International Journal of Nanomedicine

Dovepress
Taylor & Francis Group

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REVIEW

Advancements in Nanocarrier Delivery Systems for Photodynamic Therapy in Lung Cancer

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Abstract: Photodynamic therapy (PDT), as a non-invasive treatment modality, has shown potential as an alternative to traditional therapies in lung cancer treatment. However, its clinical application is still limited by key challenges, including low photosensitizer (PS) delivery efficiency, tumor microenvironment hypoxia, and the restricted diffusion of reactive oxygen species (ROS). This review systematically discusses innovative strategies employed by nanocarrier delivery systems to overcome these bottlenecks in PDT. The first section focuses on the application and challenges of PDT in lung cancer treatment: although PDT induces localized tumor cell death through ROS generation mediated by PSs, its efficacy is hindered by the delivery barriers of hydrophobic PSs to the lung, insufficient ROS generation due to tumor hypoxia, and PS self-quenching. The second section presents nanotechnology-driven solutions: 1) using nanocarriers equipped with catalase or hemoglobin and perfluorocarbon to alleviate tumor hypoxia and enhance ROS production; 2) modifying the surface of nanocarriers with targeting ligands to improve PS accumulation in tumor tissues and reduce self-quenching effects; and 3) combining PS-loaded nanocarriers with immune checkpoint inhibitors and chemotherapy agents to synergistically enhance anti-tumor efficacy and suppress metastasis. Future research should focus on further optimizing the biocompatibility, clinical translation potential, and multimodal synergistic mechanisms of nanocarriers, to promote the widespread application of PDT in precise lung cancer treatment.

Keywords: lung cancer treatment, nanocarrier delivery systems, photodynamic therapy, photosensitizers, fighting hypoxia

Introduction

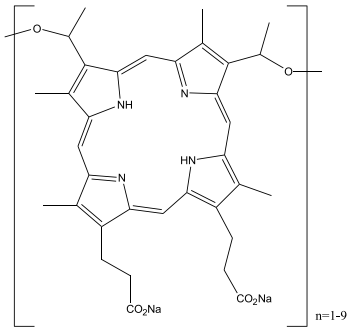
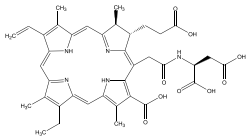
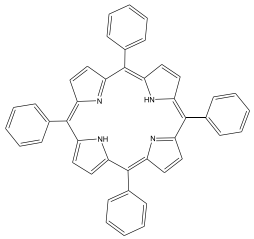
A recent report by the International Agency for Research on Cancer estimated that approximately 19.3 million new cancer cases and 9.9 million cancer-related deaths occurred globally in 2020.[1] The report also predicts a 56.4% increase in these numbers over the next 20 years.[1] Lung cancer is one of the most prevalent malignancies, accounting for 11.4% of all cases, and it remains the leading cause of cancer-related deaths, contributing to 18% of total cancer mortality.[2] Although breast cancer has surpassed lung cancer in incidence, lung cancer remains the second most frequently diagnosed cancer globally.[3] Advances in diagnostic techniques, particularly high-resolution CT imaging, have facilitated the detection of early-stage lung cancer. However, the prognosis for late-stage lung cancer remains dismal, with five-year survival rates significantly reduced due to delayed diagnoses and limited treatment efficacy. For early-stage lung cancer, surgical resection is the preferred treatment modality.[4–6] However, patients with underlying pulmonary conditions may not be suitable candidates for radical surgery, necessitating alternative therapies such as chemotherapy and radiotherapy.[7] Conventional chemotherapy and radiotherapy are associated with significant systemic toxicity and may compromise organ function,[8,9] while stereotactic ablative radiotherapy poses risks of severe radiation pneumonitis in patients with compromised respiratory function.[10] Despite progress in targeted therapies, fewer than 25% of lung cancer patients benefit from such treatments, with resistance emerging almost universally over time.[11]

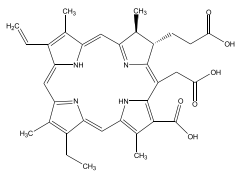
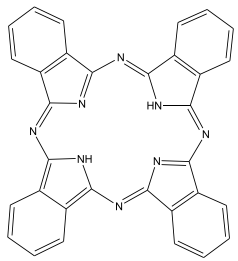
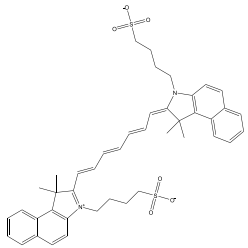
Photodynamic therapy (PDT) has emerged as a promising treatment option for lung cancer.[12–14] PDT utilizes photosensitizers (PS) (Table 1), oxygen, and specific wavelengths of light to generate reactive oxygen species (ROS), which induce tumor cell apoptosis or necrosis (Figure 1).[15–18] Compared to traditional therapies, PDT offers advantages

Received: 8 February 2025
Accepted: 7 May 2025
Published: 29 May 2025

https://doi.org/10.2147/IJN.S521444

Table 1 Photosensitizers Commonly Used in Lung Cancer Treatment

PS	Structural Formulas	WV(nm)	Major Characteristics	Pharmacokinetics	References
Porfimer		630	1. Limited light penetration depth (with the primary absorption wavelength at 630 nm), which affects the efficacy of deep tumor treatment. 2. Prolonged skin photosensitivity (requiring weeks of sunlight avoidance).	1. Preferentially accumulates in tumor tissues but can also accumulate in the skin and normal organs (such as the liver), leading to photosensitive side effects. 2. Elimination is relatively slow, requiring patients to avoid light for several weeks to prevent phototoxicity.	[20–22]
Talaporfin		664	1. A second-generation photosensitizer derived from chlorophyll-a, which, compared to the first generation (eg, Porfimer sodium), exhibits lower systemic toxicity and better tumor selectivity. 2. Primarily localizes in early endosomes and lysosomes within tumor cells, where it generates reactive oxygen species (ROS) upon light activation to induce cell death.	Plasma clearance is rapid, with a short half-life, requiring light exposure within a specific time window (eg, 2–4 hours) after administration to maximize therapeutic efficacy.	[23,24]
TPP		600–700	1. Strong absorption in the visible light region, with some derivatives exhibiting dual absorption bands, making them suitable for multi-wavelength PDT applications. 2. Modifications to the phenyl ring can improve water solubility, targeting ability, and photodynamic activity. 3. Some derivatives (eg, tetraphenyl-tetraphenylporphyrin) can extend their absorption to the 700–800 nm range through structural modifications.	Hydrophobic with a short in vivo circulation time, requiring the use of nanocarriers to improve pharmacokinetics.	[25,26]

Chlorin e6		660	1. Hydrophobic in nature, but water solubility and targeting ability can be improved through chemical modifications, such as conjugation with polysaccharides, amino acids, or targeting molecules. 2. A second-generation photosensitizer with high singlet oxygen ($^1O_2$) generation efficiency, exhibiting excellent photodynamic effects under near-infrared laser irradiation. 3. In addition to PDT, Ce6 can also be used in sonodynamic therapy (SDT), fluorescence navigation, and antibacterial treatments.	1. Ce6 accumulates significantly more in tumor tissues than in normal tissues. 2. Excreted via the hepatobiliary route, with a short half-life; modification (eg, encapsulation in nanocarriers) can extend the circulation time.	[27–29]
Phthalocyanine		600–750	1. Possesses a high molar absorption coefficient and efficient singlet oxygen ($^1O_2$) generation capacity, making it an ideal photosensitizer. However, its high hydrophobicity causes phthalocyanine to aggregate in aqueous solutions, reducing photosensitizing efficiency. 2. Strong chemical modifiability, allowing the introduction of various substituents to adjust its hydrophilicity, targeting ability, and photosensitive activity.	1. Phthalocyanine, due to its hydrophobicity, is easily cleared by the mononuclear phagocyte system and requires nanocarriers (eg, liposomes, magnetic nanoparticles) to improve in vivo circulation and tumor accumulation. 2. Phthalocyanine exhibits low toxicity in the absence of light, but prolonged retention may lead to skin photosensitivity side effects.	[30,31]
ICG		~800	1. Soluble in water and methanol, but almost insoluble in most organic solvents. 2. Capable of generating reactive oxygen species (ROS), although the quantum yield of triplet and singlet oxygen is relatively low. 3. Prone to aggregation (singlet oxygen generation decreases at high concentrations), with poor tumor targeting ability, low in vivo stability, and rapid degradation and clearance (short plasma half-life).	The accumulation ability in tumors is limited and requires the use of nanocarriers (eg, liposomes, polymers) to enhance targeting efficiency.	[32,33]

(*Continued*)

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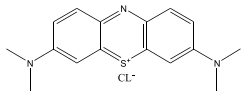
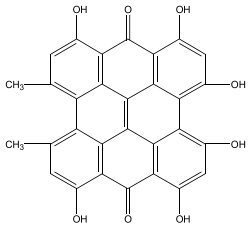
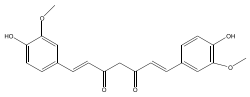
Table 1 (Continued).

