

Review

Tumor-microenvironment activatable organic photosensitizers for cancer photodynamic therapy

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Abstract Photodynamic therapy (PDT) represents a clinically approved anticancer modality but suffers from the inherent limitations of nonspecific photosensitizer toxicity to healthy tissues, restricted light penetration depth, oxygen dependency, prolonged photosensitivity, and tumor resistance mechanisms. This review systematically summarizes the rapidly evolving field of tumor microenvironment (TME)-activatable organic photosensitizers, focusing on their rational design principles, cancer treatment applications, and light source selection. These advanced molecular systems exhibit selective activation in response to TME-specific hallmarks such as acidic pH, hypoxia, elevated redox species, and overexpressed enzymes, thereby enabling precise spatiotemporal control of PDT and minimizing off-target side effects. Through comprehensive analysis of representative strategies for engineering stimuli-responsive photosensitizers, the structure-activity relationships and activation mechanisms are highlighted. The selection of light source and light delivery approaches that enhance the performance of organic photosensitizers for PDT is discussed in detail. Finally, current challenges and future directions are critically evaluated, with particular emphasis on their clinical translation potential, to guide advancing smart photosensitizers from bench to bedside and usher in a new era of precision PDT.

Keywords tumor microenvironment (TME), activatable, organic photosensitizers, photodynamic therapy (PDT), cancer

1. Introduction

1.1 Photodynamic therapy for cancers

Cancer represents a heterogeneous group of diseases characterized by the uncontrolled proliferation of cells that acquire the ability to evade growth-suppressive signals, resist apoptosis, induce angiogenesis, and promote invasion and metastasis [1-3]. Despite advances in early detection and multimodal therapies, including surgery, chemotherapy, radiotherapy, and immunotherapy, significant challenges persist [4]. Conventional treatments often suffer from the drawbacks of systemic toxicity, off-target effects, and limited efficacy against metastatic or recurrent tumors [5]. For instance, chemotherapy indiscriminately targets rapidly dividing cells, damaging healthy tissues, and triggering severe side effects [6]. Therefore, the development of novel therapeutic approaches for cancer has consistently been a major focus of scientific research.

Photodynamic therapy (PDT) is a light-activated treatment that employs photosensitizers to produce cytotoxic reactive oxygen species (ROSs) upon irradiation at specific wavelengths, inducing targeted cellular destruction [7-12]. PDT is clinically approved for treating superficial or accessible cancers, including esophageal, endobronchial, skin (e.g., basal cell carcinoma), head and neck, and cholangiocarcinoma, often targeting early-stage lesions or providing palliative care for obstructing tumors [13-15]. Compared with conventional chemotherapy and radiotherapy, PDT demonstrates significant clinical potential in biomedicine due to its advantages, including non-invasiveness, spatiotemporal controllability, low systemic toxicity, broad applicability, absence of drug resistance, and repeatable treatment protocols. Particularly in cancer therapeutics, PDT-generated ROS effectively induces tumor cell apoptosis, disrupts tumor vasculature, and promotes tumor necrosis and sloughing, enabling rapid anticancer effect while circumventing limitations of traditional modalities (surgical resection [16], radiotherapy [17], and chemotherapy

[18]) such as high recurrence rates, severe side effects [19], and drug [20] resistance development [21].

Currently, PDT has been clinically implemented for superficial tumors, including esophageal carcinoma and non-melanoma skin cancers [22]. However, its broader clinical translation is hindered by suboptimal therapeutic outcomes, which mainly arise from three critical limitations: (1) insufficient tumor-targeting specificity of photosensitizers, leading to nonspecific accumulation in healthy tissues and consequent phototoxic side effects; (2) shallow light penetration depth due to tissue scattering and hemoglobin absorption, restricting treatment efficacy to superficial tumors; and (3) oxygen-dependent ROS generation that is inefficient under hypoxic tumor microenvironments (TMEs), thereby requiring higher photosensitizer doses and raising safety concerns.

