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REVIEW

# Novel Strategies for Precision Diagnosis and Treatment of Prostate Cancer Based on Multifunctional Nanocarrier Systems

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**Abstract:** Prostate cancer (PCa) is one of the most common malignancies in men worldwide, and its current diagnostic and therapeutic methods still face severe challenges in terms of specificity, efficacy, and toxicity. The emergence of nanotechnology provides a powerful platform to overcome these obstacles. Through the design of sophisticated nanocarriers, targeted delivery and controlled release of therapeutic agents, as well as the synergy of multiple treatment modalities, can be achieved, thereby significantly improving efficacy and reducing side effects. Meanwhile, nanotechnology shows great potential in developing highly sensitive diagnostic tools and theranostic platforms, laying the foundation for early detection and precise treatment of PCa. Although challenges such as scalability and safety remain to be addressed before clinical translation, nanotechnology is undoubtedly reshaping the landscape of PCa management and driving the field towards personalized medicine. This review aims to provide a systematic overview of significant advancements in nanotechnology for the diagnosis and treatment of PCa over the past three years. It focuses on innovative research in novel nanocarrier design, targeting strategies, and the construction of integrated diagnostic and therapeutic platforms. Furthermore, current challenges and future directions for clinical translation are discussed, with the aim of offering valuable insights and references for researchers and clinicians in this field.

**Keywords:** prostate cancer, nanocarriers, targeted delivery, theranostics

## Introduction

PCa is the second most common cancer in men, with persistently high global incidence and mortality rates. Data indicates that PCa has become the most frequently diagnosed cancer in men globally, ranking first in male cancer incidence in 112 out of 185 countries. Concurrently, it is also the leading cause of male cancer death in a quarter of countries.[1] Looking ahead, the global burden of PCa is projected to increase significantly in the coming decades. According to an important forecast, the annual number of new PCa cases worldwide may double by 2040, with a substantial rise in deaths.[2] Regarding treatment, conventional approaches include surgery, radiotherapy, chemotherapy, and endocrine therapy, yet they face numerous challenges. Chemotherapeutic drugs like docetaxel and doxorubicin suffer from low bioavailability, significant systemic toxicity, and a propensity to induce drug resistance. Furthermore, patients with advanced disease often progress to castration-resistant prostate cancer (CRPC), leading to limited treatment options and poor prognosis.[3] Diagnostic bottlenecks also exist. Commonly used methods like Prostate-Specific Antigen (PSA) testing lack sufficient specificity for accurately distinguishing malignant lesions at an early stage, often resulting in unnecessary invasive biopsies and potential delays in treatment.[4]

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The rise of nanotechnology offers revolutionary tools to overcome these challenges. Nanocarrier systems (size range 1–100 nm) can passively target tumor tissues through the Enhanced Permeability and Retention (EPR) effect and achieve active targeting via surface functionalization (eg, with antibodies, aptamers, or peptide ligands), significantly enhancing drug accumulation at the lesion site. Since the discovery of liposomes in the 1960s, nanocarrier systems have evolved into various types, including organic carriers (liposomes, polymer nanoparticles, protein nanoparticles), inorganic carriers (metal and non-metal nanoparticles), and organic-inorganic hybrid carriers, each with unique advantages: Liposomes and Lipid Nanoparticles (LNPs) can efficiently encapsulate hydrophobic drugs and nucleic acids, with LNPs already approved for clinical small interfering RNA (siRNA) delivery;[5] Polymer nanoparticles (eg, Poly(lactic-co-glycolic acid) (PLGA)) offer controllable degradation and good biocompatibility, and are easily modified for environmentally responsive drug release;[6] Inorganic nanoparticles (eg, gold, silica) possess optical, catalytic, and imaging functionalities, making them suitable for multimodal theranostics.[7] Recently, biomimetic strategies (eg, cell membrane-camouflaged nanocarriers) have further enhanced carrier immune evasion and targeting precision by mimicking natural biological structures.[8] Smart responsive nanosystems have further advanced precision therapy. By responding to tumor microenvironment (TME) characteristics (eg, low pH, high reducibility, specific enzyme expression) or external stimuli (eg, light, ultrasound), these systems enable on-demand drug release, minimizing damage to normal tissues.[9] Concurrently, applications of nanotechnology in diagnostics—such as highly sensitive biomarker detection, targeted imaging contrast agents, and circulating tumor cell (CTC) capture platforms—provide new avenues for early diagnosis and real-time monitoring of PCa.[10] Nanotheranostic platforms that integrate diagnostic imaging and therapeutic functions represent the future direction of personalized medicine.

This review aims to comprehensively summarize recent advances in nanocarrier systems for PCa therapy, covering carrier design principles, functionalization strategies, therapeutic applications, and diagnostic innovations. It also discusses current challenges and future directions, intending to provide a systematic reference for researchers and clinicians and to promote the clinical translation of nanomedicine in the PCa field.

# Nanocarrier Systems for PCa Therapy

## Organic Nanocarriers

### Liposomes

Liposomes are vesicles with a closed bilayer structure formed by the spontaneous assembly of phospholipid molecules in an aqueous phase. Since their discovery in the 1960s, they have rapidly become one of the most influential and widely used nanocarriers in Drug Delivery Systems (DDS).[5] Their widespread application stems from their unique physicochemical properties and biological characteristics, which can effectively improve the pharmacokinetic profile of drugs, enhance efficacy, and reduce toxic side effects.[11] The core mechanism of liposomal therapy lies in leveraging the physiological characteristics of tumor tissue, namely the EPR effect. Due to the incomplete structure and increased permeability of neovasculature in tumor sites, coupled with impaired lymphatic drainage, nano-sized liposomes can selectively extravasate and accumulate in tumor tissue, achieving passive targeting of cancer cells.[12] This mechanism not only helps increase drug concentration at the lesion site but also significantly reduces systemic toxicity to normal tissues. Building on this key advantage, researchers are continuously expanding the frontiers of liposome applications in delivering traditional chemotherapeutic drugs, novel gene-editing tools, and gene silencing therapies.

Traditional chemotherapy is a cornerstone of PCa treatment, but drugs like dexamethasone and doxorubicin face challenges of low bioavailability and significant systemic toxicity, limiting their clinical efficacy.[13,14] Liposomal drug delivery systems provide an effective solution to overcome these hurdles. By encapsulating these chemotherapeutic drugs within the liposomal interior, they not only achieve drug accumulation in tumors via the EPR effect but also effectively protect the drugs from premature degradation during circulation, thereby improving the therapeutic window.

However, modern PCa treatment strategies have moved beyond the delivery of single cytotoxic agents towards more precise, molecular biology-based combination therapies. Studies show that combining chemotherapy with genetic intervention can produce synergistic anti-cancer effects.[15] In this context, the long non-coding RNA (lncRNA) MALAT1 has been identified as a key molecule in PCa progression, with its elevated expression closely related to

tumor invasion and metastasis, making it a promising diagnostic biomarker and therapeutic target.[16] Simultaneously, gene-editing technologies like Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR)-CRISPR-associated protein 9 (Cas9) offer unprecedented tools for fundamentally correcting oncogenes.[17] For instance, by designing specific guide RNA (gRNA), the CRISPR-Cas9 system can precisely knock out or modify key microRNAs (eg, miR-205, miR-221) involved in PCa development, thereby blocking their pro-cancer functions.[18]

Based on this rationale, a comprehensive study designed a multifunctional liposomal system delivering dexamethasone, doxorubicin, and the natural anti-cancer compound curcumin. The experimental results were encouraging; this liposomal nano-formulation not only effectively exerted the cytotoxic effects of traditional chemotherapy but also demonstrated multiple regulatory functions at the molecular level. It significantly suppressed MALAT1 expression, effectively modulated the gene-editing activity of the CRISPR-Cas9 system, and successfully blocked the crucial PI3K/AKT survival signaling pathway in tumor cells.[19] This study fully demonstrates that the liposomal platform can serve as an ideal carrier for integrating chemotherapeutic drugs, gene-editing tools, and targeting non-coding RNAs. This strategy combining drug delivery, gene editing, and biomarker monitoring not only greatly enhances anti-tumor efficacy but also opens promising new paths for the precise diagnosis and individualized treatment of PCa.

Beyond delivering small molecule drugs and CRISPR systems, liposomes and their derived LNPs also show great potential in delivering RNA interference (RNAi) therapeutics, particularly siRNA. RNAi works by using siRNA to specifically degrade target messenger RNA (mRNA) in the cytoplasm, achieving gene silencing, which is a highly promising therapeutic strategy.[20] In fact, LNP-based siRNA drugs have received FDA approval for clinical use, marking the maturity and safety of this technology platform.

Although LNPs can efficiently encapsulate and protect fragile siRNA molecules from degradation by nucleases in the bloodstream, their therapeutic efficacy is limited by a core bottleneck: "endosomal escape." When LNPs enter cells via endocytosis, they are trapped within endosomes. The siRNA must escape from the endosome into the cytoplasm to exert its biological function. However, this process is highly inefficient, with estimates suggesting only 1%–2% of siRNA successfully escapes, while the majority is degraded in lysosomes, greatly limiting the ultimate efficacy of RNAi therapy.[21] To overcome this challenge, various strategies have been developed, among which Photochemical Internalization (PCI) is a classic method that uses a photosensitizer (PS) activated by specific wavelength light to produce reactive oxygen species (ROS) that disrupt the endosomal membrane.[22] However, traditional PCI strategies have several drawbacks, such as uneven distribution of the PS and therapeutic drug within cells, complex synthesis of the delivery system, and potential biological toxicity.

To address these issues, an innovative study proposed a novel mechanism called "Light-Activated siRNA Endosomal Release (LASER)".[23] The ingenuity of this strategy lies in integrating porphyrin lipids with photosensitive properties directly as structural components into the LNP construction, forming a porphyrin-LNP composite system. This design fundamentally ensures the precise co-localization of the photosensitive unit and the siRNA payload at the nanoscale. When this system is delivered to tumor cells and internalized into endosomes, applying external, non-invasive near-infrared (NIR) light irradiation causes the porphyrin lipids within the LNP to efficiently generate ROS. These ROS oxidize and disrupt the endosomal membrane in situ and specifically, enabling efficient, controllable release of siRNA. The study confirmed that the LASER strategy significantly enhances cytoplasmic delivery efficiency of siRNA and subsequent gene silencing effects. This "smart" design not only provides an elegant and efficient solution to the endosomal escape bottleneck but also represents the development direction of a new generation of spatiotemporally precise, light-controlled RNA delivery systems, offering a more powerful and controllable technological platform for PCa gene therapy. Of course, the aforementioned nanodelivery system based on liposomes still has its limitations. For instance, the CRISPR-Cas9 system typically comprises the relatively large Cas9 protein (~160 kDa) and a guide RNA (sgRNA), forming a substantial ribonucleoprotein complex. Liposomes, particularly conventional ones, face significant challenges in efficiently encapsulating and protecting such large and complex biomacromolecules, often resulting in low encapsulation efficiency and leakage during storage and systemic circulation. Furthermore, the Cas9 protein may cleave at unintended genomic sites under the guidance of sgRNA, leading to off-target mutations. This off-target effect could potentially activate proto-oncogenes or inactivate tumor suppressor genes, thereby introducing new oncogenic risks. The liposomal delivery system itself cannot address this issue of molecular-level precision. Additionally, porphyrin

compounds are metabolized slowly in vivo, meaning patients may need to avoid direct sunlight exposure for a period after treatment to prevent skin photosensitivity reactions, which can significantly impact quality of life. Moreover, while ROS can disrupt endosomal membranes, they may also damage normal organelles (such as mitochondria and the nucleus), triggering oxidative stress and leading to unintended apoptosis or inflammatory responses. The risk of cumulative oxidative damage to cells from long-term or repeated LASER therapy remains unclear.

