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REVIEW

Subcellular Organelle-Targeted Drug Delivery of Photodynamic Therapy and Gas-Photodynamic Combination Therapy

Xuhui Zhang[1,*], Jing Wang[1], Sijia Wang[1], Lei Fu[1], Xiaofan Du[1,2], Qiangzhou Rong[1], Cuiping Yao[1], Jing Xin[1,*]

[1]Key Laboratory of Biomedical Information Engineering of Ministry of Education, Institute of Biomedical Photonics and Sensing, School of Life Science and Technology, Xi'an Jiaotong University, Xi'an, Shaanxi, 710049, People's Republic of China; [2]Department of Hepatobiliary Surgery, The First Affiliated Hospital of Xi'an Jiaotong University, Xi'an, 710061, People's Republic of China

*These authors contributed equally to this work

Correspondence: Jing Xin; Cuiping Yao, Email xinjing@mail.xjtu.edu.cn; zsycp@mail.xjtu.edu.cn

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Abstract: Photodynamic therapy (PDT), as a clinically viable non-invasive modality for tumor treatment, is characterized by precise spatiotemporal control with minimal systemic toxicity. The therapeutic efficacy of PDT is critically contingent upon subcellular photosensitizer localization, attributable to the restricted diffusion radius of reactive oxygen species (ROS, 20–40 nm). Consequently, the development of organelle-targeted drug delivery systems constitutes an essential strategy for PDT optimization. Nevertheless, the clinical translation of PDT remains constrained by inherent physicochemical and pathophysiological barriers, even following targeting refinement. These constraints—predominantly limited tissue penetration depth (<1 cm) and hypoxia-mediated therapeutic resistance—have driven the development of combinatorial therapeutic approaches. Among emerging strategies, gas-enhanced PDT has gained prominence due to its bifunctional capacity to modulate tumor pathophysiology and potentiate photosensitizer activity. The application of biocompatible gaseous agents enhances therapeutic outcomes through enhanced tumoral drug accumulation, amplified ROS generation, tumor microenvironment modulation, and reversal of multidrug resistance mechanisms. This review systematically evaluates organelle-targeted PDT delivery mechanisms, advanced strategies for gas-PDT synergistic therapy, and spatiotemporally controlled gas prodrug platforms. Collectively, these approaches establish subcellular precision medicine as a transformative paradigm for tumor therapy.

Keywords: photodynamic therapy, gas therapy, subcellular organelle-targeted

Introduction

PDT utilizes photosensitizing agents in combination with light irradiation and molecular oxygen to generate cytotoxic singlet oxygen ($^1O_2$) and reactive oxygen species (ROS, eg, hydroxyl radicals, superoxide anions, hydrogen peroxide), which mediate oxidative damage to cellular membranes, proteins, lipids, and nucleic acids, ultimately triggering cell death.[1] Mechanistically, photoexcitation induces the transition of photosensitizers from their ground state to triplet excited states via intersystem crossing (ISC). The excited-state photosensitizers subsequently engage in two distinct reaction pathways: energy transfer to molecular oxygen, generating singlet oxygen ($^1O_2$), or electron/hydrogen transfer reactions with biological substrates, yielding secondary ROS.[2]

As a precision therapeutic modality, PDT efficacy is governed by three critical parameters: photosensitizer biodistribution, localized light activation, and tissue oxygenation status.[3] Clinically approved photosensitizers predominantly exert their effects through singlet oxygen ($^1O_2$) generation, which exhibits an ultrashort diffusion radius (10–20 nm) due to its transient lifetime (nanosecond scale).[4–6] This spatial constraint necessitates precise subcellular targeting of photosensitizers.[7] Present research demonstrates that numerous hydrophobic photosensitizers (such as phthalocyanine

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PC4 and benzoporphyrin derivative monoacid ring A) can localize in mitochondrial membranes and induce cytochrome C release from the mitochondria into the cytosol, triggering rapid apoptosis.[8–10] Some hydrophobic photosensitizers can localize in the plasma membrane and initiate a cascade of signaling pathways that lead to rapid cell necrosis with shorter irradiation times.[11] Several photosensitizers localized in lysosomes could lead to the release of lysosomal enzymes into the cytosol to cause slow apoptosis.[12,13] These findings underscore the imperative for organelle-selective delivery strategies to optimize PDT outcomes. Consequently, advancing targeted modification approaches for photosensitizer localization represents a pivotal research direction in PDT development.

Beyond photosensitizer localization, tissue oxygen concentration serves as a critical determinant of PDT efficacy, demonstrating dose-dependent sensitivity.[14] Progressive hypoxia in advanced tumors substantially impairs PDT outcomes by limiting oxygen-dependent ROS generation, thereby promoting therapeutic resistance and tumor recurrence.[15] To address hypoxia-related limitations in PDT, multiple strategies have been investigated over recent decades. Among these, combination therapies with PDT have shown additive or synergistic effects, significantly improving anti-tumor efficacy while reducing therapeutic resistance.[16,17] A wide range of clinical and preclinical therapeutic modalities—including chemotherapy, immunotherapy, photothermal therapy, antiangiogenic therapy, and gas therapy—have been explored in combination with PDT.[18–23] Notably, gas therapy has gained increasing attention for its high biocompatibility profile.[24] It can achieve direct or indirect delivery of O_2 to tumor tissues, thereby improving the microenvironment for enhanced PDT efficacy.[25] Alternatively, nitric oxide (NO) may react with ROS to generate highly reactive peroxynitrites ($ONOO^-$), amplifying oxidative stress and potentiating PDT effects.[26] Notably, the therapeutic action of gaseous agents similarly relies on precise subcellular organelle targeting.[27] This review systematically examines strategies and enhancement mechanisms for organelle-specific PDT delivery, explores advanced targeting methodologies in gas-PDT combination therapy, and discusses spatiotemporally controlled gas prodrugs integrated with subcellular targeting strategies to achieve precise therapeutic modulation.

Detailed search strategies are provided in the Supplementary Material.

Subcellular Organelle-Targeted Drug Delivery for PDT

Mechanism of PDT

PDT functions through two distinct mechanisms (Figure 1). The first involves photosensitizer-mediated energy transfer to biomolecules, generating free radicals (eg, photosensitizer-substrate complexes and anion radicals) via electron/hydrogen abstraction, termed Type I PDT. The second mechanism entails direct energy transfer to molecular oxygen, producing cytotoxic singlet oxygen ($^1O_2$), which characterizes Type II PDT.[28]

Both pathways induce oxidative damage to essential cellular components—proteins, nucleic acids, and membranes—through ROS. This damage initiates diverse cell death modalities: apoptosis, autophagy, and inflammatory necrosis. Notably, necrotic processes disrupt tumor vasculature, leading to nutrient deprivation and impaired tumor survival.[29,30]

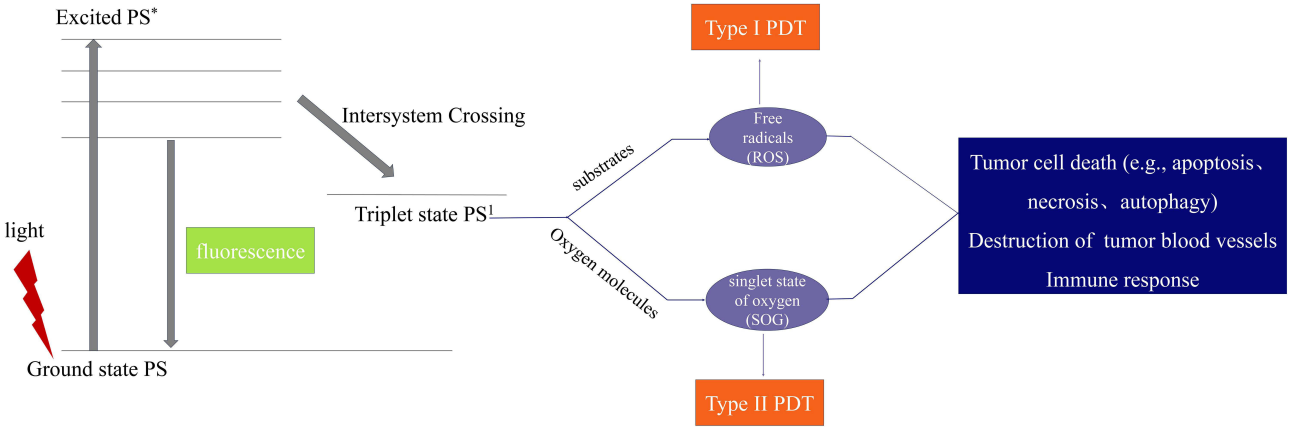

Figure 1 The Mechanism of PDT.

Concurrently, PDT activates innate immunity by releasing damage-associated molecular patterns, recruits immune cells, and stimulates antitumor immunity, albeit with potential immunosuppressive effects from immune cell apoptosis.[31] Thus, PDT exerts antitumor effects via three synergistic pathways: direct tumor cell killing, vascular system destruction, and immunomodulation.[32]

Organelle-Targeted PDT

The elevated levels of ROS and $^1O_2$ generated during PDT exert antitumor effects through oxidative damage to intracellular macromolecules, ultimately suppressing tumor growth and inducing cellular senescence or death.[33] Notably, $^1O_2$—the predominant cytotoxic oxidant produced by clinically approved photosensitizers—exhibits limited diffusion capacity (approximately 20 nm lifetime radius) with differential oxidative susceptibility across subcellular compartments.[5,6] Consequently, the organelle-specific localization of photosensitizers critically determines both the spatial patterns of PDT-induced damage and the activation pathways of cell death.[34–37] Mechanistic studies identify mitochondria, plasma membranes, endoplasmic reticulum, and lysosomes as primary targets for $^1O_2$/ROS-mediated PDT cytotoxicity.[7]

Mitochondria

Mitochondria, as multifunctional organelles, regulate cellular energy production, redox homeostasis, and survival pathways, rendering them critical targets under oxidative stress.[38] Their heightened sensitivity to $^1O_2$ and ROS enables mitochondria-targeted PDT to selectively eradicate tumor cells while sparing normal tissues. As demonstrated in Figure 2, mitochondrial targeting significantly enhances PDT efficacy compared to non-targeted approaches.[39,40] Photoactivation-induced $^1O_2$ generation at mitochondrial sites triggers permeability transition pore opening, cytochrome C release, and subsequent caspase activation. This cascade suppresses cellular respiration, depletes adenosine triphosphate

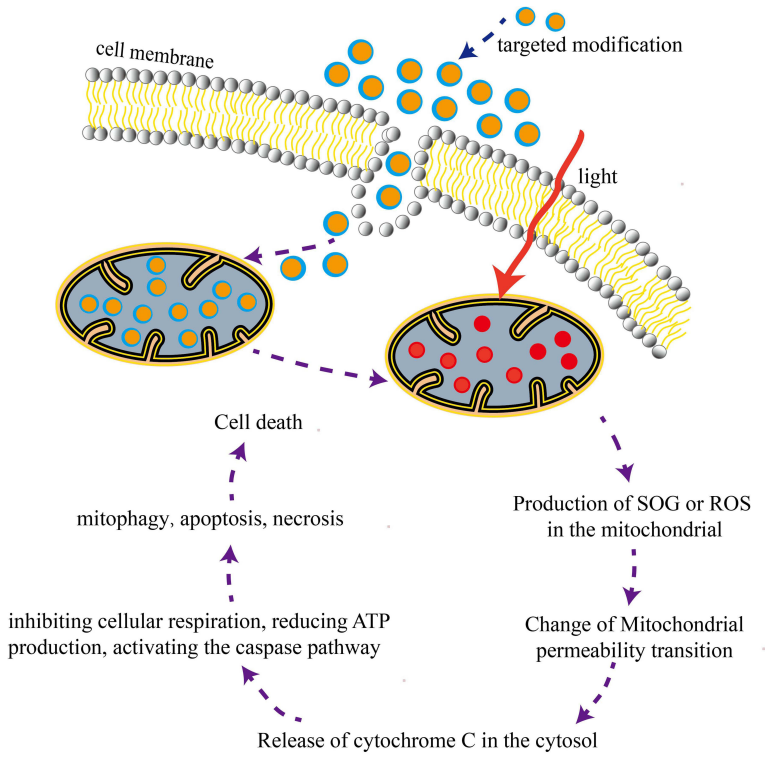

Figure 2 Modification and mechanism of Mitochondrial-targeting PDT. Blue background Orange circle: Mitochondrial-targeted photosensitizer. Red circle: Excited photosensitizer. Red solid arrow: Excitation light. Purple dashed arrow: Path. Targeting mitochondria methods: Photosensitizer itself has mitochondrial targeting ability. Positive charge modification. Increase of lipophilicity. Mitochondrial targeting peptides modification. Mitochondrial targeting protein/carrier modification.

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(ATP), and initiates rapid apoptosis or necrosis.[39,40] Concurrently, $^1O_2$/ROS-mediated lipid peroxidation disrupts mitochondrial membranes, promoting mitophagy and irreversible organelle damage.[41,42]

Mitochondrial-targeted drug delivery exploits photosensitizer physicochemical properties.[43] For instance, cationic photosensitizers like IR780 (an indocyanine derivative) accumulate in mitochondria via electrostatic attraction to the negatively charged mitochondrial matrix, synergized by the enhanced permeability and retention (EPR) effect for tumor targeting.[44,45] Wang et al developed IR780-based nanoplatforms to overcome hypoxic tumor resistance through mitochondrial-specific PDT.[46] In an advanced strategy, Sun et al engineered folic acid (FA)-conjugated bovine serum albumin nanoparticles (FA-BCNID-NPs) co-loaded with IR780 and 5-nitro-8-hydroxyquinoline (NQ)-Cu(II) complexes. This system achieved dual targeting (FA-mediated tumor homing and IR780-driven mitochondrial localization), lysosome escape, mitochondrial destruction via PDT/photothermal therapy (PTT), and inhibition of P-glycoprotein drug efflux, demonstrating potent antitumor synergy.[47]

Mitochondrial-targeted drug delivery can be achieved through multiple strategies, including charge modification (eg, guanidine, biguanide, or triphenyl phosphonium (TPP) conjugation) and lipophilicity enhancement.[48,49] Sun et al developed guanidine-functionalized cyclometalated iridium(III) complexes for mitochondrial-specific imaging and PDT, demonstrating potent cytotoxicity across cancer cell types via ROS-mediated mitochondrial apoptosis pathways.[50] Shen Jianliang's team engineered biguanide-modified chitosan (Bi-Ch) to disrupt mitochondrial function at reduced dosages, simultaneously alleviating tumor hypoxia and downregulating multidrug resistance protein 1 (MDR-1) expression to inhibit drug efflux.[51] Zhong et al designed TPP-conjugated 5-aminolevulinic acid (5-ALA) derivatives with butoxycarbonyl (Boc) modifications to enhance mitochondrial membrane penetration. Encapsulated within folic acid (FA)-functionalized bovine serum albumin nanoparticles, this Boc-ALA-TPP system promoted cellular internalization via FA receptors and induced mitochondrial oxidative phosphorylation collapse through localized ROS generation, ultimately improving PDT efficacy under hypoxic conditions.[52]

Mitochondrial-targeting peptides (MTPs), particularly mitochondrial-penetrating peptides (MPPs), offer an alternative strategy with high specificity, low toxicity, and synthetic accessibility.[53–55] Positively charged recombinant peptides or engineered nanocages further expand this approach.[56] For instance, Wang et al constructed tumor/mitochondria-dual-targeting nanocages by fusing LinTT1 peptide with human heavy-chain ferritin (HFtn) to encapsulate aggregation-induced emission luminogens (AIEgens). These AIEgen-loaded nanocages generated substantial intramitochondrial ROS, inducing mitochondrial dysfunction, apoptosis, and tumor growth suppression.[57]

However, current mitochondrial targeting strategies face limitations: cationic small molecules may exhibit poor biocompatibility due to excessive positive charges; peptides are prone to enzymatic degradation; and most approaches lack tissue specificity, necessitating supplementary targeting mechanisms.

Lysosomes

Lysosomes are heterogeneous, single-membrane-bound organelles exhibiting diversity in subcellular localization, morphology, dimensions, and enzymatic composition (containing ≥60 hydrolytic enzymes).[58] As central regulators of cellular homeostasis, they orchestrate critical processes including apoptosis, autophagy, tumor metastasis, membrane repair, signal transduction, and differentiation.[59,60] Notably, cancer cells exhibit elevated lysosomal abundance compared to normal cells,[61] positioning lysosomal targeting as a strategic approach to enhance PDT efficacy.[62,63] PDT-induced lysosomal rupture releases protons and hydrolases, triggering subcellular dysfunction and autolytic cell death,[64,65] with lysosome-targeted PDT demonstrating superior photokilling efficiency.[66] This provides a robust theoretical foundation for developing lysosome-directed phototherapy-gas therapy integrated systems.

