and releases hydrogen peroxide to activate effector T cells, enhance their infiltration and cytokine secretion, alleviate immunosuppression, and synergize with checkpoint inhibitors to improve therapeutic efficacy.[31]

For controlling off-target toxicity and systemic immune-related adverse events (irAEs), nanocapsules improve safety through targeted accumulation and stimuli-responsive release. The enhanced permeability and retention (EPR) effect or active targeting modification elevates intratumoral drug concentrations and reduces exposure to normal tissues, thereby lowering irAE incidence. External stimuli (eg, temperature, ultrasound, light) or TME-specific cues (eg, low pH, high reactive oxygen species levels) trigger on-demand drug release, allowing precise regulation of immune response intensity and avoiding severe toxicities such as cytokine release syndrome (CRS) induced by excessive immune activation. A reported example involves radiation-responsive nanocapsules that release copper ions for tumor-specific activation, eliminating systemic copper ion exposure.[32]

This review provides a comprehensive overview of the roles and mechanisms of various nanocapsule systems in cancer immunotherapies. It examines bacterial-, protein-, lipid-, inorganic-, and polymer-based nanocapsules along with their integration into multimodal treatment regimens. The review also highlights the current challenges and future directions for optimizing nanocapsule use in clinical oncology.

Types and Challenges of Immunotherapy

Immune Checkpoint Inhibitors

Immune checkpoint inhibitors (ICIs), have demonstrated remarkable efficacy in treating various cancers.[33,34] Their mechanism primarily involves blocking immune suppression signaling pathways to enhance T cell anti-tumor activity.[35–

[37] Specifically, ICIs work by targeting cytotoxic T lymphocyte-associated antigen 4 (CTLA-4) and programmed death protein 1 (PD-1) along with their ligand PD-L1, thereby releasing the suppression on T cell activation and facilitating immune system attacks against tumor cells.[38,39]

In clinical practice, Immune Checkpoint Inhibitors (ICIs) have been approved by the US Food and Drug Administration (FDA) for treating various cancers, including malignant melanoma and non-small cell lung cancer (NSCLC).[40] These drugs include CTLA-4 inhibitors such as ipilimumab, PD-1 inhibitors like nivolumab and pembrolizumab, as well as PD-L1 inhibitors such as atezolizumab.[41,42]

Although immune checkpoint inhibitors (ICIs) have shown durable efficacy in multiple cancers, their clinical use is limited by low response rates (only ~20–30% of patients benefit), frequent primary and acquired resistance, and a lack of reliable predictive biomarkers. Resistance arises through complex mechanisms: immune-desert/excluded tumor microenvironments (T-cell absence or physical sequestration by stroma/macrophages), up-regulation of alternative checkpoints (LAG-3, TIM-3, TIGIT), IFN-γ/PD-L1 feedback loops, antigen-presentation defects (B2M, JAK1/2 mutations), and metabolic/hypoxic immunosuppression. These multi-layered escape pathways render single-agent ICIs insufficient, underscoring the need for combination strategies and individualized immune archetyping to guide therapy.[43]

Chimeric Antigen Receptor T-Cell Therapy

Over the past 20 years, the field of chimeric antigen receptor (CAR) T cell therapy has witnessed remarkable advancements, particularly in the management of hematological malignancies.[44] This innovative treatment modality involves the use of genetically engineered T cells to specifically target antigens that are overexpressed on the surface of tumor cells.[45,46] While CAR-T cells are commonly derived from the patient themselves (autologous), they can also be sourced from a donor (allogeneic).[47,48] The core of this therapy is the CAR, a synthetic receptor protein that enables T cells to precisely target a specific antigen and eliminate cancer cells.[49] CAR-T cell therapy is primarily indicated for hematologic malignancies, including acute lymphoblastic leukemia, diffuse large B-cell lymphoma, and chronic lymphocytic leukemia.[48,50] Furthermore, active exploration is underway to apply CAR-T therapy in certain solid tumors such as hepatocellular carcinoma and urological tumors.[51,52] In these applications, CAR-T cells exert their antitumor effects by recognizing tumor-specific or tumor-associated antigens. However, due to the complexity and diversity of solid tumors, further research and optimization are required for the clinical application of CAR-T therapy in these areas.[53] A recent review provides a detailed overview of six FDA-approved CAR-T cell therapies—such as Tisagenlecleucel, Axicabtagene ciloleucel, and Brexucabtagene autoleucel—including their indications, dosing regimens, clinical trial outcomes, pharmacokinetics, efficacy metrics (eg, ORR, CR, PFS, OS), and side effects (eg, CRS, ICANS, infections).[54]

Studies have shown that extracellular vesicles (EVs) serve as a novel strategy to enhance CAR-T efficacy.[55] EVs can replace conventional viral vectors, thereby avoiding their associated immunogenicity, insertional mutagenesis, and high costs. By engineering EVs—such as virus-mimetic fusogenic EVs—to deliver CAR genes directly to T cells, in vivo generation of CAR-T cells can be achieved, eliminating the need for ex vivo manufacturing. As "natural nanocapsules", EVs provide valuable insights for the application of synthetic nanocapsules in CAR-T therapy.

CAR-T cell therapy is distinguished by its high specificity and potent anti-tumor efficacy. However, this treatment carries associated adverse effects such as cytokine release syndrome (CRS) and neurotoxicity, which may pose safety risks to patients.[56] To address these challenges, researchers are developing multiple strategies including combination therapies with immune checkpoint inhibitors and structural optimizations of CAR-T cells.[57] Additionally, the immunogenicity of CAR-T cells remains a critical concern, as it could lead to treatment failure or severe immune reactions.[58]

Monoclonal Antibodies

The mechanisms and clinical applications of monoclonal antibodies in cancer immunotherapy have become a focal point in current oncology research. By recognizing and binding to specific antigens on tumor cell surfaces, these antibodies effectively orchestrate immune system attacks against cancer cells.[59] Not only do they directly eliminate tumor cells, but they also enhance immune responses through mechanisms such as complement activation and antibody-dependent cell-mediated cytotoxicity (ADCC).[60] Furthermore, monoclonal antibodies can activate immune checkpoints like PD-1, PD-

L1, and CTLA-4 to break tumor-mediated immune suppression, thereby restoring the anti-tumor activity of immune cells.[61]

In clinical practice, monoclonal antibodies have been extensively utilized in treating various solid tumors and hematologic malignancies. For instance, trastuzumab (anti-HER2), when administered to HER2-positive breast cancer patients, has significantly improved survival rates.[62] Similarly, cetuximab (anti-EGFR) and palmitimab (anti-EGFR) have demonstrated remarkable efficacy in managing metastatic colorectal cancer.[63] However, the therapeutic outcomes of monoclonal antibody therapies vary across patients due to factors such as individual differences, tumor microenvironment, and pharmacokinetic characteristics of the antibodies.[64]

While monoclonal antibodies show tremendous promise in cancer treatment, their clinical application faces several challenges. First, these therapies may trigger immune-related adverse events (irAEs), which require close monitoring and prompt intervention by clinicians. A comprehensive review of the benefits and safety profile of monoclonal antibodies further highlights the importance of managing these adverse events while maximizing therapeutic outcomes in cancer immunotherapy.[62] Second, the high cost and complex manufacturing processes of monoclonal antibodies limit their widespread use.[65] To address these challenges, researchers are exploring combination therapies—such as pairing monoclonal antibodies with other immunotherapies or chemotherapy drugs—to enhance efficacy and reduce adverse effects.[66]

Cancer Vaccines

The core logic of cancer vaccines is to transform "tumor antigens" into "self-vaccines". After subcutaneous or intravenous injection, antigens are taken up by dendritic cells, processed into peptides and loaded onto MHC-I and MHC-II molecules. DCS migrate to lymph nodes and provide costimulatory signals and cytokines to activate naive $CD8^+$ cytotoxic T cells and $CD4^+$Th1 cells. The expanded effector T cells enter the tumor through the blood stream and kill cancer cells through multiple mechanisms including perforin granzyme, Fas/FasL and IFN-γ. Some T cells further differentiate into memory phenotype and provide long-term immune surveillance.[67]

According to antigen form and delivery vector, tumor vaccines can be roughly classified into several major categories: cell vaccines, peptide/protein vaccines, nucleic acid vaccines, viral or bacterial vector vaccines, and in situ vaccines. The greatest advantage of tumor vaccines lies in their high specificity and low off-target toxicity, which can mobilize the body to form a pool of memory T cells, thereby eliminating residual lesions while reducing the risk of long-term recurrence.[68] When combined with immune checkpoint inhibitors, radiotherapy or ADCs, they can also amplify the overall therapeutic effect through the "abscopal effect".

Efficient lymph-node (LN)-targeted delivery of cancer vaccines via nanotechnology and tissue-engineering approaches markedly potentiates antitumor immunity. Changing nanocapsule size, shape, surface chemistry and stiffness enhances lymphatic drainage and dendritic-cell (DC) uptake; biomimetic strategies such as cell-membrane coating or DC-receptor ligands further enrich vaccines in tumor-draining LNs. Moreover, ex-vivo antigen-loaded DC vaccines, porous scaffolds, decellularized LN scaffolds that reconstruct artificial immune niches, and in-situ induction of tertiary lymphoid structures all effectively replicate or replace LN function, overcome immunosuppression, and improve cancer immunotherapy outcomes.[69]

However, the immunosuppressive microenvironment, including Tregs, MDSCs and the IDO pathway, often weakens the function of T cells induced by vaccines.[70,71] The prediction of neoantigens and the GMP preparation cycle are relatively long, and personalized mRNA still takes four to six weeks, which may delay the treatment of patients with rapid disease progression.[72] The objective response rate of single-agent therapy is generally less than 20%, and the effect is particularly insufficient for tumors with low mutation burden or antigen loss. Future trends will focus on multi-epitope - multi-platform sequential therapy, intraoperative real-time algorithms, in situ vaccines combined with ICIs, and universal vaccines that can cover common HLA supertypes, in order to improve efficacy while shortening the preparation time and reducing production costs.

Emerging Roles of Nanocapsules in Cancer Immunotherapy

Nanocapsules have gained prominence in modern oncological therapy owing to their versatile drug-release mechanisms, which can be categorized into several types. Passive Targeting: This mechanism exploits the

enhanced permeability and retention (EPR) effect typically present in tumor vasculature, enabling nanocapsules to accumulate selectively in tumor tissues.[73] The vascular structural basis of EPR effect is the enlarged endothelial gap (100–780 nm) of tumor neovascularization, basement membrane defect, pericyte and smooth muscle layer loss. Under the synergistic action of permeability regulators such as VEGF, NO, and bradykinin, it leads to the selective extravasation and retention of nanoscale drugs in tumor tissues to achieve passive targeting.

Active Targeting: In this approach, nanocapsules are functionalized with specific ligands, such as antibodies or receptor-targeting molecules that recognize and bind to antigens on tumor cell surfaces (eg, HER2, EGFR, CD44).[74] This targeted interaction facilitates increased drug accumulation within cancerous cells, enhancing the therapeutic outcomes.