PS	Structural Formulas	WV(nm)	Major Characteristics	Pharmacokinetics	References
MB		660	1. High hydrophilicity, but poor cell membrane permeability, requiring enhancement of delivery through nanocarriers (eg, liposomes, ZrP nanoparticles). 2. Can target mitochondria and exert effects through the mitochondrial apoptosis pathway.	1. Accumulates in tumor tissues due to high vascular permeability (EPR effect), but the hypoxic environment may affect its therapeutic efficacy. 2. Prone to rapid reduction by enzymes, requiring nanocarriers (eg, poly(lactic-co-glycolic acid) (PLGA) coating) to extend its half-life.	[34,35]
Hypericin		590–600	1. Natural hypericin has poor water solubility and requires carriers (such as liposomes or polymer nanoparticles) to improve delivery efficiency. 2. Selectively taken up by tumor cells, with differentiated intracellular accumulation, particularly in lung cancer cells (eg, A549). 3. In addition to direct phototoxicity, it can regulate protein and gene expression (eg, SOD-2, caspase 3/7), enhancing chemotherapy sensitivity (eg, when combined with oxaliplatin).	1. After intravenous injection, the compound distributes systemically, but the local concentration in tumors is significantly influenced by the carrier. 2. In a lung cancer model (A549), the intracellular steady-state concentration is directly related to the phototoxic effect. 3. Hydrophobicity leads to slow clearance, which may cause skin photosensitivity side effects; local administration (eg, bronchial application) or carrier encapsulation is necessary to reduce systemic risks.	[36,37]
Curcumin		470	1. A hydrophobic polyphenolic compound with advantages such as low toxicity, high biocompatibility, and low cost. 2. In its natural state, it has drawbacks such as low water solubility, rapid metabolism, poor photostability, and low bioavailability, which limit its clinical application.	1. After oral administration, the absorption rate is low, and it is rapidly metabolized by the liver (eg, glucuronidation), resulting in a short plasma half-life (approximately 2–3 hours), with difficulty reaching effective therapeutic concentrations in tumor tissues. 2. Its hydrophobicity causes aggregation in physiological environments, reducing photosensitizing efficiency.	[38,39]
Metal-based complexes	/	650–850	1. Responsive to near-infrared light (NIR), with a penetration depth of several centimeters, making it suitable for deep lung cancer treatment. 2. Metal nanoparticles (eg, silver, gold, platinum) enhance singlet oxygen ($^1O_2$) generation efficiency through surface plasmon resonance effects, overcoming the poor photostability and oxygen-dependence limitations of traditional photosensitizers.	1. Nanocarriers (eg, iridium complexes encapsulated in BSA) can extend the blood half-life and enhance tumor accumulation through the EPR effect. 2. The metabolic pathways of metal nanoparticles vary by material; for instance, gold nanoparticles are cleared via the hepatobiliary system, while some degradable materials (eg, MnO_2) can be metabolized into non-toxic products.	[40–42]

AIE	/	<600	1. Molecular design (eg, D-π-A structure) extends the absorption/emission wavelengths to 700–850 nm. 2. Fluorescence and reactive oxygen species (ROS) generation abilities are significantly enhanced in aggregated states, overcoming the aggregation-caused quenching (ACQ) problem seen in traditional photosensitizers. 3. Combines both fluorescence imaging and photodynamic therapy functions, enabling integrated diagnosis and treatment. 4. Molecular design enables specific targeting of organelles like mitochondria (eg, TPE-4QL targeting mitochondria), allowing selective cancer cell killing without the need for additional targeting ligands. 5. Some AIE-PSs can simultaneously generate type I ($^{\cdot}OH$) and type II ($^1O_2$) ROS, enhancing the killing effect on hypoxic tumors.	1. AIE molecules have strong hydrophobicity and low in vivo delivery efficiency, requiring the use of nanocarriers (eg, polymer micelles, metal-organic frameworks (nMOFs)) to improve solubility and tumor accumulation. 2. Most AIE-PSs exhibit low cytotoxicity in the absence of light.	[43–45]
F-aza-BODIPY	/	650–850	1. Fluorine modification significantly red-shifts the absorption/emission wavelengths of aza-BODIPY to the near-infrared region (700–900 nm), enhancing tissue penetration depth, making it suitable for deep tumor treatments (eg, lung cancer). 2. The introduction of fluorine-containing groups, such as trifluoromethyl (CF_3), increases singlet oxygen ($^1O_2$) production yield, thereby enhancing photodynamic killing effects. 3. Some fluorinated derivatives (eg, BDPF) possess multifunctional capabilities, including near-infrared fluorescence (NIRF), photoacoustic (PA), and ^{19}F magnetic resonance imaging (MRI), enabling integrated diagnosis and therapy. 4. Hydrophilic modifications (eg, triethylene glycol chains) reduce dark toxicity while maintaining nanomolar photodynamic activity.	1. Fluorine atoms can prolong in vivo circulation time by reducing the metabolic rate, though specific data requires further animal studies for validation. 2. Fluorination can adjust the balance between lipophilicity and hydrophilicity, improving tumor-selective uptake.	[46–48]

Abbreviations: PS, Photosensitizer; WV, wavelength; AIE, Aggregation-induced emission; F-aza-BODIPY, Fluorinated aza-BODIPY derivatives; ICG, Indocyanine green; MB, Methylene Blue; TPP, Tetraphenylporphyrin.

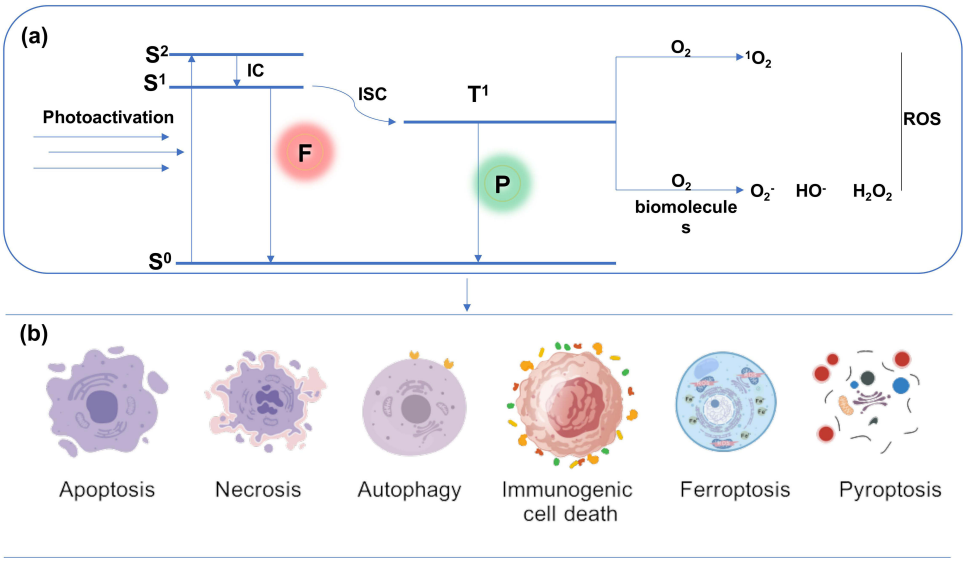


Figure 1 Schematic Illustration of Photochemical Reaction Mechanisms in PDT.[15–18] (**a**) The PS absorbs light at specific wavelengths, transitioning from the ground state (S^0) to the first singlet excited state (S^1) or the second singlet excited state (S^2). The S^2 state rapidly decays to S^1 through internal conversion (IC). From S^1, the PS can return to S^0 by emitting fluorescence (F) to release excess energy or undergo intersystem crossing (ISC) to form the more stable triplet excited state (T^1). The T^1 state can relax back to S^0 via phosphorescence (P) or transfer energy to molecular oxygen (O_2), generating singlet oxygen ($^1O_2$) in the Type II PDT process. Additionally, the T^1 state can engage in electron transfer with intracellular biomolecules (such as nucleic acids, proteins, and lipids), producing superoxide anion radicals. These radicals further react with H_2O_2 or O_2 to generate other ROS, including hydroxyl radicals (OH), defining the Type I PDT process. Currently, most PSs predominantly operate through the Type II PDT mechanism. (**b**) Six types of cell death induced by PDT. Created with BioGDP.com.[49]

such as reduced invasiveness, enhanced selectivity, and minimized damage to surrounding healthy tissues.[19] It is particularly effective in reducing the size of inoperable tumors and improving patient quality of life.