1.2 Essential components of photodynamic therapy

The Jablonski energy diagram offers a powerful tool to illustrate the photodynamic mechanism (Figure 1). In the ground state (S_0), the photosensitizer molecule's paired electrons reside in low-energy orbitals with opposite spins, forming a stable singlet state. Upon photon absorption, one electron is excited to a higher energy level, generating an unstable singlet excited state (S_1), which exhibits a short lifetime ($\sim 10^{-6}$ s). The unpaired electrons maintain antiparallel spin alignment, and the electron in the S_1 state undergoes relaxation processes, potentially transitioning via intersystem crossing (ISC) to a more stable triplet excited state (T_1) with a significantly prolonged lifetime ($\sim 10^{-2}$ s). The electrons in the T_1 state may undergo radiative decay, emitting phosphorescence. Alternatively, non-radiative decay causes localized temperature elevation, inducing thermoelastic expansion accompanied by acoustic wave generation. Notably, the spin angular momentum conversion during ISC enables T_1 -state electrons to initiate chemical reactions. Depending on the distinct reaction routes, PDT can be mechanistically classified as Type I and Type II pathways [23–25]. Regarding the Type I pathway, the photosensitizer in its triplet-state ($^3PS^*$) interacts with ambient oxygen species or biomolecular substrates (e.g., cell membrane components, proteins, lipids) via proton or electron transfer,

producing radical ions. These initially generated radicals propagate reaction cascades, sequentially generating superoxide anion radicals ($\bullet O_2^-$), hydrogen peroxide (H_2O_2), and the highly reactive hydroxyl radical ($\bullet OH$). These oxidizing species disrupt tumor cell structures, mediating PDT efficacy [26–30]. The type II pathway relies on energy transfer between $^3PS^*$ and ground-state O_2 [31–33]. Due to the matched spin multiplicities, $^3PS^*$ efficiently transfers energy to O_2 , exciting it to singlet oxygen ($^1O_2$) by overcoming an energy gap of ~ 0.98 eV. The generated $^1O_2$, as a potent electrophile, functions as a pivotal cytotoxic agent in PDT [34]. Its extremely short half-life (< 0.04 μs) and limited diffusion radius (< 0.02 μm) in biological environments confine cytotoxic effects to photosensitizer-proximal regions, thereby protecting adjacent healthy tissue to some extent [35–39]. Collectively, these characteristics demonstrated how PDT ingeniously orchestrates the interplay of three essential components: light, oxygen, and photosensitizer [40–42].

1.2.1 Light

Light plays a vital role in the efficient activation of organic photosensitizers for PDT [22,43]. The organic photosensitizers absorb light spanning the visible spectrum to the near-infrared (NIR) range. The NIR spectrum is subdivided into NIR-I (750–1,000 nm), NIR-II (1,000–1,350 nm), and NIR-III (1,350–1,870 nm). Conventional light sources for visible, NIR-I, and NIR-II regions include diode lasers, dye lasers, alexandrite lasers, and neodymium-doped yttrium aluminium garnet (Nd:YAG) lasers. In contrast, longer wavelength generation relies on optical parametric amplification or an oscillation system, where a short-wavelength laser provides pump photons. Notably, longer-wavelength light exhibits a larger penetration depth. For clinical PDT protocols, these light sources are used to directly irradiate the photosensitizer-enriched superficial tumor lesion [44–46]. To improve PDT efficiency, light arrays are customized and applied for treating tumors within superficial tissues. However, the limited tissue penetration depth of these light sources fundamentally restricts effective energy delivery to deeper anatomical regions [47,48]. This challenge is addressed by advanced fiber optic systems featuring losses in light transmission, small volume,