Stimuli-Responsive Release: Certain nanocapsules are designed to release their payloads upon encountering specific internal cues within the tumor microenvironment, such as acidic pH, elevated temperatures, or enzymatic activity. For instance, Wang et al demonstrated that nanogels containing hydrazone linkages undergo degradation in acidic lysosomes. This triggers nanocapsule disintegration, rupture of the lysosomal membrane, and cytoplasmic release of ovalbumin (OVA) antigens, thus promoting enhanced antigen presentation.[75]

Controlled Release: Through strategic engineering of capsule composition—modifying aspects such as porosity, degradability, and drug-carrier interactions—researchers can fine-tune the drug release profile.[76] Such a control improves therapeutic precision, reduces systemic toxicity, and enhances clinical efficacy.

Given these functional advantages, nanocapsules are promising vectors for cancer immunotherapy. They are capable of efficiently delivering antigens and vaccines, and when co-administered with immune checkpoint inhibitors, they significantly enhance drug delivery efficiency, limit adverse effects, and strengthen anti-tumor immune responses.[77] The therapeutic activities of various nanocapsule types are summarized in Table 1. Table 2 compares the advantages and disadvantages of different nanocapsules.

Bacterial Vector-Based Nanocapsules

Nanocapsules employing bacterial carriers represent a novel and highly adaptable platform for cancer immunotherapy, offering the dual advantages of precise drug delivery to tumor tissues and modulation of immune responses. For instance, the probiotic strain *E. coli* Nissle 1917 has been engineered as a targeted vehicle to deliver tumor suppressor p53 and the anti-angiogenic protein Tum-5 to solid tumors, demonstrating the therapeutic potential of bacterial vectors in cancer treatment.[89] These systems are engineered to transport diverse therapeutic agents, including antigens, immune adjuvants, and cytotoxic drugs, to enhance the capacity of the host to detect and eliminate malignant cells.

One of the primary benefits of bacterial-derived nanocapsules is their ability to target antigen-presenting cells (APCs) such as dendritic cells, which initiate and orchestrate immune responses. Direct antigen delivery to APCs can significantly improve antigen presentation, leading to potent T cell activation and tumor-specific immune reactions. For instance, outer membrane vesicles (OMVs) derived from *Escherichia coli* (*E. coli*) were bioengineered to present E7 early protein from human papillomavirus type 16 (HPV16E7). The vesicular structure of OMV contributes to its efficient uptake by DCs. OMV surface contains pathogen-associated molecular patterns (PAMPs), such as lipopolysaccharide (LPS), which are recognized by pattern recognition receptors (such as Toll-like receptors, TLRs) on the surface of DCS to activate signaling pathways within DCs (such as the NF-κB pathway), thereby promoting DC maturation. In murine models bearing TC-1 tumors, OMVs induced robust E7-specific cellular immunity and suppressed tumor progression, demonstrating their potential as cancer vaccine platforms.[90]

Bacterial vector-based nanocapsules can enhance immunogenicity by mimicking natural microbial structures, stimulating both the innate and adaptive immune responses. In a study by Zhang et al, attenuated *Salmonella typhimurium* strain VNP20009 was employed as an immunomodulatory vector. After Salmonella lysis-inducing nanocapsules (SLINs) are taken up by Glioblastoma multiforme (GBM) cells, they degrade to release Gasdermin D (GSDMD) and L-arabinose, activating caspase-1 to cleave GSDMD; the resulting GSDMD-N forms pores in the membrane that trigger pyroptosis and discharge Damage-associated molecular pattern (DAMPs) such as ATP and HMGB1. Concomitant bacterial lysis releases Pathogen-associated molecular pattern (PAMPs) including LPS and DNA, stimulating macrophage Toll-like receptors, up-regulating TNF-α and IL-12, promoting DC maturation ($CD80^+CD86^+$), enhancing cross-presentation of tumor antigens, expanding Granzyme-B^+ $CD8^+$ T cells, and establishing immune memory. When combined with SLINs

Table 1 Evaluation of the Anticancer Immune Response of Different Nanocapsules in Tumor Models

Types	Shell	Particle Size (nm)	Targeting	Core	Encapsuled Molecules	Effects	Tumor Models	Refs
Bacterial vector	Exosome membrane	100	P-selectin	—	L-arabinose	Induced pyroptosis in GBM cells; Activated innate and adaptive immunity; Prevented postoperative GBM relapse	Glioblastoma	[78]
	DH5α Omp	120	Anti-GRP94	PLGA	EMB	Efficient BBB penetration; Targeted delivery to brain metastases; Reduced neuroserpin in cancer cells, restored plasmin activity; Inhibited vascular cooption, induced apoptosis	Breast cancer brain metastases	[79]
Protein	Protamine	100	HA-Man	Vitamin E and TPGS	Poly(I:C) and R848	Reprogrammed TAMs to M1-like phenotype; Reduced tumor growth and metastasis in mice; Increased secretion of pro-inflammatory cytokines (CXCL10, CCL5, IL-6).	Lung cancer	[80]
	Vault Protein	—	—	—	CCL21 packaged via fusion with the INT domain	Enhanced leukocyte infiltration ($CD3^+$ T cells, DCs); Reduced immunosuppressive cells (MDSCs, Tregs); Induced systemic antitumor T cell responses.	Lewis Lung Carcinoma	[81]
Lipid	Poly(ε-caprolactone)	208±15	—	—	AcE	Enhanced Tumor Sensitivity; Reduced secretion of pro-tumor factors; Metastasis Suppression	Melanoma	[82]
	Poly(ε-caprolactone)	214±18	—	—	MTX	BBB Penetration; Tumor Inhibition; Mitigation of systemic toxicity	Glioblastoma	[83]
	Polyethylene glycol (15)-hydroxystearate	90 ± 5	—	Medium-chain triglycerides	PTX; SAL	Enhanced cytotoxicity; Apoptosis induction; Reduced stemness expression; Mammosphere inhibition	Breast Cancer	[84]
	mPEG-b-pAsp	207.9 ± 3.5	FA	Hybrid lipid core	DOX; TNP	DOX and TNP released sequentially under different pH; Enhanced cellular uptake; Synergistic Cytotoxicity	Breast cancer, Lung cancer	[85]
Polymer	PMPC-b-PApm/Glu	46 ± 10	PBA	nBSA-PBA-IgG	—	pH/SA-responsive PMPC shell disassembly in tumors; In situ NK cell activation via IgG-CD16 binding; Tumor growth inhibition	Breast cancer; melanoma	[86]
Inorganics	Silica	150	FA	Miglyol 812 oil	—	Stiff nanocapsules had higher macrophage uptake but better receptor-mediated tumor cell targeting; Soft nanocapsules evaded immune clearance and penetrated deeper into tumors.	Breast cancer, ovarian cancer	[87]
	Covalent Organic Framework	186.7	—	Zr-based MOF	77	Suppressed tumor growth; Promoted apoptosis; Activated immune response (increased CD8+ T cells, reduced Tregs); Inhibited lung metastasis	Fibrosarcoma	[88]

Notes: The Table 1 summarizes nanocapsule-based strategies for enhancing anticancer immune responses, categorized by shell composition (bacterial vectors, proteins, lipids, polymers, and inorganic materials). Key immunological outcomes include macrophage reprogramming (M2 to M1 phenotype), dendritic cell activation, enhanced cytotoxic T lymphocyte infiltration, and suppression of immunosuppressive cell populations (MDSCs and Tregs).

Abbreviations: GBM, glioblastoma; DH5α Omp, DH5α outer membrane proteins; GRP94, glucose-regulated protein 94; PLGA, poly(lactic-co-glycolic acid); EMB, embelin; BBB, blood-brain barrier; HA-Man, hyaluronic acid-mannose; TPGS, d-α-tocopheryl polyethylene glycol 1000 succinate; Poly(I:C), polyinosinic-polycytidylic acid; R848, resiquimod; TAMs, tumor-associated macrophages; INT, internal binding domain; DCs, dendritic cells; MDSCs, myeloid-derived suppressor cells; Tregs, regulatory T cells; AcE, acetaldehyde; MTX, methotrexate; PTX, paclitaxel; SAL, salinomycin; pAsp, poly(aspartic acid); FA, folic acid; DOX, doxorubicin; TNP, thiol-reactive prodrug; PMPC, poly (2-(methacryloyloxy)ethyl phosphorylcholine); PApm, poly(N-(4-aminophenyl) methacrylamide); PBA, phenylboronic acid; nBSA, nanoparticle bovine serum albumin; SA, sialic acid; MOF, metal-organic framework.

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Table 2 Comparison of Different Types of Immunotherapeutic Nanocapsules

Evaluation Dimension	Lipid Nanocapsules	Protein Nanocapsules	Polymeric Nanocapsules	Inorganic Nanocapsules
Structure/ Composition	Oil core + lecithin + PEG surfactant	Natural protein wall (albumin, casein, etc.) encapsulating aqueous/ lipid core	Biodegradable polymer shell (PLGA, PCL, etc.) encapsulating aqueous/lipid core	Rigid shell of silica, calcium phosphate, gold, MOFs, etc.
Biocompatibility	Natural lipids, very low toxicity	Non-toxic metabolites, low immunogenicity	Synthetic polymer, PEGylation needed to reduce immunogenicity	Non-biodegradable, potential long-term toxicity, surface coating required
Stability	Prone to oxidation & hydrolysis, short shelf-life	Susceptible to enzymatic degradation, short half-life	High mechanical strength, stable in vivo	Resistant to heat, acids & bases, long-term structural integrity
Drug Loading	Compatible with hydrophilic & hydrophobic drugs	Low encapsulation efficiency for macromolecules	High capacity, versatile for various drugs	Surface/pore adsorption, moderate loading
Targeting Modification	Abundant surfactant sites, easy conjugation of antibodies/ligands	Protein rich in NH_2/COOH, easy chemical modification	Terminal functional groups of polymer easy to modify	Rich silane/ligand chemistry, high-density modification
Key Advantages	High biosafety, good oral absorption, easy surface modification	Natural & non-toxic, suitable for protein drugs, immune tolerance	High mechanical strength, precise controlled release, versatile loading	Structural rigidity, easy surface functionalization, ideal for theranostics
Main Drawbacks	Membrane instability, burst release, narrow process window	Low drug loading, enzymatic degradation, high cost	Potential acid-induced inflammation, immunogenic risk of synthetic materials	Non-biodegradable, potential toxicity, poor controlled release, high cost

Notes: Table 2 conducts a parallel comparison of different types of nanocapsules in terms of structure, biocompatibility, stability, drug loading, targeting modification, advantages and disadvantages. By comparing this table, you can understand the characteristics of different nano capsules.
Abbreviations: PEG, Polyethylene glycol; PLGA, Poly(lactic-co-glycolic acid); MOFs, Metal-organic frameworks; PCL, polycaprolactone.

and delivered using ATP-sensitive hydrogels, flow cytometry showed that the number of CD4+ T cells was significantly increased in IASNDS@gel group, which was 6.62 times higher than that in control group. Bioluminescence imaging (BLI) showed that the tumor signal of the IASNDS@gel group was significantly lower than that of the other groups, and the tumor volume growth was significantly inhibited.[78] (Figure 1a).