However, the efficacy of PDT is limited by challenges such as poor solubility, low bioavailability, and non-specific distribution of PS, alongside the hypoxic nature of the tumor microenvironment (TME), which restricts oxygen availability for ROS generation. Nanocarrier delivery systems (NDSs) provide a potential solution to these limitations by enhancing the solubility, stability, and tumor-targeting capability of PS, as well as improving oxygenation at tumor sites through various mechanisms (Table 2). Strategies such as enzyme-catalyzed oxygen generation, direct oxygen delivery, and stimuli-responsive materials have been developed to overcome hypoxia and enhance the therapeutic efficacy of PDT. This review explores the clinical applications and limitations of PDT in lung cancer and discusses recent advancements in NDSs as a means to address these challenges. By synthesizing cutting-edge research, we aim to provide meaningful insights and references for advancing PDT in lung cancer therapy.

Applications and Constraints of PDT in Lung Cancer Therapy

PDT as an Alternative Therapeutic Approach

In the 1970s, PDT gradually emerged as a novel technique for cancer treatment. In 1994, Japan approved the use of Sodium Porfimer for PDT in central early-stage lung cancer.[65] In 2002, Japanese lung cancer treatment guidelines recommended PDT as an option for early-stage central lung cancer.[66] The 2013 guidelines from the American College of Chest Physicians recommended PDT for curative treatment of central-type lung cancer patients with mucosal layer-restricted lesions (Grade 1C) and early-stage squamous cell carcinoma, with regular bronchoscopic monitoring advise.[67] The 2019 guidelines from the National Comprehensive Cancer Network recommended PDT for treating non-small cell lung cancer (NSCLC) patients experiencing airway obstruction or severe hemoptysis due to local symptoms or recurrence.[3]

PDT in clinical applications for lung cancer primarily targets superficial NSCLC that has not spread beyond the lungs and early-stage central lung cancer.[68] However, most lung cancer cases in clinical practice involve larger, peripheral, and advanced-stage tumors, which limits the standalone use of PDT.[12,69] Consequently, PDT is often integrated into multimodal treatment regimens to restore airway patency obstructed by tumors or convert initially inoperable tumors into resectable

Table 2 Nanocarrier Delivery Systems for PDT

Category	Nanocarrier Delivery Systems	Inference	References
Inorganic Nanocarrier Systems	Metal Nanoparticles	Exhibit surface plasmon resonance effects, enhancing light absorption efficiency. Dual-functional agents for both PTT and PDT, providing better therapeutic efficacy.	[51,52]
	Mesoporous Silica Nanoparticles	Used to load hydrophobic photosensitizers, improving solubility and targeting.	[53]
	Manganese Ferrite Silica Nanoparticles	Continuously release oxygen to alleviate tumor hypoxia, enhancing PDT efficacy.	[54]
	Cerium Oxide Nanoparticles	Possess catalytic oxygen-generating ability, improving the tumor microenvironment.	[55]
Organic Nanocarrier Systems	Polymer Nanoparticles	Degrade slowly, extending the circulation time of photosensitizers and preventing rapid clearance.	[56,57]
	Liposome Nanoparticles	Enhance biocompatibility and improve photosensitizer delivery efficiency.	[58]
Carbon-based Nanoparticles	Graphene and Graphene Oxide	High surface area and photothermal conversion efficiency, suitable for combined PTT/PDT therapy.	[59,60]
Multifunctional Composite Nanoparticles	Environment-Responsive	pH or enzyme-sensitive materials that specifically release drugs in the tumor microenvironment (low pH, high enzyme activity).	[56,61]
	X-ray Excited Nanoparticles	Combines radiotherapy (RT) and PDT to overcome tissue penetration limitations.	[62,63]
	Two-Photon Activated Nanoparticles	Enhance deep tissue activation through two-photon fluorescence dyes.	[64]

ones, thus improving therapeutic outcomes. Kato et al reported a representative case involving a 79-year-old patient with squamous cell carcinoma of the lung, presenting with an obstruction of the right B1 bronchus.[66] The carcinoma exhibited proximal invasion extending to the carina and distal extension reaching the intermediate bronchus. After PDT, the patient underwent only a right upper sleeve lobectomy, and histological examination of the bronchial stump showed no evidence of residual tumor cells. Jung et al applied intraoperative PDT to both the lumen and outer wall of the bronchi and distal trachea to achieve local tumor control in a patient for whom complete anatomical resection by pneumonectomy was not feasible.[70] At 13 months of follow-up, the patient remains alive with no evidence of disease recurrence. A similar improvement was reported by the Ohio State University Medical Center in 2006, where 41 patients with locally advanced, non-metastatic central-type non-small cell lung cancer (NSCLC) were treated with preoperative PDT.[71] In this study, 60% of patients were initially considered inoperable due to extensive invasion of the carina or severe endobronchial obstruction. However, after preoperative PDT combined with chemotherapy and/or radiation, 50% of these patients became eligible for surgery. Furthermore, 27% of patients who were initially scheduled for pneumonectomy were able to undergo lobectomy instead. Among the 22 patients who underwent surgery, 14 showed a lower pathological stage than their preoperative clinical staging, with 4 patients having no residual tumor at the bronchial margin.[71] In a small retrospective study by Mehta et al, 10 out of 11 patients did not experience local recurrence at the irradiation site within two years after undergoing post-operative bronchoscopic PDT. In another study evaluating the effectiveness of bronchial PDT in preventing NSCLC recurrence, it was found that the 5-year survival rate for patients with positive bronchial margins who received post-operative PDT was 12 out of 17, with only one case of margin recurrence.[72] Chhatre et al analyzed data from the National Cancer Database (2004–2016) to examine the relationship between PDT and mortality in patients with stage III–IV NSCLC.[73] Their study found that, compared to the radiation therapy alone group, the PDT group had a 50% reduction in mortality rates. Kimura et al also demonstrated that PDT combined with chemotherapy significantly improved airway stenosis in patients with advanced

NSCLC as early as one week post-treatment, with the improvements largely maintained after one month.[74] Additionally, the oxidative stress induced by PDT and some PS may generate novel and distinct tumor antigens. This unique mechanism renders PDT-treated cancer cells more immunogenic compared to cells eliminated through other treatments.[75,76] While PDT alone has a limited ability to induce systemic antitumor immunity, combining it with conventional immune checkpoint inhibitors or immunoadjuvants can significantly enhance its efficacy, offering unique advantages in managing metastatic lung cancer.[77,78] The study by Gao et al demonstrated that PDT combined with immune checkpoint inhibitors effectively treats both primary tumors and metastatic lesions.[79]

Persistent Challenges in PDT

PDT induces apoptosis by generating ROS.[80] Compared to other lung cancer treatments, PDT is less invasive than traditional surgical resection, exhibits stronger targeting capabilities than chemotherapeutic agents, and has minimal risk of resistance.[81,82] Moreover, PDT can be performed on an outpatient basis and leaves no scars after healing.[83,84] However, conventional PDT faces several limitations. The limited tissue penetration of PS reduces their efficiency in inducing tumor cell apoptosis, while their low selectivity for tumor cells further compromises efficacy. Patients undergoing PDT must also avoid sunlight exposure until the PS is fully eliminated to prevent phototoxicity.[85] Additionally, oxygen consumption and vascular damage during the PDT process may exacerbate tumor hypoxia, potentially shifting its effect from pro-apoptotic to anti-apoptotic.[86,87] Bush et al demonstrated that the spatial distribution of hypoxia during PDT significantly impacts tumor destruction and vascular damage.[88] Therefore, it is crucial to utilize n NDSs to target PS specifically to tumor sites, minimizing phototoxicity in other organs.[89,90] These systems can also increase oxygen levels at the tumor site, reverse the hypoxic microenvironment, inhibit tumor metastasis and recurrence, and enhance the overall therapeutic efficacy of PDT.[91]