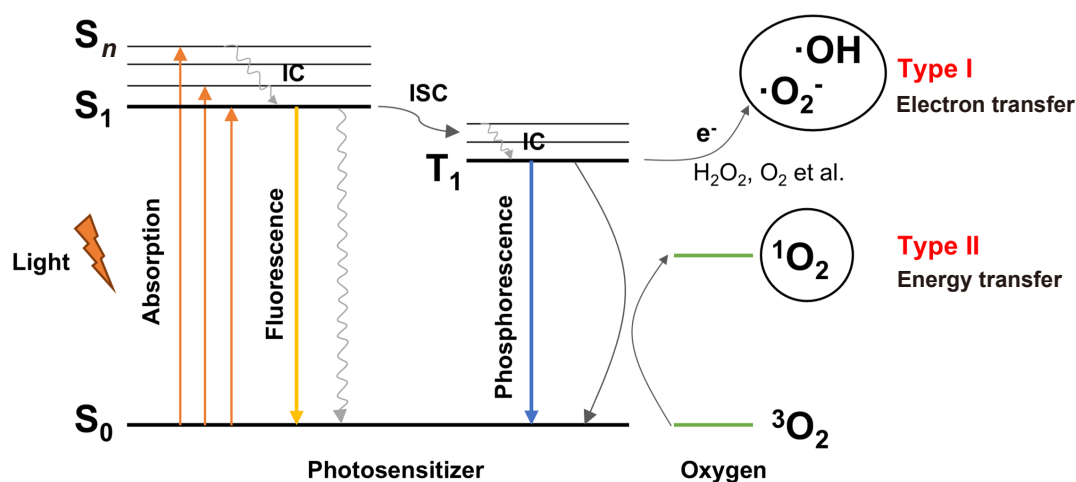


Figure 1 The photochemical reaction pathways in PDT. IC: internal conversion.

and biocompatibility. The multichannel fiber optics or fiber endoscopes are further developed to transmit the light into large and deep-seated tumors [49,50], thereby expanding the therapeutic applicability of PDT from the surface tissue to the deep tissues.

1.2.2 Oxygen environment

In the PDT process, type I and type II photochemical reactions typically coexist, where their relative contributions are modulated by multiple factors, including photosensitizer properties, substrate characteristics, O₂ concentration, and photosensitizer-substrate binding affinity [51]. Notably, the majority of photosensitizers primarily function through the O₂-dependent type II pathway [52], rendering O₂ indispensable for PDT efficacy. However, the hypoxic TME, which arises from structurally and functionally compromised tumor vasculature, severely reduces O₂ delivery efficiency. Irregular vascular distribution and intermittent blood flow establish spatially heterogeneous O₂ gradients throughout the tumor mass, leaving certain regions O₂-deprived. Concurrently, rapid tumor cell proliferation escalates O₂ demand beyond the limited supply capacity of dysfunctional vasculature, exacerbating the imbalance between O₂ supply and consumption and intensifying hypoxia. Consequently, tumor tissues generally exhibit lower overall O₂ levels compared to normal tissues, with pronounced intratumoral heterogeneity: central regions often experience severe hypoxia, while peripheral zones remain relatively oxygenated [53]. Furthermore, the O₂-consuming nature of PDT itself aggravates tumor hypoxia during treatment, thereby substantially limiting the therapeutic efficacy of type II PDT [54–56]. By contrast, type I PDT is less O₂-reliant, which may mitigate hypoxia-induced resistance and expand PDT applicability to deep-seated tumors [57,58]. Overall, the O₂ environment is an essential consideration for tumor PDT.

1.2.3 Photosensitizers

The application of photosensitizers in oncological therapeutics dates back to the 1970s. First-generation photosensitizers, exemplified by hematoporphyrin derivatives (HpD), exhibited satisfactory tolerability profiles and moderate water solubility at clinically relevant doses. However, their clinical adoption was significantly limited by prolonged skin phototoxicity. Subsequent development of second-generation photosensitizers (e.g., chlorin, bacteriochlorin, and phthalocyanine derivatives) addressed these limitations by reducing photosensitivity durations and enhancing tumor selectivity. The convergence of nanotechnology with PDT has catalyzed the development of third-generation photosensitizers [10]. These advanced systems not only enhance photosensitizing efficacy, tumor-targeting specificity, and biocompatibility but also facilitate controlled PS delivery and release. Despite the successful application of these organic photosensitizers in treating specific tumors, the majority of these photosensitizers depend primarily on passive accumulation at tumor sites through the enhanced permeability and retention (EPR) effect. This inefficient passive targeting leads to systemic photosensitizer distribution, with residual photosensitizers in non-target tissues posing risks of off-target phototoxicity upon light activation. To overcome these limitations, much effort has been devoted to conjugating photosensitizers with targeting

moieties (e.g., antibodies, peptides) to improve tumor-specific enrichment [59]. Alternatively, stimuli-responsive photosensitizers have emerged as promising alternatives due to their ability to exhibit distinct photophysical properties pre- and post-activation [3,60]. TME-specific conditions provide a biochemical foundation for the precise activation of photosensitizers, enabling spatially and temporally controlled therapeutic interventions while minimizing collateral damage to healthy tissues [61].