Such nanocapsules can be co-administered with chemotherapeutics to achieve synergistic effects. For example, combining bacterial vesicles with anticancer drugs has been shown to sensitize tumor cells to cytotoxic T lymphocytes, reducing melanoma growth and metastasis.[91] This multimodal strategy integrates the strengths of chemotherapy and immunotherapy, potentially achieving more effective tumor control.

The efficiency of drug delivery is another advantage of using bacterial nanocarriers. One approach involves coating *E. coli* DH5α outer membrane proteins (with lipopolysaccharides removed) onto poly(lactic-co-glycolic acid, PLGA) nanocapsules, creating biomimetic nanovesicles (Omp@NC) that target GRP94. In vivo brain distribution experiment showed that the fluorescence intensity of IR780 labeled Omp@NC in the brain was much higher than that of RBCM@NC. In vivo co-localization experiments, Omp@DOX mainly co-localized with GFP-labeled 231Br cells, and rarely co-localized with neurons, astrocytes, microglia, or endothelial cells. In contrast, A-NP was mainly distributed in neurons, further demonstrating the targeting specificity of Omp@NC.[79]

The modular nature of bacterial vector-based nanocapsules allows the incorporation of targeting ligands and immunostimulatory agents to enhance precision and potency. This adaptability positions them as promising candidates for personalized cancer immunotherapy, allowing customization according to patient-specific tumor characteristics.[22,92]

Protein-Based Nanocapsules

Protein-based nanocapsules have received significant attention owing to their excellent biocompatibility, biodegradability, and effectiveness in transporting therapeutic agents. These features make them attractive candidates for various applications in cancer immunotherapies. Protein nanocapsules are capable of encapsulating diverse therapeutic payloads, including small-molecule drugs, peptides, and proteins, thus forming a versatile delivery system aimed at tumor-specific targeting.

Targeted delivery is a key advantage of protein-based nanocapsules. Functionalized systems such as those incorporating the neuropilin-1 binding peptide (iRGD) have shown the ability to specifically recognize and deliver drugs to

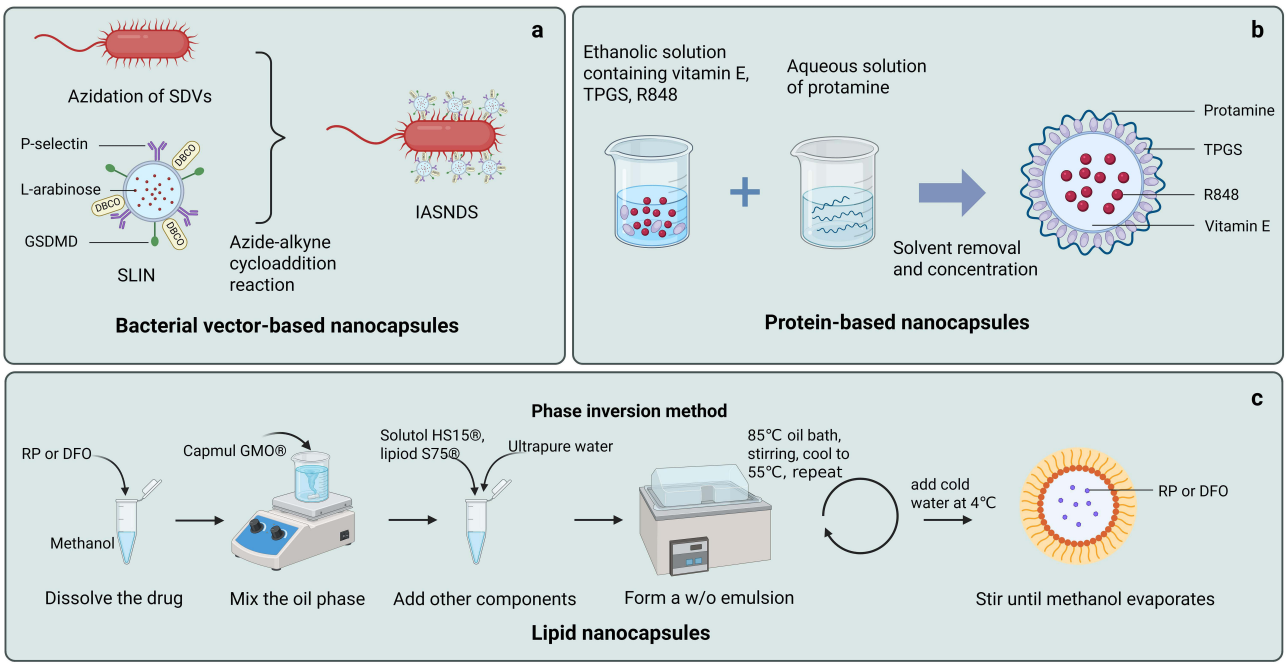

Figure 1 Design schemes of various nanocapsules. (**a**) Schematic representation of IASNDS construction. Salmonella delivery vehicles (SDVs) were azidated and conjugated with nanocapsules bearing L-arabinose via click chemistry to form immunostimulatory autolysing Salmonella nanocapsule delivery systems (IASNDS). L-Arabinose activates the pBAD promoter in SDVs, inducing LysE expression and consequent bacterial lysis. GSDMD is the key executor of pyroptosis. After cleavage, the generated GSDMD-N domain forms pores in the plasma membrane, triggering cellular pyroptosis. (**b**) Protamine-based nanocapsules were synthesized by mixing vitamin E, D-α-tocopheryl polyethylene glycol 1000 succinate (TPGS), sodium taurocholate, and R848 in ethanol (organic phase), followed by the addition of an aqueous protamine solution under stirring. After solvent evaporation, the resulting nanocapsules were concentrated via ultrafiltration. (**c**) Schematic diagram of the preparation method for phase inversion temperature (PIT) lipid nanocapsules (LNCs) that contain RP (retinol) or DFO (deferoxamine). This process begins by dissolving the drug (RP or DFO) in methanol. Additionally, the oil phase is formed by mixing Capmul GMO (glycerol monooleate). Then, the drug solution is added to the oil phase while stirring. Solutol HS15 (a non-ionic surfactant) and Lipoid S75 (soybean phospholipid) are added, and the mixture is heated in an oil bath to 85°C to form an oil-in-water (w/o) emulsion. The emulsion is cooled to 55°C, and the heating-cooling cycle is repeated to ensure homogeneity. Finally, cold ultrapure water (4°C) is rapidly added to induce inversion, thereby forming stable lipid nanocapsules.
Abbreviations: GSDMD, Gasdermin D; SLIN, Salmonella lysis-inducing nanocapsules.

pancreatic cancer cells, improving therapeutic efficacy while minimizing off-target effects.[93] Such targeted approaches are essential for reducing the collateral damage commonly seen in traditional cancer therapies.

In addition to serving as delivery vehicles, protein nanocapsules can function as immune adjuvants. For instance, protamine-based nanocapsules possess favorable physical properties, including size, surface charge, and colloidal stability, which enable efficient interactions with immune cells. R848, also known as resiquimod, is a synthetic small molecule compound of the imidazoquinolinamine class. Studies have shown that human macrophages (HMDMs) treated with poly(I:C)+R848 secreted high levels of CXCL10, CCL5 and IL-6, which are typical marks of M1-type macrophages. Additionally, the nanocapsules showed significant anti-tumor growth and anti-metastasis ability in a variety of mouse models.[80] Figure 1b illustrates the preparation of the core nanocapsules via the solvent-displacement method, aiming to encapsulate the TLR agonist imiquimod (R848) into the core of the nanocapsules.

Nanocapsules carrying chemokine CCL21 (CCL21-vaults) have demonstrated the ability to increase the migration of CCR7-expressing T2 hybridoma cells in vitro, a process inhibited by neutralizing antibodies against CCL21, confirming the chemokine's specific role.[81] These nanocarriers also improved dendritic cell-mediated antigen processing and presentation, subsequently activating $CD8^+$ T cells to secrete IL-2, a response that was similarly suppressed by anti-CCL21 antibodies. In flow cytometry analysis, the CCL21-vault group showed a significant increase in the proportion of $CD4^+$ and $CD8^+$ T cells, a noticeable increase in the number of dendritic cells, and a decrease in the number of MDSCs and Tregs.

The potential of the protein nanocapsules was further amplified using combination therapies. Co-loading multiple agents within a single nanocapsule enables synergistic effects that enhance the immunotherapeutic efficacy. For example, Paßlick et al engineered a protein nanovaccine containing two adjuvants, muramyl dipeptide (MDP) and R848, along

with the antigen OVA. This formulation robustly activated dendritic cells and triggered antigen-specific responses in both $CD4^+$ and $CD8^+$ T cells, resulting in greater immune stimulation than traditional vaccination strategies.[28]

Protein nanocapsules can remodel the tumor microenvironment, increase tumor cell immunogenicity, and improve treatment outcomes. Their multifunctional nature enables a broad range of uses, from targeted drug delivery to immune modulation, making them promising and adaptable tools for advancing cancer immunotherapy.

Lipid Nanocapsules

Lipid nanocapsules (LNCs) are gaining prominence in drug delivery owing to their distinctive physicochemical properties and versatility. They can encapsulate both hydrophilic and lipophilic compounds, thus offering a broad range of drug compatibility.[94] LNCs exhibit high encapsulation efficiency and enhanced drug stability compared to other nanocarrier systems, making them particularly well suited for cancer immunotherapy. Their production is rapid, solvent-free, and scalable, and their characteristics can be tailored to optimize delivery, especially for central nervous system (CNS)-targeted therapies.[95]

A notable application involves methotrexate-loaded LNCs (MTX-LNCs) developed using poly(ε-caprolactone) as the lipid matrix. These MTX-LNCs demonstrated the ability to cross the BBB following oral or intravenous administration without compromising its integrity.[83] Their favorable size (~200 nm) and surface charge contribute to their effective brain distribution and absorption. Additionally, glioma (GL261) and microglial (BV2) cells internalize MTX-LNCs via endocytosis and vesicle-mediated pathways, potentially enhancing drug bioavailability in brain tissue.