## Polymer Nanoparticles

With the continuous advancement of nanotechnology, nano-delivery systems based on biodegradable polymers have become an important research direction in tumor therapy. Among them, PLGA is widely used as a material for constructing anticancer drug carriers due to its excellent biocompatibility, controllable degradation rate, and safety profile approved by the FDA for use in humans.[6] PLGA nanoparticles can effectively encapsulate drugs within their core, protecting them from premature degradation during systemic circulation and achieving passive accumulation in tumor tissue via the EPR effect. Furthermore, by precisely tuning the structure and surface chemistry of the nanoparticles, co-delivery of drugs, active targeting, and intelligent responses to TME characteristics can be achieved, opening new avenues for treating malignancies like PCa.[24]

In the treatment of CRPC, resistance to the endocrine therapy drug Enzalutamide (Enz) and bone metastasis are major clinical challenges. Studies have found that the histone methyltransferase EZH2 and WNT5A in the non-canonical WNT pathway are highly expressed in CRPC, not only closely associated with Enzalutamide resistance but also promoting bone metastasis. In this mechanism, miR26a acts as a key regulator, directly targeting and inhibiting the expression of EZH2 and WNT5A. Experiments further revealed that miR26a restores sensitivity to Enz and inhibits tumor invasion and metastatic capacity by regulating the EZH2/SFRP1/WNT5A axis. To achieve efficient co-delivery of Enz and miR26a, researchers developed a core-shell structured biomimetic nanosystem: Bm@PT/Enz-miR26a.[25] This system uses PLGA as the carrier for Enz, forms a complex with miR26a via a cationic peptide CT, and is coated with a bone marrow mesenchymal stem cell membrane possessing bone-targeting functionality, thereby endowing it with active targeting capability towards tumors and bone metastatic sites. This nanosystem demonstrated synergistic effects in reversing drug resistance and inhibiting tumor growth and metastasis, providing a new strategy for treating Enz-resistant bone-metastatic CRPC. However, it is crucial to recognize the limitations of the aforementioned nano-delivery systems. Systemic or local high-dose delivery of miR-26a mimics may interfere with other critical cellular pathways, leading to unpredictable off-target effects and disruption of normal physiological functions in healthy cells. Furthermore, the mechanisms underlying enzalutamide resistance are exceedingly complex and diverse. Restoring the expression of a single miRNA to reverse resistance may only be effective for specific tumor subpopulations with particular resistance mechanisms. Additionally, tumor heterogeneity and adaptability could rapidly drive the emergence of new resistance pathways.

Natural plant active ingredients like Berberine and Hesperidin have attracted attention due to their diverse anticancer activities, including inducing apoptosis, inhibiting metastasis, and modulating key signaling pathways (eg, NF-κB, p53, PI3K/AKT).[26,27] However, these components generally suffer from poor water solubility, low oral absorption, and insufficient bioavailability, limiting their clinical application. To overcome these obstacles, a research team utilized PLGA nanoparticles to construct a delivery system co-encapsulating Berberine and Hesperidin.[28] The prepared nanoparticles had an average size below 200 nm, uniform distribution (Polydispersity Index, PDI < 0.1), and an encapsulation efficiency of approximately 70%. In vitro release experiments showed significantly accelerated drug release under acidic conditions mimicking the TME (pH 5.5), exhibiting pH-responsive characteristics, with release behavior fitting the Higuchi model. Furthermore, the nanoparticles maintained good colloidal stability after 30 days of storage. Notably, this co-loaded nanoparticle demonstrated the strongest synergistic anti-tumor effect when combined with the conventional chemotherapeutic drug doxorubicin, not only enhancing the efficacy of the natural drugs but also showing potential as a chemosensitizer, helping to reduce chemotherapy drug dosage and mitigate toxic side effects. Although PLGA is widely recognized for its favorable safety profile, the local accumulation of its degradation products (lactic acid and glycolic acid) may induce specific immune or inflammatory responses. Moreover, the two drug molecules compete for the limited space within the PLGA carrier, resulting in a reduced actual loading capacity for each drug. To achieve the

same dosage as single-drug nanoparticles, a larger number of nanoparticles must be administered, which could exacerbate the potential burdens and immunogenic risks associated with PLGA.

Active targeting is a key strategy for improving the precision of nanodrug delivery, and its efficiency is influenced by the density, spatial orientation, and accessibility of targeting ligands on the particle surface. Traditional methods often use flexible Polyethylene Glycol (PEG) chains to link ligands, but this can lead to random ligand orientation, limiting effective binding to target receptors.[29] To address this issue, one study innovatively used DNA oligonucleotide strands as rigid scaffolds to precisely arrange ligands targeting Prostate-Specific Membrane Antigen (PSMA), specifically the ACUPA ligand, on the surface of PLGA nanoparticles.[30] By varying the ACUPA density (0–1600 ligands per particle), they found that cell uptake efficiency was highest with 100–200 ligands per particle, a density highly matched to the receptor density on the surface of PSMA-high expressing cells (approximately 1000–1700/$\mu m^2$). Further comparison showed that particles presenting ACUPA via rigid DNA strands had about 3 times higher cellular uptake than those modified with flexible PEG, indicating that the rigid scaffold helps maintain an ideal ligand conformation. Simultaneously, introducing non-targeting single-stranded DNA on the particle surface further increased uptake efficiency, suggesting that flexible non-targeting strands might promote particle interaction with the cell membrane. This DNA scaffold strategy provides a new method for precisely controlling ligand arrangement, aiding in the development of highly selective nanodrugs.

In summary, PLGA nano-delivery systems significantly enhance the efficiency and safety of drugs in cancer therapy through multiple mechanisms including encapsulation protection, targeting modification, and intelligent responsive release. From co-delivering natural active ingredients to precisely controlling targeting ligand arrangement, and leveraging the TME for controlled drug release, these strategies collectively advance the development of nanodrugs in the treatment of PCa and other malignancies, laying a solid foundation for future clinical translation.

## Protein Nanoparticles

Proteins, as fundamental units of life activities, exhibit natural advantages in drug delivery. For instance, proteins derived from biological sources like Human Serum Albumin (HSA) and transferrin possess very low toxicity and immunogenicity, enabling them to effectively evade recognition and clearance by the immune system, thereby significantly prolonging the circulation time of drugs in the body.[31] Furthermore, protein nanocarriers can achieve initial accumulation of drugs in tumor sites via the EPR effect. Their surfaces are rich in functional groups (eg, amino, carboxyl), facilitating chemical modification for further conjugation of targeting ligands like antibodies, peptides, or aptamers, endowing the carriers with the ability to actively recognize and target PCa cells.[32]

The development of PCa is closely related to cellular metabolic reprogramming, with a typical feature being the "warburg effect" – where cancer cells preferentially utilize glycolysis over oxidative phosphorylation for rapid energy production even under oxygen-sufficient conditions.[33] This metabolic shift is critically regulated by Pyruvate Dehydrogenase Kinase 1 (PDK1). PDK1 inhibits the activity of Pyruvate Dehydrogenase (PDH), blocking the entry of pyruvate into the tricarboxylic acid (TCA) cycle, thereby promoting tumor cell survival, invasion, metastasis, and drug resistance.[34] Notably, PDK1 is highly expressed in PCa tissues and is associated with poor patient prognosis, making it a highly promising therapeutic target.[35] Some PDK1 inhibitors (eg, dichloroacetate, DCA) have shown anti-tumor potential in research, but their clinical application is limited by the need for high doses (millimolar range), poor water solubility, low stability, and significant neurological and gastrointestinal toxicity. Another inhibitor, dichloroacetophenone (DAP), demonstrated superior inhibitory activity to DCA in vitro, but its poor solubility and pharmacokinetic properties also limit direct application.[36]

Therefore, a research team developed a lactoferrin-wrapped DAP nanoparticle (DAP-LF-NP).[37] Lactoferrin, a natural glycoprotein, can specifically recognize and bind to transferrin receptors highly expressed on the surface of PCa cells, enabling precise targeted drug delivery.[38] This nano-delivery system effectively interfered with the glycolytic and oxidative phosphorylation metabolic pathways of cancer cells by downregulating PDK1 protein expression, inhibiting PDH phosphorylation, and reducing Hypoxia-Inducible Factor 1-alpha (HIF-1α) levels, thereby exerting anti-tumor effects. Although lactoferrin receptors are overexpressed on PCa cells, they are also widely present in normal tissues, particularly in intestinal epithelial cells, hepatocytes, brain capillary endothelial cells, and immune cells. This co-

expression can lead to nonspecific uptake of nanoparticles by non-target organs, reducing tumor-targeting efficiency and potentially causing hepatotoxicity or other organ toxicities. Therefore, long-term toxicity assessments in normal tissues—especially the liver, kidneys, and nervous system—are a critical component of preclinical studies.

Protein-based nano-delivery systems, leveraging their good biocompatibility and modifiability, offer promising strategies for targeted therapy of PCa and show potential application value in regulating tumor metabolism.

In summary, thanks to their excellent biocompatibility, design flexibility, and powerful functionalization capabilities, organic nanocarriers have become an ideal platform for achieving precise, efficient, and safe drug delivery, demonstrating broad application prospects in fields such as cancer therapy, infectious disease prevention and treatment, gene therapy, and regenerative medicine (Figure 1).

## Inorganic Nanocarriers

### Metal Nanoparticles

Gold Nanoparticles (AuNPs) are among the most extensively studied and widely applied metal nanocarriers. Their popularity stems from their high biocompatibility, chemical stability, ease of surface functionalization, and unique

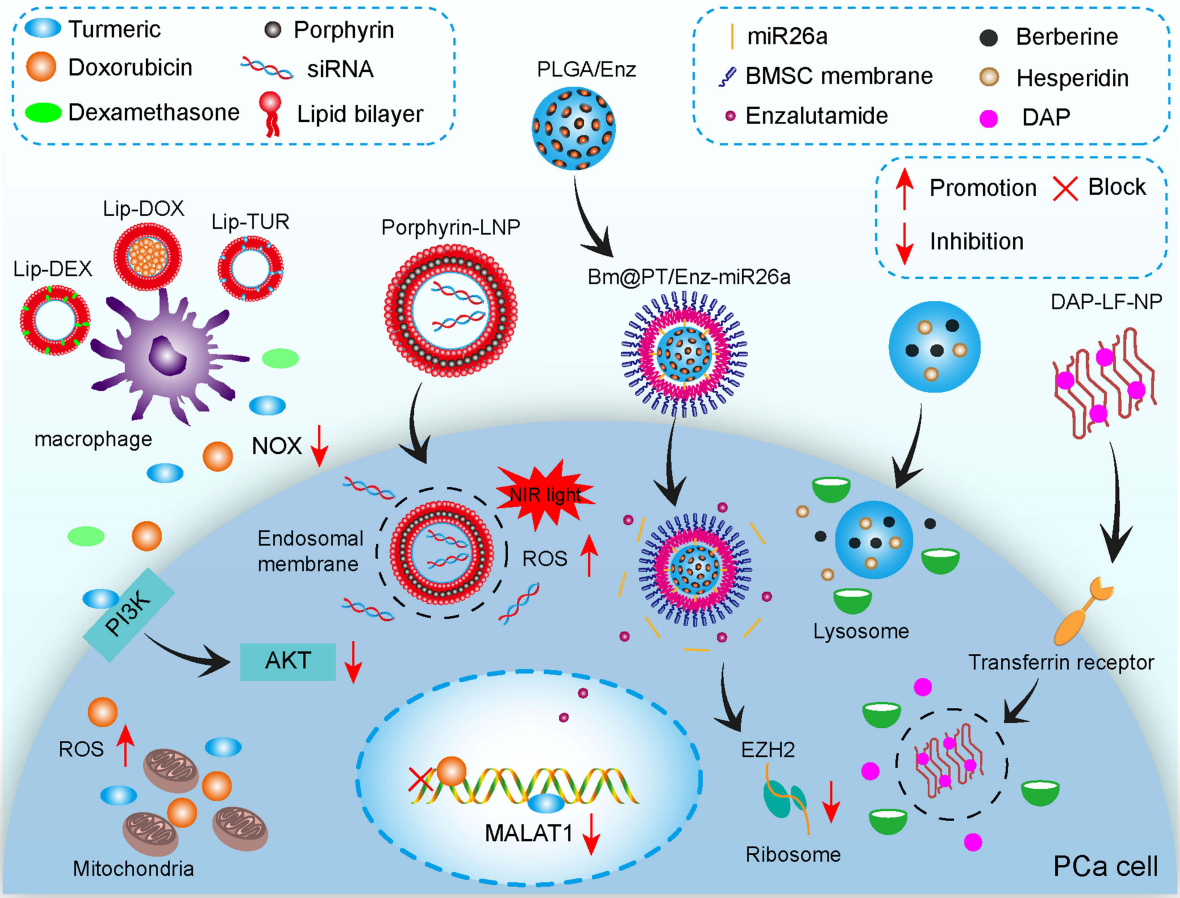


**Figure 1** Organic nanocarriers, primarily including liposomes, polymer nanoparticles, and protein nanoparticles, provide versatile and highly biocompatible delivery platforms for prostate cancer treatment. Liposomes and their derived LNPs can not only achieve targeted delivery of chemotherapeutic drugs (such as dexamethasone, doxorubicin) via the EPR effect to reduce systemic toxicity but also synergize with gene-editing tools (CRISPR-Cas9) or RNAi therapeutics (siRNA). Through innovative mechanisms (eg, the LASER strategy), they overcome the bottleneck of endosomal escape, enabling precise regulation at the genetic level. Polymer nanoparticles (represented by PLGA) employ strategies such as core-shell structures, pH-responsive release, and surface modification with precise targeting ligands to efficiently co-deliver chemotherapeutic drugs, natural active ingredients (eg, berberine and hesperetin), and nucleic acid drugs (eg, miR26a). These systems demonstrate synergistic effects in reversing enzalutamide resistance and inhibiting bone metastasis. Protein nanoparticles (eg, lactoferrin-wrapped nanosystems) leverage their natural targeting capability (eg, towards transferrin receptors) and low immunogenicity to achieve efficient delivery of inhibitors targeting key enzymes in tumor metabolism (eg, PDK1) and enable precise metabolic regulation.