The TME is a complex and dynamic ecosystem that plays a critical role in cancer progression and therapy resistance [62]. Unlike normal tissues, TME exhibits distinct biochemical features, including acidic pH, hypoxia, elevated levels of glutathione (GSH)/H₂O₂, and overexpressed enzymes [63]. These characteristics arise from the high metabolic demand and aberrant proliferation of tumor cells. Specifically, the acidic extracellular pH (6.5–6.9) results from increased glycolysis and poor vascular perfusion, leading to lactate accumulation; Hypoxia, caused by insufficient vascularization, further promotes tumor aggressiveness and resistance to therapies [64]. The overexpression of GSH, a key antioxidant, helps cancer cells evade oxidative damage [65,66]. Meanwhile, the accumulation of H₂O₂ due to oxidative stress provides another target for TME-responsive therapeutic strategies [67]. Additionally, overexpressed enzymes in TME contribute to tumor invasion and metastasis [68]. TME-specific activatable photosensitizers [69], constructed through molecular engineering approaches including but not limited to photoinduced electron transfer (PET) or intramolecular charge transfer (ICT) mechanism, demonstrate negligible phototherapeutic activity in normal tissues but regain PDT functionality upon interaction with tumor-specific biomarkers (e.g., pH, overexpressed redox species, enzymes). This tumor-specific activation mechanism enables targeted tumor ablation while minimizing both systemic toxicity and off-target effects during *in vivo* therapeutic delivery [70,71]. Consequently, compared to conventional “always-on” photosensitizers, TME-activatable photosensitizers demonstrate enhanced safety profiles with diminished collateral damage, thereby advancing the clinical translation of precision medicine [72,73].

This review comprehensively summarizes recent advances in TME-activatable photosensitizers, with a particular focus on their molecular design strategies, activation mechanisms, and PDT applications (Figure 2, Table 1). Significant progress has been made in developing TME-responsive photosensitizers that achieve tumor-selective activation through TME triggers while remaining inactive in healthy tissues. It is hoped that this will guide the future development of TME-activatable photosensitizers from laboratory to clinical.

2. Tumor microenvironment-activatable organic photosensitizers

2.1 pH-activatable organic photosensitizers

The acidic TME (pH 6.5–6.8), resulting from enhanced glycolysis and lactate accumulation, provides a biochemical basis for developing pH-activatable photosensitizers. These smart photosensitizers incorporate proton-responsive groups (e.g., amino or phenolic hydroxyl) that undergo pH-dependent