Nanotechnology-Driven Strategies to Overcome Key Barriers

Over the past few decades, NDSs have gained widespread use as platform carriers in cancer treatment due to three key physicochemical properties: (1) a high surface-to-volume ratio, which enhances therapeutic efficacy while reducing biotoxicity;[92,93] (2) excellent multi-functionalization capabilities, particularly through the incorporation of disease-specific targeting ligands, thereby increasing the targeting precision and functionality of NDSs;[94,95] and (3) the ability to protect drugs from enzymatic or chemical degradation, preventing premature clearance and ensuring sufficient drug doses reach the tumor site (Figure 2).[96–98] These properties enable NDSs to overcome significant limitations of traditional delivery systems, providing controlled and localized drug release while minimizing systemic side effects. Oxygen-dependent NDSs can enhance oxygen levels in tumor regions, enabling PS to generate ROS under specific wavelengths of light. This process directly induces oxidative stress in tumor cells or sensitizes cancer tissues to achieve desired therapeutic outcomes.[99–101] NDSs are designed to deliver PS to tumor sites in a controlled and targeted manner, ensuring the stability, plasma half-life, and bioavailability of the PS. These systems protect PS from enzymatic or chemical degradation before reaching the target tumor tissues. Furthermore, NDSs enhance the solubility, improve stability, and increase tumor-targeting efficiency of PS, as demonstrated by functionalized nanomaterials like liposomes, polymeric nanoparticles, and metal-based nanozymes.[102,103]

Fighting Hypoxia with Nanocarrier Delivery Systems to Enhance PDT

Hemoglobin-and Perfluorocarbon-Based Oxygen Delivery

Hemoglobin (Hb) serves as the primary carrier for oxygen transport and exchange in the body,[50] and perfluorocarbons (PFCs) are commonly used artificial oxygen carriers, boasting an oxygen solubility approximately twice that of normal blood.[104] However, free Hb has a short circulation time in the bloodstream, is highly unstable, and tends to form dimers that cause renal toxicity.[105] Similarly, PFCs may prematurely release oxygen, triggering allergic reactions, making both inadequate for optimal PDT outcomes.[106] NDSs have been developed to address these challenges by delivering oxygen-loaded PFCs and Hb to target sites, thereby enhancing Hb stability and reducing premature oxygen release from PFCs.[107] Xavierselvan et al fabricated nanodroplets using perfluoropentan, benzoporphyrin derivatives, and indocyanine green (ICG), controlling particle size to approximately 200 nm. Upon intravenous injection and subsequent laser irradiation at

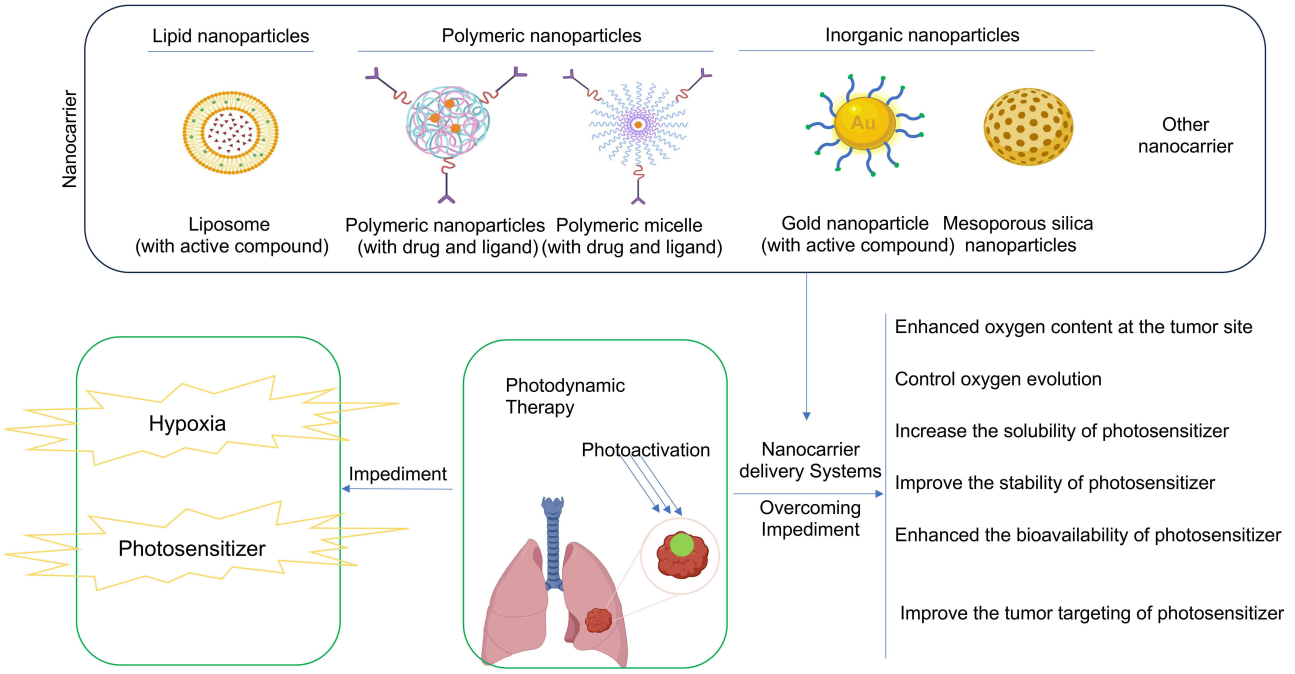


Figure 2 Advantages of Nanocarrier Delivery Systems in PDT for Lung Cancer.[49,96–98]

690 nm, these nanodroplets selectively accumulated at tumor sites. The perfluoropentan and ICG enabled synchronized oxygen release during PDT, ensuring effective intratumoral oxygen supply.[108] Guo et al engineered liposomal NDSs by encapsulating oxygen-loaded Hb and ICG complexes. This system effectively extended the circulation half-life of Hb in vivo. Post-injection, oxygen and PS effectively accumulated in deep tumor regions. T2-weighted MRI and immunohistochemical analyses revealed significantly enhanced intratumoral oxygen levels, along with a marked downregulation of hypoxia-inducible factor-1α (HIF-1α) and vascular endothelial growth factor, leading to improved PDT efficacy (Figure 3a).[109] To further enhance tumor specificity and pH responsiveness, Ma et al developed a pH-sensitive nanoplatform by incorporating hydrophobic IR780 dye, functionalized fluorocarbon nanoparticles, and tumor-penetrating peptide iRGD. This system selectively accumulated in deep tumor regions, where pH-triggered drug release occurred. Encapsulating oxygen and IR780 in a single core accelerated singlet oxygen generation, substantially boosting PDT efficiency.[110] To mitigate immune responses triggered by nanomaterials, biomimetic delivery systems, such as those utilizing red blood cell (RBC) membranes or exosomes, have been employed. Ding et al constructed an RBC membrane-coated nanovesicle, integrating Hb and semiconducting polymer nanoparticles. This system enhanced photostability, PS targeting, and oxygen self-supply, achieving prolonged circulation and efficient tumor accumulation through immune evasion.[111]

Catalase-Mediated Oxygen Generation

Due to the abnormal metabolism of tumor cells, the intracellular hydrogen peroxide (H_2O_2) levels are higher than those in normal tissues. In the presence of catalase (CAT), H_2O_2 can be catalyzed to produce oxygen, alleviating tumor hypoxia. Several studies have focused on employing NDSs loaded with catalysts to promote the decomposition of H_2O_2 and generate oxygen (Figure 3b). For example, a pH-responsive smart drug delivery system was developed using silica nanoparticles loaded with CAT, chlorin e6 (Ce6), and an anti-cancer drug. In vivo photoacoustic imaging experiments demonstrated that this system increased tumor oxygenation levels from 1.5% to 12.6%, significantly improving the hypoxic microenvironment.[54] To enhance the targeting specificity of NDSs, researchers have designed hyaluronic acid (HA)-modified systems, where IR820 and CAT were incorporated into biocompatible PLGA nanoparticles. This system leverages CD44 receptor-mediated endocytosis to facilitate tumor cell uptake and catalyze endogenous H_2O_2 conversion to oxygen.[113] To further improve the stability of CAT, Wang et al performed vinylation of the primary amines on the