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photophysical properties derived from the Surface Plasmon Resonance (SPR) effect.[39] These properties make them exhibit excellent performance in drug delivery, photothermal therapy (PTT), radiosensitization, and bioimaging. In PCa treatment strategies, AuNPs can passively accumulate in tumor tissue via the EPR effect and can also achieve active targeting by modifying their surface with specific ligands (eg, antibodies or aptamers targeting PSMA), significantly improving treatment precision.[40]

Radioactive gold-198 ($^{198}$Au) is an ideal theranostic nuclide; its emitted beta rays (max energy 0.96 MeV) can cause local DNA damage, while the accompanying gamma rays (412 keV) can be used for non-invasive imaging tracking; its relatively short physical half-life (2.7 days) also helps reduce long-term radiation exposure risk.[41] A research team innovatively combined the natural polyphenol compound resveratrol with radioactive gold nanoparticles to create a novel "green" nanomedicine RESV–$^{198}$AuNP.[42] Resveratrol not only participated in the green synthesis of the AuNPs as a reducing and stabilizing agent but, more importantly, significantly enhanced the overall anti-tumor effect by leveraging its multiple biological activities, including antioxidant, anti-inflammatory, pro-apoptotic, and radiosensitizing properties.[43] As a "green shell," resveratrol itself is a potent bioactive molecule. It possesses significant antioxidant, anti-inflammatory, and direct pro-apoptotic activities. More importantly, studies indicate that resveratrol can act as an efficient radiosensitizer, amplifying the radiotherapeutic effect of $^{198}$Au by mechanisms such as modulating the cell cycle and inhibiting DNA damage repair, achieving a synergistic "1+1>2" effect. While the β-rays emitted by $^{198}$Au can locally destroy tumor cells, they may also cause radiation damage to surrounding normal tissues, particularly when off-target accumulation occurs. Furthermore, although resveratrol exhibits anti-inflammatory and immunomodulatory properties, its pharmacodynamics and synergistic mechanisms with radiation in a radioactive microenvironment remain unclear, leading to uncertainty in its therapeutic efficacy. More comprehensive studies are therefore warranted in the future. In summary, RESV–$^{198}$AuNP was successfully prepared via a green nano-process, demonstrating good biocompatibility, excellent tumor targeting ability, and significant therapeutic efficacy, offering a highly clinically translatable new approach for the precise treatment of PCa and other solid tumors.

While research on AuNPs is maturing, other noble metal nanomaterials, such as Palladium Nanoparticles (PdNPs), are also opening new research paths in tumor therapy due to their unique catalytic and optical properties. PdNPs possess good biocompatibility, significant photothermal conversion efficiency, and unique photocatalytic and enzyme-mimicking activities, making them ideal candidates for constructing novel multimodal nano-therapeutic systems.[44]

Cisplatin (CisPt) is a widely used first-line chemotherapeutic drug. It works by binding to DNA, forming cross-links that hinder DNA replication and transcription, ultimately inducing apoptosis. However, its severe side effects, including nephrotoxicity and neurotoxicity, as well as the increasingly prominent issue of drug resistance, greatly limit its clinical application.[45] To overcome these obstacles, researchers designed a hybrid nanosystem combining PdNPs with Cisplatin: Pd@CisPt.[46] The PdNP itself exhibits Superoxide Dismutase (SOD)-like activity, able to modulate intracellular redox homeostasis. More importantly, under specific conditions, it can catalytically generate ROS. High levels of ROS cause severe oxidative stress, leading to protein misfolding or unfolding and directly causing DNA damage, weakening cancer cell viability from both organelle and molecular levels. The loaded Cisplatin is released upon entering the tumor cell, executing its classic DNA cross-linking damage function.

However, it should be noted that, although this direction shows great innovative potential, current in vivo research data on the Pd@CisPt hybrid nanosystem in the PCa field remains relatively limited. Its drug loading efficiency, precise release kinetics in the TME, in vivo targeting efficiency, long-term biosafety, and ultimate therapeutic efficacy in animal models all require more systematic and in-depth investigation for clarification and validation.

## Non-Metal Nanoparticles

Non-metal nanoparticles, by virtue of their unique physicochemical properties, highly tunable surface chemistry, and ability to efficiently accumulate in tumor tissue via the EPR effect, are becoming key platforms for developing novel targeted therapeutics. Focusing on two representative non-metal nanoparticles – Silica and Selenium nanoparticles – we delve into their application examples, advantages, and challenges in constructing multifunctional targeted delivery systems and enabling novel therapeutic molecules.

Antibody-Drug Conjugates (ADCs) represent a targeted therapy strategy that precisely kills tumor cells by conjugating specific antibodies with highly potent cytotoxic drugs.[47] However, ADCs still have limitations regarding drug loading capacity, systemic stability, and tumor selectivity. A study developed a multimodal targeted delivery system based on fluorescent PEGylated silica nanoparticles, integrating targeting, drug release, and imaging functions.[48] This system employed a "stepwise construction" strategy, integrating three functional units onto a single platform: using silica nanoparticles with good biocompatibility and intrinsic fluorescence as the core carrier for real-time tracking; selecting an anti-PSMA monoclonal antibody as the targeting headgroup to specifically recognize the highly expressed PSMA antigen on PCa cell surfaces; and conjugating the cytotoxic drug Monomethyl Auristatin E (MMAE) to the antibody via a cleavable dipeptide linker (valine-citrulline), enabling specific drug release within tumor cells. Although preliminary studies showed significant potential in targeting capability and imaging applications, the cytotoxicity of this nanosystem was still lower than that of traditional ADCs, suggesting a need for further optimization in drug loading efficiency and release kinetics.

On the other hand, p300, as a key co-activator of the Androgen Receptor (AR), plays a central role in both AR-dependent and independent oncogenic signaling pathways, making it a highly promising therapeutic target.[49] To target p300, a research team designed a peptide-based Proteolysis-Targeting Chimera (PROTAC) molecule targeting its CH1 domain. However, peptide drugs generally face challenges such as poor membrane permeability and low serum stability. To overcome these limitations, the researchers covalently conjugated this p300-targeting peptide PROTAC with a selenium nanoparticle delivery system.[50] Characterization results showed that the constructed nanodrug had a uniformly dispersed morphology, an average size of about 178 nm, and a low PDI, indicating good physical stability. Further serum stability assessment revealed that after modification with selenium nanoparticles, the half-life of the peptide drug was significantly extended to 10.19 hours, suggesting better stability and sustained action potential in vivo. Additionally, the selenium nanoparticles carried a positive surface charge, which could promote interaction with negatively charged cell membranes via electrostatic forces, significantly enhancing cellular internalization efficiency. Regarding in vivo distribution, this nanosystem effectively utilized the EPR effect characteristic of solid tumor tissues, achieving specific drug accumulation at the tumor site. Notably, the retention time of this nanodrug in the tumor area was significantly longer than in normal tissues like the liver, predicting potentially low liver toxicity risks alongside potent anti-tumor effects, indicating a favorable safety profile.

Represented by silica and selenium nanoparticles, non-metal nanoparticles provide powerful and flexible engineering platforms to overcome key bottlenecks in current cancer therapy. Silica nanosystems demonstrate potential beyond traditional ADCs by integrating multiple functional modules, with future development key focusing on further optimizing drug loading and release efficiency. The selenium nanoparticle platform successfully enables the difficult-to-drug peptide PROTAC molecules, paving the way for their clinical application. Simultaneously, addressing challenges such as long-term biosafety of nanomaterials, scalable production processes, and clinical translation will be essential steps to move these innovative therapies from the laboratory to the clinic, ultimately benefiting a broad range of cancer patients.

In summary, inorganic nanocarriers demonstrate immense application potential in drug delivery, molecular imaging, and combination therapy due to their unique physicochemical properties and powerful functional integration capabilities (Figure 2).

## Organic-Inorganic Hybrid Composite Nanoparticles

With the deep integration of nanotechnology and biomedicine, organic-inorganic hybrid composite nanoparticles, as an emerging class of intelligent biomaterials, are leading a paradigm shift in the field of tumor therapy.[51] These materials ingeniously combine the functional diversity of inorganic nano-cores (eg, Metal-Organic Frameworks (MOFs), mesoporous silica, noble metals) with the biocompatibility and functional specificity of organic molecules (eg, polymers, biomacromolecules, targeting ligands), constructing multifunctional platforms integrating drug delivery, environmental response, multi-modal therapy, and diagnostic imaging. Particularly in complex malignancies like PCa, where traditional therapies face bottlenecks such as significant drug toxicity, easy development of resistance, and low treatment efficiency, hybrid nanoparticles leverage their unique physicochemical properties to achieve precise spatiotemporal controlled

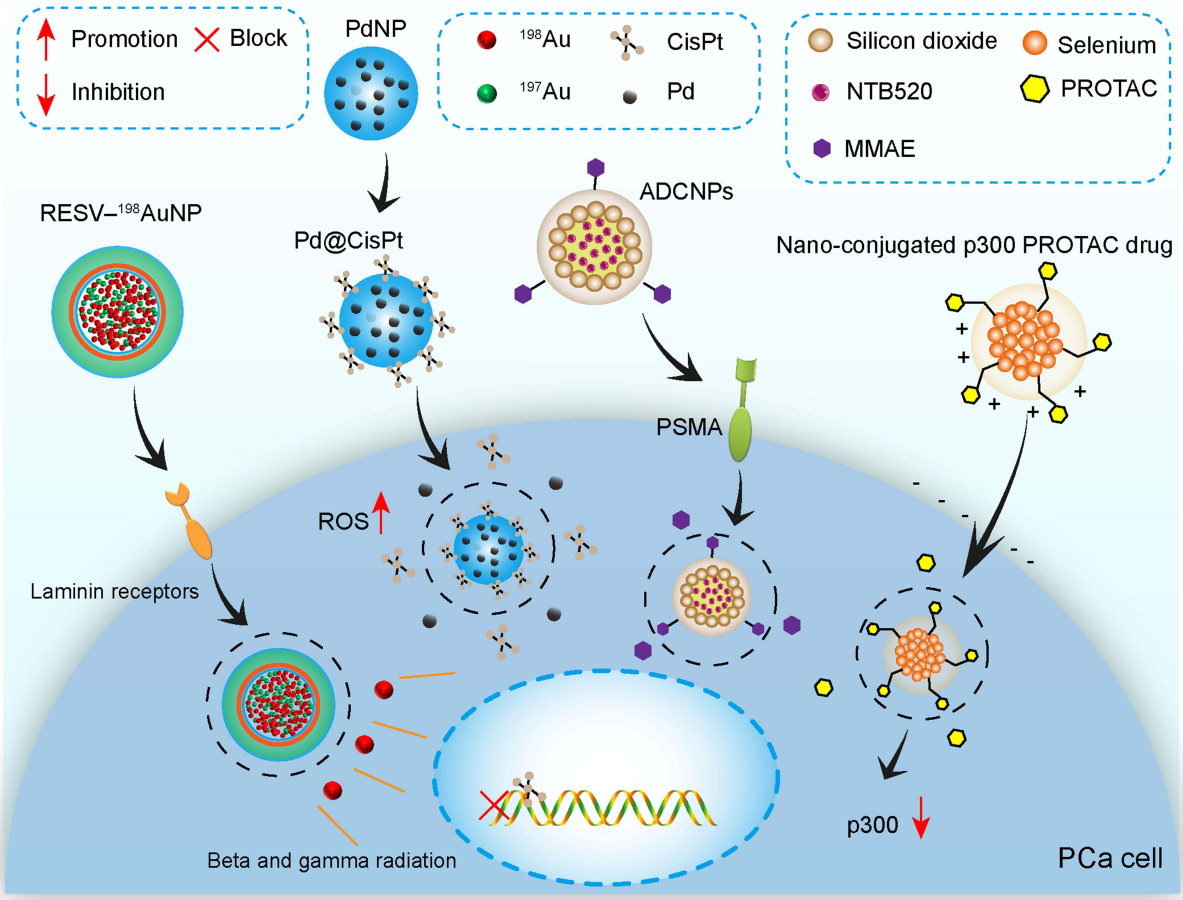


**Figure 2** Inorganic nanocarriers, mainly comprising metallic and non-metallic types, show great potential in prostate cancer treatment. Gold nanoparticles, owing to their ease of modification, biocompatibility, and unique photophysical properties, achieve tumor enrichment through passive (EPR effect) and active targeting. They have been integrated with radionuclides (eg, 198Au) and resveratrol to construct theranostic platforms with synergistic therapeutic effects. Meanwhile, palladium nanoparticles, by forming hybrid systems with cisplatin and utilizing their enzyme-like catalytic activity to generate reactive oxygen species, enhance chemotherapy efficacy. Among non-metallic nanoparticles, silica nanoparticles are used to construct multifunctional targeted delivery systems to improve the performance of antibody-drug conjugates, while nano-selenium effectively addresses the poor druggability of peptide-based PROTAC molecules through covalent conjugation, significantly enhancing their stability and cellular internalization efficiency.