Lysosome-targeted PDT is achieved primarily through two interconnected mechanisms (shown in Figure 3). The first leverages the inherent endolysosomal trafficking pathway, which serves as the primary route for intracellular transport of membrane-bound components. Nanotherapeutic systems, influenced by particle size and entry mechanisms (including pinocytosis, phagocytosis, and receptor-mediated endocytosis), are naturally directed toward lysosomal compartments. This intrinsic biological process explains why nanoparticles like polyethyleneimine-modified PEGylated nanographene (PPG-Ce6) loaded with chlorin e6 (Ce6) demonstrate enhanced lysosomal accumulation. Subsequent modifications with tumor-targeting ligands such as folic acid further improve cellular internalization and tumor-specific delivery.[67–73]

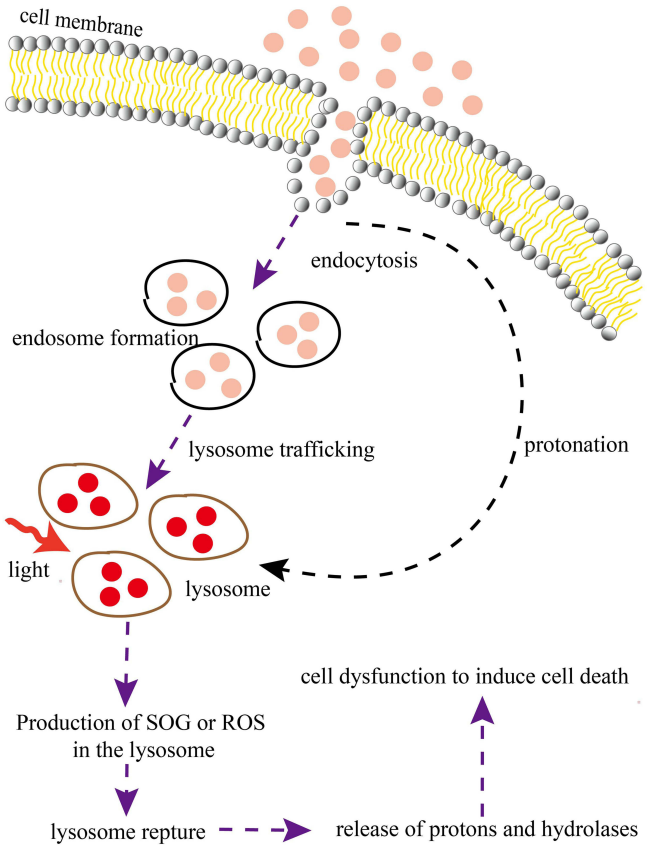

Figure 3 Modification and mechanism of Lysosome-targeting PDT. Pink circle: Lysosome-targeting photosensitizer. Red circle: Excited photosensitizer. Purple dashed arrow: Path. Black irregular round shape: Endsome. Brown irregular circle: Lysosome. Black dashed arrow: another path of targeting Lysosome methods (protonation of basic photosensitizers drives their selective accumulation): Lipophilic amine modification (such as: morpholine, tertiary amines, dimethylamine benzene). Increasion of lipophilicity.

The second mechanism capitalizes on lysosomal acidity (pH 4.5–5.5), where protonation of basic photosensitizers drives their selective accumulation. Structural modifications with lipophilic amines—including morpholine derivatives, tertiary amines, and dimethylaminobenzene—enhance lysosomal targeting efficiency. Morpholine-functionalized agents (eg, BODIPY, porphyrins) and engineered nanoparticles like DSPE@M-SiPc (morpholine-substituted silicon phthalocyanine encapsulated in 2-distearoyl-sn-glycero-3-phosphoethanolamine) exemplify this strategy, combining near-infrared imaging capabilities with potent PDT effects. Advanced systems such as diketopyrrolopyrrole (DPP)-based nanoparticles (DPP-NF NPs) further integrate NO donors, achieving lysosomal activation under acidic conditions to synergistically enhance $^1O_2$ generation and photothermal therapy.[6,74–77]

Compared to lysosomes in normal cells, those in cancer cells exhibit significantly elevated viscosity.[78] To exploit this property, Song et al developed a lysosome-targeted bifunctional fluorescent probe for simultaneous viscosity imaging-guided cancer diagnosis and dual-mode PDT. This probe employs a donor-π-acceptor (D-π-A) molecular architecture comprising triphenylamine (electron donor), thiophene (π-bridge), and benzothiazolium salt (electron acceptor). The benzothiazolium ammonium moiety enhances acidic lysosomal accumulation and enables targeted photosensitizer delivery, generating both Type I/II ROS under viscosity-activatable conditions.[79]

Lysosomal targeting represents a pivotal strategy for enhancing PDT efficacy, as the organelle's acidic microenvironment and elevated viscosity provide critical parameters for photosensitizer/carrier design. While ROS-induced lysosomal membrane disruption permits subsequent photosensitizer redistribution to other organelles, this translocation occurs at markedly slower kinetics compared to mitochondrial redistribution processes.[80]

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Nucleus

The nucleus, as the central organelle in eukaryotic cells, serves as the primary repository of genetic material and regulates critical cellular processes including proliferation, metabolism, and cell cycle progression. It also functions as the principal site of interaction for therapeutic agents such as chemotherapeutics, nucleic acids, free radicals, and hyperthermia-based treatments.[81] Nuclear-targeted PDT demonstrates enhanced efficacy compared to conventional approaches due to direct ROS-mediated damage to nuclear DNA, RNA, and proteins. Furthermore, photoactivated sensitizers can inactivate DNA repair enzymes, arrest cell cycles, and stimulate antitumor immunity (as shown in Figure 4). However, achieving effective nuclear delivery faces substantial challenges: photosensitizers must bypass cytoplasmic barriers (eg, endosomal entrapment, lysosomal degradation) and overcome nucleocytoplasmic transport restrictions to accumulate at nuclear targets.[82]

Nuclear entry is governed by nuclear pore complexes (NPCs)—bidirectional channels spanning the double-layered nuclear envelope. With a central pore diameter of ~70 nm, nuclear pore complexes permit passive diffusion of molecules <9 nm (eg, small gold nanoparticles) or <60 kDa (eg, doxorubicin, paclitaxel).[83] For photosensitizers, Liu et al developed an aggregation-induced emission (AIE)-active nuclear-targeted agent (MeTPAE) that inhibits histone deacetylases and induces telomeric DNA damage via precision PDT.[84] Light irradiation can also trigger nuclear translocation of certain photosensitizers. Anionic TPPS4 redistributes from lysosomes to nuclei in proliferating cells, a process dependent on cell-cycle status.[85,86] Cationic pyridinium zinc phthalocyanine selectively accumulates in nucleoli post-irradiation, while anionic sulfonated and glycine-conjugated Zn-phthalocyanines migrate from lysosomes to nuclei under low-dose irradiation.[87]

Given the rapid systemic clearance and limited efficiency of passive nuclear transport, active nuclear-targeted drug delivery systems utilizing nuclear localization sequences (NLS) — such as SV40 T antigen, adenovirus-derived peptides, and TAT transduction domains — demonstrate enhanced therapeutic potential.[81] Li et al engineered a nucleus-targeting system (PHSA-ICG-TAT) by conjugating TAT peptides with polyethylene glycol 4000 (PEG4000) and human serum albumin (HSA), enhancing both the aqueous solubility of indocyanine green (ICG) and its nuclear localization efficiency. This TAT-functionalized system exhibited superior cytotoxicity compared to free ICG, with combined DNA damage and

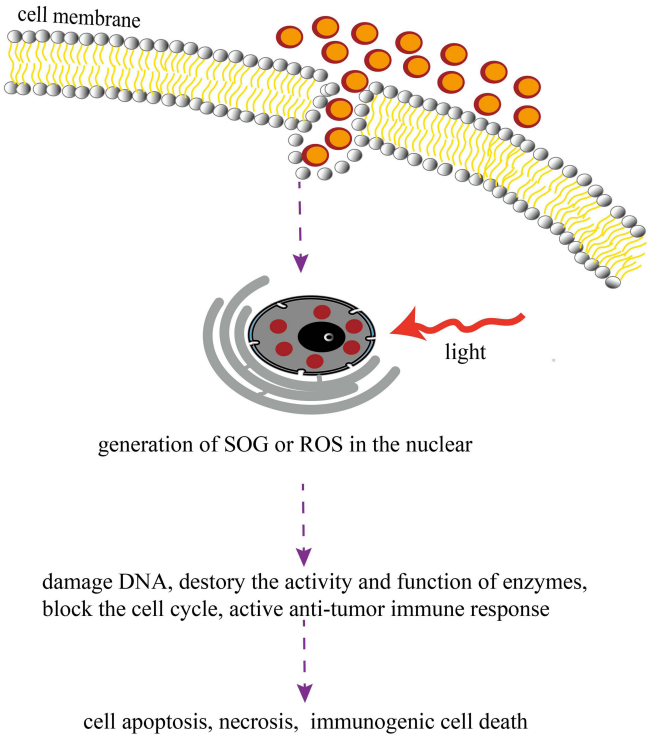

Figure 4 Modification and mechanism of Nucleus-targeting PDT. Orange Circle: Nucleus-targeting photosensitizer. Red circle: Excited photosensitizer. Purple dashed arrow: Path. Methods for targeting the cell nucleus: Nuclear localization sequences (eg, SV40 T antigen, adenovirus, TAT peptide). Disruption of nuclear membrane integrity. Passive diffusion (drug diameter should be less than 9 nm or drug molecular weight should be less than 40 kDa).

localized hyperthermia significantly amplifying PDT/photothermal therapy (PTT) efficacy.[88] Although amino-rich cationic polymers enable nuclear targeting, their clinical translation is constrained by systemic toxicity.[89] Alternative strategies include lectin-mediated glycosylation-dependent nuclear entry, where carbohydrate-protein interactions facilitate nuclear translocation of glycosylated cargos.[90]

Notably, nuclear membrane destabilization offers another targeting avenue. Wu et al developed polyamine-functionalized polyhedral oligomeric silsesquioxane (POSS) nanoparticles (PPR NPs) incorporating polyethylene glycol (PEG) chains and the photosensitizer rose bengal (RB). Light-induced $^1O_2$ generation first disrupts lysosomal membranes for nanoparticle release. Subsequent irradiation triggers nuclear membrane lipid peroxidation, enabling active nuclear penetration through envelope destabilization, thereby enhancing intranuclear therapeutic accumulation.[91]

Endoplasmic Reticulum

The endoplasmic reticulum (ER), the largest intracellular organelle, functions as the primary site for protein synthesis, folding, and transport; lipid and steroid biosynthesis; carbohydrate metabolism; and calcium ion storage.[92] In cancer cells, excessive protein synthesis often leads to unfolded protein accumulation—a hallmark of malignancy—triggering ER stress-mediated apoptotic pathways.[93] During ER-targeted PDT, generated ROS impair ER protein-folding capacity, inducing pathological ER stress that activates pro-apoptotic signaling cascades such as the PERK-eIF2α-ATF4-CHOP axis, ultimately causing cell death.[94,95] Under severe ER stress caused by high ROS levels, pro-survival autophagy transitions to autophagy-dependent cell death, a process requiring high-dose PDT.[96,97]

ER-targeted PDT also induces immunogenic cell death (ICD) through ROS-driven ER stress. This mechanism promotes calreticulin (CRT) translocation to the cell surface, where it acts as an "eat-me" signal by activating dendritic cell maturation, thereby enhancing antitumor immunity.[98] Furthermore, ER photodamage initiates paraptosis—a non-apoptotic death mode characterized by cytoplasmic vacuolization and loss of cellular integrity.[99] Additionally, ER-generated ROS exacerbate ferroptosis via lipid peroxidation, leveraging the ER's central role in lipid biosynthesis.[100] Collectively, ER stress modulation through PDT enables multimodal tumor suppression via apoptosis, autophagy, immunogenic cell death, paraptosis, and ferroptosis (Figure 5).

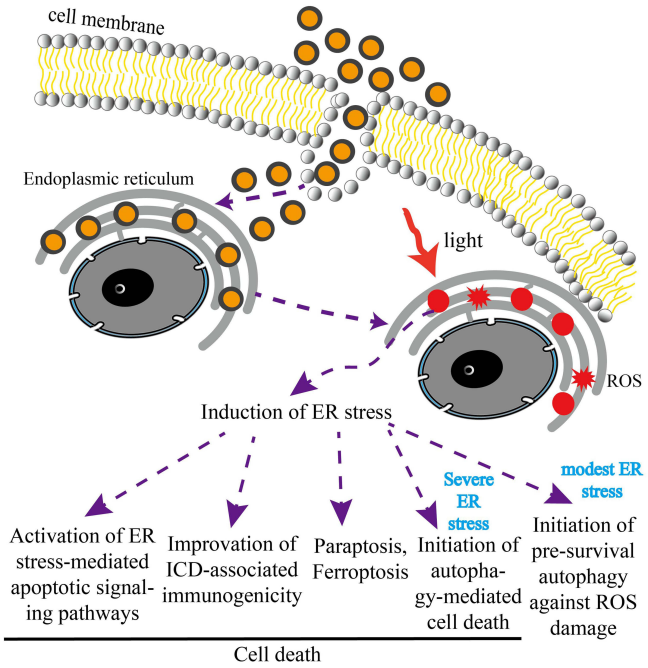

Figure 5 Modification and mechanism of ER-targeting PDT. Orange Circle: ER-targeting photosensitizer. Red circle: Excited photosensitizer. Red irregular firework-shaped figure: ROS. Purple dashed arrow: Path. Black horizontal line: Induction, indicating that the above four situations all lead to cell death. Endoplasmic reticulum targeting methods: Targeted nanocarriers (receptors, lipophilic membranes, metabolic enzymes, etc.) for endoplasmic reticulum via small molecule modifications. Modification of endoplasmic reticulum targeting peptides (PA, KDEL, FEHDEL, etc). Modification of endoplasmic reticulum targeting ligands (sulfonylethylenediamine, sulfonamide ligands, etc).

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ER-targeted delivery strategies comprise three principal approaches: small molecule-modified nanocarriers utilizing ligand-receptor binding, lipophilic modifications, or metabolic enzyme targeting; peptide-based systems incorporating PA, KDEL, and FEHDEL motifs; and engineered ER ligands such as tosyl ethylenediamine and sulfonamide derivatives.[101]

Guo et al developed NBS-ER, incorporating p-methylbenzenesulfonamide for ER targeting, which demonstrated reduced dark toxicity and enhanced ER localization compared to the non-targeted NBS-NH2 control. Post-PDT analysis revealed downregulation of ER stress sensors (ATF6, IRE1α), suppression of anti-apoptotic Bcl-xL, and activation of caspase-9 cleavage, confirming ROS-mediated ER stress apoptosis.[102] Similarly, You et al designed FAL-ICG-HAuNS nanosystems combining pardaxin (FAL) peptides, indocyanine green (ICG), hollow gold nanospheres, and hemoglobin-loaded liposomes to alleviate hypoxia. This platform induced significant CHOP upregulation and caspase-3 activation under near-infrared irradiation, demonstrating ER stress-driven mitochondrial apoptosis and synergistic PDT/photothermal efficacy.[98] Moreover, ER-targeted PDT effectively promoted calreticulin (CRT) exposure—a marker of immunogenic cell death—thereby enhancing dendritic cell maturation, CD8+ T cell proliferation, cytotoxic cytokine secretion, and activating systemic immune responses.

Lipid Droplet

Ferroptosis, an iron-dependent programmed cell death mechanism, is regulated by ferrous ions (Fe^2+) that catalyze the Fenton reaction—a process converting excess hydrogen peroxide (H_2O_2) into hydroxyl radicals (·OH) and oxygen (O_2) within tumor microenvironments.[102] These hydroxyl radicals initiate free radical chain reactions, driving lipid peroxide accumulation in cellular membranes and triggering phospholipid damage that culminates in ferroptosis. Concurrently, depletion of intracellular glutathione (GSH) and inhibition of glutathione peroxidase 4 (GPX4) lead to the production of cytotoxic phospholipid hydroperoxides (PLOOH), causing membrane rupture and irreversible cell death.[103]

Emerging evidence demonstrates that PDT induces ferroptosis through lethal lipid ROS accumulation.[104] Lipid ROS-mediated ferroptosis can originate at cellular membranes or subcellular organelles membranes (endoplasmic reticulum, mitochondria, lysosomes). However, rapid necrosis or apoptosis caused by acute ROS oxidation at these sites often overshadows the slower ferroptotic process.[105]

Lipid droplets (LDs), highly dynamic organelles serving as lipid storage hubs, play multifaceted roles in membrane synthesis, energy homeostasis, vesicular trafficking, and proteostasis.[106,107] Crucially, LDs regulate ferroptosis by enabling photoinduced oxidation of polyunsaturated fatty acid phospholipids (PUFA-PLs) to peroxidized derivatives, establishing them as promising PDT targets for ferroptosis induction.[108,109]

LDs are structurally composed of a neutral lipid core (primarily triacylglycerols and sterol esters) surrounded by a phospholipid monolayer embedded with regulatory proteins such as perilipins.[108,109] The phospholipid hydrophilic heads face the cytosol, while their hydrophobic alkyl chains anchor into the neutral lipid core (Figure 6). This architecture enables hydrophobic interactions as a key mechanism for LD targeting. Fluorescent precursors with tailored hydrophobicity—including BODIPY, coumarin, and benzoxadiazole derivatives—demonstrate inherent LD affinity.[110,111] Structural modifications such as long alkyl chain incorporation, styryl additions, or fluorine substitutions further enhance targeting specificity.