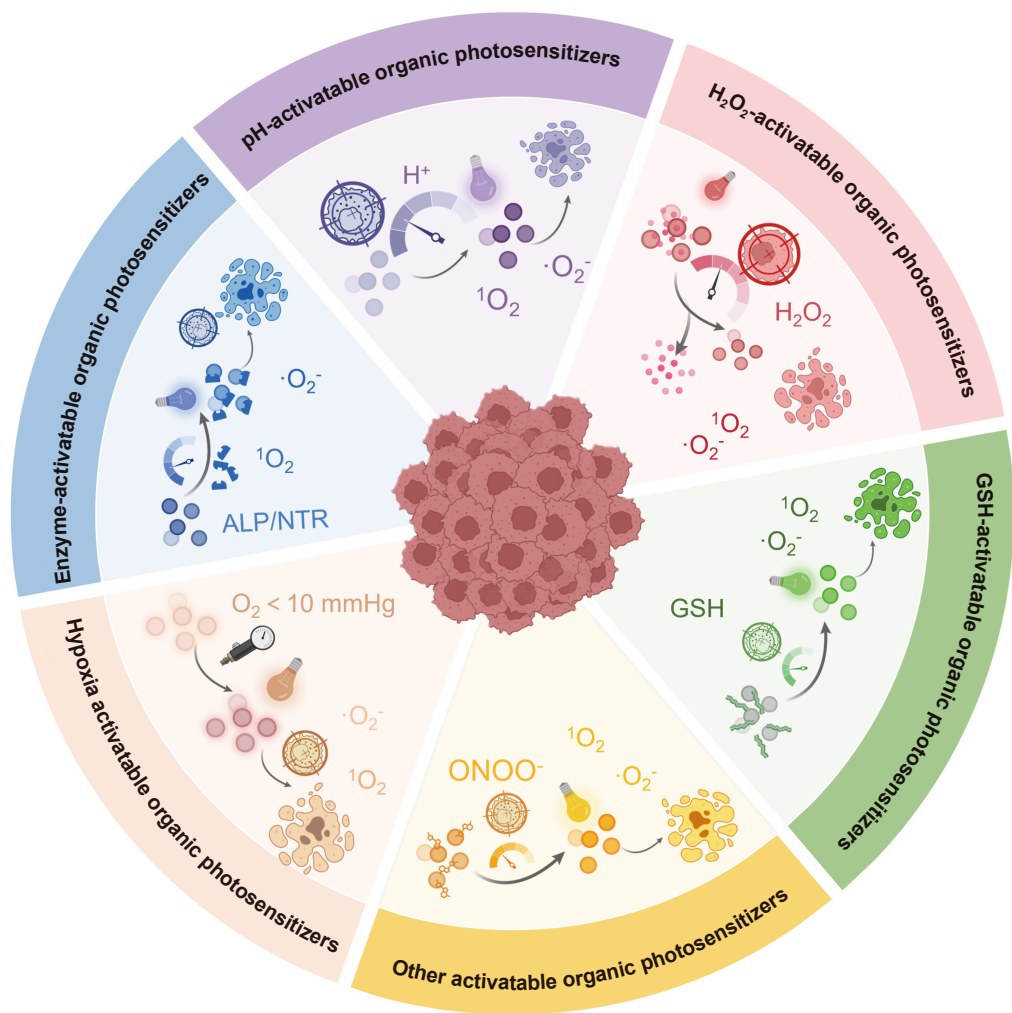


Figure 2 Schematic illustration of tumor microenvironment-activatable organic photosensitizers and their stimuli-responsive activation for theranostic applications.

Table 1 Summary of activatable organic photosensitizers for tumor-specific PDT^{a)}

Photosensiti- zers	Stimulus	$\lambda_{\text{Abs}}/\lambda_{\text{Em}}$ (nm)	Light source (nm)	Light dose (W/cm ²)	Administra- tion mode	Coating material	Dosage	$t_{1/2}$ (h)	Tumor model	Photother- nostic application	Tumor inhibition rate	Ref.
RBT-pH-1	pH	730/1,000– 1,300	808	0.8	IV injection	DSPE-PEG _{5k}	5 mg/kg	N.R.	HepG2	NIR-II FLI/ PDT	–	[74]
BT-TPE	pH	465/680	465	0.2	IV injection	N.R.	1.0 μmol/L	N.R.	HepG2/ 4T1/HeLa	PDT/CDT	–	[75]
LET-I-FA	pH	808/830– 850	808	0.2	IV injection	DSPE-PEG _{2k}	10 μmol/kg	6.35	4T1	FLI/PAI PDT	–	[76]
LET-15	pH	680/710	660	0.5	IV injection	DSPE-PEG _{2k}	50 μL 1 mmol/L	N.R.	4T1	FLI/PDT	81%	[77]
M-TPE-P	Hypoxia	480/620	480	0.05	N.R.	N.R.	50 μmol/L	N.R.	4T1	FLI/PDT	–	[78]
NFh-NTR	Hypoxia	660/690	980/660	0.5/0.2	IV injection	N.R.	300 μmol/L	N.R.	4T1/A549/ HeLa	FLI/PDT	80%	[79]
Pro-I-PSs	Hypoxia	660–680/ 700–720	660	0.5	IV injection	N.R.	100 μL 1 mmol/L	8.2±0.7	MCF-7	FLI/PAI/ PDT	92.1%	[80]
TPFN- AzoCF3	Hypoxia	550/650	550	0.1–0.5	IV injection	DSPE-PEG _{2k}	5 mg/kg	N.R.	4T1/ HeLa	FLI/PDT	–	[81]
TBPPN	GSH	470/680	470	0.01–0.05	IV injection	N.R.	50 μL 2 mg/mL	N.R.	A549	FLI/PDT	–	[82]

(Continued)