release of drugs, synergize multiple treatment modalities, and specifically target cancer cells, thereby enhancing efficacy while significantly reducing damage to normal tissues, showing broad clinical translation prospects.[52]

Among numerous inorganic nanocarriers, MOFs have attracted much attention due to their tunable pore structures and surface chemistry. Among them, Zeolitic Imidazolate Framework-8 (ZIF-8) is a nano-scale, porous crystalline structure formed by the self-assembly of zinc ions and 2-methylimidazole ligands. It is widely used in constructing drug delivery systems due to its high specific surface area, good biocompatibility, ease of functionalization, and degradability in acidic environments.[53] Taking the long non-coding RNA SNHG15 as an example, it is highly expressed in various malignancies including PCa and plays a role in promoting tumorigenesis and progression.[54] Although siRNA can specifically silence this gene, it faces problems like poor stability, susceptibility to nuclease degradation, and limited cell membrane penetration, urgently requiring efficient nanocarriers for effective protection and precise delivery. ZIF-8 can efficiently load negatively charged siRNA via electrostatic adsorption and gradually degrade in the acidic environment within tumor cells, releasing siRNA to achieve gene silencing effects. To further enhance stability and targeting capability, PEG and specific targeting ligands can be modified on the ZIF-8 surface. For instance, researchers constructed a targeted nano-delivery platform by optimizing the mass ratio of ZIF-8 to siRNA, achieving a 94% loading efficiency to form siRNA@ZIF-8 complexes, then coating them with bifunctional PEG to form PEG-siRNA@ZIF-8, significantly


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enhancing colloidal stability and biocompatibility. Further covalent modification of the surface with an Epithelial Cell Adhesion Molecule (EpCAM)-specific aptamer constructed Apt-PEG-siRNA@ZIF-8, enabling specific recognition and efficient internalization by EpCAM-high expressing PCa cells.[55] This system can safely and efficiently silence the oncogene SNHG15, demonstrating significant anti-tumor effects in experiments, providing a new strategy for precise gene therapy of tumors. Nevertheless, the targeting efficiency of this nanodelivery system warrants further improvement. Intratumoral heterogeneity may result in the absence of EpCAM expression in certain cancer cells, thereby compromising the overall therapeutic outcome. Although the acidic environment facilitates siRNA release, the complexity of the in vivo tumor microenvironment may affect the precision and efficiency of this release. Future studies should focus on in-depth optimization and validation of these aspects to advance its clinical translation.

Beyond gene therapy, nanotechnology also shows great potential in novel tumor strategies like PTT and Chemodynamic Therapy (CDT), but their practical application still faces numerous challenges: the high temperatures induced by traditional PTT can easily damage surrounding normal tissues, while the efficacy of CDT is limited by the insufficient endogenous hydrogen peroxide ($H_2O_2$) and suboptimal pH conditions in the TME.[56,57] Therefore, developing a new nano-platform that efficiently catalyzes in the acidic tumor environment and achieves precise therapy under mild photothermal conditions holds significant research value. To address the aforementioned challenges, a research team designed and synthesized a sulfur and palladium co-modified Prussian blue analogue nanocomposite (Pd-S-CNMF).[58] This material uses a Prussian blue analogue as the base skeleton, with $S^{2-}$ and Pd nanoparticles synchronously introduced into its structure via a wet chemical method, significantly enhancing the material's responsiveness in acidic environments, endowing it with multiple enzyme-mimicking activities, enhanced Magnetic Resonance Imaging (MRI) performance, and excellent photothermal conversion efficiency. To further enhance the therapeutic effect on PCa, researchers also loaded the Heat Shock Protein 90 (HSP90) inhibitor Tanespimycin onto Pd-S-CNMF, constructing a functionally enhanced nanosystem 17Pd-S-CNMF, aiming to enhance the sensitivity and efficacy of subsequent PTT by inhibiting HSP90 expression. The therapeutic mechanisms of this nanosystem mainly include: reshaping the TME via multiple enzyme-mimicking activities, such as mimicking catalase to decompose $H_2O_2$ producing oxygen to alleviate tumor hypoxia; mimicking Glutathione Peroxidase (GPx) to consume reduced Glutathione (GSH); and mimicking peroxidase under acidic conditions to catalyze the generation of highly toxic ROS, thereby enhancing CDT efficacy. Simultaneously, leveraging its excellent photothermal properties, it achieves mild and efficient photothermal ablation under NIR laser irradiation. Additionally, the Pd nanoparticles also exhibited Cytochrome c Oxidase (COX)-mimicking activity, enabling mitochondrial targeting, inducing mitochondrial membrane potential collapse and apoptosis, further strengthening the anti-tumor effect. It is worth mentioning that this material also possesses good $T_1$-weighted MRI capability, serving as a theranostic platform for real-time visual guidance of the treatment process.

In terms of drug therapy, endocrine therapy is primary for initial PCa, but most patients eventually progress to CRPC. At this stage, docetaxel chemotherapy becomes the standard treatment. However, this drug faces issues such as low cellular uptake efficiency, requirement for high doses, significant systemic toxicity (eg, immunosuppression, neurotoxicity), and a tendency to induce early resistance, severely limiting its clinical application.[59] Studies show that the oncogene Pituitary Tumor-Transforming Gene 1 (PTTG1) plays a key role in the proliferation, migration, and drug resistance mechanisms of PCa, and its silencing is expected to have synergistic anti-tumor effects with docetaxel.[60] However, due to the negative charge of siRNA itself, susceptibility to enzymatic degradation, and difficulty in effectively entering cells, there is an urgent need to construct a nano-system capable of efficiently and stably co-delivering docetaxel and siPTTG1. For this purpose, a study developed a multifunctional nano-platform based on mesoporous polydopamine nanoparticles – MDS@LA.[61] Its construction strategy included: selecting mesoporous polydopamine nanoparticles (MPDA) as the carrier, known for good biocompatibility, high drug loading capacity, easy surface modification, and excellent photothermal conversion performance; loading docetaxel into the MPDA pores and immobilizing siPTTG1 on the particle surface via electrostatic adsorption; coating the drug-loaded MPDA with PEGylated liposomes to form MDS@L, and further linking the PSMA-specific aptamer A10-3.2 on its surface to obtain the final product MDS@LA, achieving efficient targeted recognition and internalization by PCa cells. Experimental results showed that the constructed nanoparticles had uniform size (~190 nm), good dispersity, exhibited pH-responsive drug release behavior in acidic environments, and possessed good NIR photothermal performance. MDS@LA effectively downregulated PTTG1,

B-cell lymphoma 2 (BCL-2), and AR protein expression while upregulating Caspase-3 activity, indicating it exerts synergistic therapeutic effects by promoting apoptosis and inhibiting proliferation pathways. This system successfully achieved the synergistic delivery and precise release of docetaxel and siPTTG1, coupled with a PTT enhancement effect, demonstrating excellent targeting, anti-tumor efficacy, and biosafety in both in vitro and in vivo experiments.

From ZIF-8-based targeted gene silencing platforms, to Pd-S-CNMF theranostic systems integrating multiple enzyme activities and mild PTT, to mesoporous polydopamine nano-platforms for synergistic delivery of chemotherapeutic drugs and siRNA, these advanced organic-inorganic hybrid nanotechnologies all demonstrate great potential in the precise treatment of PCa (Figure 3). Through ingenious design, they successfully overcome many bottlenecks of traditional therapies and single treatment modalities, exhibiting excellence in improving drug delivery efficiency, achieving controllable release, reducing systemic toxicity, and synergizing multiple treatment strategies. With deepening research and continuous technological optimization, these intelligent, multifunctional nano-platforms are expected to propel tumor therapy towards a new stage of precision, efficiency, and personalization, providing more powerful solutions for the clinical management of PCa and other malignancies.

## Biomimetic Nanocarriers

The emergence of nanodrug delivery systems offers new possibilities for improving therapeutic efficacy and reducing toxic side effects. However, conventional synthetic nanocarriers are often rapidly recognized and cleared by the body's

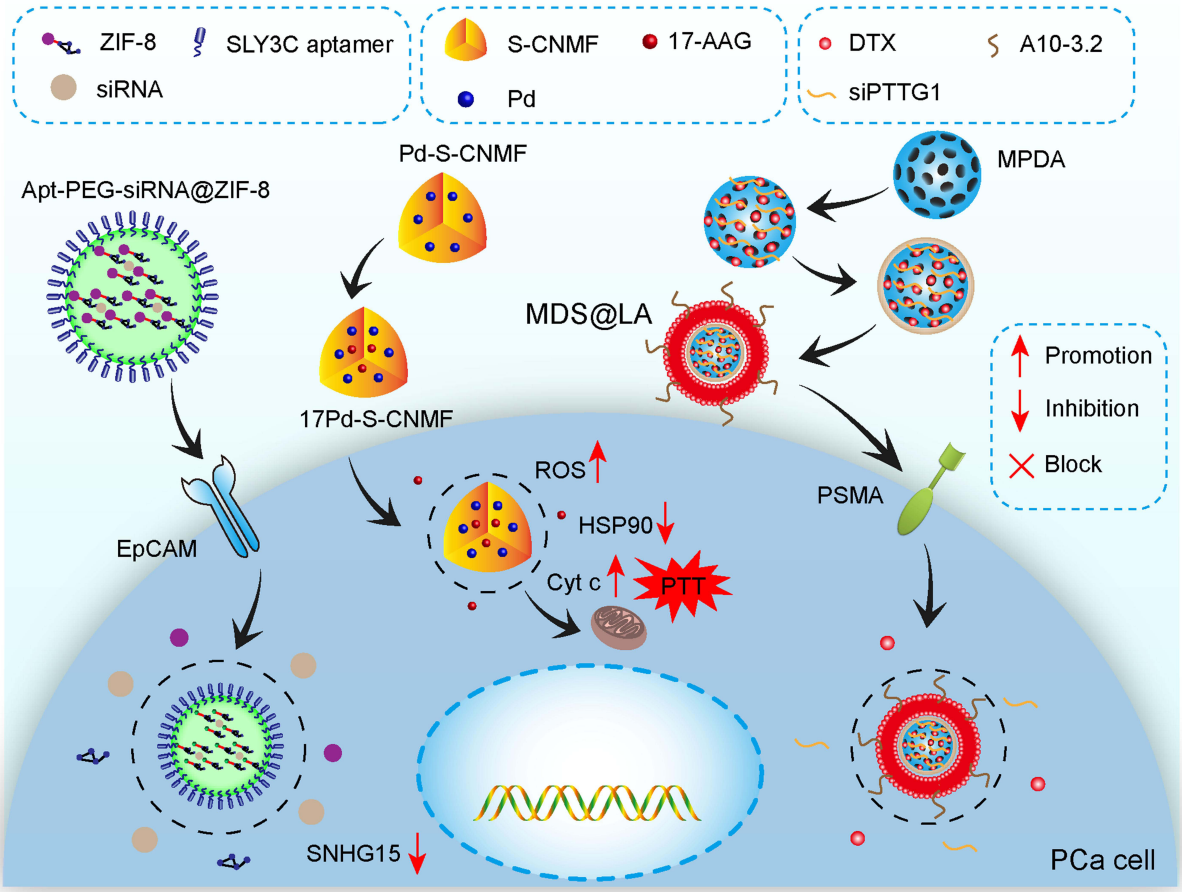


**Figure 3** Organic-inorganic hybrid composite nanoparticles integrate the biocompatibility and functionality of organic components (eg, polymers, targeting ligands) with the unique catalytic, optical, and porous channel properties of inorganic components (eg, ZIF-8, Prussian blue, mesoporous polydopamine). They construct multifunctional precision platforms combining targeted delivery, environmentally responsive release, multi-modal synergistic therapy, and theranostics. Specifically, they achieve efficient gene silencing (eg, siRNA) through response to the acidic microenvironment, utilize multiple enzyme activities and mild photothermal effects to synergistically enhance therapeutic efficiency, and leverage drug-loading pores and surface modifications for the co-delivery of chemotherapeutic drugs and nucleic acids. Thereby, they significantly overcome the bottlenecks of traditional prostate cancer therapies regarding targeting, drug resistance, and systemic toxicity.