For instance, Peng et al engineered an LD-targeting photosensitizer (BODSel) by integrating a selenomorpholine group into the BODIPY core. This modification optimized lipophilicity-hydrophilicity balance for improved LD localization, while iodine atom incorporation via the heavy atom effect enhanced intersystem crossing efficiency and singlet oxygen generation. The resulting BODSel exhibited low dark toxicity, high biocompatibility, and potent LD-specific PDT efficacy.[112]

Similarly, Wang et al developed sulfur-substituted coumarin photosensitizers through π-conjugation extension and donor-acceptor optimization. Replacing carbonyl oxygen atoms with sulfur not only amplified intersystem crossing and ROS production but also conferred LD-targeting capability.[113]

In addition, decreasing the interaction of photosensitizers with water through intramolecular hydrogen bonds (H-bonds) can improve the LD-targeting ability. Peng et al designed the first lipid droplet-targeting type I photosensitizer (MNBS) by substituting the benzophenothiazine structure with a morpholine group in a donor-

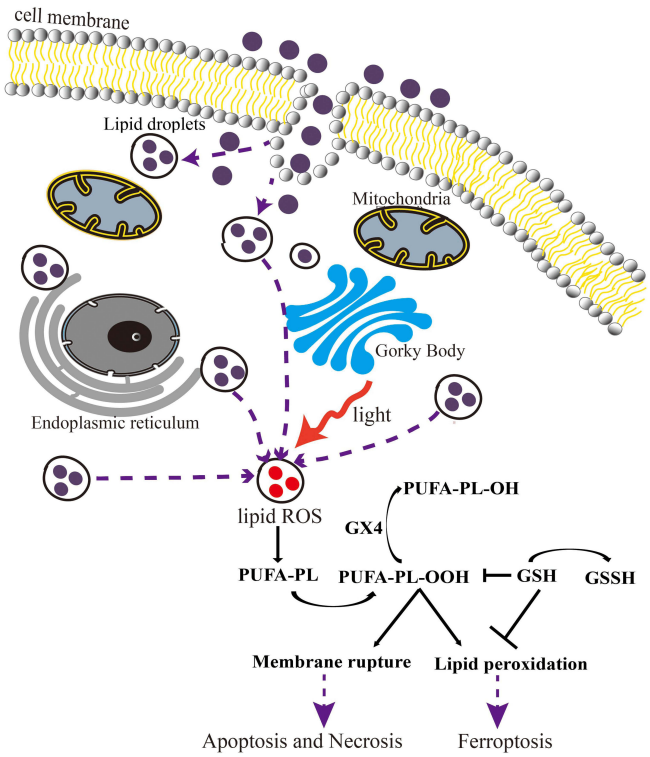

Figure 6 Modification and mechanism of LDs-targeting PDT. Deep purple circle: LDs targeted photosensitizer. Red circle: Excited photosensitizer. Purple dashed arrow: Path. Black irregular circle: Lipid Droplets. LDs targeting methods: Targeted modification through hydrophobic interactions. Targeted modification by regulating intramolecular hydrogen bonds. Targeted based on aggregation-induced emission materials. Solid black arrows and corresponding text: LDs regulate ferroptosis by photoinducing the oxidation of polyunsaturated fatty acid phospholipids (PUFA-PLs) into peroxidation derivatives. Meanwhile, the consumption of glutathione (GSH) and the inhibition of glutathione peroxidase 4 (GPX4) lead to the production of cytotoxic lipid hydroperoxides (PLOOH), resulting in membrane rupture and irreversible cell death.

acceptor (D-A) system to enhance superoxide anion (O_2^-) production.[104] The incorporation of morpholine not only increased hydrophobicity but also improved the H-aggregation tendency, thereby dispersing molecular electrostatic distribution. MNBS accumulated in LDs and induced ferroptosis-mediated PDT, achieving highly efficient antitumor effects under both hypoxic and normoxic conditions.

Novel photosensitizers with AIE features have been designed for LD targeting. For example, Tang's group synthesized an LD-targeting AIE luminogen (AIEgen) to induce adipocyte apoptosis via type I PDT. They further developed biomimetic AIE photosensitizers (DC@AIEdots) by coating dendritic cell membranes onto nano-aggregated AIEgens, enabling LD targeting and activating photodynamic immunotherapy.[112] Zhang et al synthesized an LD-targeting fluorescent material with AIE properties for integrating cancer diagnosis (via LD visualization) and treatment (via apoptosis induction through PDT).[113] Hua et al designed three D-A-structured dihydrodibenzo[a,c]phenazine (DHP)-based photosensitizers (DP-CNPY, SMP-CNPY, and DMP-CNPY) by introducing methyl groups into the DHP donor and 2-(pyridin-4-yl)acetonitrile as a strong electron acceptor.[114] Among these, SMP-CNPY exhibited LD-targeting ability and strong ROS production, thereby enhancing PDT efficacy under hypoxia.

Li et al reported a series of AIE-active photosensitizers (AIE-Cbz-LD-Cn, n = 1, 3, 5, 7, OMe) through conjugation of quinoline-malononitrile (QM) with carbazole.[115] These compounds (AIE-Cbz-LD-C3, C5, and C7) demonstrated LD-targeting specificity, with AIE-Cbz-LD-C7 further inducing lipophagy and ferroptosis in live cells. Liu et al synthesized triphenylamine-based AIE molecules with a D1-D2-π-A structure and intramolecular charge transfer (ICT) properties.[116] Modification of D2 with functional groups (phenyl, thiophene, and furan) allowed tuning of donor-acceptor interactions. All molecules displayed high LD-targeting capability and excellent ROS generation efficiency, enhancing PDT within LDs.[117]

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Cell Membrane

The cell membrane, as the primary protective barrier of cells, isolates intracellular components from the external environment and maintains cellular integrity and metabolism. Additionally, the cell membrane regulates substance exchange through pinocytosis, phagocytosis, exocytosis, and protein secretion/transport.[7] Intracellular drug accumulation critically depends on cell membrane fluidity, which determines therapeutic efficacy.[118] Membrane-targeted drugs bypass transmembrane transport, thereby avoiding drug efflux.[119] Furthermore, membrane homeostasis is essential for regulating cellular processes. Disruption or damage to membrane function triggers signaling pathways that induce cell death (eg, apoptosis, necrosis, autophagy, and ferroptosis) (shown in Figure 7). Membrane rupture rapidly releases cellular contents, provoking immunogenic cell death to enhance antitumor immunity and therapeutic outcomes.[120] Thus, the cell membrane is a promising target for PDT.

The amphiphilic cell membrane, composed of phospholipids, glycoproteins, and glycolipids arranged in a bilayer, carries abundant negative charges.[121] Membrane-targeted PDT can exploit these amphiphilic and electrostatic properties. Sun et al designed two molecular rotor-based self-reporting photosensitizers to disrupt membrane integrity via electrostatic/hydrophobic interactions with phospholipid bilayers during PDT.[122] Zhang et al developed a charge-reversible self-delivery chimeric peptide (C16-PRP-DMA) for sustained membrane targeting. This peptide integrates four functional segments: palmitic acid as a lipophilic moiety enabling membrane insertion and self-assembly, a DMA-modified tetrapeptide (RRKK) enhancing membrane affinity via electrostatic interactions while reducing nonspecific in vivo adsorption, polyethylene glycol (PEG) improving biocompatibility and prolonging blood circulation half-life, and protoporphyrin IX (PPIX) generating ROS to directly disrupt membranes and induce rapid necrosis. This design significantly enhanced PDT efficacy.[123] Zhang's group further engineered a self-delivery chimeric peptide for combined low-

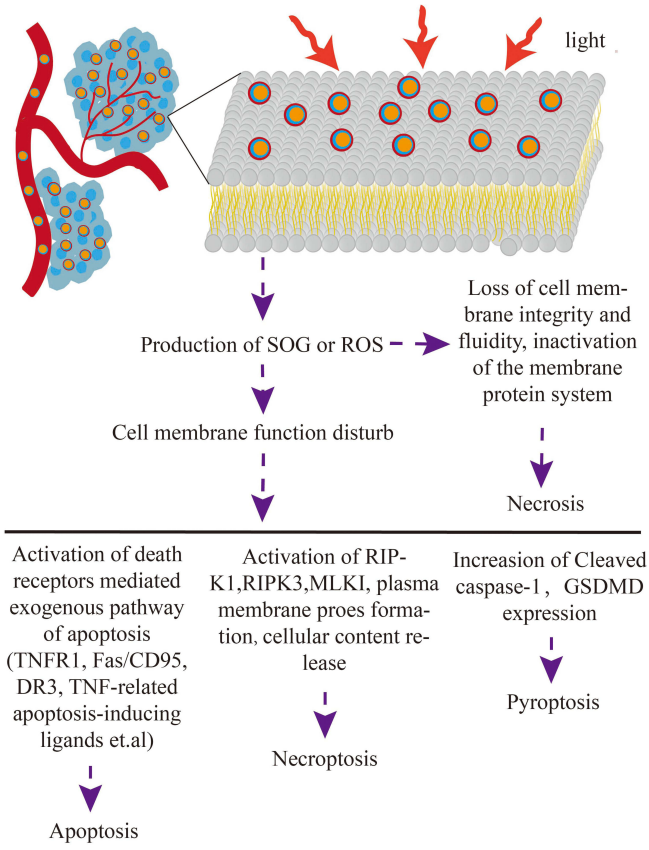

Figure 7 Modification and mechanism of cell membrane-targeting PDT. Orange Circle: Cell membrane targeted photosensitizer. Red circle: Excited photosensitizer. Purple dashed arrow: Path. Targeted strategies for cell membranes: Positive charge modification. Hydrophobic interactions with cell membrane. Lipid analog design: such as Fluorescence strategy. Biospecific recognition strategy: receptor ligand targeting, enzyme driven membrane localization. Amino acid and glycosylation modification strategies. New materials and intelligent design strategies: AIEgens (aggregation induced luminescent materials) and others.

temperature photothermal therapy (LTPTT) and PDT. Localized ROS generation and mild heating (<45 °C) at the membrane induced rupture and activated antitumor immunity, suppressing metastasis.[124]

Novel AIEgens-based membrane-targeted photosensitizers have also emerged. Tang et al synthesized a near-infrared (NIR)-emissive AIE photosensitizer (TBMPEI) by cationizing pyridine units. TBMPEI selectively accumulates on membranes, inducing necroptosis via membrane rupture and DNA degradation upon irradiation.[125] Qi et al designed AIE-active photosensitizers (DCTPys) that disrupt membranes under mild conditions to trigger necrosis.[126]

Lipid mimics designed for cell membrane targeting often lack cancer cell selectivity, leading to unintended damage to normal cells. Perfluorocarbons are known to accumulate in the central lipid layer of cell membranes. Based on this property, Chen et al proposed a fluorination strategy for plasma membrane-targeted PDT in cancer cells, disrupting membrane integrity and inducing pyroptosis to enhance therapeutic efficacy.[127] Awazu et al employed replication-deficient hemagglutinating virus of Japan (HVJ; Sendai virus) envelopes (HVJ-E) as membrane-targeted drug carriers to deliver photosensitizers, achieving cancer-selective apoptosis and antitumor immunity for amplified PDT effects.[128]

Specific membrane targeting can be achieved through protein receptors, peptides, amino acids, or glycosylated chlorin compounds. For instance, folate receptors are overexpressed in approximately 40% of human cancers, making them viable targets for folate-modified PDT systems.[129] Zhang's group developed a protein farnesyltransferase (PFTase)-driven plasma membrane (PM)-targeted chimeric peptide based on a K-Ras-derived sequence (KKKKKKSKTKC-OMe). This system initiates lipid peroxidation and membrane rupture at nanomolar concentrations during PDT. Damaged membranes further release damage-associated molecular patterns, activating antitumor immunity to suppress metastatic tumors.[130]

Simple amino acid modifications can enhance noncovalent interactions between photosensitizers and membranes. Li's team conjugated protoporphyrin IX (PPIX) to the ε-amine of lysine and modified it with arginine or glutamic acid, enabling single-arginine-level membrane targeting and light-induced membrane disruption.[131] Drain et al demonstrated that glycosylated chlorin compounds localized transiently at membranes activate necrosis upon irradiation, despite initial targeting via surface saccharide receptors followed by rapid internalization into the endoplasmic reticulum.[11]

Organelle-Targeted Gas-Photodynamic Combination Therapy

Despite continuous technological advancements, particularly in subcellular organelle-targeted photosensitizer delivery systems, the efficacy of PDT has been substantially improved. However, challenges such as limited light penetration depth (<1 cm), tumor hypoxia, and ROS quenching have hindered the clinical translation and broad application of PDT.[132] To address these limitations, synergistic strategies combining PDT with other modalities (eg, chemotherapy, radiotherapy, photothermal therapy, immunotherapy, sonodynamic therapy, and gas therapy) have emerged as effective solutions.[16,23,133,134] Among these, gas therapy utilizing gaseous signaling molecules—such as NO, carbon monoxide (CO), hydrogen (H_2), and hydrogen sulfide (H_2S)—demonstrates selective pro-apoptotic effects on cancer cells, modulates tumor vasculature, and protects normal tissues within specific concentration and temporal windows.[135] Thus, the integration of PDT with gas therapy represents a promising strategy to enhance antitumor efficacy with significant developmental potential.

Gas Therapy and Mechanisms of Action

NO, CO, H_2, and H_2S are critical gaseous signaling molecules that regulate cellular biology and signaling pathways.[136] At specific concentrations, these gases inhibit tumor migration, reverse the Warburg effect in cancer cells to modulate cell death, and exert anti-inflammatory effects.[137] Their ultralow molecular weights enable diffusion into tumor interstitium and penetration across biological membranes, thereby targeting deep-seated cancer cells.[138] The antitumor mechanisms of these gases are summarized in Table 1. Similar to PDT, gas therapy exhibits low systemic toxicity, minimal off-target effects on normal tissues, and reduced risk of drug resistance.[139–141] As a minimally invasive and biocompatible strategy, gas therapy induces biochemical and physiological alterations in tumor microenvironments, achieving precise tumor suppression.

Table 1 Therapeutic Mechanisms of Different Gases

Gas	Mechanism of Treatment	References
CO	Prevents cytochrome C oxidase and mitochondrial electron transfer. Normal cells: Enhances the ability of mitochondria to produce ROS Tumor cells: Induces apoptosis by elevating oxygen concentration, generating excessive ROS, suppressing tumorigenesis/ proliferation/ migration/ angiogenesis, and enhancing drug accumulation/penetration.	[141]
NO	Increases oxidative stress, inhibits cellular respiration and DNA synthesis/repair, disrupts mitochondrial integrity, and reacts with superoxide radicals to form toxic peroxynitrite anions ($ONOO^-$). Additionally, NO downregulates the expression of P-gp and MRPs, thereby suppressing multidrug resistance.	[142]
H_2	Decreases vascular endothelial growth factor (VEGF) expression, triggers Gasdermin D-mediated pyroptosis, selectively scavenges hydroxyl radicals and peroxynitrite anions ($ONOO^-$), activates endogenous antioxidant enzymes (SOD and CAT), exerts anti-inflammatory effects, and sensitizes drug-resistant cells.	[143]
H_2S	Physiological concentrations: Exhibits antioxidant, angiogenic, vasodilatory, anti-inflammatory, and anti-apoptotic properties. Exogenous low concentrations: Induces angiogenesis and anti-apoptosis, accelerates cell cycle progression, and promotes tumorigenesis. Exogenous high concentrations: Inhibits cancer cell growth, arrests the cell cycle, and induces apoptosis via intracellular acidification.	[144]
SO_2	Anti-inflammatory, vasorelaxation-promoting, cardiovascular-regulating, bactericidal, and cytoprotective. In a hyperoxidized state, endogenous SO_2 induces oxidative stress and cellular damage while reversing multidrug resistance.	[145,146]

Abbreviations: P-gp, P-glycoprotein; MRPs, Multidrug resistance proteins; SOD, Superoxide Dismutase; CAT, Catalase.

Gas-Photodynamic Combination Therapy and Mechanisms of Action

Although nanocarriers and targeted drug delivery systems enhance the efficacy of PDT, several inherent limitations remain unresolved. For instance, the limited penetration depth of excitation light persists despite optimization through near-infrared irradiation, fiber optics, or light-emitting diodes. Moreover, skin photosensitivity, thermal damage, and localized heating induced by prolonged light exposure cannot be fully addressed by current strategies. Combining PDT with other therapeutic modalities is critical to reduce photosensitizer toxicity and amplify photodynamic effects. Gas therapy synergizes profoundly with PDT through mechanisms such as ROS sensitization, tumor vascular disruption, and enhanced intracellular drug accumulation, as summarized in previous sections. These interactions establish a robust foundation for achieving therapeutic synergy. Consequently, integrating gas therapy with PDT holds significant potential in advancing antitumor treatment paradigms.