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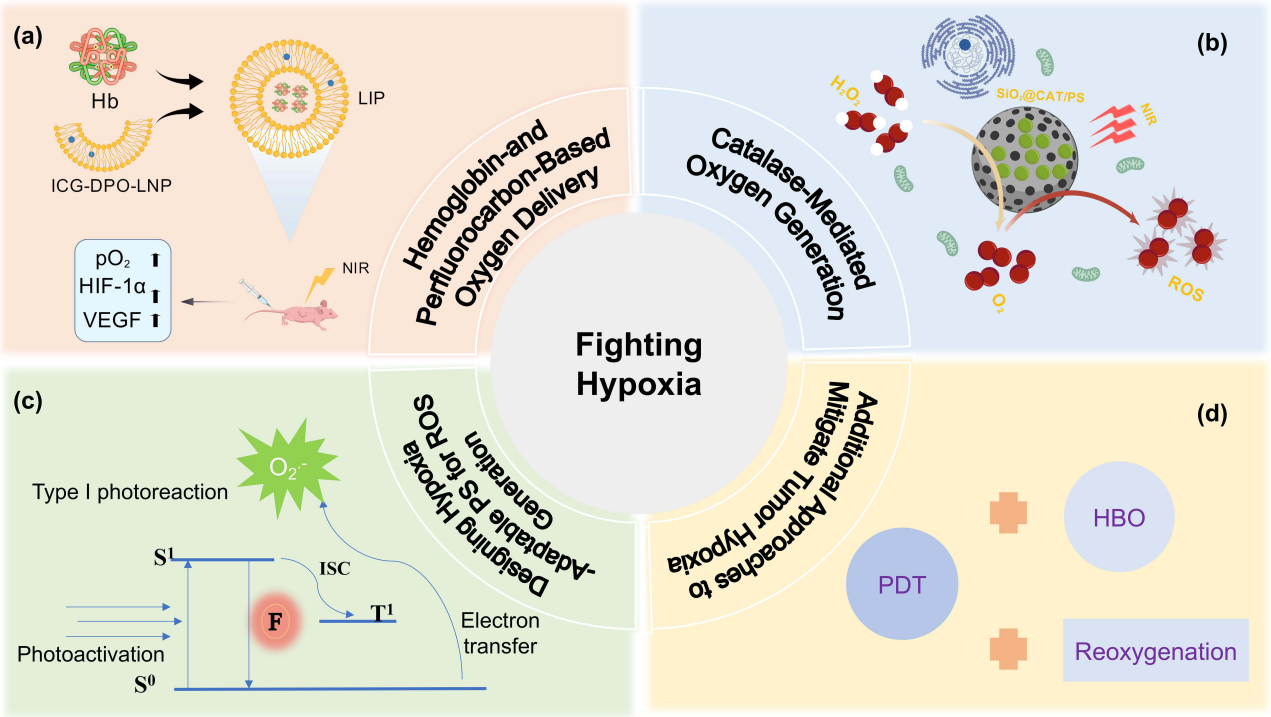

Figure 3 Fighting Hypoxia with Nanocarrier Delivery Systems to Enhance PDT. (**a**) Schematic illustration of alleviation of tumor hypoxia and enhanced PDT based on PS and hemoglobin co-loaded liposomes.[109] (**b**) Schematic illustration of alleviating tumor hypoxia and enhancing PDT using a catalase-based NDSs. (**c**) The Type I-dominated PS with small ΔEST. It has a low enough reduction potential in the ground state and a high enough reduction potential in the triplet excited state.[112] (**d**) hyperbaric oxygenation (HBO) and interval-based illumination for tissue reoxygenation, have been explored to counteract the hypoxic conditions exacerbated by PDT itself. Created with BioGDP.com.[49]

lysine residues of CAT, followed by in situ free-radical polymerization with acrylamide monomers and crosslinking with the Ce6. The resulting protein nano-capsules significantly enhanced the catalytic oxygen production capacity of CAT under physiological conditions.[114] Manganese dioxide (MnO_2) nanoparticles can also catalyze the decomposition of H_2O_2 to generate oxygen, with the reaction byproducts being harmless Mn^{2+} ions that are water-soluble and easily excreted via the kidneys. However, MnO_2 nanoparticles can damage normal tissues. To improve colloidal stability, prolong blood circulation time, and reduce toxicity, polyelectrolytes synthesized from alkynyl-modified carboxymethyl cellulose and azide-modified gelatin were employed for the in-situ growth of MnO_2 nanoparticles. Alternatively, MnO_2 has been assembled into nanozymes that exhibit excellent PDT efficacy under white-light illumination.[115]

Designing Hypoxia-Adaptable PS for ROS Generation

Most existing PDT approaches rely on Type II photoreactions, which are highly dependent on oxygen levels and involve significant oxygen consumption. This dependence on oxygen can exacerbate tumor hypoxia during PDT, especially due to oxygen consumption and microvascular damage, resulting in suboptimal therapeutic outcomes. In contrast, Type I PSs work differently by transferring electrons to molecular oxygen to produce superoxide anions. These anions undergo further cascade reactions mediated by superoxide dismutase (SOD), generating highly cytotoxic hydroxyl radicals that synergistically damage intracellular lysosomes and induce apoptosis in tumor cells (Figure 3c).[112] For example, Zhao et al developed a silicon phthalocyanine derivative (NanoPcAF), which demonstrates efficient Type I photoreaction capabilities. Unlike conventional Type II PSs, NanoPcAF generates a significant amount of superoxide anions even under hypoxic conditions. Their research demonstrated that NanoPcAF achieved 3.4 times higher superoxide anion production compared to conventional methylene blue under similar hypoxic conditions, while its photothermal conversion efficiency was 2.4 times higher than ICG. Preclinical trials revealed excellent tumor accumulation and no significant systemic toxicity.[116] Similarly, Tamoxifen (TAM), commonly known as an anti-estrogen drug, was observed to alleviate intrinsic

tumor hypoxia by modulating mitochondrial electron transport and reducing oxygen consumption rates. TAM also downregulated HIF-1α, further enhancing the therapeutic potential of PDT in hypoxic environments.[117]

Additional Approaches to Mitigate Tumor Hypoxia

PDT effectiveness is significantly influenced by the availability of molecular oxygen in the TME. Strategies to increase oxygen supply, such as hyperbaric oxygenation (HBO) and interval-based illumination for tissue reoxygenation, have been explored to counteract the hypoxic conditions exacerbated by PDT itself (Figure 3d). Tomaselli et al conducted a study involving 30 patients (22 males, 8 females; mean age 68.8 years) with inoperable NSCLC and endobronchial stenosis, assessing the acute effects of combined PDT and HBO. Patients were sensitized with hematoporphyrin derivative (2 mg/kg BW) 48 hours before treatment, and a light dose of 300 J/cm was delivered. At one and four weeks after the treatment, patients reported significant improvements in dyspnea and hemoptysis. Objective measures, such as reductions in tumor stenosis and resolution of post-stenotic pneumonia, supported these findings. The combined therapy achieved notable tumor stenosis reduction ($p < 0.05$) and an increase in Karnofsky performance status without treatment-related complications.[118] In addition to HBO, pulsed illumination has been proposed to enhance oxygenation during PDT. By delivering light in intervals, tissue reoxygenation can occur between exposures, mitigating hypoxia-induced therapy resistance. Such methods offer a promising approach to improve PDT outcomes by sustaining oxygen availability during treatment.[86]

Improving PS with Nanocarrier Delivery Systems to Enhance PDT

Traditional Unmodified Nanocarrier Delivery Systems

Nanomedicine offers substantial advantages in improving the solubility of hydrophobic drugs, enhancing biodistribution and pharmacokinetics, and enabling preferential accumulation at target sites. Commonly used nanocarriers include lipid nanoparticles, polymeric nanoparticles, and inorganic nanoparticles.