LNCs are also advantageous for combination therapies because of their capacity to co-deliver multiple agents. One study formulated LNCs encapsulating paclitaxel (PTX) and salinomycin (SAL) to target breast cancer cells and breast cancer stem cells (bCSCs). The IC50 value of RP-LNCs in MTT cytotoxicity assay was 10.86 ± 0.98 μg/mL (RP pure drug: 29.4 ± 0.98 μg/mL). Annexin V-FITC/PI flow cytometry showed that RP/DFO-LNCs group had the highest apoptosis rate (about 27.14% apoptosis and 29.54% necrosis). RP-LNCs and DFO-LNCs significantly reduced the level of Cyclin D1 (1.4 and 2.0 ng/mg, respectively), which was lower than that of the control group.[84] These nanocapsules were produced using the Phase Inversion temperature (PIT) method, yielding particles with a mean diameter of 90 nm and over 98% drug encapsulation efficiency (Figure 1c). In another study, a strong Dil fluorescence signal was observed in both MCF-7 monolayer cells and BCSCs-enriched mammospheres (3D model), indicating that LNCs effectively penetrated and entered tumor cells and stem cell spheres. In the mammosphere inhibition assay, the combination of PTX +SAL (especially LNC-PTX-SAL) almost completely destroyed the sphere structure and significantly reduced the number and size. Cellular uptake studies have confirmed their efficient internalization and reduced systemic toxicity. Importantly, this dual-drug delivery system showed synergistic effects, inducing apoptosis and suppressing tumor spheroid growth in vitro.[85]

To enhance the specificity, LNCs can be modified using targeting ligands. For instance, folate receptor-targeted hybrid LNCs have been developed to sequentially deliver doxorubicin and tanipimicin, improving their cytotoxic efficacy against breast and lung cancer cells while minimizing off-target interactions.[96]

In addition to drug delivery, LNCs can modulate immune function. Sandri et al demonstrated that poly(ε-caprolactone)-based LNCs were readily taken up by human immune cells and exhibited no cytotoxic effects.[82] The secretion of IL-10, IL-8 and TNF-α was inhibited after LNCs treatment. Under inflammatory conditions, these nanocapsules suppressed mitogen-driven lymphocyte proliferation, cytokine production, and leukocyte migration primarily by downregulating the MAPK pathway and reducing intracellular calcium signaling. Similarly, acetoeugenol-loaded LNCs were found to influence neutrophil activity and melanoma cell signaling, suggesting their potential for treating melanoma by modulating TME.[97]

In conclusion, LNCs offer a multifunctional and tunable platform for enhancing drug delivery, regulating immune responses, and achieving precise targeting in cancer immunotherapies. As research in this area progresses, LNCs are expected to play a key role in the development of next-generation nanomedicines that improve therapeutic outcomes and patient prognosis.

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Metal Nanocapsules

Metal-based nanocapsules offer considerable promise for cancer immunotherapy because of their multifunctionality and distinctive physicochemical characteristics. One of their core advantages lies in enhancing the targeted delivery and therapeutic potency of the immunomodulatory agents. For example, metal-organic frameworks (MOFs) modulate the immunometabolic tumor microenvironment by delivering IDO1 inhibitors (eg, NLG919) to block tryptophan catabolism and suppress regulatory T-cell expansion, while concurrently releasing chemotherapeutic agents to induce immunogenic cell death, thereby activating dendritic cells and $CD8^+$ T lymphocytes, ultimately enhancing immunotherapeutic efficacy.[30] (Figure 2a).

Innovative formulations that integrate multiple therapeutic modalities have also emerged. A notable example is the ZTN@COF@Poloxamer nanocapsule, which synergistically combines photodynamic therapy with poly(ADP-ribose) polymerase (PARP) inhibition for the treatment of soft tissue sarcomas. The ZTN@COF@poloxame group showed a continuous decrease in tumor volume over 15 days, significantly better than the other groups. Flow cytometry showed that CD8+ T cells (CTL) increased significantly (from 13.1% to 24.0%), and Treg cells ($CD25^+Foxp3^+$) decreased significantly (from 27.8% to 9.69%). After MCA-205 cells were injected into the tail vein to establish a lung metastasis model, it was found that there were almost no obvious nodules on the lung surface of the ZTN@COF@poloxame group. Both in vitro and in vivo findings have confirmed its potent tumor-suppressive effects, accompanied by enhanced immune activation and significant inhibition of metastasis, while maintaining a favorable safety profile.[98]

Biomembrane-coated metal nanocapsules represent further advancement, offering improved compatibility with biological systems and increased delivery efficiencies. A recent development involves a zinc–phenol-based nanocapsule (RMP@Cap) designed for immunotherapeutic management of triple-negative breast cancer (TNBC).[88] This system

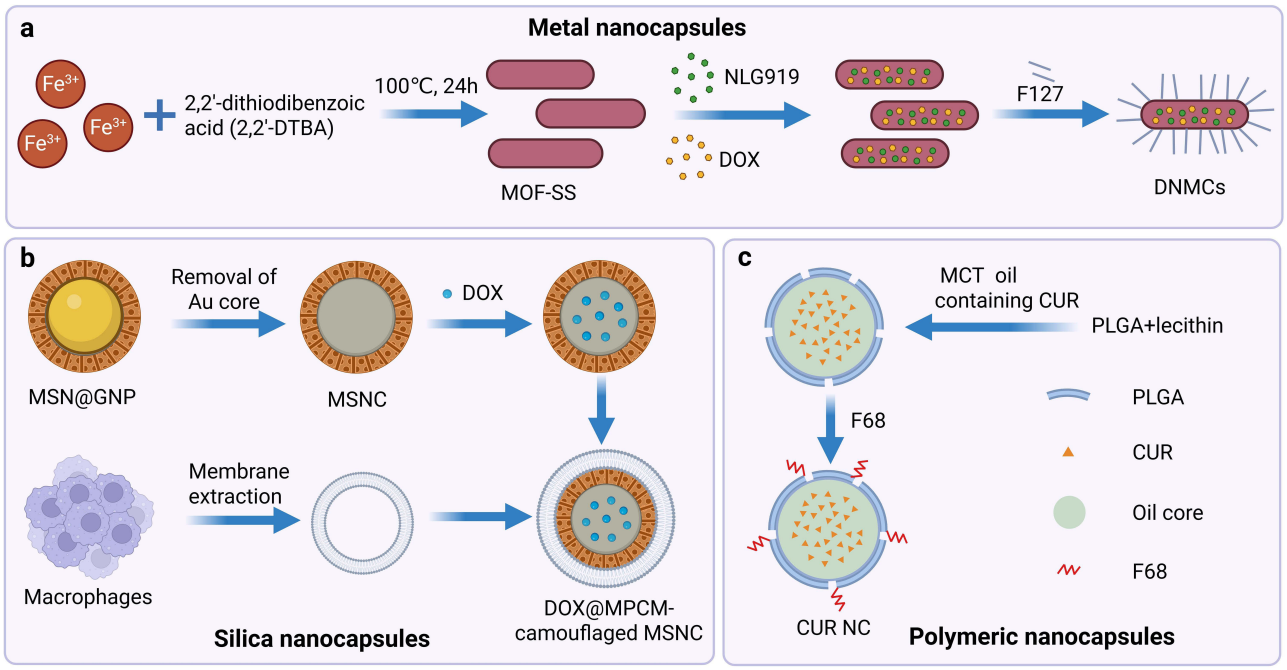

Figure 2 Fabrication of the nanocapsule systems. (**a**) DNMCs were prepared by first solvothermally synthesizing MOF-SS nanorods from $FeCl_3 \cdot 6H_2O$ and 2,2′-DTBA in DMF/NaOH at 100 °C for 24 h. After washing, the rods were dispersed in methanol containing DOX, NLG919 and Et_3N, stirred overnight, evaporated, stabilized with aqueous F127, and finally isolated by centrifugation and vacuum drying. (**b**) Mesoporous silica nanocapsules (MSNCs) were first synthesized by CTAB-templated coating of gold nanocapsules with silica, followed by calcination to remove the template and aqua regia etching to eliminate the gold core. Macrophage cell membrane (MPCM) was extracted via hypotonic lysis and differential centrifugation, then extruded into vesicles. After loading DOX into MSNCs via incubation, the MPCM vesicles were fused with DOX@MSNCs by extrusion to obtain MPCM-camouflaged DOX-loaded MSNCs. (**c**) Curcumin-loaded nanocapsules (CUR NCs) were synthesized using a modified solvent displacement method. PLGA and lecithin were dissolved in acetone and ethanol and mixed with curcumin in MCT oil. This solution was injected into an aqueous solution of poloxamer 188 to form the final formulation.

Abbreviations: DNMC, DOX+NLG919@MOF-SS nanocapsules; MOF-SS, Metal-Organic Framework-Disulfide; 2,2′-DTBA, 2,2′-Dithiodibenzoic acid; DMF, N, N-Dimethylformamide; DOX, Doxorubicin; NLG919, IDO1 inhibitor; Et_3N, Triethylamine; F127, Poloxamer 407(polyethylene oxide-polypropylene oxide-polyethylene oxide); CTAB, Cetyltrimethylammonium bromide; MCT, Medium-Chain Triglycerides; F68, Poloxamer 188(Lutrol®F68).

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encapsulates mitoxantrone (MTO) and an anti-PD-L1 antibody (aPD-L1) and is cloaked onto a red blood cell (RBC) membrane layer. The encapsulated formulation induces pyroptosis in tumor cells, leading to the release of mitochondrial DNA (mtDNA) and subsequent activation of the STING signaling pathway, which enhances tumor immunogenicity and initiates robust anti-tumor immunity. The RBC membrane coating prolongs systemic circulation and facilitates improved tumor localization. Experimental data demonstrated that RMP@Cap exerts significant antitumor and antimetastatic activities in both cellular and animal models, while exhibiting excellent biocompatibility.

Overall, metal nanocapsules serve as multifunctional platforms that not only boost drug delivery and immune regulation but also offer opportunities for combinatory therapeutic strategies. With the continuing advancements in nanotechnology, metal-based nanocapsules are expected to play an increasingly vital role in designing more precise and effective cancer immunotherapies.

Silica Nanocapsules

Silica, an inorganic nonmetallic material, is frequently utilized in the fabrication of nanocapsules owing to its excellent biocompatibility and chemical robustness. Other inorganic nanomaterials such as layered double hydroxides have also shown great promise in biomedical applications, highlighting the broad potential of inorganic nanomaterial platforms.[99] Smart inorganic nanomaterials represent a powerful platform for tumor microenvironment modulation, offering unique opportunities for cancer immunotherapy.[100] These properties contribute to the safety profile of in vivo applications. The porous architecture of silica nanocapsules enables them to achieve high drug-loading efficiency, making them well suited for transporting therapeutic agents. Furthermore, the surface of silica nanocapsules is readily modifiable, allowing functionalization with targeting ligands to enhance selective delivery to specific tissues or cell types and to reduce off-target effects.

In another study, silica nanocapsules (SiNCs) were evaluated for their ability to deliver small interfering RNA (siRNA) to $CD8^+$ T cells. Using techniques such as flow cytometry and confocal microscopy, researchers confirmed the efficient cellular uptake and favorable biocompatibility of SiNCs, supporting their use in immune-targeting applications.[101]

Mesoporous silica nanocapsules (MSNCs) also exhibit favorable interactions with other biological materials, thus enabling multifunctional design. In a study conducted by Xuan et al, researchers encapsulated macrophage plasma membranes (MPCM) within MSNCs to form a biomimetic drug delivery system[102] (Figure 2b). The mesoporous structure allowed for high drug loading and controlled sustained release. Meanwhile, the MPCM coating served as a camouflage, extending the nanocapsule circulation time and promoting accumulation at the breast tumor sites. This cell membrane disguising strategy not only enhanced in vivo stability but also improved the drug delivery efficiency. The combination of silica nanocapsules with biologically derived membranes is a promising strategy to boost the performance of nanomedicine platforms.