Six gaseous agents—oxygen (O_2), CO, NO, hydrogen (H_2), hydrogen sulfide (H_2S), and sulfur dioxide (SO_2)—are predominantly employed in gas-photodynamic combination therapy. The mechanisms of gas-PDT synergy include ROS amplification through oxidative stress enhancement, sensitization of drug-resistant cells, inhibition of malignant cell and tissue proliferation, anti-inflammatory modulation, and tumor microenvironment reprogramming, as illustrated in Figures 8 and 9. Subsequent sections critically evaluate gas-PDT combination strategies organized by these mechanistic categories.[147–152]

Promotes Oxidative Stress

O_2

The generation of $^1O_2$ or ROS to induce cancer cell death represents a core mechanism of PDT. However, the rapid proliferation of tumor cells creates an imbalance between oxygen supply and consumption, resulting in tumor hypoxia.[153] Hypoxia not only restricts ROS production during PDT but also promotes tumor progression, metastasis, and radioresistance. Consequently, tumor reoxygenation strategies are essential to overcome this limitation. Current approaches include endogenous oxygen supplementation; exogenous oxygen delivery; and in situ oxygen regeneration via catalytic reactions.[154–158]

Endogenous oxygen supplementation modulates the hypoxic microenvironment through tumor vascular normalization, degradation of dense tumor stroma, or hyperthermia-induced oxygen release. Exogenous delivery relies on

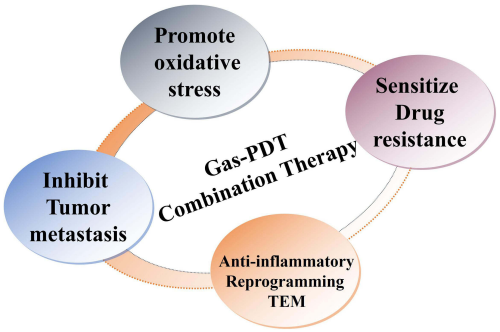

Figure 8 The possible main mechanism of Gas-PDT combination therapy.

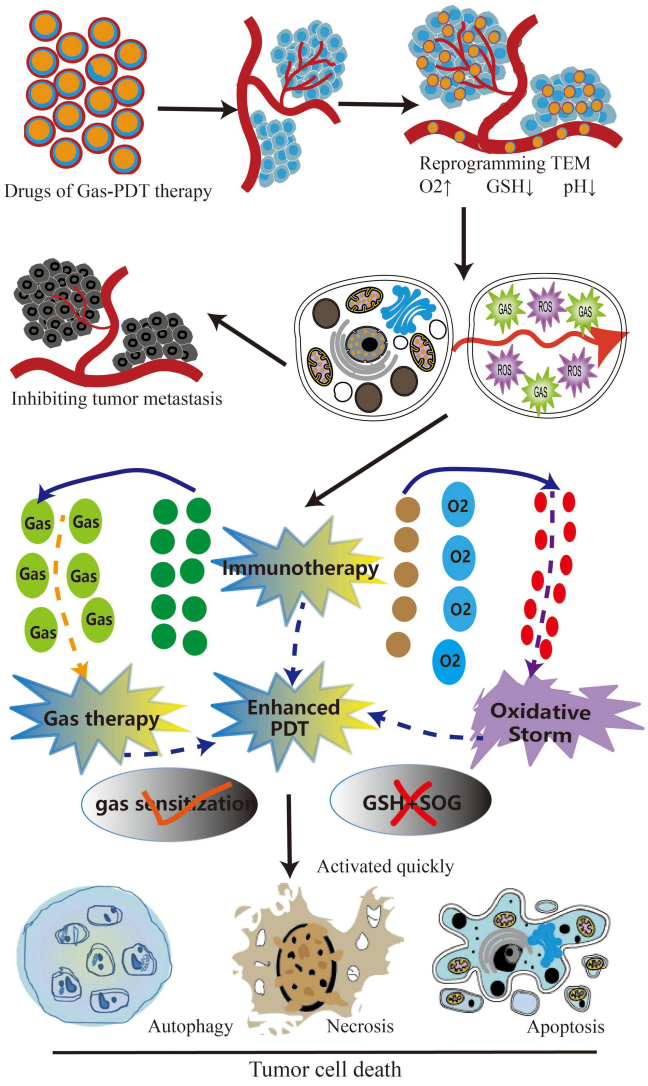

Figure 9 The enhancement of Gas-PDT combination therapy. Red circle: Photosensitizers. Green circle: Gas prodrugs. Brown circle: Oxygen precursors. Black solid line arrow: Leads to. Blue solid line arrow: Transforms into. Yellow, purple, blue dashed line arrows: Lead to. Black horizontal line: Here refers to Autophagy, Necrosis, Apoptosis ultimately leading to tumor cell death.

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oxygen nanocarriers such as perfluorocarbons (PFCs), erythrocytes, hemoglobin (Hb), and metal-organic frameworks (MOFs).

Red blood cells (RBCs), the primary oxygen carriers in mammals, exhibit high oxygen-binding capacity, biocompatibility, and immunomodulatory functions. Zhang et al engineered an RBC-derived vehicle co-loaded with hemoglobin, chlorin e6, and sorafenib, which enhances PDT efficacy by boosting intratumoral oxygen/iron levels and triggering ferroptosis.[159] To address hemoglobin's auto-oxidation and nephrotoxicity risks, Wang et al developed a chemiluminescence-driven PDT system using hemoglobin-conjugated conjugated polymer nanoparticles (Hb-CPNs). This system generates ROS via luminol-catalyzed chemiluminescence absorbed by CPNs, eliminating the need for external light. Encapsulation of Hb-CPNs within biomimetic liposomal polymers further improves hemoglobin stability and oxygen-loading capacity, achieving superior therapeutic outcomes.[160]

PFCs are FDA-approved oxygen carriers that physically dissolve substantial oxygen via weak van der Waals interactions and passively diffuse it into hypoxic tumors. Compared to hemoglobin (Hb), PFCs exhibit twice the oxygen capacity, unique electronic structures, high gas solubility, and chemical inertness, making them clinically validated for oxygen delivery.[161–164] Current PFC-based systems include liposomes, nanoparticles, and micelles. Wu et al engineered core-shell nanoparticles emulsified with perfluorotributylamine (PFTBA) and Ce6, augmenting PDT efficacy by leveraging PFCs to capture oxygen from photosynthetic chlorella gel under light.[165] Studies confirm that PFC content in nanoplatforms directly correlates with $^1O_2$ yield. Hu et al developed oxygen self-enriching PDT (Oxy-PDT) using PFC nanodroplets loaded with photosensitizers, demonstrating amplified ROS generation and cytotoxicity.[166] However, PFCs' side effects—arterial hypotension, pulmonary injury, thrombocytopenia, and flu-like symptoms—remain understudied.

MOFs, highly ordered porous structures formed by metal ions and organic ligands, enhance photosensitizer delivery via high porosity, surface area, and EPR effects.[167,168] Their nanoscale tunability further optimizes tumor accumulation. Zhao et al integrated Ce6 with Zn-MOFs, which disrupt bacterial membranes, amplify ROS production, and enable pH-responsive Ce6 release.[169] Despite these advantages, challenges persist in preventing premature drug leakage and improving tumor-targeted oxygen delivery.

In situ oxygen regeneration employs catalytic nanoparticles (eg, CaO_2, Cu_2O, Pt, Fe) or enzymes to decompose tumor H_2O_2/H_2O into oxygen. Manganese dioxide (MnO_2) is widely utilized; Cong et al encapsulated MnO_2, paclitaxel, and Ce6 in liposomes, where MnO_2 releases oxygen to enhance PDT while synergizing with chemotherapy.[170] Catalase (CAT)-based systems, such as Zhang's Nb@HCC platform (CAT, Ce6, human serum albumin, and nanobody), boost ROS under 660 nm light for ovarian cancer therapy.[171] However, CAT's high molecular weight and instability limit tumor penetration, whereas metal nanoparticles (eg, MnO_2) offer cost-effectiveness and stability despite potential cytotoxicity risks.[172–178]

NO

NO, an endogenous multifunctional signaling molecule, regulates vascular relaxation, neuromodulation, bone metabolism, and tumor progression. Its synthesis originates from precursors such as S-nitrosothiols (SNOs), L-arginine (L-Arg), nitroglycerin, N-nitrosamines, nitro compounds, diazeniumdiolates (NONOates), and metal nitroso complexes. Among these, L-Arg—a natural amino acid—exhibits superior biocompatibility and efficient NO generation via inducible nitric oxide synthase (iNOS) or ROS-driven oxidation, despite challenges like premature release and toxic byproduct formation compared to NONOates and SNOs.[179]

NO potentiates oxidative stress to amplify antitumor therapy through three interconnected mechanisms: competitive binding to mitochondrial complex IV reduces oxygen consumption and enhances PDT efficacy; reaction with superoxide radicals forms cytotoxic peroxynitrite ($ONOO^-$); and vasodilation-mediated hypoxia alleviation synergizes with PDT. For instance, Li et al combined perfluorocarbon (PFC) nanoliposomes (FI@Lip) with S-nitrosated human serum albumin (HSA-SNO), where HSA-SNO releases NO to inhibit mitochondrial respiration and deplete GSH, restoring $^1O_2$ levels, while PFCs directly deliver oxygen to boost $^1O_2$ generation, collectively enhancing tumor suppression.[180] Similarly, Zhang et al designed an arginine-loaded gelatin-coated PCN-224 system (Arg-PCN@Gel), leveraging arginine-derived NO to produce $ONOO^-$, disrupt biofilms, and enhance ROS penetration, achieving targeted cascade PDT against methicillin-resistant Staphylococcus aureus (MRSA).[181] Despite these advances, NO-PDT integration faces limitations:

NO's short half-life (<5 s) and restricted diffusion range (20–160 μm) necessitate subcellular targeting strategies (eg, mitochondrial or nuclear localization) to optimize therapeutic precision.

CO

Similar to NO, CO modulates tumor viability by amplifying oxidative stress. CO inhibits cytochrome c oxidase and mitochondrial electron transport, thereby disrupting tumor cell survival and protein synthesis. The therapeutic effects of CO exhibit dual functionality: in normal cells, CO mildly enhances mitochondrial ROS production; in cancer cells, it induces apoptosis through oxygen concentration elevation, excessive ROS generation, and mitochondrial dysfunction.

While low-dose CO inhalation is a potential delivery method, its systemic toxicity and poor targeting limit clinical utility. Current strategies prioritize nanocarrier-mediated delivery of CO-releasing molecules (CORMs), primarily transition metal carbonyl compounds that release CO under exogenous (light, heat, magnetic fields) or endogenous (ROS, acidic pH) stimuli.[182–188] For example, Li et al engineered human serum albumin (HSA)-stabilized MnO_2 nanoparticles (HIM-MnO_2) co-loaded with the CORM MnCO and mitochondrial-targeting photosensitizer IR780. The nanoparticles' photothermal effect triggers CO release, while IR780's mitochondrial localization directs CO to impair respiratory function, synergistically inducing tumor cell death.[189]

H_2S

Similar to CO, H_2S exhibits biphasic effects. At physiological concentrations, it demonstrates antioxidant, angiogenic, vasodilatory, anti-inflammatory, and anti-apoptotic properties. Conversely, high exogenous H_2S concentrations or prolonged exposure arrest the cell cycle, induce intracellular acidification, dysregulate signaling pathways, and trigger mitochondrial dysfunction and apoptosis.[135,150]

The concentration-dependent effects of H_2S lead to variable PDT synergies. Yang et al synthesized FTEP-TBFc NPs via alkyne-azide click chemistry, integrating NIR-II imaging with HPTT/CDT/PDT/GT. Under 808 nm light, the NPs generate fluorescence, heat, and $^1O_2$. Tumor GSH cleaves trisulfide bonds, releasing H_2S to suppress COX IV and HSP70, enhancing apoptosis. H_2S also inhibits catalase, reducing H_2O_2 consumption and increasing intratumoral O_2 to amplify PDT.[190]

Ye et al designed acid-responsive 1-JK-PS-FA NPs using JK-2 (H_2S donor), a reducible chromophore, NIR775, and FA. FA-mediated targeting and EPR enhance tumor accumulation. The acidic microenvironment triggers JK-2 to release H_2S, promoting angiogenesis, alleviating hypoxia, and improving NP uptake. This reprograms the tumor microenvironment, boosting PDT-induced apoptosis and immune activation while suppressing metastasis.[191]

Similarly, Wang et al developed a novel nanoplatform that enables cascade photo-immunotherapy through tumor-specific responsive reactions.[192] Its tetrasulfide-bridged silica-based core releases an AIEgen and manganese carbonyl (MnCO) upon glutathione (GSH) triggering, simultaneously generating hydrogen sulfide (H_2S). Under near-infrared light irradiation, the AIEgen mediates photodynamic therapy and triggers the decomposition of MnCO, releasing CO and manganese ions (Mn^2+). The synergistic action of H_2S and CO disrupts mitochondrial integrity, leading to mitochondrial DNA (mtDNA) leakage into the cytoplasm. Meanwhile, Mn^2+ enhances the activation of the cGAS–STING pathway, promoting type I interferon production and potentiating antitumor immunity.

However, Saenz et al reported H_2S-mediated PDT resistance. NaHS pretreatment reduces $^1O_2$ generation via upregulated GSH and catalase, while inhibiting protoporphyrin IX synthesis in ALA-PDT, thereby attenuating cytotoxicity.[193]

SO_2

Endogenous SO_2 in a hyperoxidized state induces cellular oxidative stress and damage due to its tetravalent sulfur properties.[194] This occurs primarily through two pathways: acting as an oxidant to elevate intratumoral GSH levels or generating free radicals within biological systems.[195] Zhang et al developed an injectable hydrogel (TBH) co-delivering the AIE-based theranostic agent TOCAc and the SO_2 donor benzothiazole sulfinate (BTS). The TBH gel's photothermal effect under irradiation triggers localized warming, dissolving and releasing BTS and TOCAc aggregates. Cationic TOCAc selectively targets mitochondrial membranes of cancer stem/non-stem cells, enabling simultaneous type I PDT

and photothermal therapy (PTT). Concurrent SO_2 release depletes intratumoral GSH, amplifying PDT efficacy and eradicating cancer stem cells to prevent recurrence.[140]

Similarly, Wang et al synthesized CyI-DNBS by conjugating 2,4-dinitrobenzenesulfonyl chloride (DNBS) to the photosensitizer Cyl-OH. GSH-mediated cleavage releases both SO_2 and Cyl-OH, activating PDT under red light.[196] Li et al engineered gold nanorod-polydopamine nanocapsules (GPBRs) doped with BTS. Near-infrared irradiation induces photothermal effects, while the acidic tumor microenvironment and hyperthermia synergistically promote SO_2 diffusion. SO_2-derived ROS ($SO_3^{\cdot-}$) upregulates pro-apoptotic proteins (p53, Bax, caspase-3) and suppresses anti-apoptotic Bcl-2, driving apoptosis.[137]

Sensitize Drug-Resistant Cells

Multidrug resistance (MDR) remains a critical challenge in oncology, contributing significantly to therapeutic failure and tumor recurrence.[197] MDR mechanisms are multifactorial and heterogeneous, encompassing upregulated drug efflux (eg, P-gp overexpression), impaired drug influx, apoptosis resistance, enhanced DNA repair, drug target modifications, and enzymatic detoxification. Current strategies to overcome MDR include tumor vascular normalization, stromal cell reprogramming, DNA repair inhibition, and intratumoral drug concentration escalation.[198] Integrating gas therapy with structurally optimized nanomedicine offers a promising approach to reverse MDR synergistically.

Inhibits Drug Excretion

Drug efflux is a major contributor to MDR, primarily mediated by ABC transporters. Key members include P-gp, BCRP, and MRP1.[199] Given the ATP-dependent nature of these transporters, gases impairing mitochondrial function (eg, CO, NO, H_2S) suppress ABC activity, overcoming MDR. Furthermore, SO_2 directly inhibits P-gp-mediated efflux.[200]

Normalizes Tumor Blood Vessels

In tumor systems, hypoxia-inducible factors (HIF) drive abnormal vasculature formation through upregulation of angiogenic factors, exacerbating hypoxia and promoting uncontrolled metastasis. Excessive angiogenesis in tumors and inflammatory tissues results in enlarged vascular fenestrations—a hallmark of the EPR effect—enabling selective nanoparticle accumulation in tumors.[201] However, hypoxia not only enhances nanoparticle retention but also diminishes PDT efficacy and exacerbates MDR. Tumor vascular normalization has emerged as a strategic approach to counteract MDR.

As previously discussed, O_2 supplementation and CO's competitive inhibition of mitochondrial respiration alleviate hypoxia, while NO downregulates HIF-1α expression, collectively promoting vascular normalization and reversing MDR.[202]

Nevertheless, achieving optimal therapeutic outcomes requires careful balance between vascular normalization and EPR preservation. While normalized vasculature improves drug distribution uniformity, it may compromise EPR-mediated nanoparticle accumulation. Precise gas dosage and temporal control remain critical parameters requiring systematic evaluation.