Photosensiti- zers	Stimulus	$\lambda_{\text{Abs}}/\lambda_{\text{Em}}$ (nm)	Light source (nm)	Light dose (W/cm ²)	Administra- tion mode	Coating material	Dosage	$t_{1/2}$ (h)	Tumor model	Photother- nostic application	Tumor inhibition rate	Ref.
NBSCEA	GSH	660/710	660	0.1–0.3	IV injection	DSPE-PEG _{2k}	100 μ L 100 μ mol/L	N.R.	4T1	FLI/PDT	70%	[83]
MB-SS-CPT	GSH	660/690	660	0.2	IV injection	N.R.	10 mmol/L	N.R.	HepG2	FLI/PDT	60%	[84]
a-NA-PSNP	GSH	680/720	660	0.1–0.5	IV injection	BSA	200 μ L 40 mg/mL	N.R.	4T1/HeLa /MCF-7	NIR-II FLI/ PDT	–	[85]
Pro-Dye	GSH	672/786	660	N.R.	IV injection	DSPE-PEG _{5k}	200 μ L 0.83 mmol/L	N.R.	4T1	FLI	–	[86]
PBE-AMF	H ₂ O ₂	488/515	488	N.R.	N.R.	N.R.	10 μ mol/L	N.R.	MCF-10A/ MDA-MB- 231/ A4549/ HeLa	FLI	70%	[87]
DCzIBr	H ₂ O ₂	680/950	–	N.R.	IV injection	F-127	N.R.	N.R.	CT26	FLI/CLI/ PDT	70%	[88]
NBS-TK-PTX	ROS	660/720	660	0.3	IV injection	Gox	N.R.	N.R.	4T1/ HEK293T	FLI/PAI/ PDT	98%	[89]
ALPIN-6I	ALP	750/820	730	0.2	IV injection	N.R.	0.4 μ mol/kg	N.R.	HepG2	FLI/PDT	–	[90]
NFh-Br ₁₁	ALP	650/670	980/650	0.5/0.1	IV injection	N.R.	300 μ mol/L	N.R.	HeLa/ A549	FLI/PDT	60%	[91]
Hypocrellin B	Cys	580/650	580	0.1	N.R.	N.R.	N.R.	N.R.	MCF-7/ HeLa/ A549	FLI/PDT	–	[92]
NPA-ONOO –	ONOO [–]	710/820	730	0.15	IV injection	N.R.	20 μ L 500 μ mol/L	N.R.	4T1	FLI/PDT	–	[93]

Note: N.R. means not reported; $t_{1/2}$ represents elimination half-life; IV injection means intravenous injection.

protonation, modulating the PET process to selectively enhance ROS generation in acidic tumors while remaining inert in normal tissues (pH 7.4) [94,95].

Indocyanine green (ICG) is a clinically used cyanine dye for biomedical imaging and therapy. However, most cyanine-based photosensitizers are limited by the low ¹O₂ yield, due to their low energy gaps between the highest occupied molecular orbital (HOMO) and the lowest unoccupied molecular orbital (LUMO). Through integrating pH-sensitive spiro-ring switching units and iodine atoms at the meso-position of the cyanine scaffold, pH-responsive NIR photosensitizer LET-I was synthesized for 808 nm laser-induced PDT (Figure 3a) [76]. Under acidic conditions, LET-I undergoes a structural transition to its ring-open form, which exhibits significantly enhanced photodynamic performance. Its singlet oxygen quantum yield increased to 3.25 times that of ICG, and the fluorescence quantum yield reached 0.28. Furthermore, LET-I was encapsulated using folic acid-modified 1,2-distearoyl-sn-glycero-3-phosphoethanolamine-N-[methoxy(poly-ethylene glycol)-2000] (DSPE-PEG₂₀₀₀-FA) to form tumor-targeting nanoparticles (LET-I-FA), improving specific accumulation at the tumor site. Pharmacokinetic studies further demonstrated that LET-I-FA exhibits a blood circulation half-life ($t_{1/2}$) of 6.35 h. This system enables high-contrast photoacoustic and fluorescence dual-modal imaging and achieves complete tumor ablation under 808 nm laser irradiation at a power density of 0.2 W/cm² through enhanced PDT. This molecular design, which combines the heavy-atom effect, pH-responsive activation, and active tumor targeting, represents a

notable advancement in precision PDT.