Polymeric Nanocapsules

Polymeric nanocapsules, composed of a core–shell architecture in which a liquid or solid interior is enclosed by a polymeric membrane, offer distinct advantages in cancer drug delivery. These include enhanced drug stability, controlled release, improved bioavailability, and targeted accumulation in tumor tissues, reducing the systemic toxicity often associated with traditional chemotherapy.[103]

A major strength of these systems is their ability to improve the solubility and bioavailability of hydrophobic compounds, which typically exhibit poor aqueous solubility and rapid metabolic degradation. For instance, curcumin, a naturally derived compound with established anticancer potential, has been successfully incorporated into PLGA-based nanocapsules. This formulation enhanced the solubility of curcumin by approximately 1500-fold and enabled sustained drug release, with nearly 50% of the active compound released over 10 days[104] (Figure 2c). Beyond serving as structural materials, natural polymers such as polysaccharides from Gynura divaricata have also demonstrated direct antitumor activity, highlighting their dual potential as both therapeutic agents and components in nanocapsule design.[105]

In another approach, researchers utilized poly(RGD) protein polymers to fabricate nanocapsules co-loaded with doxorubicin (Dox) and tumor necrosis factor-related apoptosis-inducing ligand (TRAIL). This dual delivery system was designed to stabilize TRAIL and attenuate the side effects of doxorubicin, showing therapeutic promise in the management of ovarian cancer.[106] The development of such nanocapsule systems is particularly relevant given the unique

challenges of the ovarian cancer microenvironment and the need for innovative immunotherapeutic strategies in this malignancy.[107] The nanocapsule developed by Yanqi Ye's team uses hyaluronic acid as a carrier, co-loading the IDO inhibitor (1-MT) and encapsulating the anti-PD-1 antibody (aPD-1).[108] When delivered to the tumor site via a microneedle patch, the hyaluronidase highly expressed in the tumor microenvironment degrades the capsules, triggering the synergistic release of the two drugs: aPD-1 releases the "brake" on T cells (by blocking the PD-1/PD-L1 pathway), while 1-MT clears away the immunosuppressive metabolic environment for T cells (by inhibiting the IDO pathway). This dual blockade significantly enhances the infiltration and function of cytotoxic T cells within the tumor while reducing immunosuppressive cells, thereby potently activating antitumor immune responses and reducing systemic toxicity (Figure 3).

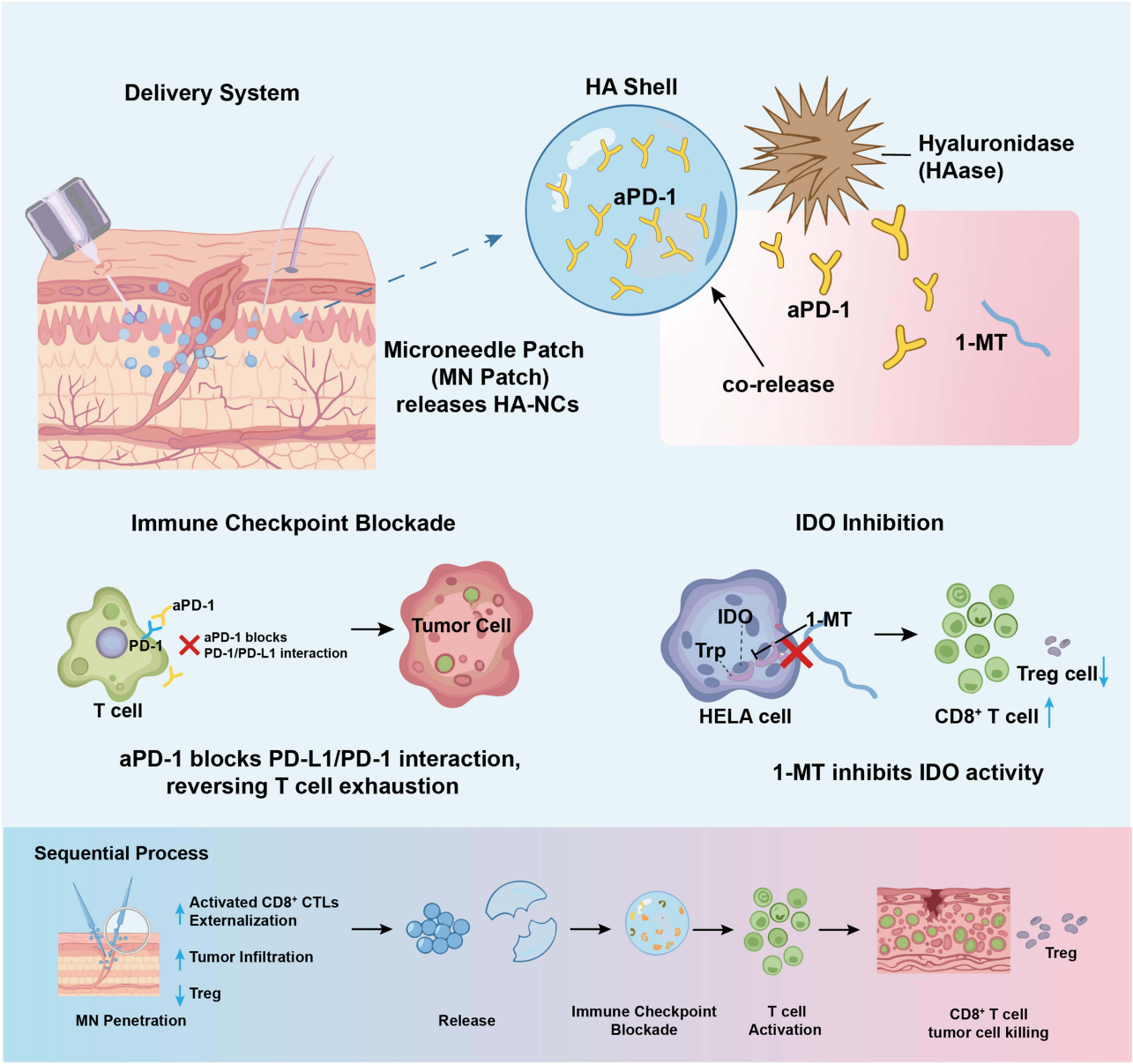

Figure 3 Schematic illustration of the synergistic transcutaneous immunotherapy strategy. The Microneedle patch penetrates the skin and releases hyaluronic acid nanocapsules (HA-NCs) encapsulating aPD-1 and conjugated with 1-MT. In the tumor microenvironment, overexpressed hyaluronidase (HAase) degrades the HA matrix, triggering co-release of aPD-1 and 1-MT. aPD-1 blocks the PD-1/PD-L1 interaction, reversing T cell exhaustion and restoring cytotoxic T lymphocyte (CTL) activity. 1-MT inhibits IDO activity, reducing tryptophan depletion and suppressing regulatory T cell (Treg) recruitment. Collectively, these effects enhance CD8+ T cell infiltration and activation, leading to improved antitumor immune responses and tumor cell killing.
Abbreviations: aPD-1, anti-PD1 antibody; HA-shell, Hyaluronic Acid-shell; 1-MT, 1-methyl-DL-tryptophan; IDO, indoleamine 2,3-dioxygenase.

Surface functionalization strategies have been employed to further enhance the targeting specificity. For example, folic acid has been attached to nanocapsule surfaces to recognize folate receptors that are overexpressed in TNBC cells (MDA-MB-231). Folic acid-modified Dox nanocapsules significantly improved cellular uptake, suppressed migration and colony formation, and induced apoptosis in cancer cells, with a reduced impact on the surrounding healthy tissues.[109]

Recent advancements have also explored the use of polymer nanocapsules for combination drug delivery. One such formulation encapsulated both curcumin and methotrexate using an interfacial deposition technique. The resulting nanocapsules (NCUR/MTX-2) exhibited favorable release kinetics and notable cytotoxic effects against Calu-3 cells. At low drug concentrations, the co-delivery system induced apoptosis and demonstrated synergistic antitumor activity, suggesting its potential to overcome chemoresistance and enhance treatment efficacy.[110]

Overall, polymer nanocapsules represent a highly adaptable and effective therapeutic platform for oncology. Their ability to enhance drug solubility, target cancer cells precisely, and control drug release positions them as critical tools in the evolution of cancer nanomedicine.[86] As research progresses, polymer nanocapsules are expected to play an increasingly significant role in the development of tailored combination-based cancer therapies.

Nanocapsules in Combination with Other Therapeutic Strategies and Immunotherapy

Nanocapsules have significant potential in cancer therapy, particularly when integrated into multimodal treatment regimens. Their ability to be co-administered with various therapeutic approaches enhances their clinical efficacy and may help overcome the limitations of monotherapies.

When used alongside chemotherapy, nanocapsules enable precise drug delivery to tumor sites, minimizing exposure to healthy tissues, reducing systemic toxicity, and helping circumvent drug resistance mechanisms. This targeted approach enhances the therapeutic index and reduces adverse side effects.

In radiotherapy, nanocapsules can be employed to investigate the impact of different administration techniques, such as stereotactic injection (SI), on the spatial distribution of radiation and its immunological consequences.[111] These combinations could potentially amplify radiation-induced immunogenic cell death and improve immune activation. In targeted therapies, nanocapsules serve as efficient carriers for molecularly targeted agents. The therapeutic precision and efficacy of treatment can be significantly improved by directing these drugs to specific receptors or markers expressed on the cancer cells.[112]

Overall, nanocapsule-assisted combination strategies represent a promising strategy for cancer treatment. By enhancing drug delivery, reducing toxicity, and improving therapeutic specificity, these integrated approaches have the potential to improve the clinical outcomes and quality of life of patients with cancer. Next, we would like to discuss the therapeutic effects produced by nanocapsules when used in combination with other traditional cancer treatment methods and immunotherapy.

Chemotherapy

Integrating nanocapsules with chemotherapy is an effective strategy for enhancing treatment efficacy while minimizing adverse effects. By encapsulating anticancer drugs, nanocapsules offer advantages, such as targeted delivery, improved pharmacokinetics, and controlled release. These features not only increase the therapeutic concentrations at tumor sites but also limit systemic toxicity.