Target Glutathione

The elevated reactivity and concentration of GSH in tumor cells contribute to drug resistance by reducing PDT efficacy (dependent on oxidative stress) and promoting MRP2-mediated drug efflux.[203] In 2018, Chen et al synthesized a GSH-responsive polymeric SO_2 prodrug, demonstrating that SO_2 restores cancer cell sensitivity to doxorubicin (DOX) through GSH depletion and ROS elevation.[204] Similarly, Xuan et al engineered poly(disulfide)-based polymers (PSSD) conjugated with DOX, which deplete GSH and amplify chemotherapy efficacy.[205]

Inhibits DNA Repair

DNA repair dysfunction contributes to MDR. Beyond gases that suppress DNA repair via inhibition of cellular respiration and ATP synthesis, NO further disrupts repair processes through oxidative/nitrosative stress induction and S-nitrosation-mediated inactivation of key proteins (eg, PARP-1, XRCC1), impairing base excision repair (BER) and promoting DNA damage accumulation.[206,207]

In summary, gas-PDT combination therapy enhances oxidative stress and chemosensitization at optimized concentrations. However, clinical application demands precise spatiotemporal control of gas donor delivery. Current strategies

predominantly exploit the EPR effect for tumor accumulation, yet achieving subcellular-targeted delivery (eg, nuclei, mitochondria) with controlled release kinetics remains a critical challenge.

Subcellular-Targeted Gas-Photodynamic Combination Therapy

Current studies demonstrate progress in subcellular-targeted gas-photodynamic combination therapy. He et al engineered a photoconversion peptide (TPP-RRRKLVFFK-Ce6), where the oligoarginine domain RRR serves as a NO donor, TPP enables mitochondrial targeting, and light-induced $ONOO^-$ generation enhances cytotoxicity. Irradiation-triggered nanosphere-to-nanorod structural transformation further improves intratumoral drug accumulation and efficacy.[179] Li et al utilized IR780's mitochondrial localization to guide nanoparticles (HIM-MnO_2), where MnO_2 catalyzes H_2O_2 decomposition to alleviate hypoxia, while MnCO releases CO to induce apoptosis via mitochondrial damage.[189]

Lysosomal targeting strategies have also been explored. Wang et al developed a near-infrared (NIR)-responsive nanocarrier (DPP-NF, diketopyrrolopyrrole conjugated with NIR-activatable NO donor NF) by integrating pH-sensitive dimethylaminophenyl groups. Acidic lysosomal conditions activate ROS production, and NIR-controlled NO release triggers DNA damage-mediated apoptosis, demonstrating potent phototoxicity.[77]

ER-targeted approaches show emerging potential. Hu et al synthesized photosensitizers with ortho-thiophene diamine derivatives to enhance electron density and NO responsiveness.[208] The diamine moiety directs ER localization, enabling targeted cancer cell ablation through photosensitization.

Although subcellular-targeted gas-photodynamic studies remain limited (summarized in Table 2), their organelle-specific delivery strategies mirror conventional PDT paradigms. A critical challenge lies in achieving spatiotemporal control of gas release at designated subcellular sites to optimize therapeutic precision.

Table 2 Subcellular-Targeted Gas-Photodynamic Combination Therapy

Gas	Donors	Targeting Mode	Gas Therapy Mechanism	References
NO	SNOs	None	Inhibits mitochondrial respiration	[180]
	L-Arg	Gelatin selectively adheres to autolysin	Produces ONOO- and destroys biofilms	[181]
CO	MnCO	IR780	Mitochondrial dysfunction	[189]
	FeCO	HA +TPP	Mitochondrial dysfunction	[209]
	Butoxy carbonyl	FA +TPP	Oxidative phosphorylation of mitochondria is disrupted	[52]
O_2	Hb	Tumor cell homologous fusion liposomes	Increases ROS production	[160]
	CAT	Anti-HER-2 Nanobody targeting TEM	Breaks down intratumoral hydrogen peroxide and relieves tumor hypoxia	[178]
	Chlorella gel and PFC	None	Increases oxygen	[165]
SO_2	BTS	The cationic properties of TDCAc target mitochondria	Consumption of intratumoral glutathione	[140]
H_2S	Trisulfide	None	Inhibits the expression of cytochrome c oxidase (COX IV) and HSP70	[190]
	JK-2	FA	Promotes angiogenesis, alleviates tumor hypoxia, and increases the accumulation of nanodrugs	[191]

Abbreviations: SNOs, S-nitrosothiols; ONOO-, Peroxynitrite anion; HA, hyaluronic acid; TPP, triphenyl phosphonium; FA, folic acid; Hb, hemoglobin; CAT, Catalase; HER-2, Human epidermal growth factor receptor 2; TEM, Tumor microenvironment; PFC, Perfluorocarbon; BTS, Benzothiazole sulfinate; HSP70, Heatshockprotein70; JK-2, A hydrogen sulfide donor based on thioester phosphate.

Precise Controlled Release of Subcellular Organelle-Targeted Drug Delivery Strategy

Numerous gas prodrugs exhibit light sensitivity. In PDT, light serves as an essential component. Therefore, selecting or developing novel photo-responsive gas prodrugs combined with subcellular organelle-targeting strategies may enable spatiotemporally controlled gas-PDT delivery. Furthermore, certain gas prodrugs are ROS-activatable, aligning with the inherent ROS production in PDT. Integrating ROS-responsive prodrugs with organelle-targeting strategies could achieve cascade drug release for synergistic gas-PDT. For example, Feng et al developed a high-efficiency nanoplatform ($TPyNO_2$-FeCO NPs) that triggers robust ROS generation and CO release for PDT/CO gas synergistic therapy.[210] This system establishes a self-amplifying ROS-CO-ROS feedback loop, where CO induces intracellular oxidative stress, depolarizes mitochondrial membrane potential, and inhibits ATP production, thereby amplifying ROS generation. Pei et al synthesized photo-triggered ROS-responsive supramolecular nanoprodrugs (BNN6@GBTC NPs) via supramolecular self-assembly of an amphiphilic prodrug (GBTC) and an NO donor (BNN6).[211] These NPs achieve galactose receptor-mediated membrane targeting, where light irradiation generates ROS to release camptothecin (CPT) and activate BNN6 for NO production, enhancing anticancer efficacy through chemo-PDT-gas tri-therapy while minimizing normal cell damage.

The tumor microenvironment (TME) provides endogenous triggers for controlled drug release. TME comprises tumor cells, fibroblasts, immune cells, extracellular matrix, and vasculature, exhibiting unique pathological features: overexpression of tumor-promoting enzymes, progressive hypoxia from aberrant vasculature and rapid oxygen consumption, acidic pH due to lactic acid accumulation via glycolysis, and redox imbalance with elevated glutathione peroxidase and GSH levels. Xiao et al developed GSH-responsive nanoparticles (NP-DN) from an amphiphilic SO_2 prodrug (mPEG-PLG(DNs)), enabling nuclear-targeted PDT/SO_2 combination therapy.[195] Cellular studies demonstrated nuclear-targeted accumulation of porphyrin (Por) photosensitizer, which induces apoptosis through concurrent ROS generation and SO_2 release, exemplifying subcellular-precision gas-PDT synergy.

The Combination of CRISPR/Cas9 with PDT and Gas Therapy

In recent years, the rapid development of Clustered Regularly Interspaced Short Palindromic Repeats / CRISPR-associated protein 9 (CRISPR-Cas9) gene editing technology has brought breakthrough progress in the field of cancer therapy, particularly demonstrating significant potential in enhancing strategies such as gas therapy and PDT.

The CRISPR-Cas9 system originates from the adaptive immune system of bacteria and archaea. This system utilizes sgRNA to guide the Cas9 nuclease to perform targeted cleavage of specific genomic sequences, inducing DNA double-strand breaks. These breaks are then repaired by cellular mechanisms—either non-homologous end joining (NHEJ) or homology-directed repair (HDR)—enabling gene knockout, knock-in, or precise point mutations.[212,213] Due to its high efficiency and specificity, this technology has been widely applied in precision gene interference for cancer treatment.

In cancer therapeutic applications, CRISPR-Cas9 primarily functions through two strategies: First, direct editing of key genes in tumor cells—such as those affecting cell survival, proliferation, or drug resistance (eg, PRMT5 in pancreatic ductal adenocarcinoma and SLC5A3/MARCH5 in acute myeloid leukemia)—to inhibit tumor growth and enhance treatment sensitivity. For instance, knocking out NRF2 reduces tumor cells' tolerance to ROS, thereby improving their response to photodynamic therapy or gas therapy. Second, engineering immune cells to optimize adoptive cell therapy (ACT). Examples include knocking out the TRAC locus in CAR-T cells to reduce the risk of graft-versus-host disease (GVHD), disrupting PD-1 to alleviate immune suppression, and knocking out endogenous TCRαβ chains to enhance the expression and cytotoxicity of exogenous tumor-specific TCRs.[212–215]

In combination with gas therapy, the CRISPR-Cas9 system can knock out genes associated with stress response (eg, NRF2) in tumor cells, weakening their defense mechanisms and creating a synergistic antitumor effect with gas molecules such as CO and NO, which induce intracellular disruption and oxidative stress. For example, Li et al constructed a pH/GSH dual-responsive nanoplatform using $CaCO_3$ as a carrier to co-deliver glucose oxidase (Gox), MnCO (a CO donor), and Cas9/sgRNA complexes. This system decomposes in the tumor microenvironment, enabling simultaneous controlled release of CO and knockout of the NRF2 gene, significantly enhancing tumor cell killing efficacy.[216]

In combined strategies with photodynamic therapy, CRISPR-Cas9 is used to address two major limitations of PDT: tumor hypoxia and activation of antioxidant pathways. By editing genes related to antioxidant responses or angiogenesis, researchers not only increase tumor sensitivity to reactive oxygen species (ROS) but also improve local oxygen supply. For instance, Song et al developed a DNA-based complex system using upconversion nanoparticles (UCNPs) for coordinated delivery of CRISPR-Cas9, hemin, and protoporphyrin (PP).[217] This system employs Cas9 RNP to knock out the Nrf2 gene, enhancing cellular sensitivity to ROS, while utilizing G-quadruplex/hemin DNAzyme to catalyze endogenous H_2O_2 decomposition into oxygen, alleviating tumor hypoxia and thereby significantly improving PDT efficacy in breast cancer models. Another study utilized Pluronic F127 to encapsulate chlorophyll (Chl) and Cas9/sgRNA, constructing a micellar system that simultaneously generates ROS and performs NRF2 and APE1 gene editing under laser excitation, thereby disrupting oxidative defense mechanisms and increasing oxygen accumulation, leading to effective reprogramming of the tumor microenvironment.[218] Wang et al developed TCPH nanoparticles integrating an AIE photosensitizer with CRISPR-Cas9.[219] Under photoexcitation, these nanoparticles produce reactive oxygen species and generate a photothermal effect, while simultaneously achieving targeted knockout of the PD-L1 gene to reverse immune suppression. This approach demonstrated significant therapeutic efficacy and inhibited recurrence in multiple tumor models.

Currently, there are not many studies on the combination of CRISPR/Cas9 with PDT and gas therapy, but the precision medical characteristics of CRISPR/Cas9 in gene editing and its mechanisms for regulating the generation of gases in vivo demonstrate its infinite potential.

Future Perspectives and Challenges

Despite the promising advancements in subcellular organelle-targeted gas-PDT synergistic therapy, several pivotal challenges and exciting opportunities lie ahead, shaping the future trajectory of this field.

Pursuing Ultimate Precision: Multi-Stage Targeting and Smart Release

The next generation of platforms must achieve unparalleled specificity through intelligent design. Future efforts should focus on engineering multi-stage targeting systems that sequentially overcome biological barriers: first, accumulating in the tumor via the EPR effect or active targeting ligands; second, being internalized into specific cells via receptor-mediated endocytosis; and third, escaping endo/lysosomes to reach and release their cargo within a designated organelle (eg, mitochondria, ER). This necessitates the development of novel stimuli-responsive gas prodrugs activated by a unique combination of biomarkers present only in the target organelle's milieu (eg, specific pH, enzyme concentration, or redox potential). For instance, a prodrug designed for mitochondrial activation could require both high GSH levels and a high transmembrane potential for triggering, minimizing off-target release.

Harnessing the Synergy with Anti-Tumor Immunity

The intrinsic ability of both PDT and certain gas molecules (eg, CO, H_2S) to induce immunogenic cell death (ICD) and modulate the tumor immune microenvironment (TIME) presents a monumental opportunity. Future research should explore gas-PDT-immunotherapy triple-combination strategies. A promising direction, as illustrated by platforms that release mtDNA and Mn^{2}+ to activate the cGAS-STING pathway, is to design organelle-targeted systems that not only kill cancer cells directly but also function as in situ vaccines and reverse immunosuppression. The combination with immune checkpoint inhibitors (ICIs) could be particularly effective in converting "cold" tumors into "hot" ones, leading to robust and systemic anti-tumor immunity.

Bridging the Translational Gap: From Bench to Bedside

For these sophisticated nanoplatforms to transition from proof-of-concept studies to clinical applications, critical translational challenges must be addressed. Comprehensive and long-term biosafety evaluations of the degradation products of novel carriers (eg, tetrasulfide-based organosilica) and gas molecules at high doses are imperative. Scalable and reproducible manufacturing processes that ensure batch-to-batch consistency of complex multi-component systems need to be established. Furthermore, identifying predictive biomarkers for patient stratification

will be crucial to select those most likely to benefit from these targeted therapies, ensuring clinical trial success and future personalized medicine applications.

Conclusion

PDT, as a minimally invasive therapeutic method, can precisely induce tumor tissue damage and cell death. Subcellular organelle-targeted drug delivery strategies for PDT can be designed to significantly enhance the cytotoxic efficacy of singlet oxygen within its limited diffusion range and short lifetime. In this review, we systematically analyze subcellular targeting sites, organelle-specific delivery methodologies, and molecular mechanisms underlying enhanced therapeutic outcomes in PDT. Furthermore, gas therapy shares similar advantages with PDT, including minimal toxicity, reduced side effects, and low drug resistance, while addressing inherent limitations of PDT such as limited light penetration depth and hypoxia-induced treatment resistance. We comprehensively evaluate current progress in subcellular-targeted gas-PDT combination therapy, advanced delivery systems enabling dual-modality targeting, and responsive gas prodrugs integrated with organelle-targeting strategies. Although preliminary successes have been achieved, critical challenges remain in enhancing targeting precision for photosensitizers and gas molecules, achieving spatiotemporal control of therapeutic agent release, developing real-time monitoring systems for dosage optimization, and elucidating synergistic mechanisms between gas molecules and photosensitizers.

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Disclosure

The authors declare no conflicts of interest in this work.

References

1. Austin E, Wang JY, Ozog DM, Zeitouni N, Lim HW, Jagdeo J. Photodynamic therapy: overview and mechanism of action. *J Am Acad Dermatol*. 2025;20(25):00321–00324.
2. Yao L, Xie S, Liu Y, Mengqi L, Xia J, Lu B. Singlet oxygen storage and controlled release for improving photodynamic therapy. *Chem Commun*. 2024;60(95):14012–14021. doi:10.1039/D4CC04619F
3. Zhao W, Wang L, Zhang M, et al. Photodynamic therapy for cancer: mechanisms, photosensitizers, nanocarriers, and clinical studies. *MedComm*. 2024;5(7):e603. doi:10.1002/mco2.603
4. Li B, Lin L, Lin H, Wilson BC. Recent advances in nanomedicines for photodynamic therapy (PDT)-driven cancer immunotherapy. *J Biophotonics*. 2016;9(11–12):1314–1325. doi:10.1002/jbio.201600055
5. Przygoda M, Bartusik-Aebisher D, Dynarowicz K, Cieślar G, Kawczyk-Krupka A, Aebisher D. Cellular mechanisms of singlet oxygen in photodynamic therapy. *Int J Mol Sci*. 2023;24(23):16890. doi:10.3390/ijms242316890
6. Mehraban N, Freeman H. Developments in PDT sensitizers for increased selectivity and singlet oxygen. *Materials*. 2015;8(7):4421–4456. doi:10.3390/ma8074421
7. Wang R, Li X, Yoon J. Organelle-targeted photosensitizers for precision photodynamic therapy. *ACS Appl Mater Interfaces*. 2021;13(17):19543–19571. doi:10.1021/acsami.1c02019
8. Granville DJ, Carthy CM, Jiang H, Shore GC, McManus BM, Hunt DWC. Rapid cytochrome c release, activation of caspases 3, 6, 7 and 8 followed by Bap31 cleavage in HeLa cells treated with photodynamic therapy. *FEBS Lett*. 1998;437(1–2):5–10. doi:10.1016/S0014-5793(98)01193-4
9. Peng T-I, Chang C-J, Guo M-J. Mitochondrion-targeted photosensitizer enhances the photodynamic effect-induced mitochondrial dysfunction and apoptosis. *Ann N Y Acad Sci*. 2005;1042(1):419–428. doi:10.1196/annals.1338.035
10. Bhattacharyya A, Jameei A, Saha R, Garai A, Karande AA, Chakravarty AR. BODIPY-linked cis-dichlorido zinc(ii) conjugates: the strategic design of organelle-specific next-generation theranostic photosensitizers. *Dalton Trans*. 2021;50(1):103–115. doi:10.1039/D0DT03342A
11. Thompson SA, Aggarwal A, Singh S, Adam AP, Tome JPC, Drain CM. Compromising the plasma membrane as a secondary target in photodynamic. *Bioorg Med Chem*. 2018;26(18):5224–5228. doi:10.1016/j.bmc.2018.09.026
12. Chiu S-M, Xue L-Y, Lam M. A requirement for Bid for induction of apoptosis by photodynamic therapy with a lysosome- but not a mitochondrion-targeted photosensitizer. *Photochem Photobiol*. 2010;86(5):1161–1173. doi:10.1111/j.1751-1097.2010.00766.x
13. Li Y-H, Jia H-R, Wang H-Y, Hua X-W, Bao Y-W, Wu F-G. Mitochondrion, lysosome, and endoplasmic reticulum: which is the best target for phototherapy? *J Control Release*. 2022;351:692–702. doi:10.1016/j.jconrel.2022.09.037
14. Hong L, Li JM, Luo YL, et al. Recent advances in strategies for addressing hypoxia in tumor photodynamic therapy. *Biomolecules*. 2022;12(1):81. doi:10.3390/biom12010081
15. Larue L, Myrzakhmetov B, Ben-Mihoub A. Fighting hypoxia to improve PDT. *Pharmaceuticals*. 2019;12(4):163. doi:10.3390/ph12040163
16. Zhang Q, Li L. Photodynamic combinational therapy in cancer treatment. *J Buon*. 2018;23(3):561–567.