Furthermore, taking advantage of the pH-sensitive spiro-ring switching property, a smart pH-activatable NIR photosensitizer hemicyanine, namely LET-15' with mitochondria-targeting activity, was developed for fluorescence imaging-guided tumor PDT (Figure 3b) [77]. Upon reaction with the proton in the TME, ring-closing structured dye (LET-15) was converted to the ring-opening hemicyanine (LET-15') with a cationic indolium unit. Therefore, the ICT process of LET-15' was significantly promoted, with the absorption band redshifted from 400 nm to 700 nm and the fluorescence band peaked at 742 nm, enhanced 3-fold. Moreover, the singlet oxygen generation capability of photosensitizer LET-15' was restored. Owing to the cationic indolium unit in LET-15', nanophotosensitizer nLET-15 fabricated through encapsulating LET-15' with DSPE-PEG₂₀₀₀, enabled mitochondria-targeted precision cancer PDT with fluorescence imaging navigation.

Interconversion between the Rhodamine and its spirolactam form can be triggered through the pH tuning [96]. Taking advantage of this interconversion, pH-responsive NIR-II nano-photosensitizer RBT-pH-1 NPs were designed for PDT (Figure 3c) [74]. To enhance tumor specificity and improve drug delivery efficiency, RBT-pH-1 NPs were prepared through encapsulation of RBT-pH-1 dye with DSPE-mPEG_{5k}. Spirolactam RBT-pH-1, with a pK_a of 6.78, demonstrated optimal activation under acidic conditions, where partial spirolactam ring opening to generate RBT-Br, accompanied by NIR-II fluorescence enhancement and increased ROS production. Under 730 nm irradiation, simulta-

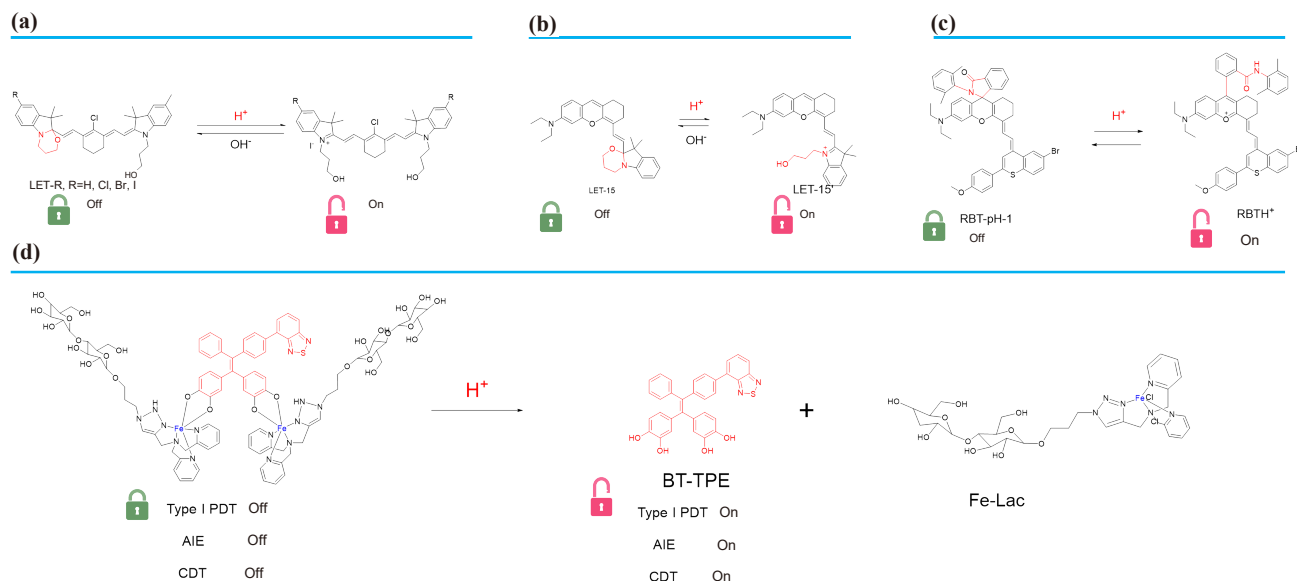


Figure 3 **a.** Chemical structures for pH-responsive LET-R, and its application for activatable FL/PA imaging-guided PDT [76]. **b.** pH-responsive hemicyanine-based system for mitochondria-targeted tumor therapy with NIR fluorescence imaging guidance [77]. **c.** Schematic illustration of reversible pH-responsive NIR-II photosensitizer (RBT-pH-1 NPs) for tumor-specific imaging and PDT [74]. **d.** pH-responsive active targeting nanoparticles with an “on/off” function. Mechanism of PDT combined with chemodynamic therapy for tumor treatment [75].