One study explored lipid nanocapsules co-loaded with paclitaxel and SaL for breast cancer therapy. This dual delivery system targeted both bulk tumor cells and cancer stem cells, which are typically responsible for recurrence and treatment resistance. The formulation demonstrated superior cytotoxic effects and significant tumor suppression, highlighting its potential as an advanced chemotherapeutic agent.[85]

Another study examined the use of protamine–carboxymethyl cellulose-based magnetic nanocapsules to treat doxorubicin-resistant cervical cancer.[113] These doxorubicin-loaded nanocapsules modified with Fe_3O_4 nanoparticles were evaluated in vitro and in vivo (Figure 4). Under the influence of an external magnetic field, doxorubicin-loaded magnetic nanocapsules (Dox-MNCs) significantly enhance cellular drug uptake, increase intracellular accumulation, and

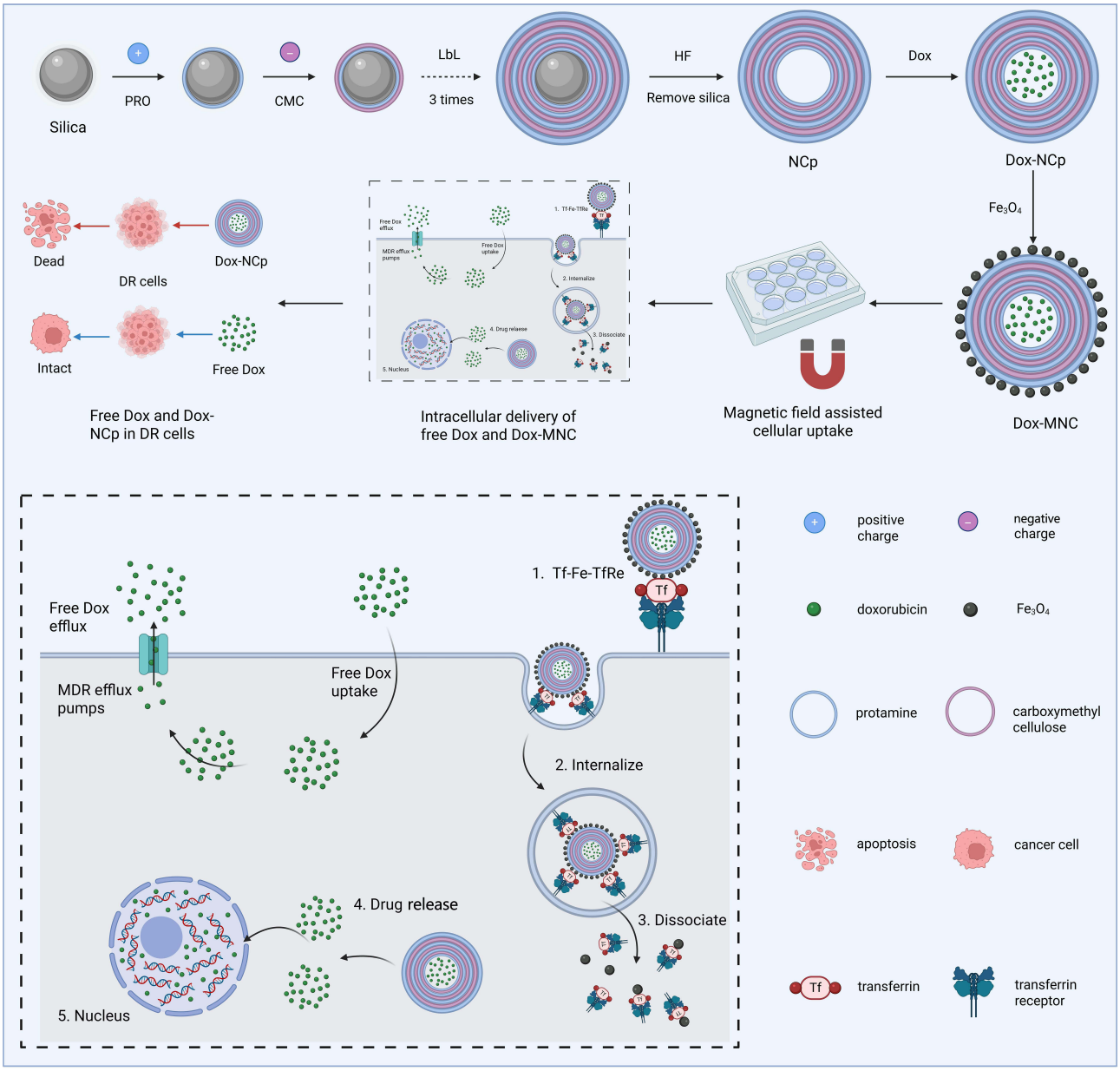

Figure 4 Synthesis of magnetic nanocapsules for chemotherapy. Nanocapsules (NCp) are fabricated by sequentially depositing positively charged protamine (PRO) and negatively charged carboxymethyl cellulose (CMC) onto silica nanoparticles via the layer-by-layer assembly technology (LbL). The core template was etched to create hollow nanocapsules for doxorubicin loading (Dox-NCp). Ferrite nanoparticles were anchored on the surface to construct doxorubicin magnetic nanocapsules (Dox-MNC), enabling magnetic field (MF)-assisted targeting. The cellular uptake of Dox-MNC by drug-resistant cells proceeds via the following five steps: (1) Transferrin binds to the Fe_3O_4 particles on the surface of Dox-MNC to form Tf-Fe conjugates, and subsequently interacts with the transferrin receptors on the cell membrane. (2) The Tf-Fe-TfRe complex is internalized through clathrin-mediated endocytosis. (3) The Tf-Fe-TfRe complex dissociates within late endosomes. (4) Doxorubicin (Dox) is released from the nanocarriers (NCp) into the cytoplasm. (5) Doxorubicin translocates into the cell nucleus. Cells treated with free doxorubicin expel the drug out of the cell via multidrug resistance (MDR) efflux pumps. Hence, in drug-resistant (DR) cancer cells, free doxorubicin had limited efficacy, while Dox-NCp induced apoptosis, demonstrating the effectiveness of magnetic-assisted delivery.

promote apoptosis in resistant HeLa cells. Animal experiments have confirmed improved drug localization and therapeutic efficiency, suggesting that magnetic guidance could be a viable method to overcome multidrug resistance. In a similar vein, precisely tailored doxorubicin prodrugs have been designed to form stable nanoassemblies with rapid activation and enhanced antitumor effects, offering another promising strategy to improve the therapeutic profile of doxorubicin.[114]

Controlled release is a defining advantage of nanocapsule-based drug delivery systems. One study introduced a multifunctional nanocapsule with a tunable internal structure capable of a magnetically triggered release. The surface was functionalized with RGD peptides targeting integrins to promote efficient cellular uptake. Drug release was successfully controlled in living cells with minimal toxicity.[115] Additionally, pH-responsive nanocapsules show promise for site-specific delivery. In gastric cancer therapy, a liposomal system has been designed to release apatinib and cinobufacini under acidic conditions typical of the tumor microenvironment.[116]

Co-delivery systems using nanocapsules have been widely studied for their ability to enhance chemotherapeutic efficacy. For instance, Fourniols et al developed lipid nanocapsules encapsulating acriflavine (ACF) and paclitaxel (PTX) to target both cancer-associated fibroblasts (CAFs) and tumor cells in a colorectal cancer spheroid model. While LNC-ACFs selectively suppressed CAFs, LNC-PTX acted broadly on tumor spheroids. Although no synergy was observed between the two, the study presented a novel CAF-targeted strategy using nanotechnology.[117]

Doudou Hu's team developed a reactive oxygen species (ROS)-responsive, synergistic delivery system (pep-PAPM @PTX) by co-loading the chemotherapeutic drug paclitaxel (PTX) and a surface-modified anti-PD-L1 peptide into nanomicelles, enabling combined chemotherapy and immunotherapy.[118] This system targets PD-L1 on tumor cells, directing it to lysosomal degradation, thereby reversing PTX-induced PD-L1 upregulation, enhancing T-cell infiltration and the expression of immune-activating factors, and significantly improving antitumor efficacy in a triple-negative breast cancer model. Notably, the pep-PAPM@PTX combination group achieved a tumor inhibition rate of 78%, markedly higher than that of the pep group (anti–PD-L1 peptide alone, 30%) and the Taxol group (paclitaxel alone, 41%). Another team has developed an MRI-visible, locally deliverable immune checkpoint blockade nanocarrier (Fer-ICB-UPMSNP).[119] After cabazitaxel chemotherapy-induced immunogenic cell death (ICD) and upregulation of PD-L1, MRI-guided intratumoral delivery was performed in a Tramp C1 prostate cancer mouse model. Fer-ICB-UPMSNP simultaneously achieves a favorable immune signature—2.5-fold more $CD8^+$ T-cell infiltration, a 5-fold reduction in suppressive Tregs, and a 2.4-fold higher $CD8^+$/Treg ratio—outperforming both systemic immunotherapy and chemotherapy alone. The tumor suppression effect was markedly superior to that of systemic immunotherapy following chemotherapy, offering a novel sequential chemo-immunotherapy approach for "cold tumors".

In summary, the combination of nanocapsules and chemotherapeutic agents addresses key obstacles in oncology, including drug resistance, limited selectivity, and uncontrolled drug distribution. These advanced delivery platforms hold great potential to improve the therapeutic index of chemotherapy while reducing systemic toxicity, setting the stage for more precise and patient-friendly cancer treatments.

Radiotherapy

The integration of nanocapsules with radiotherapy has gained increasing attention in recent years, owing to its potential to enhance therapeutic outcomes. Owing to their multifunctional capabilities, nanocapsules can act as radiosensitizers or drug carriers, amplifying radiation-induced tumor cell death while protecting the surrounding healthy tissues and ultimately improving the therapeutic index.

Nanocapsules capable of co-loading hydrophilic and hydrophobic agents have opened new possibilities for combinational cancer therapy. These systems can be engineered to release their therapeutic payload in response to specific stimuli such as ionizing radiation, thus enhancing the synergy between radiotherapy and chemotherapy.[109] In another innovative application, hybrid nanocapsules incorporating gold nanoshells were designed for dual functionality of imaging and treatment. These nanocapsules were applied to HER2-positive breast cancer and exhibited enhanced therapeutic performance through NIR-triggered photothermal effects combined with chemotherapeutic action.[120]

Recent research has revealed that post-radiotherapy tumors may exhibit elevated expression of cuproptosis-related proteins such as ferredoxin 1 (FDX1) and lipoic acid synthase (LIAS), rendering them more sensitive to copper-induced cell death.[32] To overcome this vulnerability, researchers have developed copper-loaded polyoxometalate nanocapsules (PWCu) that precisely release copper ions in response to X-ray exposure. This targeted release activates the cuproptosis pathway, effectively overcoming radiotherapy resistance in breast cancer. Moreover, PWCu treatment not only improved local tumor control, but also induced systemic immune responses capable of suppressing untreated metastatic lesions,

with a documented cure rate of 40%. This approach represents a promising direction for integrating targeted radiotherapy with immunomodulation.

Recently, there have also been studies focusing on enhancing the anti-tumor immune efficacy through the combination of radiotherapy and immunotherapy. Jiali Sun reported a radio-activatable R848 prodrug nanomedicine (MAL-NPs) that, when combined with radiotherapy (RT) and anti-PD-1 immune checkpoint blockade, markedly potentiates antitumor immunity.[121] Upon RT-induced tumor antigen release, MAL-NPs enrich within the tumor by capturing these antigens via maleimide moieties; RT then triggers on-site reduction of the R848 prodrug to active R848, activating dendritic cells to cross-present antigens and initiate $CD8^+$ T-cell responses. Concurrent anti-PD-1 alleviates T-cell suppression, amplifying and sustaining systemic antitumor immunity.

Photodynamic Therapy and Photothermal Therapy

Nanocapsules have emerged as promising delivery systems for both photodynamic therapy (PDT) and photothermal therapy (PTT), offering significant improvements in the solubility, stability, and bioavailability of photosensitizing and sonosensitizing agents. These features are crucial for optimizing the therapeutic efficacy of these modalities for cancer treatment.