17. Adnane F, El-Zayat E, Fahmy HM. The combinational application of photodynamic therapy and nanotechnology in skin cancer treatment: a review. *Tissue Cell*. 2022;77:101856. doi:10.1016/j.tice.2022.101856
18. Li Z, Lai X, Fu S. Immunogenic cell death activates the tumor immune microenvironment to boost the immunotherapy efficiency. *Adv Sci*. 2022;9(22):e2201734. doi:10.1002/advs.202201734
19. Peng C-L, Lin H-C, Chiang W-L. Anti-angiogenic treatment (Bevacizumab) improves the responsiveness of photodynamic therapy in colorectal cancer. *Photodiagnosis Photodyn Ther*. 2018;23:111–118. doi:10.1016/j.pdpdt.2018.06.008
20. Ji B, Wei M, Yang B. Recent advances in nanomedicines for photodynamic therapy (PDT)-driven cancer immunotherapy. *Theranostics*. 2022;12(1):434–458. doi:10.7150/thno.67300
21. Chai J, Zhu J, Tian Y, Yang K, Luan J, Wang Y. Carbon monoxide therapy: a promising strategy for cancer. *J Mater Chem B*. 2023;11(9):1849–1865. doi:10.1039/D2TB02599J
22. Yi J, Liu L, Gao W. Advances and perspectives in phototherapy-based combination therapy for cancer. *J Mater Chem B*. 2024;12(26):6285–6304. doi:10.1039/D4TB00483C
23. Yan Z, Liu Z, Zhang H. Current trends in gas-synergized phototherapy for improved antitumor theranostics. *Acta Biomater*. 2024;174:1–25. doi:10.1016/j.actbio.2023.12.012
24. Chen L, Zhou S-F, Su L, Song J. Gas-mediated cancer bioimaging and therapy. *ACS Nano*. 2019;13(10):10887–10917. doi:10.1021/acsnano.9b04954
25. Song L, Wang G, Hou X. Biogenic nanobubbles for effective oxygen delivery and enhanced photodynamic. *Acta Biomater*. 2020;108:313–325. doi:10.1016/j.actbio.2020.03.034
26. Shi H, Xiong C-F, Zhang L-J. Light-triggered nitric oxide nanogenerator with high l -arginine loading for synergistic photodynamic/gas/photothermal therapy. *Adv Healthc Mater*. 2023;12(20):e2300012. doi:10.1002/adhm.202300012
27. Gong W, Xia C, He Q. Therapeutic gas delivery strategies. *Wiley Interdiscip Rev Nanomed Nanobiotechnol*. 2022;14(1):e1744. doi:10.1002/wnan.1744
28. Kwiatkowski S, Knap B, Przystupski D. Photodynamic therapy - mechanisms, photosensitizers and combinations. *Biomed Pharmacother*. 2018;106:1098–1107. doi:10.1016/j.biopha.2018.07.049
29. Agostinis P, Berg K, Cengel KA. Photodynamic therapy of cancer: an update. *CA Cancer J Clin*. 2011;61(4):250–281. doi:10.3322/caac.20114
30. Sun B, Bte Rahmat JN, Zhang Y. Advanced techniques for performing photodynamic therapy in deep-seated tissues. *Biomaterials*. 2022;291:121875. doi:10.1016/j.biomaterials.2022.121875
31. Cramer GM, Cengel KA, Busch TM. Forging forward in photodynamic therapy. *Cancer Res*. 2022;82(4):534–536. doi:10.1158/0008-5472.CAN-21-4122
32. Gunaydin G, Gedik ME, Ayan S. Photodynamic therapy-current limitations and novel approaches. *Front Chem*. 2021;9:691697. doi:10.3389/fchem.2021.691697
33. Zhang Z-J, Wang K-P, Mo J-G, Xiong L, Wen Y. Photodynamic therapy regulates fate of cancer stem cells through reactive oxygen. *World J Stem Cells*. 2020;12(7):562–584. doi:10.4252/wjsc.v12.i7.562
34. Kessel D. Death pathways associated with photodynamic therapy. *Med Laser Appl*. 2006;21(4):219–224. doi:10.1016/j.mla.2006.05.006
35. Kessel D. Apoptosis, paraptosis and autophagy: death and survival pathways associated with photodynamic therapy. *Photochem Photobiol*. 2019;95(1):119–125. doi:10.1111/php.12952
36. Kessel D. Death pathways associated with photodynamic therapy. *Photochem Photobiol*. 2021;97(5):1101–1103. doi:10.1111/php.13436
37. Kessel D, Oleinick NL. Cell death pathways associated with photodynamic therapy: an update. *Photochem Photobiol*. 2018;94(2):213–218. doi:10.1111/php.12857
38. Kadkhoda J, Tarighatnia A, Nader ND, Aghanejad A. Targeting mitochondria in cancer therapy: insight into photodynamic and photothermal therapies. *Life Sci*. 2022;307:120898. doi:10.1016/j.lfs.2022.120898
39. Yaqoob MD, Xu L, Li C, Leong MML, Xu DD. Targeting mitochondria for cancer photodynamic therapy. *Photodiagnosis Photodyn Ther*. 2022;38:102830. doi:10.1016/j.pdpdt.2022.102830
40. Li X, Zhao Y, Zhang T, Xing D. Mitochondria-specific agents for photodynamic cancer therapy: a key determinant to boost the efficacy. *Adv Healthc Mater*. 2021;10(3):e2001240. doi:10.1002/adhm.202001240
41. Yang Y, Wang S, Chen X, et al. Acid triggering highly-efficient release of reactive oxygen species to block mitochondrial-mediated homeostasis maintenance for accelerating cell death. *Anal Chim Acta*. 2025;1340:343645. doi:10.1016/j.aca.2025.343645
42. Hsieh CW, Yang WY. Triggering mitophagy with photosensitizers. *Methods Mol Biol*. 2019;1880:611–619.
43. Zhao X, Yang Y, Yu Y, Guo S, Wang W, Zhu S. A cyanine-derivative photosensitizer with enhanced photostability for mitochondria-targeted photodynamic therapy. *Chem Commun*. 2019;55(90):13542–13545. doi:10.1039/C9CC06157F
44. Bao JH, Zhao YA, Xu J, Guo YQ. Design and construction of IR780-and EGCG-based and mitochondrial targeting nanoparticles and their application in tumor chemo-phototherapy. *Journal of Materials Chemistry B*. 2021;9(48):9932–9945. doi:10.1039/D1TB01899J
45. Yang ZY, Wang JF, Liu S, et al. Defeating relapsed and refractory malignancies through a nano-enabled mitochondria-mediated respiratory inhibition and damage pathway. *Biomaterials*. 2020;229:119580. doi:10.1016/j.biomaterials.2019.119580
46. Wen J, Luo Y, Gao H, et al. Mitochondria-targeted nanoplatforms for enhanced photodynamic therapy against hypoxia tumor. *J Nanobiotechnology*. 2021;19(1):440. doi:10.1186/s12951-021-01196-6
47. Liu G, Wen Z, Liu F, Xu Y, Li H, Sun S. Multisubcellular organelle-targeting nanoparticle for synergistic chemotherapy and photodynamic/photothermal tumor therapy. *Nanomedicine*. 2023;18(7):613–631. doi:10.2217/nnm-2023-0021
48. Sandoval-Acuña C, Fuentes-Retamal S, Guzmán-Rivera D, et al. Destabilization of mitochondrial functions as a target against breast cancer progression: role of TPP-linked-polyhydroxybenzoates. *Toxicol Appl Pharm*. 2016;309:2–14. doi:10.1016/j.taap.2016.08.018
49. Huang MF, Myers CR, Wang YA, You M. Mitochondria as a novel target for cancer chemoprevention: emergence of mitochondrial-targeting agents. *Cancer Prev Res*. 2021;14(3):285–306. doi:10.1158/1940-6207.CAPR-20-0425
50. Song X-D, Chen -B-B, He S-F. Guanidine-modified cyclometalated iridium(III) complexes for mitochondria-targeted imaging and photodynamic therapy. *Eur J Med Chem*. 2019;179:26–37. doi:10.1016/j.ejmech.2019.06.045
51. Zhou Z, Zheng C, Liu Y, Luo W, Deng H, Shen J. Chitosan biguanide induced mitochondrial inhibition to amplify the efficacy of oxygen-sensitive tumor therapies. *Carbohydr Polym*. 2022;295:119878. doi:10.1016/j.carbpol.2022.119878

52. Bai XS, Lin Y, Gong LY, et al. Nanoparticles that target the mitochondria of tumor cells to restore oxygen supply for photodynamic therapy: design and preclinical validation against breast cancer. *J Controlled Release*. 2023;362:356–370. doi:10.1016/j.jconrel.2023.07.064
53. Wu J, Li J, Wang H, Liu CB. Mitochondrial-targeted penetrating peptide delivery for cancer therapy. *Expert Opin Drug Deliv*. 2018;15 (10):951–964. doi:10.1080/17425247.2018.1517750
54. Ehsan S, Covarrubias-Zambrano O, Bossmann SH. Mitochondrial targeting peptide-based nanodelivery for cancer treatment. *Curr Protein Pept Sci*. 2022;23(10):657–671. doi:10.2174/1389203723666220520160435
55. Farsinejad S, Gheisary Z, Ebrahimi Samani S, Alizadeh AM. Mitochondrial targeted peptides for cancer therapy. *Tumour Biol*. 2015;36 (8):5715–5725. doi:10.1007/s13277-015-3719-1
56. Zhou L, Liu JH, Ma F, et al. Mitochondria-targeting photosensitizer-encapsulated amorphous nanocage as a bimodal reagent for drug delivery and biodiagnose in vitro. *Biomed Microdevices*. 2010;12(4):655–663. doi:10.1007/s10544-010-9418-1
57. Wang DP, Zheng J, Jiang FY, et al. Facile and green fabrication of tumor- and mitochondria-targeted AIEgen-protein nanoparticles for imaging-guided photodynamic cancer therapy. *Acta Biomater*. 2023;168:551–564. doi:10.1016/j.actbio.2023.06.048
58. Yang CL, Wang XC. Lysosome biogenesis: regulation and functions. *J Cell Biol*. 2021;220(6):e202102001. doi:10.1083/jcb.202102001
59. Daugelaviciene N, Grigaitis P, Gasiule L, Dabkeviciene D, Neniskyte U, Sasnauskiene A. Lysosome-targeted photodynamic treatment induces primary keratinocyte differentiation. *J Photochem Photobiol B*. 2021;218:112183. doi:10.1016/j.jphotobiol.2021.112183
60. Pu J, Guardia CM, Keren-Kaplan T, Bonifacino JS. Mechanisms and functions of lysosome positioning. *J Cell Sci*. 2016;129(23):4329–4339. doi:10.1242/jcs.196287
61. Eriksson I, Öllinger K. Lysosomes in cancer-at the crossroad of good and evil. *Cells*. 2024;13(5):459. doi:10.3390/cells13050459
62. Liu X, Yu S, Zhang Y. pH-sensitive and lysosome targetable photosensitizers based on BODIPYs. *J Fluoresc*. 2025;35(2):779–787. doi:10.1007/s10895-023-03562-z
63. Piao S, Amaravadi RK. Targeting the lysosome in cancer. *Ann N Y Acad Sci*. 2016;1371(1):45–54. doi:10.1111/nyas.12953
64. Koshkaryev A, Piroyan A, Torchilin VP. Increased apoptosis in cancer cells in vitro and in vivo by ceramides in transferrin-modified liposomes. *Cancer Biol Ther*. 2012;13(1):50–60. doi:10.4161/cbt.13.1.18871
65. Towers CG, Thorburn A. Targeting the lysosome for cancer therapy. *Cancer Discov*. 2017;7(11):1218–1220. doi:10.1158/2159-8290.CD-17-0996
66. Sun Q, Yang J, Wu Q, Shen W, Yang Y, Yin D. Targeting lysosome for enhanced cancer photodynamic/photothermal therapy in a "one stone two birds" pattern. *ACS Appl Mater Interfaces*. 2024;16(1):127–141. doi:10.1021/acsami.3c13162
67. Dos Reis SB, Silva JD, Garcia-Fossa F, et al. Mechanistic insights into the intracellular release of doxorubicin from pH-sensitive liposomes. *Biomed Pharmacother*. 2021;134:110952. doi:10.1016/j.biopha.2020.110952
68. Sun Y, Sha Y, Cui G, Meng F, Zhong Z. Lysosomal-mediated drug release and activation for cancer therapy and immunotherapy. *Adv Drug Deliv Rev*. 2023;192:114624. doi:10.1016/j.addr.2022.114624
69. Tian XX, Shi AH, Yin H, et al. Nanomaterials respond to lysosomal function for tumor treatment. *Cells*. 2022;11(21):3348. doi:10.3390/cells11213348
70. Banushi B, Joseph SR, Lum B, Lee JJ, Simpson F. Endocytosis in cancer and cancer therapy. *Nat Rev Cancer*. 2023;23(7):450–473. doi:10.1038/s41568-023-00574-6
71. Stern ST, Adiseshaiah PP, Crist RM. Autophagy and lysosomal dysfunction as emerging mechanisms of nanomaterial toxicity. *Part Fibre Toxicol*. 2012;9(1):20. doi:10.1186/1743-8977-9-20
72. Li Y, Yu Y, Kang L, Lu Y. Effects of chlorin e6-mediated photodynamic therapy on human colon cancer SW480 cells. *Int J Clin Exp Med*. 2014;7(12):4867–4876.
73. Zeng YP, Luo SL, Yang ZY, et al. A folic acid conjugated polyethylenimine-modified PEGylated nanographene loaded photosensitizer: photodynamic therapy and toxicity studies in vitro and in vivo. *J Mater Chem B*. 2016;4(12):2190–2198. doi:10.1039/C6TB00108D
74. Zou J, Wang P, Wang Y, et al. Penetration depth tunable BODIPY derivatives for pH triggered enhanced photothermal/photodynamic synergistic therapy. *Chem Sci*. 2019;10(1):268–276. doi:10.1039/C8SC02443J
75. Gao J, Luan T, Lv J, Yang M, Li H, Yuan Z. An oxygen-carrying and lysosome-targeting BODIPY derivative for NIR bioimaging and enhanced multimodal therapy against hypoxic tumors. *J Photochem Photobiol B*. 2023;241:112666. doi:10.1016/j.jphotobiol.2023.112666
76. Yu H, Chen J, Chen X, et al. Morpholinyl silicon phthalocyanine nanoparticles with lysosome cell death and two-photon imaging functions for in vitro photodynamic therapy of cancer cells. *Front Bioeng Biotechnol*. 2023;11:1181448. doi:10.3389/fbioe.2023.1181448
77. Wang Y, Huang X, Tang Y, et al. A light-induced nitric oxide controllable release nano-platform based on diketopyrrolopyrrole derivatives for pH-responsive photodynamic/photothermal synergistic cancer therapy. *Chem Sci*. 2018;9(42):8103–8109. doi:10.1039/C8SC03386B
78. Duan X, Tong Q, Fu C, Chen L. Lysosome-targeted fluorescent probes: design mechanism and biological applications. *Bioorg Chem*. 2023;140:106832. doi:10.1016/j.bioorg.2023.106832
79. Liu D, An H, Li X, et al. Lysosome-targeted bifunctional fluorescent probe and type I/II photosensitizer for viscosity imaging and cancer photodynamic therapy. *Luminescence*. 2024;39(11):e70028. doi:10.1002/bio.70028
80. Moor ACE. Signaling pathways in cell death and survival after photodynamic therapy. *J Photochem Photobiol B*. 2000;57(1):1–13. doi:10.1016/S1011-1344(00)00065-8
81. Pan L, Liu J, Shi J. Cancer cell nucleus-targeting nanocomposites for advanced tumor therapeutics. *Chem Soc Rev*. 2018;47(18):6930–6946. doi:10.1039/C8CS00081F
82. Zaitsava H, Gachowska M, Bartoszewska E, Kmiecik A, Kulbacka J. The potential of nuclear pore complexes in cancer therapy. *Molecules*. 2024;29(20):4832. doi:10.3390/molecules29204832
83. Yi X, Hussain I, Zhang P, Xiao C. Nuclear-targeting peptides for cancer therapy. *Chembiochem*. 2024;25(24):e202400596. doi:10.1002/cbic.202400596
84. Wang KN, Liu LY, Mao D, et al. A nuclear-targeted AIE photosensitizer for enzyme inhibition and photosensitization in cancer cell ablation. *Angew Chem Int Ed Engl*. 2022;61(15):e202114600. doi:10.1002/anie.202114600
85. Berg K, Madslien K, Bommer JC, Oftebro R, Winkelman JW, Moan J. Light induced relocalization of sulfonated meso-tetraphenylporphines in NHIK 3025 cells and effects of dose fractionation. *Photochem Photobiol*. 1991;53(2):203–210. doi:10.1111/j.1751-1097.1991.tb03924.x