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immune system (especially the mononuclear phagocyte system) after entering the body, resulting in short circulation times in the blood and inability to effectively accumulate at tumor sites, thus limiting their therapeutic potential.[62] To overcome these obstacles, researchers have drawn inspiration from natural biological systems, pioneering the frontier field of "biomimetic nanotechnology." This strategy involves mimicking or directly utilizing the structure and function of natural biological components (eg, cell membranes, extracellular vesicles) to modify and camouflage nanocarriers, aiming to endow them with superior biocompatibility, immune evasion capability, and precise targeting.[8]

"Camouflaging" nanocarriers with natural cell membranes is one of the most mature and widely applied strategies in the biomimetic field. This "learning from nature" approach cleverly transplants the complex surface proteins and functional molecules inherent to cell membranes onto the surface of artificial nano-cores, thereby bestowing the latter with "living" characteristics, enabling them to interact more intelligently with the internal environment.

Red Blood Cell (RBC) membranes are an ideal "cloak" for constructing long-circulating nanocarriers due to their abundant source, excellent biocompatibility, and surface enrichment of the "don't eat me" signal protein CD47.[63] The CD47 protein can bind to the Signal Regulatory Protein Alpha (SIRPα) receptor on phagocytic immune cells, transmitting an inhibitory signal for phagocytosis,[64] thereby helping nanocarriers effectively evade surveillance and clearance by the mononuclear phagocyte system, significantly prolonging their circulation half-life in the blood, creating a crucial time window for subsequent tumor targeting and accumulation.

A study targeting CRPC ingeniously utilized this characteristic, designing a biomimetic nanovesicle named FiFe@RBM.[65] This system used an RBC membrane as the shell, co-encapsulating the Fatty Acid Synthase (FASN) inhibitor IPI-9119 and Iron Oxide Nanoparticles (IONPs) internally. Its multi-level synergistic mechanism is highly innovative: Firstly, RBM camouflage ensures the long circulation and tumor accumulation of the nanovesicles in vivo. Secondly, under an external alternating magnetic field, the core IONPs can not only generate localized hyperthermia for efficient magnetic hyperthermia therapy but also release iron ions. These iron ions catalyze the Fenton reaction, producing a large amount of ROS, which directly damages tumor cells on one hand, and induces mitochondrial dysfunction and inhibits the crucial AKT-mammalian Target of Rapamycin (mTOR) survival pathway on the other, thereby promoting apoptosis. More ingeniously, the synchronously released FASN inhibitor profoundly reshapes the lipid composition of the cancer cell membrane by blocking the abnormally active de novo fatty acid synthesis pathway in cancer cells, leading to a significant increase in the proportion of polyunsaturated fatty acids and their phospholipid derivatives (PUFA-PC, PUFA-PE). This change greatly enhances the sensitivity of the cell membrane to lipid peroxidation, thereby synergistically amplifying the iron ion-induced ferroptosis effect. FiFe@RBM, by integrating immune evasion, magnetic hyperthermia, CDT (Fenton reaction), and metabolic reprogramming-enhanced ferroptosis, provides a new paradigm for efficient, precise, and synergistic treatment of refractory tumors like CRPC. This system still possesses certain limitations. Its tumor targeting primarily relies on the EPR effect, which may prove less effective against solid tumors with heterogeneous vascularization or severe fibrosis. Furthermore, the research team has only validated its efficacy in suppressing liver metastases, without addressing other prevalent metastatic sites of PCa, such as bone or lung.

Building upon the RBC membrane biomimetic strategy, another study further integrated active targeting functionality to address the poor targeting and high toxicity of traditional chemotherapeutic drugs like 10-Hydroxycamptothecin (HCPT). The research team constructed a dual-layer biomimetic nanocarrier named LHRH-RV-NG/HCPT.[66] The design of this system also embodied multi-layered ingenuity: its core used a polymer nanogel highly sensitive to the TME, cross-linked by disulfide bonds, ensuring it disintegrates only in the high GSH environment inside tumor cells, achieving on-demand precise drug release. The exterior was coated with mouse-derived RBC membrane vesicles (RVs), endowing it with long-circulating "stealth" capability. The most critical innovation was the further modification of the RBC membrane surface with Luteinizing Hormone-Releasing Hormone (LHRH) peptide. Since LHRH receptors are generally highly expressed on PCa cell surfaces, this design guides the nanocarrier to actively recognize and bind to cancer cells, achieving a leap from "passive accumulation" to "active targeting." This multifunctional integrated system significantly improved the therapeutic window of HCPT, providing a highly clinically translatable solution for precise chemotherapy of advanced PCa.

Beyond RBC membranes, the membranes of tumor cells themselves, due to their unique surface antigens and adhesion molecules, have become an attractive biomimetic material.[67] Utilizing the principle of "homotypic targeting" – where membranes derived from a certain tumor cell type are preferentially recognized and taken up by the same type of tumor cell – researchers can construct nano-delivery systems with natural affinity for specific tumors. Addressing another major challenge in PCa treatment – bone metastasis – a study cleverly employed this strategy. The research team first extracted cell membranes from human PC-3 PCa cells and coated them onto chitosan-polypyrrole nanogels (CH-PPy NGs) loaded with the chemotherapeutic drug Docetaxel (DTX) and siRNA targeting the RANK gene.[68] The resulting CH-PPy NGs/DTX/siRANK@CM composite system possessed multiple advantages: Firstly, the PC-3 cell membrane camouflage allowed it to evade immune clearance and precisely "home" to primary and metastatic PC-3 tumor lesions, greatly enhancing targeted drug accumulation efficiency. Secondly, the nanogel core possessed pH responsiveness, promoting drug release in the acidic TME. Most importantly, this system achieved potent synergy between chemotherapy and gene therapy: DTX directly killed tumor cells, while RANK siRNA effectively blocked the invasion and metastasis process of PCa cells to bone by silencing the key RANK/RANK Ligand (RANKL) signaling pathway. This "trinity" strategy combining homotypic targeting, chemotherapy, and gene silencing opened a new path for inhibiting the growth and distant metastasis of PCa.

The design philosophy of biomimetic nanocarriers is not limited to simply "borrowing" natural cell membranes. Further, researchers have begun attempting to deconstruct and reconstruct biological functions at a more fundamental level or seek inspiration from other biological phenomena, giving rise to more profound and disruptive innovations. Extracellular Vesicles (EVs) are natural messengers for intercellular communication. They possess endogenous targeting capabilities and can even penetrate physiological barriers like the blood-brain barrier, making them highly promising natural drug carriers.[69] However, the application of natural EVs faces severe bottlenecks: EVs produced by source cells are highly heterogeneous, separation and purification processes are complex with low yield, drug loading efficiency is not high, and standardization and scalable production are difficult, all of which severely hinder their clinical translation.[70] To address this challenge, research ideas are shifting from "top-down" isolation of natural EVs to "bottom-up" rational design and reconstruction of EV mimetics. A groundbreaking study focused on precisely simulating the key physicochemical properties of natural EVs, aiming to construct artificial nanocarriers with performance comparable to or even surpassing natural EVs. The research team systematically analyzed key parameters of natural EVs, including lipid composition, size distribution, surface charge, membrane fluidity, and polarity, and used this as a guide to screen for an optimal cholesterol-enhanced formulation named "CE Mimic 3" by regulating the ratios of different lipids (cholesterol, sphingomyelin, phosphatidylethanolamine, phosphatidylcholine, phosphatidylserine).[71] The nanoparticles constructed with this formulation (Chol/SM/PE/PC/PS = 30/16.1/12.9/20.9/20.1) closely matched natural EVs derived from PC3 PCa cells in multiple dimensions including size, zeta potential, coating integrity, and membrane polarity. For functionalization, the system also incorporated reducible organosilica nanocapsules responsive to reducing environments (eg, high intracellular GSH in tumor cells) as the core, enabling intelligent controlled drug release. This work not only successfully constructed highly realistic EV mimetics but, more importantly, established a set of systematic rational design principles, laying a solid technical foundation for developing standardized, scalable next-generation targeted drug delivery platforms.

In nature, pathogens have evolved highly efficient mechanisms for recognizing human cells for survival. Drawing inspiration from these unique biological phenomena can provide novel perspectives for tumor targeting therapy. Research has found that an abnormal glycosylation modification – oncofetal Chondroitin Sulfate (ofCS) – exists on the surface of various types of tumor cells. This glycosaminoglycan is almost absent in normal tissues but highly enriched in tumor tissues, constituting a highly potential broad-spectrum tumor marker.[72] An interesting biological correlation is that this ofCS marker is also present on the trophoblast cells of the human placenta,[73] which is precisely the binding site for erythrocytes infected by the parasite Plasmodium falciparum causing gestational malaria.[74] The malaria parasite binds specifically to ofCS on the placenta via its VAR2CSA protein. Based on this discovery, researchers inferred that recombinant VAR2CSA protein could also specifically recognize and bind to ofCS on the surface of various cancer cells. Experiments confirmed this hypothesis; VAR2CSA protein showed extremely high affinity for cancer cells from multiple sources, with almost no binding to normal tissues. This discovery gave rise to a novel biomimetic strategy:

constructing Malaria Mimicking Erythrocyte Nanoparticles (MMENPs).[75] The concept aims to mimic the behavior of malaria-infected erythrocytes by modifying nanoparticles with VAR2CSA protein, enabling them to precisely "capture" ofCS-expressing tumor cells like the malaria parasite, thereby achieving broad-spectrum, efficient drug delivery. This strategy breaks away from the traditional antibody-antigen or ligand-receptor targeting modes, opening a new targeting pathway based on the simulation of pathophysiological processes. Although this strategy is still in the conceptual and early validation stage, and future evaluation of its efficacy, safety, and potential immunogenicity in more complex animal models is needed, it undoubtedly provides an exciting direction for developing novel anticancer therapies with broad applicability.

In summary, biomimetic nanocarriers, as a frontier interdisciplinary field in tumor therapy, are demonstrating unprecedented vitality and potential. From utilizing RBC and cancer cell membranes for immune evasion and precise targeting, to rationally reconstructing extracellular vesicles to overcome production bottlenecks, and to mimicking pathogens to pioneer new paradigms for broad-spectrum targeting, these innovative strategies collectively point to the core development direction of future tumor therapy: smarter, more precise, and more efficient (Figure 4).