In PDT, nanocapsules can enhance the delivery and activation of photosensitizers, amplifying their phototoxic effects against tumor cells. For instance, curcumin encapsulated in colloidal nanocapsules composed of amphiphilic block copolymers demonstrated increased photodynamic efficacy and cytotoxicity against lung adenocarcinoma and melanoma cell lines upon light exposure. This illustrates how nanoscale encapsulation can substantially improve therapeutic outcomes by ensuring more efficient drug activation and targeted accumulation.[122] Another study utilized lipid nanocapsules to deliver two photosensitizers, protoporphyrin IX and hypericin, which exhibited potent in vitro phototoxicity with IC_{50} values in the nanomolar range. These nanocapsules also significantly suppressed prostate tumor growth in vivo and reduced dark toxicity. Additionally, the differential intracellular localization of photosensitizers revealed new insights into subcellular targeting strategies for enhancing PDT.[123]

Meanwhile, there have also been advancements in the research on the use of nano-capsules in the combination of immunotherapy and photothermal therapy. Yujun Bao's team recently developed a novel immune-activating nanomedicine, Fc-SS-Fe/Cu, that responsively degrades in the tumor microenvironment to release Fe/Cu ions and Fenton reaction catalysts, inducing ferroptosis, reactive oxygen species, and oxygen generation.[124] Combined with mild photothermal therapy, it triggers immunogenic cell death and significantly enhances antitumor immune responses. Moreover, by inhibiting the HIF-1α pathway, it downregulates PD-L1 expression, thereby boosting the efficacy of immune checkpoint blockade and realizing a new strategy for synergistic ferroptosis-photothermal-immunotherapy against tumors. Combined with mild photothermal therapy, it triggers immunogenic cell death and significantly enhances antitumor immune responses.[125]

In summary, the combined applications of nanocapsules with chemotherapy, radiotherapy, and photodynamic/photothermal therapy (PDT/PTT) all aim at optimized targeted delivery, reduced toxicity, and synergistic immune activation. Their common advantages stem from the structural characteristics of nanocapsules, which enable precise enrichment and controlled release of therapeutic agents, while remodeling the tumor microenvironment (TME) or inducing immunogenic cell death (ICD).

The core advantage of nanocapsule-chemotherapy combinations lies in their broad adaptability and ability to overcome drug resistance. Through co-delivery of dual drugs, targeted modification, or stimuli-responsive release, they balance cytotoxic killing and immune microenvironment improvement, are suitable for metastatic tumors and advanced solid tumors, have a solid foundation for clinical translation, and require addressing the issue of drug resistance evolution.[118] Nanocapsule-radiotherapy combinations are notably characterized by the dual synergy of radiosensitization and systemic immune activation. Via the delivery of radiosensitizers and the synergy between antigen release and immune adjuvants, they enhance local tumor control and inhibit metastasis, are applicable to locally advanced solid tumors, and the key lies in the spatiotemporal matching between radiotherapy and carrier enrichment.[126] In addition, nanocapsule-PDT/PTT combinations are corely featured by precise local killing and low systemic toxicity. Relying on the controllability of light signals to achieve specific activation, they synchronously induce ICD to enhance immune

responses, which are suitable for superficial tumors or deep tumors accessible via fiber optics.[124] But they are limited by the penetration depth of light sources and the balance of photosensitizer toxicity.

Overall, the clinical selection of the three combination strategies should be comprehensively determined based on tumor stage, anatomical location, pathological type, and immune phenotype. The chemotherapy combination strategy has the widest applicability and is more suitable for systemic treatment needs. The radiotherapy combination strategy focuses on the curative control of local tumors while concurrently inhibiting metastases. The PDT/PTT combination strategy highlights safety advantages in the treatment of superficial tumors, making it suitable for patients with low toxicity tolerance.

The application of two or more therapeutic approaches with different mechanisms of action can achieve synergistic enhancement of efficacy, overcome drug resistance, and reduce side effects. For example, PEGylated bismuth selenide hollow nanocapsules co-load the chemotherapeutic drug doxorubicin (DOX) and the photosensitizer chlorophyll e6 (Ce6), enabling triple-modal PTT/PDT/chemotherapy. Near-infrared (NIR) laser triggers photothermal effects and reactive oxygen species (ROS) generation, while on-demand drug release is achieved under the tumor microacidic environment or thermal shock, realizing efficient tumor suppression with minimized systemic toxicity.[127] The team of Wenhao Wang investigated ferroptosis-mediated multimodal therapy. In this study, epigallocatechin gallate (EGCG) and Fe^{3+} self-assembled into EFP nanocapsules, which were integrated into a microneedle patch. EGCG induces lipophagy to release free fatty acids, which serve as "fuel" for lipid peroxides (LPO) to promote ferroptosis. Meanwhile, the nanocapsules themselves possess photothermal capacity, combining ferroptosis, photothermal therapy (PTT), and immune remodeling, as well as enhancing the efficacy of PD-L1 antibodies.[128] Future research should focus on multiple therapeutic modalities to further break through the technical bottlenecks of single combination strategies.

Clinical Perspectives of Nanocapsules in Cancer Immunotherapy

Nanocapsules represent a cutting-edge drug delivery platform that has received increasing attention in oncology, particularly in immunotherapy. Their distinct physicochemical features allow them to enhance drug stability by preventing rapid degradation in biological environments, which in turn improves bioavailability and therapeutic efficacy.[129] Through surface modification, nanocapsules can be engineered for targeted delivery, directing therapeutic agents precisely to tumor tissues, while minimizing exposure to healthy cells and reducing off-target toxicity.[130] Their ability to facilitate controlled release enables drugs to be administered within optimal therapeutic windows, enhancing both effectiveness and safety.[131] The excellent biocompatibility of these carriers further supports their safe use in vivo and minimizes the risk of immune rejection.[129]

Such attributes make nanocapsules particularly suitable for cancer immunotherapy, which depends on the activation of the immune system to selectively eliminate tumor cells. They have shown potential for treating various malignancies, including bladder cancer[132] and renal cell carcinoma.[133] MT-302 (NCT05969041) and MT-303 (NCT06478693) are the two first-in-human trials that use LNP-nano-capsules to deliver mRNA for in-situ reprogramming of myeloid cells to express CARs. In the dose-escalation Phase I study of MT-302 for TROP2-positive epithelial cancers, more than 40 patients have received over 200 doses without cumulative toxicity; TROP2-CAR expression is detectable in both circulation and tumor tissue, and one confirmed partial response plus several disease-stabilizations have been observed, together with systemic, interferon-driven immune activation. MT-303, targeting GPC3-positive hepatocellular carcinoma, dosed its first patient in 2024, remains in phase I enrollment, shows preliminary safety, but efficacy data are still pending. Together these studies mark the transition of nano-capsule mRNA-based in-vivo CAR immunotherapy from concept to clinical validation.

AGuIX is a type of gadolinium-chelated polysiloxane-based nanocapsule designed to overcome tumor radiotherapy resistance.[134] The potential of AGuIX nanocapsules has been supported by preclinical and phase I clinical data. In preclinical glioblastoma multiforme (GBM) models, the combination of AGuIX with chemoradiotherapy prolonged the survival time of experimental subjects, as the nanocapsules could selectively accumulate in tumors via the enhanced permeability and retention (EPR) effect. Results from the phase I NANO-RAD trial involving patients with brain metastases demonstrated that a dose of 100 mg/kg was well tolerated; among the 14 enrolled patients, 13 achieved clinical benefits, with tumor volume reduction showing a positive correlation with the administered dose. In clinical

applications, AGuIX is indicated for newly diagnosed GBM patients with incomplete or partial tumor resection who have a poor prognosis, as it can precisely sensitize tumors to radiotherapy while reducing damage to normal tissues.

In addition, CPX-351, a liposomal nanocapsule formulation co-delivering cytarabine and daunorubicin, has exhibited superior long-term survival benefits compared with the standard 7+3 regimen in elderly patients aged 60–75 years with newly diagnosed high-risk or secondary acute myeloid leukemia (AML).[135] The 5-year overall survival rate reached 18% (95% confidence interval [CI]: 12–25%) in the CPX-351 group, whereas it was only 8% (95% CI: 4–13%) in the 7+3 group, indicating a significant and sustained long-term survival advantage. These studies address the issue of pharmacokinetic mismatch associated with traditional combination chemotherapy. By means of liposomal co-delivery, CPX-351 achieves a synergistic effect at a molar ratio of 1:5 for the two drugs, prolongs the drug exposure time in tumor tissues and reduces systemic toxicity, thereby providing a novel "high-efficiency and low-toxicity" therapeutic option for elderly patients with high-risk AML. Furthermore, these findings verify the feasibility and superiority of nanocapsule technology in the co-delivery of cytotoxic drugs, offer a reference for the dosage form optimization of other combination chemotherapy regimens, and promote the application of nanomedicines in hematological malignancies.

Despite their promising potential, several practical challenges limit the clinical application of nanocapsule-based therapies. A major concern is the risk of off-target effects, which could result in unintended toxicity and immune activation, particularly problematic when delivering potent chemotherapeutic or immunomodulatory agents.[136,137] Another issue is premature drug release, which compromises treatment efficacy and increases systemic side effects if the therapeutic agent is released before reaching the tumor site.[138] Tumor heterogeneity and the complexity of the tumor microenvironment often hinder the efficient targeting and internalization of nanocapsules, reducing therapeutic efficacy. Overcoming these biological barriers requires extensive research and technological innovation.[139]

The clinical delivery of nanocapsules is challenged by the dense stroma of solid tumors and the blood-brain barrier (BBB). In solid tumors, aberrant secretion of extracellular matrix components, including collagen and hyaluronic acid, forms a dense interstitial barrier that restricts intratumoral penetration efficiency of nanocapsules to typically less than 5%, with penetration depth limited to less than 1 mm.[140] Studies have demonstrated that pegylated lipid nanocapsules in systemic circulation can activate the complement system and promote macrophage phagocytosis, further compromising intratumoral accumulation.[141] Although nanocapsules can achieve passive accumulation via the enhanced permeability and retention (EPR) effect in solid tumors, their penetration depth remains significantly constrained by matrix density. Current optimization strategies primarily utilize collagenase or hyaluronidase to degrade tumor stroma and thereby enhance penetration depth. In comparison to solid tumors, the BBB exhibits even lower permeation efficiency for nanocapsules, which must overcome dual barriers comprising endothelial tight junctions and efflux pump systems such as P-glycoprotein, resulting in efficiency 1–2 orders of magnitude lower than that observed in solid tumors.[142] However, nanocapsules modified with transferrin or low-density lipoprotein can enhance BBB permeation efficiency through receptor-mediated transcytosis pathways.

The accelerated blood clearance (ABC) phenomenon represents a major obstacle to long-term nanocapsule therapy. The first dose can induce production of specific antibodies (such as anti-PEG IgM), and upon subsequent administration, antibody-mediated rapid clearance shortens nanocapsule half-life by more than 90%.[143] The specific impacts on long-term therapeutic efficacy are manifested as follows: first, alterations in pharmacokinetic parameters, where plasma drug concentrations are significantly reduced and tumor targeting efficiency decreases by 50%-80%; second, increased safety risks, as repeated dosing may elicit hypersensitivity reactions with clinical manifestations ranging from mild rash to severe anaphylaxis.