86. Strauss WSL, Gschwend MH, Sailer R, Schneckenburger H, Steiner R, Rück A. Intracellular fluorescence behaviour of meso-tetra(4-sulphonatophenyl)porphyrin during photodynamic treatment at various growth phases of cultured cells. *J Photochem Photobiol B*. 1995;28(2):155–161. doi:10.1016/1011-1344(94)07082-Y
87. Ball DJ, Mayhew S, Wood SR, Griffiths J, Vernon DI, Brown SB. A comparative study of the cellular uptake and photodynamic efficacy of three novel zinc phthalocyanines of differing charge. *Photochem Photobiol*. 1999;69(3):390–396. doi:10.1111/j.1751-1097.1999.tb03303.x
88. Liu J, Yin Y, Yang L. Nucleus-targeted photosensitizer nanoparticles for photothermal and photodynamic. *Int J Nanomedicine*. 2021;16:1473–1485. doi:10.2147/IJN.S284518
89. Riera R, Feiner-Gracia N, Fornaguera C, Cascante A, Borros S, Albertazzi L. Tracking the DNA complexation state of pBAE polyplexes in cells with super resolution microscopy. *Nanoscale*. 2019;11(38):17869–17877. doi:10.1039/C9NR02858G
90. Tammam SN, Azzazy HME, Lamprecht A. How successful is nuclear targeting by nanocarriers? *J Control Release*. 2016;229:140–153. doi:10.1016/j.jconrel.2016.03.022
91. Zhu YX, Jia HR, Pan GY, Ulrich NW, Chen Z, Wu FG. Development of a light-controlled nanoplatform for direct nuclear delivery of molecular and nanoscale materials. *J Am Chem Soc*. 2018;140(11):4062–4070. doi:10.1021/jacs.7b13672
92. Schwarz DS, Blower MD. The endoplasmic reticulum: structure, function and response to cellular signaling. *Cell Mol Life Sci*. 2016;73(1):79–94. doi:10.1007/s00018-015-2052-6
93. Chen X, Shi C, He M, Xiong S, Xia X. Endoplasmic reticulum stress: molecular mechanism and therapeutic targets. *Signal Transduct Target Ther*. 2023;8(1):352. doi:10.1038/s41392-023-01570-w
94. Wang M, Kaufman RJ. Protein misfolding in the endoplasmic reticulum as a conduit to human disease. *Nature*. 2016;529(7586):326–335. doi:10.1038/nature17041
95. Bonsignore G, Martinotti S, Ranzato E. Endoplasmic reticulum stress and cancer: could unfolded protein response be a druggable target for cancer therapy? *Int J Mol Sci*. 2023;24(2):1566. doi:10.3390/ijms24021566
96. Miller DR, Thorburn A. Autophagy and organelle homeostasis in cancer. *Dev Cell*. 2021;56(7):906–918. doi:10.1016/j.devcel.2021.02.010
97. Weisheit S, Wegner CS, Ailte I, et al. Inhibiting autophagy increases the efficacy of low-dose photodynamic therapy. *Biochem Pharmacol*. 2021;194:114837. doi:10.1016/j.bcp.2021.114837
98. Li W, Yang J, Luo LH, et al. Targeting photodynamic and photothermal therapy to the endoplasmic reticulum enhances immunogenic cancer cell death. *Nat Commun*. 2019;10(1):3349. doi:10.1038/s41467-019-11269-8
99. Kessel D. Detection of paraptosis after photodynamic therapy. *Methods Mol Biol*. 2022;2451:711–720.
100. Shi YY, Wang SJ, Wu JL, Jin XZ, You J. Pharmaceutical strategies for endoplasmic reticulum-targeting and their prospects of application. *J Controlled Release*. 2021;329:337–352. doi:10.1016/j.jconrel.2020.11.054
101. Li S, Chen Y, Wu Y, et al. An endoplasmic reticulum targeting type I photosensitizer for effective photodynamic therapy against hypoxic tumor cells. *Chemistry*. 2022;28(72):e202202680. doi:10.1002/chem.202202680
102. Jiang X, Stockwell BR, Conrad M. Ferroptosis: mechanisms, biology and role in disease. *Nat Rev Mol Cell Biol*. 2021;22(4):266–282. doi:10.1038/s41580-020-00324-8
103. Chang Q, Wang P, Zeng Q, Wang X. A review on ferroptosis and photodynamic therapy synergism: enhancing anticancer treatment. *Heliyon*. 2024;10(7):e28942. doi:10.1016/j.heliyon.2024.e28942
104. Xiong T, Chen Y, Peng Q, et al. Lipid droplet targeting type I photosensitizer for ferroptosis via lipid peroxidation accumulation. *Adv Mater*. 2024;36(4):e2309711. doi:10.1002/adma.202309711
105. Petan T. Lipid droplets in cancer. *Rev Physiol Biochem Pharmacol*. 2023;185:53–86.
106. Tabero A, García-Garrido F, Prieto-Castañeda A, et al. BODIPYs revealing lipid droplets as valuable targets for photodynamic theragnosis. *Chem Commun*. 2020;56(6):940–943. doi:10.1039/C9CC09397D
107. Dong B, Song W, Lu Y, Sun Y, Lin W. Revealing the viscosity changes in lipid droplets during ferroptosis by the real-time and in situ near-infrared imaging. *ACS Sens*. 2021;6(1):22–26. doi:10.1021/acssensors.0c02015
108. Zadoorian A, Du X, Yang H. Lipid droplet biogenesis and functions in health and disease. *Nat Rev Endocrinol*. 2023;19(8):443–459. doi:10.1038/s41574-023-00845-0
109. Guo Y, Liu W, Sha J, et al. Constructing lipid droplet-targeting photosensitizers based on coumarins with NIR emission. *Spectrochim Acta A Mol Biomol Spectrosc*. 2023;296:122698. doi:10.1016/j.saa.2023.122698
110. Xia X, Wang R, Hu Y, et al. A novel photosensitizer for lipid droplet-location photodynamic therapy. *Front Chem*. 2021;9:701771. doi:10.3389/fchem.2021.701771
111. Li X, Liu W, Zheng X, et al. Lipid droplet targeting-guided hypoxic photodynamic therapy with curcumin analogs. *Chem Commun*. 2023;59(28):4181–4184. doi:10.1039/D2CC07025A
112. Xu XL, Deng GJ, Sun ZH, et al. A biomimetic aggregation-induced emission photosensitizer with antigen-presenting and hitchhiking function for lipid droplet targeted photodynamic immunotherapy. *Adv Mat*. 2021;33(33):e2102322. doi:10.1002/adma.202102322
113. Pei SZ, Li HY, Chen LF, et al. Dual-functional AIE fluorescent probe for visualization of lipid droplets and photodynamic therapy of cancer. *Anal Chem*. 2024;96(14):5615–5624. doi:10.1021/acs.analchem.4c00227
114. Xu J, Jin X, Wu X, et al. Regulating donor configuration to develop AIE-active type I photosensitizers for lipid droplet imaging and high-performance photodynamic therapy under hypoxia. *J Mater Chem B*. 2024;12(26):6384–6393. doi:10.1039/D4TB00051J
115. Chen R, Li Z, Peng C, Wen L, Xiao L, Li Y. Rational design of novel lipophilic aggregation-induced emission probes for revealing the dynamics of lipid droplets during lipophagy and ferroptosis. *Anal Chem*. 2022;94(39):13432–13439. doi:10.1021/acs.analchem.2c02260
116. Zhang F, Liu Y, Yang B, et al. Tunable NIR AIE-active optical materials for lipid droplet imaging in typical model organisms and photodynamic therapy. *J Mater Chem B*. 2021;9(10):2417–2427. doi:10.1039/D0TB02801K
117. Sun ZG, Shi SM, Guan PL, Liu B. Construction of heteroaryl-bridged NIR AIEgens for specific imaging of lipid droplets and its application in photodynamic therapy. *Spectrochim Acta A*. 2022;272:120946. doi:10.1016/j.saa.2022.120946
118. Mukherjee D, Kundu N, Chakravarty L, et al. Membrane perturbation through novel cell-penetrating peptides influences intracellular accumulation of imatinib mesylate in CML cells. *Cell Biol Toxicol*. 2018;34(3):233–245. doi:10.1007/s10565-017-9414-9
119. Ma W, Sha SN, Chen PL, et al. A cell membrane-targeting self-delivery chimeric peptide for enhanced photodynamic therapy and in situ therapeutic feedback. *Adv Healthc Mater*. 2020;9(1):e1901100. doi:10.1002/adhm.201901100

120. Chen J, Duan Z, Deng L, et al. Cell membrane-targeting type I/II photodynamic therapy combination with FSP1 inhibition for ferroptosis-enhanced photodynamic immunotherapy. *Adv Healthc Mater*. 2024;13(16):e2304436. doi:10.1002/adhm.202304436
121. Wang X, Yang L, Li Y, Wang X, Qi Z. A long-retention cell membrane-targeting AIEgen for boosting tumor theranostics. *Chem Asian J*. 2024;19(12):e202400305. doi:10.1002/asia.202400305
122. Yang L, Chen Q, Gan S, Huang C, Zhang H, Sun H. Rational design of self-reporting photosensitizers for cell membrane-targeted photodynamic therapy. *Anal Chem*. 2023;95(32):11988–11996. doi:10.1021/acs.analchem.3c01659
123. Liu LH, Qiu WX, Zhang YH, et al. A charge reversible self-delivery chimeric peptide with cell membrane-targeting properties for enhanced photodynamic therapy. *Adv Funct Mater*. 2017;27(25):1700220. doi:10.1002/adfm.201700220
124. Chen PL, Huang PY, Chen JY, et al. A self-delivery chimeric peptide for high efficient cell membrane-targeting low-temperature photothermal/photodynamic combinational therapy and metastasis suppression of tumor. *Biomaterials*. 2022;286:121593. doi:10.1016/j.biomaterials.2022.121593
125. Niu N, Yu Y, Zhang Z, et al. A cell membrane-targeting AIE photosensitizer as a necroptosis inducer for boosting cancer theranostics. *Chem Sci*. 2022;13(20):5929–5937. doi:10.1039/D2SC01260J
126. Dai Y, Xue K, Zhao X, Zhang P, Zhang D, Qi Z. Rationally designed near-infrared AIEgens photosensitizer for cell membrane-targeted photo-driven theranostics. *Spectrochim Acta A Mol Biomol Spectrosc*. 2023;286:122013. doi:10.1016/j.saa.2022.122013
127. Li A, Wang F, Li Y, et al. Fluorination of Aza-BODIPY for cancer cell plasma membrane-targeted imaging and therapy. *ACS Appl Mater Interfaces*. 2025;17(2):3013–3025. doi:10.1021/acsami.4c17943
128. Inai M, Honda N, Hazama H, et al. Photodynamic therapy using a cytotoxic photosensitizer porphyrus envelope that targets the cell membrane. *Photodiagnosis Photodynamic Ther*. 2017;20:238–245. doi:10.1016/j.pdpdt.2017.10.017
129. Aung W, Tsuji AB, Hanaoka K, Higashi T. Folate receptor-targeted near-infrared photodynamic therapy for folate receptor-overexpressing tumors. *World J Clin Oncol*. 2022;13(11):880–895. doi:10.5306/wjco.v13.i11.880
130. Zhang C, Gao F, Wu W, et al. Enzyme-driven membrane-targeted chimeric peptide for enhanced tumor photodynamic immunotherapy. *ACS Nano*. 2019;13(10):11249–11262. doi:10.1021/acsnano.9b04315
131. Cheng H, Fan GL, Fan JH, et al. Epigenetics-inspired photosensitizer modification for plasma membrane-targeted photodynamic tumor therapy. *Biomaterials*. 2019;224:119497. doi:10.1016/j.biomaterials.2019.119497
132. Lin L, Song X, Dong X, Li B. Nano-photosensitizers for enhanced photodynamic therapy. *Photodiagnosis Photodynamic Ther*. 2021;36:102597. doi:10.1016/j.pdpdt.2021.102597
133. Alvarez N, Sevilla A. Current advances in photodynamic therapy (PDT) and the future potential of PDT-combinatorial cancer therapies. *Int J Mol Sci*. 2024;25(2):1023. doi:10.3390/ijms25021023
134. Hu H, Zhao J, Ma K, et al. Sonodynamic therapy combined with phototherapy: novel synergistic strategy with superior efficacy for antitumor and antiinfection therapy. *J Control Release*. 2023;359:188–205. doi:10.1016/j.jconrel.2023.05.041
135. Jing YZ, Li SJ, Sun ZJ. Gas and gas-generating nanoplatforms in cancer therapy. *J Mater Chem B*. 2021;9(41):8541–8557. doi:10.1039/D1TB01661J
136. Wang Y, Yang T, He Q. Strategies for engineering advanced nanomedicines for gas therapy of cancer. *Natl Sci Rev*. 2020;7(9):1485–1512. doi:10.1093/nsr/nwaa034
137. Lu QL, Lu T, Xu M, Yang LF, Song YL, Li N. SO_2 prodrug doped nanorattles with extra-high drug payload for "collusion inside and outside" photothermal/pH triggered-gas therapy. *Biomaterials*. 2020;257:120236. doi:10.1016/j.biomaterials.2020.120236
138. Ghaffari-Bohlouli P, Jafari H, Okoro OV, et al. Gas therapy: generating, delivery, and biomedical applications. *Small Methods*. 2024;8(8):e2301349. doi:10.1002/smtd.202301349
139. Camara R, Matei N, Camara J, Enkhjargal B, Tang J, Zhang JH. Hydrogen gas therapy improves survival rate and neurological deficits in subarachnoid hemorrhage rats: a pilot study. *Med Gas Res*. 2019;9(2):74–79. doi:10.4103/2045-9912.260648
140. Zhang T, Pan Y, Suo M, et al. Photothermal-triggered sulfur oxide gas therapy augments type I photodynamic therapy for potentiating cancer stem cell ablation and inhibiting radioresistant tumor recurrence. *Adv Sci*. 2023;10(29):e2304042. doi:10.1002/advs.202304042
141. Motterlini R, Otterbein LE. The therapeutic potential of carbon monoxide. *Nat Rev Drug Discov*. 2010;9(9):728–743. doi:10.1038/nrd3228
142. Zhou J, Cao C, Zhang X, et al. Gas-assisted phototherapy for cancer treatment. *J Control Release*. 2023;360:564–577. doi:10.1016/j.jconrel.2023.07.015
143. Li Y, Yoon B, Dey A, Nguyen VQ, Park JH. Recent progress in nitric oxide-generating nanomedicine for cancer therapy. *J Control Release*. 2022;352:179–198. doi:10.1016/j.jconrel.2022.10.012
144. Ji P, Yang KX, Xu QQ, et al. Mechanisms and application of gas-based anticancer therapies. *Pharmaceuticals*. 2023;16(10):1394. doi:10.3390/ph16101394
145. Wu Y, Yuan M, Song J, Chen X, Yang H. Hydrogen gas from inflammation treatment to cancer therapy. *ACS Nano*. 2019;13(8):8505–8511. doi:10.1021/acsnano.9b05124
146. Ohsawa I, Ishikawa M, Takahashi K, et al. Hydrogen acts as a therapeutic antioxidant by selectively reducing cytotoxic oxygen radicals. *Nat Med*. 2007;13(6):688–694. doi:10.1038/nm1577
147. Zhang C, Zheng DW, Li CX, et al. Hydrogen gas improves photothermal therapy of tumor and restrains the relapse of distant dormant tumor. *Biomaterials*. 2019;223:119472. doi:10.1016/j.biomaterials.2019.119472
148. Zhang Y, Tan S, Xu J, Wang T. Hydrogen therapy in cardiovascular and metabolic diseases: from bench to bedside. *Cell Physiol Biochem*. 2018;47(1):1–10. doi:10.1159/000489737
149. Di Masi A, Ascenzi P. H2S: a "Double face" molecule in health and disease. *Biofactors*. 2013;39(2):186–196. doi:10.1002/biof.1061
150. Ding H, Chang J, He F, Gai S, Yang P. Hydrogen sulfide: an emerging precision strategy for gas therapy. *Adv Healthc Mater*. 2022;11(4):e2101984. doi:10.1002/adhm.202101984
151. Salari M, Zare Mehrjerdi F, Yadegari M, Rezvani ME, Shahrokhi Raeini A. Antidepressant-like effect of endogenous SO(2) on depression caused by chronic unpredictable mild stress. *Naunyn Schmiedebergs Arch Pharmacol*. 2023;396(6):1325–1336. doi:10.1007/s00210-023-02405-9
152. Xu M, Lu Q, Song Y, Yang L, Li J, Li N. Enhanced Bax upregulating in mitochondria for deep tumor therapy based on SO(2) prodrug loaded Au-Ag hollow nanotriangles. *Biomaterials*. 2020;250:120076. doi:10.1016/j.biomaterials.2020.120076