## Smart Responsive Delivery Strategies

With the deep integration of nanotechnology and biomedicine, smart responsive drug delivery systems have become a frontier direction in the field of tumor precision therapy. These systems can specifically respond to intrinsic physicochemical characteristics of the TME (eg, low pH, high reducibility, specific enzyme overexpression) or externally applied physical stimuli (eg, light, ultrasound), thereby achieving precise drug release and activation at predetermined times and locations. Smart responsive delivery strategies encapsulate therapeutic agents within specially designed nanocarriers that are sensitive to specific stimuli, enabling "on-demand" release, which greatly enhances the precision and safety of treatment.[9]

### Light-Responsive Strategies

Light-responsive strategies use light of specific wavelengths as an external "switch" to control drug release or activation with extremely high spatiotemporal resolution, with Photodynamic Therapy (PDT) being a typical application.[76] PDT, as a non-invasive treatment modality, relies on a PS generating Reactive Oxygen Species (ROS) under light irradiation to induce cell death. However, traditional PDT faces three major challenges: 1) PS self-quenching due to aggregation within carriers, reducing ROS yield; 2) Extremely short ROS lifetime (<40 ns) and very small action radius (~10 nm), limiting the killing range; 3) Limited tissue penetration depth (3–5 mm) of commonly used visible light, restricting its application in deep-seated tumors.[77]

To address the first two challenges, researchers designed a novel light-responsive block copolymer – Poly(ethylene glycol)-block-poly(4,5-dimethoxy-2-nitrobenzyl methacrylate) (PEG-b-PNBMA).[78] This polymer can self-assemble into micelles or vesicles in aqueous solution, with the core PNMMA segment containing an o-nitrobenzyl group serving as the photosensitive switch. Upon irradiation with ultraviolet or violet light (eg, 405 nm), this group undergoes photolysis, transforming from hydrophobic to hydrophilic polymethacrylic acid. This fundamental change in chemical property disrupts the structural integrity of the nanocarrier, enabling precise release of the internally loaded drug. Based on this, the research team constructed smart micelles loaded with the PS Rose Bengal (RB-M). This system employed an ingenious "sequential irradiation" strategy: First, using a 405 nm LED light to irradiate the tumor site, triggering the disintegration of the PEG-b-PNBMA micelles and releasing the RB molecules, effectively solving the self-quenching problem. Subsequently, switching to a 580 nm LED light, which efficiently activates the now freely dispersed RB molecules, causing them to generate a large amount of ROS. This strategy not only significantly improved ROS generation efficiency and killing rate against tumor cells, but the study also found that the primary light-induced carrier dissociation process helped disrupt the endosomal/lysosomal structures formed after cellular internalization, thereby promoting RB escape and diffusion throughout the cytoplasm, greatly expanding the ROS action range and comprehensively enhancing PDT efficacy.

To address the insufficient penetration depth of visible light, using Near-Infrared (NIR) light as an excitation source has become a research hotspot. NIR light has lower absorption and scattering in biological tissues, with penetration depths reaching

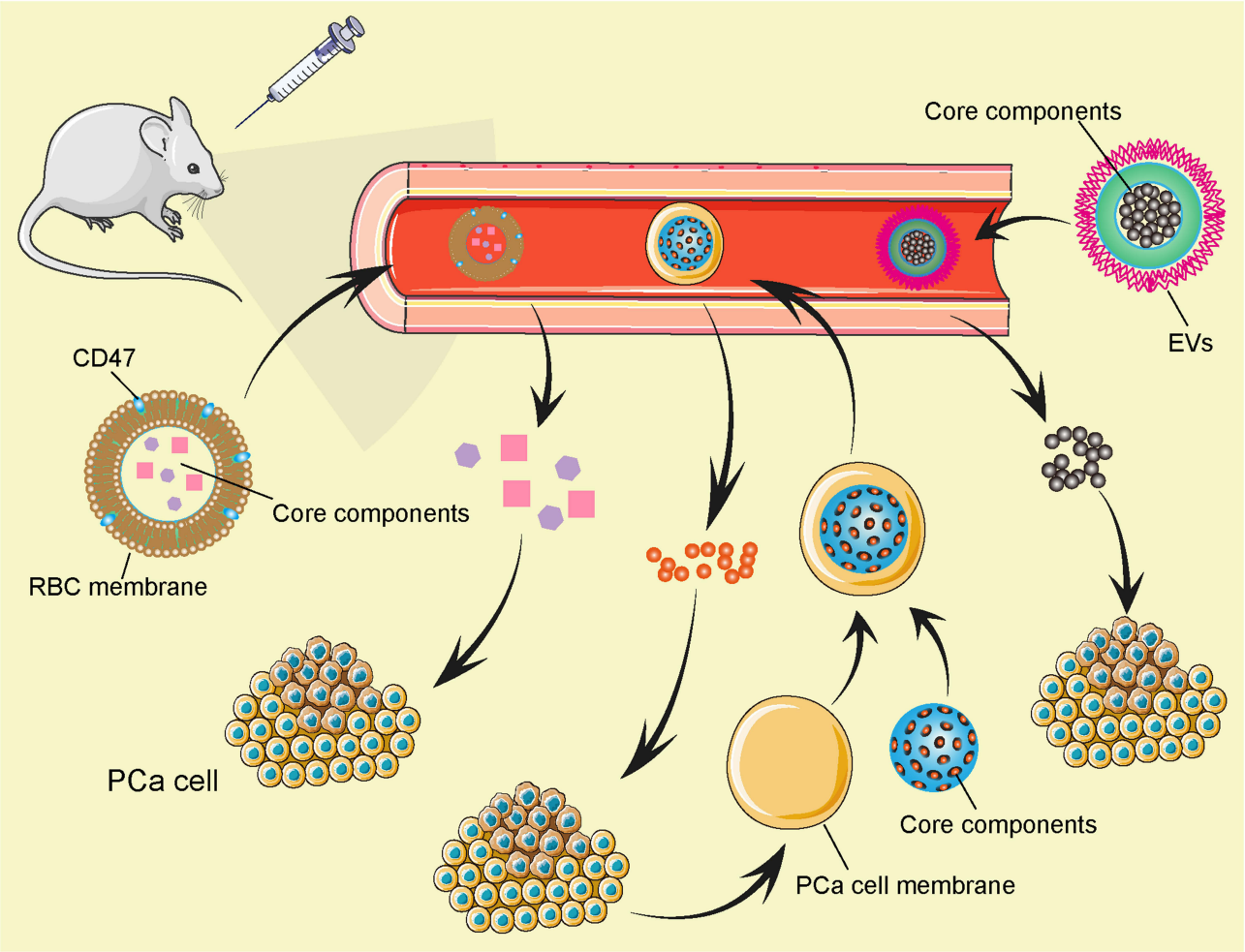


**Figure 4** The core principle of bioinspired nanomedicine delivery is to "learn from nature," constructing intelligent carriers by directly transplanting or functionally mimicking the properties of native biological components. Several key strategies have emerged: harnessing the CD47 protein on red blood cell membranes to achieve immune evasion and prolong circulation; utilizing the homotypic targeting capability of cancer cell membranes for precise tumor "homing"; rationally designing lipid formulations to reconstruct extracellular vesicle mimetics for standardized drug delivery; and simulating pathological processes, such as pathogen recognition of tumor-specific markers (eg, malaria parasite targeting), to establish novel broad-spectrum targeting pathways. Together, these approaches aim to enhance the intelligent delivery efficacy of carriers within complex biological environments.

several centimeters. Upconversion Nanoparticles (UCNPs), as excellent light conversion media, can absorb low-energy NIR light and convert it into high-energy visible light, thereby remotely activating PSs located in deep tumors.[79] A study designed and constructed core-shell-shell structured $NaYbF_4$:$Er^{3+}$ UCNPs.[80] By precisely controlling synthesis parameters like ligand ratio, reaction time, temperature, and reactant concentration, the size and morphology of the nanoparticles were optimized. Further coating with a $NaGdF_4$:$Yb^{3+}$,$Er^{3+}$ active shell and a $NaGdF_4$ inert shell not only significantly enhanced fluorescence intensity (approximately 30-fold) but also, due to the presence of gadolinium ions, enhanced MRI performance. This nanosystem was co-assembled with two functional molecules: one was JS-K, a prodrug that reacts with GSH in tumor cells, releasing nitric oxide (NO), consuming intracellular antioxidants and generating Reactive Nitrogen Species (RNS); the other was an Aggregation-Induced Emission (AIE)gen (MD), a Type I PS that effectively generates superoxide anions and hydroxyl radicals upon light irradiation. Under co-irradiation with NIR and white light, the NO released by JS-K and the superoxide anions generated by MD further react, producing highly cytotoxic peroxynitrite, forming a synergistic killing mechanism involving both ROS and RNS, thereby significantly enhancing the killing effect on PCa cells.


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## Ultrasound-Responsive Strategies

Ultrasound, due to its non-invasiveness, superior tissue penetration capability (can exceed 10 cm), and good biosafety, is an ideal external energy source for activating therapy in deep-seated tumors.[81] Sono-immunotherapy utilizes ultrasound to activate sonosensitizers to produce ROS, inducing Immunogenic Cell Death (ICD), thereby triggering a systemic anti-tumor immune response.[82] However, this therapy is still limited by low tumor immunogenicity, the immunosuppressive TME, and insufficient targeting efficiency.

To address these challenges, researchers developed a cascade-targeting nanocomposite MCTH NCs.[83] This system used mesoporous organosilica nanoparticles doped with disulfide bonds as the carrier, endowing it with GSH-responsive degradation capability; it was loaded with copper-modified protoporphyrin as the sonosensitizer, which can not only produce ROS under ultrasound but also convert $H_2O_2$ in the TME into the more toxic hydroxyl radical via a Fenton-like reaction; the surface was sequentially modified with the mitochondrial targeting molecule triphenylphosphonium and Hyaluronic Acid (HA), the latter recognizing the highly expressed CD44 receptor on tumor cells for active targeting. The cascade targeting process of MCTH NCs occurs in two stages: First, relying on the specific binding between HA and CD44 receptors, the nanoparticles accumulate at the tumor site and are internalized by cells. Subsequently, within the tumor cell, overexpressed hyaluronidase degrades the HA layer, exposing the triphenylphosphonium, guiding the particles to target mitochondria. Simultaneously, the high GSH concentration in the TME breaks the disulfide bonds, promoting nanocarrier degradation and release of the sonosensitizer, further enhancing ROS generation. Under ultrasound activation, MCTH NCs trigger severe oxidative stress at the mitochondrial site, leading to membrane potential collapse and cytochrome c release, thereby initiating the apoptosis program. Additionally, the ROS burst can induce ICD, promoting the release of Damage-Associated Molecular Patterns (DAMPs) such as calreticulin, High Mobility Group Box 1 (HMGB1), HSP90, and adenosine triphosphate. These signaling molecules effectively promote dendritic cell maturation and antigen presentation, activating $CD8^+$ T cell-mediated adaptive immunity, ultimately reshaping the tumor immune microenvironment. MCTH NCs, through their cascade targeting mechanism, precisely deliver the sonosensitizer to mitochondria, not only directly killing tumor cells but also achieving synergistic therapy by activating a systemic immune response, providing a new strategy for sono-immunotherapy of PCa.

## pH-Responsive Strategies

The TME, due to enhanced glycolysis and poor perfusion, is typically weakly acidic (pH 6.5–6.8), providing a natural target for designing pH-responsive delivery systems.[84] A study aimed at enhancing photo-immunotherapy cleverly combined pH-responsive mechanisms with various advanced treatment strategies, constructing a membrane-anchored NIR dual-type nano-photosensitizer system YBS-BMS NPs-RKC.[85] The pH-responsive principle was based on a nanocarrier system composed of a pH-responsive polymer (eg, PCL-b-PAE) and a cell membrane-anchoring peptide RKC (consisting of the positively charged amino acid sequence RKKRKRK and a hydrophobic palmitic acid fragment $C_{16}$). In the bloodstream at normal physiological pH (7.4), the hydrophobic and compact PAE structure is shielded by the PEG layer, hiding the RKC peptide inside the nanoparticle, avoiding non-specific interactions and reducing in vivo clearance. However, when the nanoparticles reach the acidic TME (pH < 6.5), the PAE undergoes protonation and a hydrophilic transition, causing the RKC peptide to be specifically exposed at the tumor site. The exposed RKC peptide electrostatically interacts with the cell membrane via its positively charged RKKRKRK sequence, while the hydrophobic $C_{16}$ fragment inserts into the cell membrane lipid bilayer, achieving prolonged anchoring of the nano-photosensitizer on the tumor cell membrane. This pH-driven phase transition process is also accompanied by a change in nanoparticle surface potential from negative to positive, further enhancing its affinity for the cell membrane. Ultimately, this membrane anchoring mechanism allows the ROS generated under NIR light irradiation to act locally on the cell membrane, effectively activating the caspase-1/Gasdermin D (GSDMD) pathway, inducing immunogenic pyroptosis, and synergizing with the immune checkpoint blocker BMS-202 to enhance anti-tumor immune responses.

## Reduction-Responsive Strategies

The reductive environment inside tumor cells, particularly the Glutathione (GSH) concentration, is much higher than in normal cells and the extracellular environment (can reach up to 10 mM), providing an ideal endogenous trigger condition

for constructing reduction-responsive delivery systems.[86] In various tumors including PCa, GSH levels can further increase with disease progression. Leveraging this concentration gradient, nanocarriers that specifically degrade within tumor cells can be designed. Based on this difference, researchers designed a reduction-responsive nanocarrier where the disulfide bonds in its structure can be cleaved in the high GSH concentration of the TME, achieving targeted drug release, while remaining stable under normal physiological conditions. A research team successfully synthesized a GSH-responsive polymer: poly-tetraethylene glycol disulfide polymer (poly-TTG-SS), and prepared Docetaxel (DTX)-loaded nanoparticles (poly-TTG-SS@DTX NPs) using the nano-precipitation method.[87] This GSH-responsive nano-delivery system exhibited good biosafety, high drug loading efficiency, and excellent TME-responsive drug release capability. Experiments showed that this system could significantly enhance the killing effect of DTX on PCa cells while effectively reducing toxic side effects on normal cells, providing a promising new therapeutic strategy for clinical chemotherapy of PCa.