Constructed from phospholipid bilayers, lipid nanoparticles are widely applied for the targeted delivery of PSs due to their ease of preparation, excellent biocompatibility, minimal side effects, and ability to extend circulation time. This enhances drug accumulation in tumors. Liu et al encapsulated Ce6 and SB-3CT within nanoliposomes, which significantly improved the stability of Ce6 and showed efficient tumor cell apoptosis upon light irradiation.[119] Similarly, Visudyne®, a clinically approved PS, addresses the aggregation issue commonly faced by PS, improving their tissue penetration capacity.[120]

Polymeric nanoparticles, synthesized from natural or synthetic polymers such as dextran, chitosan, or polyethylene glycol (PEG), offer diverse structural variations for controlled drug delivery. These systems can encapsulate drugs in polymer reservoirs, embed them within polymer matrices, or use polymer-drug conjugates for targeted delivery. Ma et al developed folate-modified PEG-b-PAsp micelles that encapsulate PS, enhancing their accumulation in tumors through folate receptor-mediated uptake and acid-triggered release.[121] Similarly, Zhang et al constructed tetraphenyl porphyrin loaded polymeric nanoparticles, achieving a high drug-loading capacity, reducing aggregation-induced quenching, and significantly improving antitumor efficacy.[122]

Inorganic nanoparticles, such as gold and silica-based systems, are known for their superior stability, tunable size, and surface modification capabilities. These properties make them suitable for designing environmentally responsive delivery systems that improve PS targeting and release control.[103] Haimov et al conjugated hydrophobic Tetrahydroxyphenylchlorin with gold nanoparticles, resulting in enhanced solubility, stable colloidal properties, and increased tumor cell uptake.[123] Similarly, mesoporous silica nanoparticles conjugated with Visudyne® significantly improved the PS's bioavailability, leading to reduced tumor lymphangiogenesis and enhanced photodynamic efficacy.[124]

Targeted Nanocarrier Delivery Systems

While the enhanced permeability and retention (EPR) effect facilitates the accumulation of PS nanoparticles in tumors, it lacks tumor cell specificity. This limitation often results in insufficient uptake by tumor cells, thereby reducing the therapeutic efficacy.[125] Tumor cells overexpress specific antigens or receptors, such as epidermal growth factor receptors, folate receptors, and low-density lipoprotein receptors. To enhance tumor-specific PS accumulation, corresponding

antibodies or ligands including small molecule ligands, peptides, or lipid-based ligands can be conjugated to the surface of nanoparticles. These ligand-receptor interactions enhance the tumor-targeting capability of nanoparticles, improving PDT outcomes.[126–128] For instance, Karges et al encapsulated a Ru(II)-based polypyridyl complex in a polymer functionalized with terminal folate groups. This system mitigated the inherent cytotoxicity of the Ru(II) complex in the dark and exhibited over an 8-fold higher selectivity toward folate receptor-overexpressing tumor cells compared to healthy cells.[129] Similarly, Sun et al employed porous Fe3O4 nanoparticles to load ICG, modifying the nanoparticle surface with HA. This HA-functionalized system demonstrated a significant increase in tumor uptake through CD44 receptor-mediated endocytosis. Moreover, under 808 nm laser irradiation, the system effectively suppressed tumor growth in animal models, showcasing the synergy between photodynamic and photothermal therapies.[130]

Beyond nanoparticle-based delivery systems, targeted PS molecules also exhibit promise. For example, biotin-a ligand for receptors overexpressed in many cancer types-has been used to enhance PS targeting.[131] Li et al synthesized a biotin-functionalized PS (ENBS-B), which demonstrated an 87-fold higher uptake in cancer cells compared to normal cells. Remarkably, ENBS-B retained its efficacy under hypoxic conditions, utilizing a Type I photodynamic mechanism to generate superoxide anions, thus overcoming the challenges posed by tumor hypoxia.[132] Similarly, mannose receptors overexpressed in certain cancer cells have been targeted using mannose-functionalized PS molecules. Zhang et al conjugated a PS with mannose and assembled it into nanoparticles, which achieved improved tumor accumulation via both the EPR effect and mannose receptor-mediated uptake, significantly enhancing PDT efficacy.[133]

Multifunctional Nanocarrier Delivery Systems

In the complex microenvironment of tumors, diverse mechanisms drive both proliferation and metastasis. These mechanisms not only include the activation of bypass signaling pathways but also involve the inactivation of downstream apoptotic signals. In recent years, combination therapies have emerged as a promising strategy to suppress tumor proliferation and metastasis. Huang et al introduced a polymeric system capable of co-delivering three therapeutic agents, including Yes-associated protein (YAP) siRNA and gefitinib (Gef). Upon internalization into NSCLC cells, this polymeric nanoplatform selectively cleaves disulfide bonds, releasing YAP-siRNA and Gef. Gef effectively blocks the epidermal growth factor receptor signaling pathway, while YAP-siRNA suppresses the bypass pathways associated with gefitinib resistance. Additionally, this system facilitates PDT, enhancing ROS production to promote tumor apoptosis. Importantly, the introduction of YAP-siRNA and Gef not only alleviates PDT-induced hypoxia but also inhibits glycolysis and downregulates HIF-1α, synergistically triggering apoptosis.[12] Guo et al developed a nanoplatform integrating PDT and immunotherapy by encapsulating ICG into hollow MnO_2 nanospheres, further encapsulated within PD-L1 antibody-modified exosomes. This system, termed ICG@MnO_2@Exo-anti-PD-L1, precisely targets PD-L1-overexpressing tumor cells, delivering anti-PD-L1 antibodies to the acidic TME to activate T-cell responses. The MnO_2 catalyzes the conversion of H_2O_2 into oxygen, mitigating hypoxia within the tumor. Under 808 nm near-infrared (NIR) irradiation, ICG utilizes the generated oxygen to produce singlet oxygen ($^1O_2$), effectively inducing tumor cell apoptosis.[134] Furthermore, the Mn^{2+} released during the reaction polarizes macrophages from the M2 phenotype to the tumor-suppressing M1 phenotype, enhancing immune activation and supporting T-cell responses.

Carrier-Free Nanocarrier Delivery Systems

In recent years, NDSs have emerged as a potent solution to address the challenges in anticancer drug delivery.[135] However, traditional NDSs often rely on encapsulating drugs within carrier materials through intermolecular interactions, such as hydrophobic forces. This approach presents several drawbacks, including premature drug leakage,[136] low drug loading, increased toxicity,[137,138] and challenges in manufacturing and clinical translation.[139]

Pure drug nano-assemblies (PANAs), which self-assemble or co-assemble directly from unmodified drug molecules, have garnered significant attention. Unlike conventional drug delivery systems, PANAs eliminate the need for carrier materials, simplifying preparation and improving drug loading to ultra-high levels-exceeding 60% or even 100%.[140,141] These assemblies can be fabricated using straightforward methods like nanoprecipitation, which offers uniform particle formation, high reproducibility, and scalability.[142] Acting as both carriers and cargos, PANAs minimize carrier-related toxicity and enhance therapeutic outcome. Zhang et al mentioned that a Förster Resonance Energy Transfer (FRET)-

based PS system has been proposed, integrating Ce6 as the FRET donor and 1,1′-dioctadecyl-3,3,3′,3′-tetramethylindotricarbocyanine iodide (DiR) as the FRET acceptor. In this design, Ce6's photodynamic activity is "switched off" until DiR is photobleached by NIR laser irradiation, ensuring controlled activation and minimizing systemic phototoxicity (Figure 4).[140] This cascaded activation mechanism not only enhances PDT outcomes but also improves patient safety by preventing unwanted side effects.