153. Mortezaee K. Normalization in tumor ecosystem: opportunities and challenges. *Cell Biol Int*. 2021;45(10):2017–2030. doi:10.1002/cbin.11655
154. Li X, Jiang C, Jia X, et al. Dual "unlocking" strategy to overcome inefficient nanomedicine delivery and tumor hypoxia for enhanced photodynamic-immunotherapy. *Adv Healthc Mater*. 2023;12(6):e2202467. doi:10.1002/adhm.202202467
155. Zhang Z, Wang Z, Xiong Y, et al. A two-pronged strategy to alleviate tumor hypoxia and potentiate photodynamic therapy by mild hyperthermia. *Biomater Sci*. 2022;11(1):108–118. doi:10.1039/D2BM01691E
156. Vaupel P, Piazena H. Hyperhydration of cancers: a characteristic biophysical trait strongly increasing O(2), CO(2), glucose and lactate diffusivities, and improving thermophysical properties of solid malignancies. *Adv Exp Med Biol*. 2023;1438:135–145.
157. Feng W, Han X, Wang R, et al. Nanocatalysts-augmented and photothermal-enhanced tumor-specific sequential nanocatalytic therapy in both NIR-I and NIR-II biowindows. *Adv Mater*. 2019;31(5):e1805919. doi:10.1002/adma.201805919
158. Moloudi K, Abrahamse H, George BP. Nanotechnology-mediated photodynamic therapy: focus on overcoming tumor hypoxia. *Wiley Interdiscip Rev Nanomed Nanobiotechnol*. 2024;16(1):e1937. doi:10.1002/wnan.1937
159. Liu W, Zhang J, Ding L, et al. RBC-derived nanosystem with enhanced ferroptosis triggered by oxygen-boosted phototherapy for synergized tumor treatment. *Biomater Sci*. 2021;9(21):7228–7236. doi:10.1039/D1BM00175B
160. Jiang LY, Bai HT, Liu LB, Lv FT, Ren XQ, Wang S. Luminescent, oxygen-supplying, hemoglobin-linked conjugated polymer nanoparticles for photodynamic therapy. *Angew Chem Int Edit*. 2019;58(31):10660–10665. doi:10.1002/anie.201905884
161. Jagers J, Wrobeln A, Ferenz KB. Perfluorocarbon-based oxygen carriers: from physics to physiology. *Pflugers Arch*. 2021;473(2):139–150. doi:10.1007/s00424-020-02482-2
162. Krafft MP. Alleviating tumor hypoxia with perfluorocarbon-based oxygen carriers. *Curr Opin Pharmacol*. 2020;53:117–125. doi:10.1016/j.coph.2020.08.010
163. Yang Y, Liu Y, Jiang Y. Recent advances in perfluorocarbon-based delivery systems for cancer theranostics. *Mol Pharm*. 2023;20(7):3254–3277. doi:10.1021/acs.molpharmaceut.3c00116
164. Hu H, Yan X, Wang H, et al. Perfluorocarbon-based O(2) nanocarrier for efficient photodynamic therapy. *J Mater Chem B*. 2019;7(7):1116–1123. doi:10.1039/C8TB01844H
165. Wang H, Guo Y, Wang C, et al. Light-controlled oxygen production and collection for sustainable photodynamic therapy in tumor hypoxia. *Biomaterials*. 2021;269:120621. doi:10.1016/j.biomaterials.2020.120621
166. Cheng Y, Cheng H, Jiang C, et al. Perfluorocarbon nanoparticles enhance reactive oxygen levels and tumour growth inhibition in photodynamic therapy. *Nat Commun*. 2015;6(1):8785. doi:10.1038/ncomms9785
167. Ye Y, Zhao Y, Sun Y, Cao J. Recent progress of metal-organic framework-based photodynamic therapy for cancer treatment. *Int J Nanomedicine*. 2022;17:2367–2395. doi:10.2147/IJN.S362759
168. Gao DR, Gao Y, Shen J, Wang QW. Modified nanoscale metal organic framework-based nanoplatforms in photodynamic therapy and further applications. *Photodiagnosis Photodynamic Ther*. 2020;32:102026. doi:10.1016/j.pdpdt.2020.102026
169. Zhang W, Wang B, Xiang G, Jiang T, Zhao X. Photodynamic alginate Zn-MOF thermosensitive hydrogel for accelerated healing of infected wounds. *ACS Appl Mater Interfaces*. 2023;15(19):22830–22842. doi:10.1021/acsami.2c23321
170. Cong C, He Y, Zhao S, et al. Diagnostic and therapeutic nanoenzymes for enhanced chemotherapy and photodynamic therapy. *J Mater Chem B*. 2021;9(18):3925–3934. doi:10.1039/D0TB02791J
171. Zhang Q, Wu L, Liu S, et al. Moderating hypoxia and promoting immunogenic photodynamic therapy by HER-2 nanobody conjugate nanoparticles for ovarian cancer treatment. *Nanotechnology*. 2021;32(42):425101. doi:10.1088/1361-6528/ac07d1
172. Sun X, Chen K, Liu Y, et al. Metal-organic framework combined with CaO(2) nanoparticles for enhanced and targeted photodynamic therapy. *Nanoscale Adv*. 2021;3(23):6669–6677. doi:10.1039/D1NA00610J
173. Wan WT, Zhen T, Zhan M, et al. Tumor-targeting multi-shelled hollow nanospheres as drug loading platforms for imaging-guided combinational cancer therapy. *Biomater Sci*. 2020;8(6):1748–1758. doi:10.1039/C9BM01881F
174. Shi X, Zhan Q, Yan X, Zhou J, Zhou L, Wei S. Oxyhemoglobin nano-recruiter preparation and its application in biomimetic red blood cells to relieve tumor hypoxia and enhance photodynamic therapy activity. *J Mater Chem B*. 2020;8(3):534–545. doi:10.1039/C8TB02430H
175. Cao HQ, Yang Y, Liang MH, et al. Pt@polydopamine nanoparticles as nanozymes for enhanced photodynamic and photothermal therapy. *Chem Commun*. 2021;57(2):255–258. doi:10.1039/D0CC07355E
176. Liu XL, Dong X, Yang SC, et al. Biomimetic liposomal nanoplatinum for targeted cancer chemophototherapy. *Adv Sci*. 2021;8(8):2003679. doi:10.1002/advs.202003679
177. Magesan P, Dhanalekshmi KI, Prabha J, et al. Photodynamic and antibacterial studies of template-assisted Fe2O3-TiO_2 nanocomposites. *Photodiagnosis Photodynamic Ther*. 2022;40:103064. doi:10.1016/j.pdpdt.2022.103064
178. Zhang YF, Ma J, Wang DW, et al. Fe-TCPP@CS nanoparticles as photodynamic and photothermal agents for efficient antimicrobial therapy. *Biomater Sci*. 2020;8(23):6526–6532. doi:10.1039/D0BM01427C
179. Jiang L, Chen D, Jin Z, et al. Light-triggered nitric oxide release and structure transformation of peptide for enhanced intratumoral retention and sensitized photodynamic therapy. *Bioact Mater*. 2022;12:303–313. doi:10.1016/j.bioactmat.2021.09.035
180. Li W, Yong J, Xu Y, et al. Glutathione depletion and dual-model oxygen balance disruption for photodynamic therapy enhancement. *Colloids Surfaces B*. 2019;183:110453. doi:10.1016/j.colsurfb.2019.110453
181. Zhang A, Wu H, Chen X, et al. Targeting and arginine-driven synergizing photodynamic therapy with nutritional immunotherapy nanosystems for combating MRSA biofilms. *Sci Adv*. 2023;9(28):eadg9116. doi:10.1126/sciadv.adg9116
182. Tien Vo TT, Vo QC, Tuan VP, Wee Y, Cheng HC, Lee IT. The potentials of carbon monoxide-releasing molecules in cancer treatment: an outlook from ROS biology and medicine. *Redox Biol*. 2021;46:102124. doi:10.1016/j.redox.2021.102124
183. Khan H, Faizan M, Niazi SUK, Muhammad N, Zhang W, Zhang W. Water-soluble carbon monoxide-releasing molecules (CORMs). *Top Curr Chem*. 2022;381(1):3. doi:10.1007/s41061-022-00413-6
184. Choi HI, Zeb A, Kim MS, et al. Controlled therapeutic delivery of CO from carbon monoxide-releasing molecules (CORMs). *J Control Release*. 2022;350:652–667. doi:10.1016/j.jconrel.2022.08.055
185. Bauer N, Yuan Z, Yang X, Wang B. Plight of CORMs: the unreliability of four commercially available CO-releasing molecules, CORM-2, CORM-3, CORM-A1, and CORM-401, in studying CO biology. *Biochem Pharmacol*. 2023;214:115642. doi:10.1016/j.bcp.2023.115642

186. Ge J, Zuo M, Wang Q, Li Z. Near-infrared light triggered in situ release of CO for enhanced therapy of glioblastoma. *J Nanobiotechnology*. 2023;21(1):48. doi:10.1186/s12951-023-01802-9
187. Liu R, Peng Y, Lu L, Peng S, Chen T, Zhan M. Near-infrared light-triggered nano-prodrug for cancer gas therapy. *J Nanobiotechnology*. 2021;19(1):443. doi:10.1186/s12951-021-01078-x
188. Ma W, Chen X, Fu L, et al. Ultra-efficient antibacterial system based on photodynamic therapy and CO gas therapy for synergistic antibacterial and ablation biofilms. *ACS Appl Mater Interfaces*. 2020;12(20):22479–22491. doi:10.1021/acsami.0c01967
189. Ren H, Yang Q, Yong J, et al. Mitochondria targeted nanoparticles to generate oxygen and responsive-release of carbon monoxide for enhanced photogas therapy of cancer. *Biomater Sci*. 2021;9(7):2709–2720. doi:10.1039/D0BM02028A
190. Wu GL, Liu F, Li N, et al. Tumor microenvironment-responsive one-for-all molecular-engineered nanoplatform enables NIR-II fluorescence imaging-guided combinational cancer therapy. *Anal Chem*. 2023;95(47):17372–17383. doi:10.1021/acs.analchem.3c03827
191. Wu LY, Liu YL, Zeng WH, et al. Smart lipid nanoparticle that remodels tumor microenvironment for activatable H2S gas and photodynamic immunotherapy. *J American Chem Soc*. 2023;145(50):27838–27849. doi:10.1021/jacs.3c11328
192. Wang K, Li Y, Wang X, et al. Gas therapy potentiates aggregation-induced emission luminogen-based. *Nat Commun*. 2023;14(1):023–38601.
193. Calvo G, Cespedes M, Casas A, Di Venosa G, Saenz D. Hydrogen sulfide decreases photodynamic therapy outcome through the modulation of the cellular redox state. *Nitric Oxide-Biol Ch*. 2022;125:57–68. doi:10.1016/j.niox.2022.06.006
194. Wang W, Wang B. SO_2 donors and prodrugs, and their possible applications: a review. *Front Chem*. 2018;6:559. doi:10.3389/fchem.2018.00559
195. Zhang Y, Shen W, Zhang P, Chen L, Xiao C. GSH-triggered release of sulfur dioxide gas to regulate redox balance for enhanced photodynamic therapy. *Chem Commun*. 2020;56(42):5645–5648. doi:10.1039/D0CC00470G
196. Wang R, Xia X, Yang Y, et al. A glutathione activatable photosensitizer for combined photodynamic and gas therapy under red light irradiation. *Adv Healthc Mater*. 2022;11(4):e2102017. doi:10.1002/adhm.202102017
197. Li Z, Yin P. Tumor microenvironment diversity and plasticity in cancer multidrug resistance. *Biochim Biophys Acta Rev Cancer*. 2023;1878(6):188997. doi:10.1016/j.bbcan.2023.188997
198. Tan H, Zhang M, Wang Y, et al. Innovative nanochemotherapy for overcoming cancer multidrug resistance. *Nanotechnology*. 2021;33(5):052001. doi:10.1088/1361-6528/ac3355
199. Bukowski K, Kciuk M, Kontek R. Mechanisms of multidrug resistance in cancer chemotherapy. *Int J Mol Sci*. 2020;21(9):3233. doi:10.3390/ijms21093233
200. Yao X, Ma S, Peng S, et al. Zwitterionic polymer coating of sulfur dioxide-releasing nanosystem augments tumor accumulation and treatment efficacy. *Adv Healthc Mater*. 2020;9(5):e1901582. doi:10.1002/adhm.201901582
201. Ikeda-Imafuku M, Wang LL, Rodrigues D, Shaha S, Zhao Z, Mitragotri S. Strategies to improve the EPR effect: a mechanistic perspective and clinical translation. *J Control Release*. 2022;345:512–536. doi:10.1016/j.jconrel.2022.03.043
202. Zhu YX, Jia HR, Duan QY, Wu FG. Nanomedicines for combating multidrug resistance of cancer. *Wiley Interdiscip Rev Nanomed Nanobiotechnol*. 2021;13(5):e1715. doi:10.1002/wnan.1715
203. Traverso N, Ricciarelli R, Nitti M, et al. Role of glutathione in cancer progression and chemoresistance. *Oxid Med Cell Longev*. 2013;2013:972913. doi:10.1155/2013/972913
204. Shen W, Liu WG, Yang HL, Zhang P, Xiao CS, Chen XS. A glutathione-responsive sulfur dioxide polymer prodrug as a nanocarrier for combating drug-resistance in cancer chemotherapy. *Biomaterials*. 2018;178:706–719. doi:10.1016/j.biomaterials.2018.02.011
205. Xiao X, Wang K, Zong Q, Tu Y, Dong Y, Yuan Y. Polyprodrug with glutathione depletion and cascade drug activation for multi-drug resistance reversal. *Biomaterials*. 2021;270:120649. doi:10.1016/j.biomaterials.2020.120649
206. Wink DA, Kasprzak KS, Maragos CM, et al. DNA deaminating ability and genotoxicity of nitric oxide and its progenitors. *Science*. 1991;254(5034):1001–1003. doi:10.1126/science.1948068
207. Khan FH, Dervan E, Bhattacharyya DD, McAuliffe JD, Miranda KM, Glynn SA. The role of nitric oxide in cancer: master regulator or not? *Int J Mol Sci*. 2020;21(24):9393. doi:10.3390/ijms21249393
208. Qin Y, Gao H, Yin Y, et al. Photo-facilitated nitric oxide-triggered turn-on photodynamic therapy for precise antitumor application. *Adv Healthc Mater*. 2025;14(6):e2404265. doi:10.1002/adhm.202404265
209. Meng J, Jin Z, Zhao P, Zhao B, Fan M, He Q. A multistage assembly/disassembly strategy for tumor-targeted CO delivery. *Sci Adv*. 2020;6(20):eaba1362. doi:10.1126/sciadv.aba1362
210. Yu Y, Zhang L, Jia H, et al. Dual-mode reactive oxygen species-stimulated carbon monoxide release for synergistic photodynamic and gas tumor therapy. *ACS Nano*. 2024;18(45):31286–31299. doi:10.1021/acsnano.4c10277
211. Shi J, Ma K, Yang Y, Pei Y, Pei Z. Photo-triggered ROS-responsive supramolecular nanoprodrugs for targeted and synergistic chemo/photodynamic/gas therapy. *Chemistry*. 2025;31(1):e202403514. doi:10.1002/chem.202403514
212. Wang S-W, Gao C, Zheng Y-M. Current applications and future perspective of CRISPR/Cas9 gene editing in cancer. *Mol Cancer*. 2022;21(1):57. doi:10.1186/s12943-022-01518-8
213. Zhan T, Rindtorff N, Betge J, Ebert MP, Boutros M. CRISPR/Cas9 for cancer research and therapy. *Semin Cancer Biol*. 2019;55:106–119. doi:10.1016/j.semcancer.2018.04.001
214. Xu X, Liu C, Wang Y. Nanotechnology-based delivery of CRISPR/Cas9 for cancer treatment. *Adv Drug Deliv Rev*. 2021;176:113891. doi:10.1016/j.addr.2021.113891
215. Du Y, Liu Y, Hu J, Peng X, Liu Z. CRISPR/Cas9 systems: delivery technologies and biomedical applications. *Asian J Pharm Sci*. 2023;18(6):100854. doi:10.1016/j.ajps.2023.100854
216. Li Y, Pan Y, Chen C. Multistage-responsive gene editing to sensitize ion-interference enhanced carbon monoxide gas therapy. *Small*. 2022;18(40):e2204244. doi:10.1002/smll.202204244
217. Song N, Fan X, Guo X. A DNA/upconversion nanoparticle complex enables controlled co-delivery of CRISPR-Cas9 and photodynamic agents for synergistic cancer therapy. *Adv Mater*. 2024;36(15):e2309534. doi:10.1002/adma.202309534
218. Zhang C, Wang X, Liu G, et al. CRISPR/Cas9 and chlorophyll coordination micelles for cancer treatment by genome. *Small*. 2023;19(17):24.
219. Wang Y, Chen P, Wen H. Advanced nanoplatform mediated by CRISPR-Cas9 and aggregation-induced emission photosensitizers to boost cancer theranostics. *ACS Nano*. 2024;18(48):33168–33180. doi:10.1021/acsnano.4c11757

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