## Novel Nanotechnologies for PCa Diagnosis

Early and accurate diagnosis of PCa is crucial for improving patient survival rates and quality of life. However, traditional diagnostic methods face severe challenges. For example, PSA serum testing, the most widely used screening tool, lacks sufficient specificity and can also be elevated in benign conditions like benign prostatic hyperplasia, leading to a large number of unnecessary invasive biopsies.[88] Imaging examinations, such as MRI, while providing anatomical information, still have room for improvement in identifying early micro-lesions and precisely assessing tumor boundaries.[89] Therefore, developing new diagnostic tools with both high sensitivity and high specificity has become a research focus in this field. Nanotechnology, by virtue of its unique size effects, surface effects, and quantum effects, enables unprecedented precise interaction with biological systems at the molecular and cellular levels. By designing functionalized nanomaterials, researchers can develop new strategies for ultrasensitive biomarker detection, targeted molecular imaging, and high-throughput cell separation.

### Optimization of Diagnostic Strategy: From Single to Dual Biomarker Detection

To overcome the limitations of single PSA detection, research has turned to multi-marker combined detection strategies. PSMA is another key biomarker, whose expression level is significantly upregulated in malignant prostate tumor tissues and is closely related to tumor aggressiveness and malignancy. Theoretically, simultaneously detecting PSA and PSMA in serum can build a more reliable diagnostic model, significantly improving early diagnostic accuracy and effectively distinguishing malignant tumors from benign lesions. Addressing this need, researchers developed a fluorescent nanoprobe based on gold-selenium (Au–Se) bonds for the simultaneous detection of PSA and PSMA in serum.[90] This nanoprobe system uses gold nanoparticles as the carrier, covalently linking selenol peptide chains labeled with fluorescent dyes FAM and 5-TAMRA to the particle surface via the more stable Au–Se bond. When not interacting with the target enzymes, the fluorescence of the dyes is quenched due to the energy transfer effect; when PSA or PSMA is present, they specifically cleave the corresponding peptide chain, releasing the fluorescent dye and restoring its emission, thereby achieving simultaneous, specific detection of the two biomarkers. This probe system performed excellently in terms of thermal stability, temporal stability, and resistance to GSH interference. Even under high temperature, prolonged reaction time, or high GSH concentration environments, its fluorescent background remained stable, demonstrating good environmental adaptability. In actual testing with clinical serum samples, this probe showed high sensitivity, accurately detecting abnormal expression of PSA and PSMA even when samples were diluted 40-fold, with results consistent with standard hospital detection methods, proving its potential for high-fidelity, simultaneous dual-marker detection in complex biological samples.

### Targeted Nano-Contrast Agents for Magnetic Resonance Imaging (MRI) Enhancement

MRI plays an important role in the localization and staging of PCa, but conventional contrast agents lack tumor specificity. Developing PSMA-targeted MRI probes is a key direction for improving imaging signal-to-noise ratio and diagnostic accuracy. However, previous studies often used targeting ligands not approved by the FDA, such as antibodies. These large molecular ligands often have weak tumor tissue penetration and tend to accumulate in non-

target organs (eg, liver, spleen), limiting their clinical translation.[91] Therefore, developing targeted contrast agents based on the approved PSMA-11 peptide holds significant clinical value. This class of ligands can guide nanoparticles to specifically aggregate in PSMA-positive tumor regions, thereby enhancing imaging signal-to-noise ratio and specificity. As negative contrast agents, Superparamagnetic Iron Oxide Nanoparticles (IONPs) reduce signal intensity in $T_2$ or $T_2$*-weighted images by disrupting local magnetic field uniformity. Their surfaces are often modified with biocompatible materials (eg, Bovine Serum Albumin (BSA) or carboxymethyl dextran) to enhance stability, reduce aggregation, and provide a platform for conjugating targeting molecules. Researchers constructed two targeted IONPs: TBNPs (BSA-coated IONPs conjugated with PSMA-11-HBED) and TDNPs (carboxymethyl dextran-coated IONPs conjugated with PSMA-11-HYNIC).[92] Experimental results showed that both exhibited excellent targeted imaging performance in PSMA-positive PCa models. The targeted nanoparticles caused significant signal attenuation in the tumor region, with TBNPs performing better than TDNPs. Relative Signal Enhancement (RSE) analysis further confirmed that the tumor-to-muscle contrast in the targeted groups was significantly higher than in the non-targeted groups. Additionally, the targeted nanoparticles had higher iron accumulation levels within the tumor. Notably, the targeting strategy greatly improved the efficiency of contrast agent use: TBNPs and TDNPs reduced the required dose of their non-targeted counterparts to 1/3 and 1/2, respectively. The PSMA-11 targeted iron oxide nanoparticle system developed in this study, while enhancing MRI specificity and contrast, significantly reduced the contrast agent dose, showing good clinical translation prospects and providing a new strategy for early and precise diagnosis of PCa.

### Biomimetic Magnetic Nanoparticles for Efficient Capture of Circulating Tumor Cells (CTCs)

CTCs are tumor cells that detach from the primary tumor and enter the peripheral blood, serving as "seeds" for tumor metastasis.[93] Capturing and analyzing CTCs through "liquid biopsy" technology can provide key information for early cancer diagnosis, prognosis assessment, and treatment efficacy monitoring. Especially when PSA levels are in the "gray zone" of 4–10 ng/mL,[94] CTC count has been proven to be a powerful tool for distinguishing benign from malignant lesions and aiding diagnostic decisions.[95] However, CTCs are extremely rare in the blood (only a few to dozens per milliliter of blood), and traditional immunomagnetic bead separation techniques, primarily relying on antibody-antigen interactions at the molecular level, still have room for improvement in capture efficiency and specificity. A research team, inspired by the filopodia structures on immune cell surfaces, designed and prepared magnetic particles with nanofilamentous structures (NFMPs).[96] Just as immune cells enhance their capture ability for target cells via filopodia, NFMPs achieve topological matching with CTCs through surface nanofilamentous structures, enhancing capture efficiency. Their structure mimics the filopodia on immune cell surfaces, with an average diameter of about 105 nm, similar to the diameter of natural immune cell filopodia. Experiments showed that NFMPs achieved a capture efficiency as high as 86.5% for PCa cell lines, significantly higher than smooth magnetic particles. Their efficient capture is attributed to the synergy of topological matching and molecular recognition: filopodia on the cell surface can more effectively "grab" the nanofilamentous structures on the NFMP surface. Furthermore, NFMPs showed good specificity, with low capture efficiency for non-specific cell lines, and cell viability remained good after capture. In clinical samples, NFMPs combined with machine learning algorithms achieved high-precision diagnosis for patients in the PSA gray zone. By integrating PSA level, Free-to-Total PSA (F/T-PSA) ratio, and CTC count, a Support Vector Machine (SVM) model achieved 100% sensitivity and 93.3% specificity, with an Area Under the Curve (AUC) value of 98.1%, significantly superior to single PSA or F/T-PSA detection. This platform provides an efficient and reliable tool for liquid biopsy-based early cancer diagnosis and prognosis assessment.

## Nanotheranostic Platforms for PCa

The rapid development of nanotechnology provides an ideal solution for realizing novel "theranostic" technical platforms, which has become a key direction for improving PCa treatment efficacy and patient prognosis. Through precise design and functionalization, nanoparticles can serve as multifunctional carriers, integrating imaging contrast agents, therapeutic drugs, and targeting molecules into a single nano-platform. These platforms can not only provide

complementary, high-precision anatomical and functional information about the tumor through multimodal imaging techniques but also precisely deliver therapeutic agents to the tumor site, thereby achieving "visualized therapy" while maximizing efficacy and minimizing toxic side effects.

## Active and Passive Targeting Strategies in Nanotheranostic Platforms

Active targeting strategies, by modifying the nanoparticle surface with ligands that specifically recognize and bind to receptors highly expressed on tumor cell surfaces, achieve precise "locking onto" tumor cells, greatly enhancing the efficiency and specificity of drug delivery. To address the challenge of separated traditional diagnostic modes, a research team constructed a nanotheranostic system named AMNDs-LHRH.[97] The core of this system is gold/manganese composite nanodots (Au/Mn Nanodots), whose design ingeniously integrates multiple functions. The system is based on gold nanodots (Au Nanodots), which themselves possess excellent optical properties and X-ray attenuation capacity, serving as contrast agents for both fluorescence imaging and Computed Tomography (CT) imaging, respectively. Simultaneously, by introducing paramagnetic manganese ions ($Mn^{2+}$), the nanodots gained the capability to serve as $T_1$-weighted MRI contrast agents. This clever combination allows a single nanoparticle to simultaneously support fluorescence, CT, and MRI three imaging modes, achieving complementary advantages of structural and functional information: MRI provides high-resolution soft tissue anatomical structure, CT provides high-contrast density information, and fluorescence can provide real-time optical guidance during surgery. To achieve precise targeting of PCa, the system surface was modified with Luteinizing Hormone-Releasing Hormone (LHRH) as the targeting ligand. LHRH can specifically bind to Gonadotropin-Releasing Hormone Receptors (GnRH-R) highly expressed on the surface of PCa and other reproductive system tumor cells, while receptor expression in normal tissues is low, thereby guiding the nanosystem to accumulate efficiently at the tumor site. On the therapeutic front, the core gold nanodots possess excellent photothermal conversion efficiency. When irradiated with an 808 nm NIR laser, AMNDs-LHRH can rapidly convert light energy into heat, raising the local tumor temperature to about 50°C, effectively inducing tumor cell apoptosis and achieving precise PTT.

Furthermore, PSMA is an important specific biomarker for PCa, possessing folate hydrolase activity and thus considered an ideal molecular target for targeted therapy. Based on the high affinity of PSMA for Folic Acid (FA), researchers designed an FA-modified nano-hydroxyapatite (nHA) delivery system.[98] nHA material has good biocompatibility, a mineral composition similar to bone tissue, and a porous structure, making it very suitable for use as a drug carrier. In this system, researchers co-loaded the chemotherapeutic drug Doxorubicin (DOX), the therapeutic radionuclide $^{32}P$, and the diagnostic radionuclide $^{99m}Tc$ into nHA nanoparticles. Surface modification with folate-PEG further enhanced its targeted delivery capability. Among them, $^{32}P$, as a beta emitter, can effectively kill tumor cells through internal radiation effects; while $^{99m}Tc$ is used for Single-Photon Emission Computed Tomography (SPECT) to track the distribution of the nanocarrier in real-time and non-invasively and assess its tumor targeting efficiency. Ultimately, the researchers successfully constructed a multifunctional nano-delivery system ($^{32}P$/DOX-FA-PEG-nHA) integrating active targeting, therapy, and diagnosis. This system, leveraging folate-mediated active targeting, achieved efficient killing and precise imaging of PSMA-positive PCa, while showing reduced toxicity to normal tissues in animal experiments, providing a new strategy and platform for the precise treatment of PCa.

Unlike active targeting, passive targeting primarily relies on the physiological characteristics of tumor tissue. IR780-MNCs is a self-assembled magnetic nanocarrier based on PLGA, internally encapsulating Iron Oxide Nanoparticles ($Fe_3O_4$ NPs) and the NIR dye IR780 iodide.[99] In therapeutic applications, this nanocarrier accumulates at the tumor site via the EPR effect. Under 808 nm laser excitation, IR780 can efficiently convert light energy into heat, thereby performing PTT and inducing tumor cell apoptosis. In diagnostics, the encapsulated $Fe_3O_4$ NPs serve as $T_2$-weighted MRI contrast agents, used for real-time, non-invasive visualization of tumor morphology and the distribution/accumulation process of the nanocarrier in vivo. By integrating PTT and MRI navigation functions, IR780-MNCs achieves integrated synergy between diagnosis and therapy.

Nanotheranostic platforms, through ingenious structural design and functional integration, successfully achieve efficient synergy between diagnosis and therapy. Whether based on ligand-mediated active targeting or utilizing the

EPR effect for passive targeting, these systems demonstrate great potential in improving the precision, efficacy, and safety of PCa diagnosis and treatment, opening new paths for the development of precision medicine in oncology.