The clinical application of nanocapsules remains a critical and urgent issue to be addressed, as the therapeutic efficacy varies significantly with different administration routes. Studies have confirmed that the maximum tolerated dose (MTD) of paclitaxel lipid nanocapsules (paclitaxel LNCs) reaches 96 mg/kg, which is substantially higher than that of conventional paclitaxel injection (Taxol, 12 mg/kg).[144] This discrepancy directly verifies that the nanocapsule formulation can markedly reduce the systemic toxicity of drugs and broaden the safe dosage range for clinical application. In the field of oral administration, relevant studies have demonstrated that docetaxel nanocapsules encapsulated in hydrogel matrices can be absorbed via the lymphatic system, leading to a significant improvement in oral bioavailability with

therapeutic efficacy comparable to that of intravenous injection.[145] This finding provides a novel feasible strategy for the transformation of chemotherapeutic drugs into oral formulations.

Long-term clinical toxicity monitoring needs to focus on the following core issues.[146] Firstly, the organ accumulation effect: nanocapsules with a particle size > 100 nm or surface-charged particles tend to accumulate in organs such as the liver, spleen and kidney, which may induce long-term organ damage. Secondly, the immunogenicity risk: polyethylene glycol (PEG)-modified or surface-functionalized nanocapsules may activate the complement system, induce cytokine release and trigger hypersensitivity reactions. Thirdly, dose-dependent toxicity: formulations containing cationic lipids or high concentrations of polysorbates can disrupt cell membrane structures, thereby inducing oxidative stress responses and mitochondrial damage. At present, data regarding the long-term toxicity of nanocapsules are still scarce. Most studies on lipid nanocapsules (LNCs) have only focused on short-term efficacy evaluation, with a lack of systematic toxicity monitoring data involving follow-up periods exceeding 6 months.

Regulatory and standardization requirements present additional barriers to their clinical application. There are four major complexities in the clinical trial design of nanocapsules for personalized tumor immunotherapy: firstly, the inter-patient, intra-tumor, and spatiotemporal heterogeneity of tumors increases the difficulty of personalized precise matching; secondly, the differential uptake of nanocapsules by immune cells as well as the risk of immunogenicity raises the threshold for safety assessment; thirdly, it is necessary to establish a multi-dimensional evaluation system based on immune-related biomarkers, rendering traditional tumor size indicators no longer applicable; fourthly, personalized immunotherapy with nanocapsules usually requires combination with other therapeutic modalities, which further increases the complexity of clinical trial design. A robust chemistry, manufacturing, and control (CMC) framework is necessary to guarantee product quality, safety, and efficacy. Nanocapsules must be formulated with pharmaceutical-grade excipients and produced using scalable and reproducible methods.[147] Designing clinical trials for nanocapsule-based therapies can also be complex, particularly for personalized immunotherapies, in which inter-individual variability must be accounted for. Innovations in formulation design, adaptive manufacturing processes, and scalable production technologies are essential to bridge the gap between laboratory research and clinical implementation.[148]

Nonetheless, several hurdles remain in the path toward clinical translation. One of the main technical challenges is the complexity of the large-scale manufacturing process. Maintaining batch-to-batch consistency is vital to ensure uniform quality and performance, but the production process is highly sensitive to changes in formulation parameters.[149] For nanocapsules cloaked on cell membranes, the extraction and encapsulation processes must preserve membrane protein integrity and achieve uniform coating, which are essential factors for targeting efficiency and compatibility.[150] Stability during storage is another concern. The bioactive compounds within nanocapsules can degrade over time, potentially compromising their safety and efficacy. Freeze-drying techniques are often used to extend shelf life, but they may inadvertently introduce instability by altering the key physical or chemical properties.[151] Consequently, research is now focused on the development of novel production and preservation strategies to enhance long-term stability and drug retention.

Discussion

Nanocapsule size is a key determinant for controlling drug release profiles and tissue penetration. Smaller nanocapsules typically possess a higher surface-area-to-volume ratio, which facilitates faster drug diffusion and improved interactions with cancer cells. For example, smaller nanocapsules encapsulating γ-cyhalothrin have been reported to exhibit greater toxicity than their larger counterparts, emphasizing the role of size in modulating drug bioactivity.[152] Size also affects immune interactions and barrier penetration. During the development of paclitaxel nanoformulations, particle size was found to play a crucial role in colloidal stability and therapeutic efficacy, likely due to altered immune system interactions and tumor distribution.[153]

The surface charge is another vital parameter that dictates the interaction of nanocapsules with target cells and immune components. In a study focused on LNCs for glioblastoma therapy, researchers modulated both the particle size and zeta potential to selectively target immunosuppressive myeloid-derived suppressor cells (MDSCs) and tumor-associated macrophages (TAMs). The study found that Monocytes preferred neutral particles, while positively charged nanocapsules were more readily internalized by macrophages and tumor cells.[154] Another study used polyacrylic acid

(PAA) polymerized on liposomal surfaces to tune surface potential. Neutral nanocapsules exhibit reduced cytotoxicity, indicating better biocompatibility for clinical use.[155] Thus, controlling the surface charge plays a critical role in fine-tuning biodistribution, minimizing toxicity, and enhancing therapeutic targeting.

The rigidity of nanocapsules influences their circulation time, biodistribution, and cellular uptake dynamics. Rigid nanocapsules have been found to undergo greater uptake by macrophages and tumor cells in vitro owing to receptor-mediated endocytosis. However, their in vivo targeting efficiency is reduced because of accelerated clearance by the spleen and impaired penetration into tumor tissues.[87] Conversely, softer nanocapsules demonstrate improved tumor accumulation and better penetration through biological barriers. One study demonstrated that calcium carbonate-templated nanorods can be transformed into nanocapsules with tunable hardness. The resulting spherical nanocapsules prolonged the circulation time and enhanced drug accumulation in breast tumors, leading to more effective tumor suppression.[156]

Currently, nanocapsule-mediated reversal strategies for cancer immunotherapy resistance have established four core technological pathways, each implementing precise targeted interventions against key pathological mechanisms of immune resistance to achieve specific regulation of the tumor immune microenvironment (TME) and immune cell functions.

Firstly, targeted regulation of tumor metabolic reprogramming to mediate resistance reversal. Abnormal accumulation of lactate within the TME creates an acidic microenvironment, which represents a key metabolic driver that induces T cell dysfunction and undermines the antitumor efficacy of immune checkpoint inhibitors (ICIs). Lactate oxidase nanocapsules (LOX-NCs) can specifically scavenge abnormally accumulated lactate in the TME, thereby effectively ameliorating the acidic microenvironment and relieving immunosuppression of T cells, while simultaneously releasing the immune-stimulatory factor hydrogen peroxide (H_2O_2) in situ to activate T cell immune responses, consequently significantly enhancing the therapeutic efficacy of ICIs.[31]

Secondly, targeted remodeling of immunosuppressive cell phenotypes and functions. Polarization of tumor-associated macrophages (TAMs) toward the M2 immunosuppressive phenotype constitutes a core cellular mechanism in establishing an immunosuppressive microenvironment and mediating immunotherapy resistance. Nanocapsule-based targeted delivery systems loaded with Toll-like receptor (TLR) agonists can specifically target M2-type TAMs, inducing their reprogramming toward the M1 pro-inflammatory phenotype.[80] This subsequently enhances macrophage antigen presentation function, activates proliferation and cytotoxic activity of effector T cells, and disrupts the local tumor immunosuppressive network.

Thirdly, precise blockade of immune checkpoint molecules synergized with activation of innate immune pathways. High expression of immune checkpoint molecules (eg, PD-L1, CD47) on tumor cells represents a core molecular mechanism mediating tumor immune evasion. In special sites such as brain tumors, the physiological barrier function of the blood-brain barrier further limits drug delivery efficiency. A class of co-delivery nanocapsules can simultaneously load anti-CD47 antibodies and the STING agonist, leveraging their unique nanocarrier properties to efficiently penetrate the blood-brain barrier and achieve targeted drug release at the tumor site.[157] This approach activates phagocytic clearance by macrophages and microglia on one hand, while inducing massive secretion of interferon-γ (IFN-γ) through STING pathway activation on the other, creating a synergistic "immune checkpoint blockade-innate immune activation" effect that substantially strengthens the intensity and durability of antitumor immune responses.

Fourthly, targeted reversal of T cell exhaustion phenotype to overcome immunotherapy resistance. Persistent tumor antigen stimulation can drive T cells into an exhaustion phenotype, characterized by high expression of inhibitory receptors and loss of proliferative capacity and cytotoxic function, representing a key T cell-level mechanism of immunotherapy resistance. Nanocapsule-based sustained-release delivery systems enabling continuous release of immunologically active cytokines such as interleukin-12 (IL-12) and interleukin-7 (IL-7) can effectively reverse the T cell exhaustion phenotype, promoting proliferation, survival, and functional maintenance of effector T cells, thereby reestablishing an efficient and durable antitumor immune response.[158]

The application of AI-driven nanostructure design strategies in optimizing nanocapsule structures represents a cutting-edge research frontier in the intersection of nanotechnology and artificial intelligence. By integrating AI technology with nanostructure design, researchers can achieve precise control over nano-capsule properties, thereby

enhancing their potential applications in biomedical fields. AI-driven reverse engineering has played a pivotal role in optimizing nanostructures. By integrating evolutionary strategies (ES) with deep learning, researchers can achieve precise design of nanostructure surface properties across multiple physical scenarios. This approach not only enhances design efficiency but also overcomes computational limitations inherent in traditional methods. Notably, parallel evolutionary strategies (parallel ES) demonstrate significant potential in accelerating AI-powered nanostructure design, markedly improving both design speed and scalability.[159] The successful application of this methodology provides robust support for advancements in nanofabrication technologies.

Secondly, the role of surface patterning in nanostructures during cell membrane remodeling has been extensively investigated. By integrating evolutionary algorithms with coarse-grained molecular dynamics simulations, the study revealed that ligand patterns play a critical role in enhancing cellular uptake. Notably, when ligand quantities are limited, elongated chain-like ligand arrangements can significantly reduce the free energy barrier for membrane penetration while increasing nanocapsule rotational freedom. This discovery not only establishes new design principles for artificial nanocapsule construction but also provides novel strategies for identifying viral entry inhibitors.[160]

Conclusion

This review highlights the emerging role of nanocapsules as promising and versatile platforms in cancer immunotherapy, particularly in addressing the limitations associated with conventional treatment modalities. Various nanocapsule systems, including those based on bacterial vectors, proteins, lipids, metals, inorganic nonmetals, and polymers, have been discussed in terms of their distinct advantages in targeted delivery, sustained drug release, and immune system modulation. These nanoscale carriers can be engineered to interact specifically with tumor cells or antigen-presenting cells, enhancing the therapeutic precision, minimizing off-target effects, and boosting the overall efficacy of immunotherapy. Nanocapsules exhibit a strong potential for combination regimens. When used alongside chemotherapy, radiotherapy, photodynamic therapy, or photothermal therapy, they contribute to synergistic therapeutic effects. Continued efforts are required to refine the design, functionality, and clinical translation of nanocapsules.

Data Sharing Statement

The data used to support this review are included in the article.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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The authors declare that there are no conflicts of interest.

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