Biomimetic Nanocarrier Delivery Systems

Biomimetic NDSs (BM-NDSs) are innovative platforms capable of mimicking biological functions, enabling them to bypass immune recognition, extend circulation time, and enhance drug accumulation at target sites.[143–145] Among the widely utilized technologies in BM-NDSs are extracellular vesicle-based formulations and cell membrane-coating strategies.[146] RBC membranes are attracting attention as stealth barriers in drug delivery systems due to their low immunogenicity, high biocompatibility, and ability to prolong systemic circulation.[147,148] By leveraging the inherent biological interfaces and self-recognition properties of RBC membranes, nanoparticles can interact effectively with their surrounding environments, enhancing retention in vivo.[149] Yang et al developed RBC membrane-modified nanoparticles loaded with NIR-II photothermal agents (IR1061) and an IDO-1 inhibitor.[150] These multifunctional nanoparticles showed targeted tumor accumulation and controlled drug release under laser irradiation, as evidenced by in vitro and in vivo

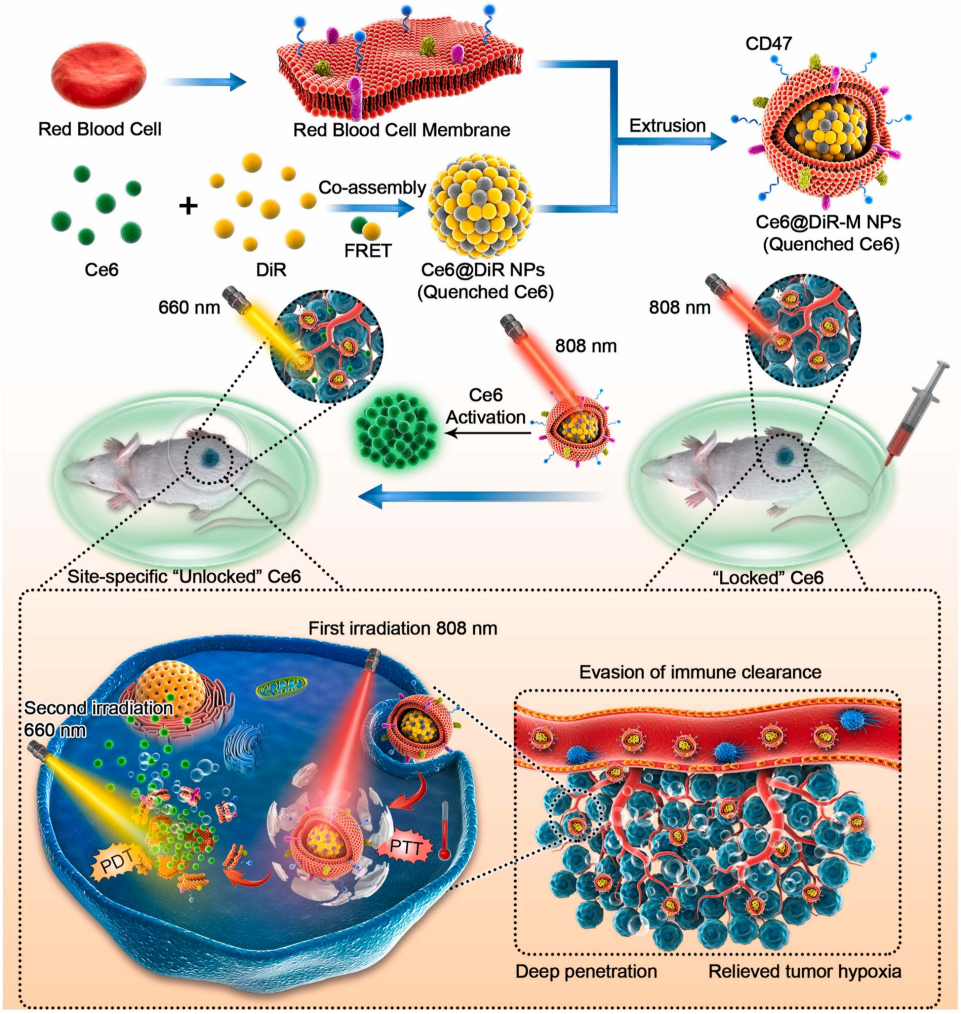

Figure 4 Schematic representation of the preparation of erythrocyte camouflaged Ce6@DiR NPs and its programmed cascade-activatable photothermal-photodynamic therapy for TNBC with low phototoxicity in normal tissues. Reprinted from Zhang X, Xiong J, Wang K, et al. Erythrocyte membrane-camouflaged carrier-free nanoassembly of FRET photosensitizer pairs with high therapeutic efficiency and high security for programmed cancer synergistic phototherapy. *Bioact Mater.* 2021;6(8):2291–2302.[140]

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results. Despite their promise, issues like ex vivo contamination and blood-type compatibility limit their large-scale use. Cancer cell membranes are another promising biomimetic approach.[151] Tumor-derived membranes enable nanoparticles to evade immune detection and exhibit homotypic targeting, owing to surface proteins such as N-cadherin and epithelial adhesion molecules.[152] Liu et al demonstrated that nanoparticles coated with HepG-2 cell membranes, encapsulating doxorubicin (DOX), showed prolonged circulation, immune evasion, and increased cellular uptake in homotypic tumor environments.[153] Similarly, mesoporous silica nanoparticles wrapped in cancer cell membranes and functionalized with $CaCO_3$ layers exhibited pH-sensitive drug release, leading to enhanced therapeutic efficacy against prostate cancer.[154] Despite significant progress, challenges such as scalability, immune reaction control, and maintaining membrane functionality remain. Innovative solutions like the use of macrophage membranes to combine immune evasion with inflammatory targeting are under exploration. The integration of such biomimetic platforms into clinical applications demands further refinement to optimize stability, loading capacity, and biocompatibility while ensuring regulatory compliance.

Nanocarrier-Based PS Delivery Systems Combined with Other Lung Cancer Treatment Modalities

The complex TME is driven by a variety of mechanisms that promote tumor proliferation and metastasis, including the activation of bypass signaling pathways and the suppression of key apoptotic pathways. In recent years, combination therapies have emerged as a promising strategy to effectively inhibit tumor growth and metastasis. By combining PDT with chemotherapy, immunotherapy, and photothermal therapy (PTT), these synergistic strategies achieve precise targeting of lung cancer and promote the reprogramming of the TME.

Combining PDT with Chemotherapy

PDT induces tumor cell death by generating ROS through PSs, while chemotherapy drugs damage DNA or inhibit cell division. Combining both therapies can overcome tumor heterogeneity and enhance the ROS-mediated killing effect. Wang et al developed charge-switchable nano-micelles (NMs) that co-deliver doxorubicin (DOX) and paclitaxel (PTX), facilitating drug delivery via endosomal escape and significantly inhibiting the growth of lung adenocarcinoma.[155] Long-term chemotherapy use often leads to multidrug resistance (MDR) in tumor cells; however, ROS generated by PDT can directly kill tumor cells, and its mechanism of action is unaffected by traditional resistance pathways. Additionally, PDT efficacy is often limited by hypoxia in the TME, but chemotherapy can alleviate this by disrupting tumor vasculature or inhibiting antioxidant systems (such as reducing glutathione levels), thereby enhancing PDT efficiency. Zhang et al designed a nanocarrier system that co-loads cisplatin and PSs to sensitize chemotherapy with PDT, reverse drug resistance, and reduce systemic side effects in NSCLC.[156] Nanocarriers or responsive drug delivery systems, such as ROS-sensitive liposomes, can precisely control drug release, minimizing systemic toxicity. Liu et al developed a pH/ROS dual-responsive nanocarrier system (ZnP-OC-M), which triggers targeted release of PSs and chemotherapy drugs within the TME, thus enhancing the efficacy of PDT.[157]

Combining PDT with Immunotherapy

PDT induces immunogenic cell death (ICD), releasing tumor-associated antigens (TAAs) and damage-associated molecular patterns (DAMPs), which activate dendritic cells (DCs) and promote T-cell infiltration (Figure 5).[158] This process disrupts the immune tolerance of tumors and creates a more sensitive microenvironment for immunotherapy, such as PD-1/PD-L1 inhibitors. Immunotherapy further amplifies the anti-tumor immune response triggered by PDT by relieving T-cell inhibition, generating systemic immune memory, and inhibiting distant metastasis and recurrence. The response rate to immune checkpoint inhibitors (ICIs) is relatively low (about 20%-30%), largely due to the "cold tumor" microenvironment. PDT can convert "cold tumors" into "hot tumors" by inducing ICD, significantly enhancing the efficacy of ICIs. Zheng et al designed a near-infrared light-responsive nanocarrier system (such as NIR-715) that induces endoplasmic reticulum (ER) stress via PDT, enhancing antigen presentation. When combined with anti-PD-1 antibodies, this system significantly inhibits the progression of "cold tumors".[159] However, it is important to note that when