## The Intrinsic Paradox in Nanotheranostic Platforms: The Conflict Between Imaging and Therapeutic Dosages

While the aforementioned nanotheranostic platforms demonstrate immense application potential, a crucial yet often overlooked scientific issue is the profound intrinsic conflict between the "optimal imaging dose" and the "optimal therapeutic dose" within a single nanocarrier.[100] This conflict stems from fundamental differences in the mechanisms of action, dosage requirements, pharmacokinetic profiles, and windows of biological effect between diagnostic imaging and therapeutic intervention. Simply "bundling" imaging and therapeutic modules together does not guarantee that both can function under optimal conditions; it may even lead to the compromise of one function for the sake of the other or result in unexpected toxic side effects.[101] This challenge represents a core obstacle that must be overcome for nanotheranostic platforms to transition from the laboratory to the clinic. This dosage conflict is not caused by a single factor but is the result of differences operating across multiple levels. If the administered dose of the nanoplatform is calibrated to meet the requirements for optimal imaging, the concentration of the therapeutic drug delivered to the tumor site will fall far below its effective therapeutic window, rendering the treatment efficacy negligible. Conversely, if the administered dose is significantly increased to achieve an effective therapeutic concentration, the dose of the imaging agent (especially radionuclides) will far exceed safety standards, potentially causing severe radiation damage or other toxic side effects to patients, thereby violating the fundamental safety principles of diagnostic imaging. Furthermore, ideal imaging agents and therapeutic agents have distinctly different, even contradictory, requirements for in vivo circulation and clearance kinetics.[102] An ideal imaging agent should possess the characteristics of "rapid targeting and rapid clearance." It needs to rapidly reach and accumulate at the tumor site while being quickly cleared from the blood and non-target tissues to achieve a high target-to-background signal ratio within a short timeframe, thereby yielding clear, high-contrast images. In contrast, most therapeutic drugs (particularly chemotherapeutic agents) require properties of "prolonged circulation and sustained release." They need a sufficiently long blood half-life to increase their opportunity for accumulation at the tumor site via the EPR effect, and they must persist within tumor tissue for an extended duration to enable sustained drug release, thereby killing cancer cells across different cell cycles. Rapid clearance would significantly reduce the cumulative therapeutic dose and efficacy of the drug.

Although no single strategy to date can perfectly resolve all these issues, and the biosafety, scalable production, and clinical translation of these advanced systems still face significant challenges, the recognition and systematic investigation of the dosage conflict problem nevertheless signify that the field of nanotheranostics is progressing from the proof-of-concept stage towards a more mature and clinically-oriented phase of development.

# Conclusion and Outlook: From Laboratory Innovation to Clinical Reality

In summary, the strategy for precise diagnosis and treatment of PCa based on multifunctional nanocarrier systems has achieved remarkable theoretical and experimental progress in recent years (Table 1). Through ingenious design of liposomes, polymers, inorganic materials, and bio-inspired systems, researchers have demonstrated immense potential in enhancing drug targeting, achieving intelligent responsive release, and synergizing multiple therapeutic modalities. Nanotechnology not only provides novel approaches to overcome the toxic side effects and drug resistance associated with conventional chemotherapy but also paves the way for the clinical application of cutting-edge strategies such as gene therapy and immunotherapy. However, despite promising laboratory data, the path to translating these complex nanosystems from "proof-of-concept" to "clinical routine" is far more rugged than initially anticipated. Currently, we must shift from optimistic expectations of fundamental theories to a profound examination of the formidable challenges in the clinical translation process. These challenges are primarily concentrated in three core areas: the validity of biological effects, the feasibility of industrial-scale manufacturing, and the safety and regulatory compliance of clinical application.

**Table 1** Basic Information of the Principal Nanodelivery Systems Mentioned in This Review

| Types of Nanocarriers | Author | Year | Country | Nanoparticle Delivery System | Targeting Strategy |
|---|---|---|---|---|---|
| Liposomes | Kadry MO | 2024 | Egypt | Liposomal-coated compounds | Passive targeting |
| Liposomes | Mo Y | 2023 | Canada | LASER | Passive targeting |
| Polymer nanoparticles | Wang Y | 2024 | China | Bm@PT/Enz-miR26a | Active targeting |
| Polymer nanoparticles | Ramezanimoladehi M | 2025 | Iran | BH-NPs | Passive targeting |
| Protein nanoparticles | Subramaniam S | 2025 | Australia | DAP-LF-NP | Active targeting |
| Metal nanoparticles | Sakr TM | 2025 | Egypt | RESV–$^{198}$AuNP | Active targeting/Passive targeting |
| Metal nanoparticles | Bellissima A | 2023 | Italy | Pd@CisPt | Passive targeting |
| Non-Metal Nanoparticles | Barattini C | 2025 | Italy | ADCNP | Active targeting |
| Non-Metal Nanoparticles | Zhang D | 2025 | China | Nano-selenium system | Passive targeting |
| Organic-inorganic hybrid composite nanoparticles | Saeinasab M | 2024 | Iran | Apt-PEG-siRNA@ZIF-8 | Active targeting |
| Organic-inorganic hybrid composite nanoparticles | Zhu S | 2025 | China | 17Pd-S-CNMF | Active targeting |
| Organic-inorganic hybrid composite nanoparticles | Dai L | 2025 | China | MDS@LA | Active targeting |
| Biomimetic nanocarriers | Cheng X | 2025 | China | FiFe@RBM | Passive targeting |
| Biomimetic nanocarriers | Liu M | 2025 | China | LHRH-RV-NG/HCPT | Active targeting/Passive targeting |
| Biomimetic nanocarriers | Yu Q | 2024 | China | CH-PPy NGs/DTX/siRANK@CM | Active targeting |
| Biomimetic nanocarriers | Rosso G | 2025 | Italy | EV Mimics | Active targeting |
| Biomimetic nanocarriers | Pihl J | 2023 | Denmark | MMENPs | Active targeting |

First, we must re-evaluate and move beyond the passive targeting paradigm founded on the EPR effect. Long regarded as the "gold standard" for tumor targeting of nanomedicines, a growing body of clinical evidence indicates that the EPR effect is far from universal or homogeneous in human tumors.[103] In contrast to rapidly growing, homogeneously abnormal vasculature in mouse xenograft models, the tumor microenvironment of human PCa (particularly low vascular density types) is extremely complex and highly heterogeneous.[104] The dense extracellular matrix, high interstitial fluid pressure, and irregular blood perfusion within the tumor collectively form formidable physical barriers that hinder the effective penetration and uniform distribution of nanoparticles.[105] Clinical imaging studies, such as PET imaging using radionuclide-labeled nanoparticles (eg, $^{64}$Cu or $^{89}$Zr), have visually revealed vast differences in nanoparticle accumulation among different patients and even among different lesions within the same patient, with uptake varying by orders of magnitude.[106] This significant heterogeneity implies that a "one-size-fits-all" strategy relying solely on the EPR effect is destined to fail clinically. Future research must pivot from blind dependence on passive targeting toward developing "intelligent" systems capable of actively overcoming these biological barriers. More crucially, advanced molecular imaging technologies should be employed as "companion diagnostic" tools to quantitatively assess the "nanomedicine accessibility" of a patient's tumor prior to treatment.[107] By screening for patient populations who can genuinely benefit from nanotherapy, we can transform nanomedicine from a generalized hope into a personalized, precise reality.

Second, scaling up from "milligram-scale" laboratory preparation to "kilogram-scale" Good Manufacturing Practice (GMP) production represents a daunting chasm in the clinical translation of nanomedicines. The intricate multi-step synthesis and modification processes often used in the laboratory encounter a series of thorny technical and economic challenges during scale-up.[108] Foremost among these are the difficulties of batch-to-batch consistency and quality control. Minor fluctuations in Critical Quality Attributes (CQAs) such as particle size, surface charge, drug loading, and ligand density can significantly impact the in vivo pharmacokinetics, targeting efficiency, and safety of nanoparticles.[109] For instance, the production of PSMA-targeted LNPs requires precise control over lipid composition, ligand conjugation efficiency, and nucleic acid encapsulation rate. Deviation in any step may lead to product failure. Ensuring high reproducibility across different batches and scales is a fundamental requirement for regulatory approval,


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yet it demands complex, expensive Process Analytical Technology (PAT) and stringent quality assurance systems.[110] Furthermore, the physical and chemical stability of the product poses another major challenge. Many nanoformulations, particularly LNPs, may undergo aggregation, fusion, drug leakage, or degradation during storage and transportation, severely affecting their shelf life and efficacy.[111] Although strategies like lyophilization can enhance stability,[112] their development and validation are also time-consuming and resource-intensive. Finally, high manufacturing costs present a direct obstacle to commercialization. Complex production processes, expensive raw materials (eg, functionalized polymers and high-purity lipids), specialized equipment, and stringent quality control procedures all contribute to production costs far exceeding those of traditional small-molecule drugs.[113] Historically, even approved nanodrugs like Doxil and Abraxane have faced severe supply disruptions or market withdrawals due to complex manufacturing and quality control issues, serving as a cautionary tale for all successors.[114,115] Therefore, future nanocarrier design must incorporate the principle of "Design for Manufacturability" from the outset, prioritizing materials and preparation methods that are process-robust, easily scalable, and cost-controllable.

Finally, a comprehensive and in-depth assessment of the long-term safety and immunogenicity of nanoformulations is paramount to their ultimate utility in humans. Once nanoparticles enter the complex in vivo environment, their interaction with blood components and immune cells (ie, the "nano-bio interface") dictates their final fate and biological effects.[116] On one hand, nanoparticles may be recognized as "foreign" by the immune system, triggering unintended immune reactions, including complement activation, cytokine storms, and even severe allergic responses.[117] Nanoplatforms designed to activate anti-tumor immunity may also induce uncontrolled systemic inflammation if not properly designed. For example, the clinical trial of the siRNA nanomedicine MRX34 was terminated due to severe immune-related adverse events, serving as a profound lesson for the field.[118] On the other hand, the accumulation of nanomaterials (especially non-degradable inorganic nanoparticles) in organs like the liver, spleen, and kidneys following long-term or repeated administration may induce chronic toxicity, for which human long-term data are extremely scarce.[119] Even for nanomedicines that have entered clinical trials, safety reports often focus on short-term adverse events, such as fatigue, nausea, and neuropathy observed in PCa patients treated with BIND-014,[120] while their long-term impact on organ function remains unknown. Consequently, future research must establish more standardized preclinical immunotoxicology and long-term toxicity evaluation systems, implementing them as mandatory early screening steps in nanomedicine development. Simultaneously, clinical trial designs must incorporate rigorous monitoring of immune-related biomarkers and follow-up on long-term organ function to construct a comprehensive safety profile, providing a solid foundation for evaluation by regulatory agencies (eg, FDA and EMA).[121]

Looking ahead, the field of PCa nanomedicine is undergoing a paradigm shift from "creating ever more complex nanoparticles" towards "solving genuine clinical problems." This signifies a strategic realignment of research priorities, where the pursuit of novel structures and functions is no longer the sole objective. Instead, greater emphasis is placed on clinical need-driven design, a deeper understanding of biological principles, and the overcoming of engineering challenges. Successful nanoplatforms will be those capable of robust performance within intricate biological realities, scalable manufacturing at controllable costs, and possessing a well-defined and acceptable safety profile. Future breakthroughs are anticipated to emerge in several interconnected directions: the stratification of patients based on biomarkers, utilizing imaging to predict nanodrug delivery efficiency and match the right nanotherapy to the right patient; the development of dynamically intelligent responsive systems, akin to "multi-stage rockets," designed to sequentially respond to multiple signals within the tumor microenvironment and overcome diverse biological barriers; the engineering of immuno-modulatory nanoplatforms that precisely control interactions with the immune system, enabling on-demand switching from "immune evasion" to "precision immune activation" or "tolerance" to synergize with immunotherapies while mitigating toxicity; and the integration of manufacturability with standardization, advancing production technologies like continuous manufacturing and microfluidics while establishing industry-wide consensus on characterization standards and methodologies. Ultimately, it is only through seamless, interdisciplinary collaboration among chemists, materials scientists, biologists, clinicians, pharmaceutical engineers, and regulatory scientists that the immense potential of nanotechnology can be translated into tangible clinical outcomes, improving the survival and quality of life for patients with PCa.

## Data Sharing Statement

Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

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## Disclosure

The authors declare no conflicts of interest in this work.

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