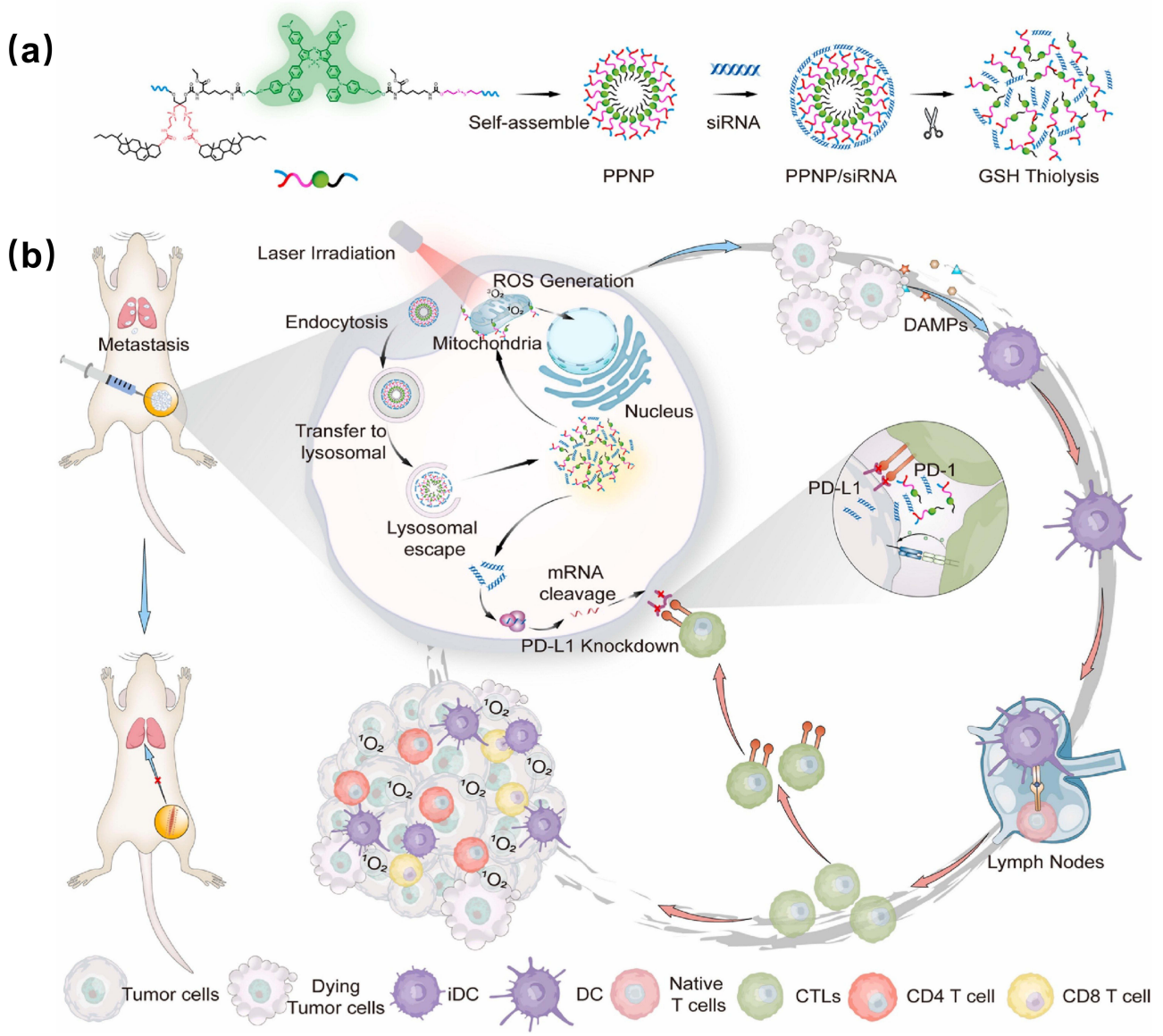

Figure 5 Illustration of near-infrared region II (NIR-II) photo-accelerated polymer nanoparticle (PPNP) enhancing tumor immunotherapy via Programmed Death-Ligand 1 (PD-L1) silencing and immunogenic cell death (ICD). (**a**) The preparation of PPNP/siRNA. (**b**) Upon activation by 808 nm laser and overexpressed GSH, PPNP/siRNA will undergo cleavage, releasing both the NIR-II PS and siPD-L1. ROS production will be stimulated, leading to tumor ICD, the release of damage-associated molecular patterns (DAMPs), recruitment of T cells to lymph nodes, activation of T cells, and initiation of T cell immune responses. Simultaneously, the released siPD-L1 will inhibit PD-L1 activity on tumor cells, enhance phagocytosis of tumor cells by T cells, activate systemic anti-tumor immune responses, and ultimately reshape the immune microenvironment. This photo-accelerated immunotherapy strategy facilitates tumor-specific immune responses and remodeling of the TME. Reprinted from Zhang T, Tang D, Wu P, et al. NIR-II photo-accelerated polymer nanoparticles boost tumor immunotherapy via PD-L1 silencing andimmunogenic cell death. *Bioact Mater.* 2025;46:285–300.[158]
Abbreviations: iDC, Immature Dendritic Cells; DC, Dendritic Cells; CTLs, Cytotoxic T Lymphocytes.

combining PDT with immunotherapy, it is crucial to optimize the co-delivery ratio of PSs and immunomodulators to avoid excessive immune activation, which could lead to a cytokine storm.[160,161]

Synergistic PDT and PTT

The photothermal effect can enhance tumor vascular permeability, promoting the accumulation of nanocarriers, and accelerate the diffusion of ROS through localized heating, thus expanding the area of tumor cell destruction. Copper nanoclusters (CuNCs) loaded with the PS Ce6 and hyaluronic acid (HA) simultaneously generate ROS and localized high temperatures under near-infrared light, disrupting tumor blood vessels and inducing apoptosis.[162] Traditional PDT/PTT

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combination therapies require lasers of two different wavelengths, but novel nanomaterials, such as SPAuNCs and Ce6-PEG-AuNR, can activate both PDT and PTT with a single wavelength laser. This reduces treatment time and minimizes the risk of skin burns. For instance, gold nanoparticles (AuNPs) can serve as carriers for both PDT and PTT, achieving dual-mode killing with a single laser exposure, thereby causing more thorough destruction of lung cancer cells.[163]

Multifunctional Nanocarrier Delivery Systems

The hypoxic TME limits the generation of ROS in PDT. Nanocarriers equipped with catalase or oxygen carriers (such as ICG@ZIF-82) can provide in situ oxygenation during PDT, while simultaneously activating hypoxia-activated chemotherapy drugs (eg, tirapazamine). This enables the synergistic effect of PDT and hypoxia-activated chemotherapy.[164,165] PDT's ability to penetrate deep tumors is often limited, but smart nanocarriers (such as mPEG-azo-HA-Ce6) can dissociate in the acidic TME, releasing the PS Ce6 and enhancing ROS accumulation. When combined with chemotherapy, this can improve penetration into deep tumor tissues.[166,167] Additionally, targeted nanocarriers can enhance tumor targeting via receptor-mediated endocytosis, reducing damage to normal tissues.[168]

Conclusion and Future Prospects

In the field of lung cancer treatment, PDT has gradually emerged as an important alternative or adjunctive treatment due to its non-invasive nature, precise targeting, and low systemic toxicity. However, traditional PDT still faces key challenges such as low PS delivery efficiency, TME hypoxia, and limited diffusion range of ROS. The introduction of nanocarrier technology has provided innovative solutions to overcome these bottlenecks, significantly advancing the clinical application of PDT. Despite the immense potential of nanocarriers in lung cancer PDT, there are still challenges in their clinical translation: 1) the stability and biocompatibility of certain nanomaterials need further verification; and 2) existing research predominantly focuses on in vitro or small animal models, necessitating large-scale clinical trials to confirm their safety and efficacy.

In conclusion, nanocarrier technology offers a novel approach to optimize lung cancer PDT through precise delivery, oxygen enhancement, and multimodal synergistic strategies. Future research should focus on addressing clinical translation barriers and promoting the development of personalized nanomedicines to achieve more efficient and precise lung cancer treatment.

Disclosure

The authors report no conflicts of interest in this work.

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