neous production of both $O_2^{\cdot-}$ and $^1O_2$ was observed, enabling efficient PDT guided by NIR-II fluorescence.

Through Fe^{3+} -coordination between aggregation-induced emission (AIE)-active dye BT-tetraphene (BT-TPE) and lactosylated amine, multifunctional nanophotosensitizer BT-TPE@Fe-Lac was synthesized for pH-activatable synergistic type I PDT and chemodynamic therapy (Figure 3d) [75]. Nanophotosensitizer BT-TPE@Fe-Lac exhibited specific tumor-targeting capability through ASGPR-mediated endocytosis, enhancing cellular uptake in HepG2 cells. Under acidic lysosomal conditions at pH 5.0, nanophotosensitizer BT-TPE@Fe-Lac underwent rapid dissociation to simultaneously release active photosensitizing dye BT-TPE with superoxide radical generation for PDT and Fe^{3+} complexes with hydroxyl radical generation for CDT.

2.2 Hypoxia-activatable organic photosensitizers

Hypoxia, a critical characteristic of the TME, refers to an inadequate oxygen supply in cells or tissues, failing to meet their metabolic demands. This condition is particularly prevalent in solid tumors due to the rapid proliferation of cancer cells, which consumes substantial oxygen, coupled with the irregular and dysfunctional vasculature within the tumor. Hypoxia not only influences the biological behavior of tumor cells but also significantly impacts therapeutic efficacy. Thus, many materials design strategies have been developed to address the hypoxia issue to improve the therapeutic efficacy [97–100]. In recent years, many hypoxia-responsive photosensitizers have been specifically designed to activate under hypoxic conditions or through other mechanisms to generate cytotoxic effects for amplified PDT.

Nitroreductase (NTR), a hypoxia-inducible flavoenzyme, reduces nitroaromatics to cytotoxic hydroxylamines via NADH-

dependent reactions. Tumor hypoxia significantly elevates NTR activity, with expression levels approximately five times higher than those observed in normoxic cells, establishing its dual role as a reliable hypoxia biomarker and promising bio-target for therapy. NTR metabolites modulate lysosomal activity, enabling dual-targeted drug designs where lysosomal delivery precedes NTR activation with enhanced tumor specificity. Current strategies employ pH/NTR-responsive nanosystems for spatially controlled drug release, particularly valuable for developing hypoxia-selective photosensitizers with minimized off-target effects. Through taking TPE as a scaffold, p-nitrobenzyl (PBN) as an NTR-activation unit, and morpholine as a lysosomal targeting group, NTR-activatable photosensitizer M-TPE-P was designed for turn-on fluorescence-guided PDT (Figure 4a) [78]. M-TPE-P had little fluorescence in its initial state but strongly emitted in the presence of NTR, maintaining high fluorescence intensity even in acidic lysosomal environments (pH 4.5–5.0). Photosensitizer M-TPE-P was highly selective and sensitive to NTR and could work effectively over a wide range of pH values. The behavior of intracellular NTR could be monitored by time-dependent fluorescence changes of M-TPE-P. Therefore, Photosensitizer M-TPE-P was not only an NTR-responsive fluorescent probe targeting lysosomes but also a potential photosensitizer for tumor PDT.

Semi-cyanine and cyanine dyes have attracted much attention in the field of functional materials because of their excellent photophysical properties [73,101]. It has a simple synthesis method, a large molar extinction coefficient, and tunable absorption and emission wavelengths ranging from visible light to the NIR region. Through the incorporation of PBN onto semi-cyanine dye NFh-NMe-2, NTR-activatable prodrug NFh-NTR was developed for tumor-specific activation of fluorescence and PDT cancer treatment while minimizing off-target effects (Figure

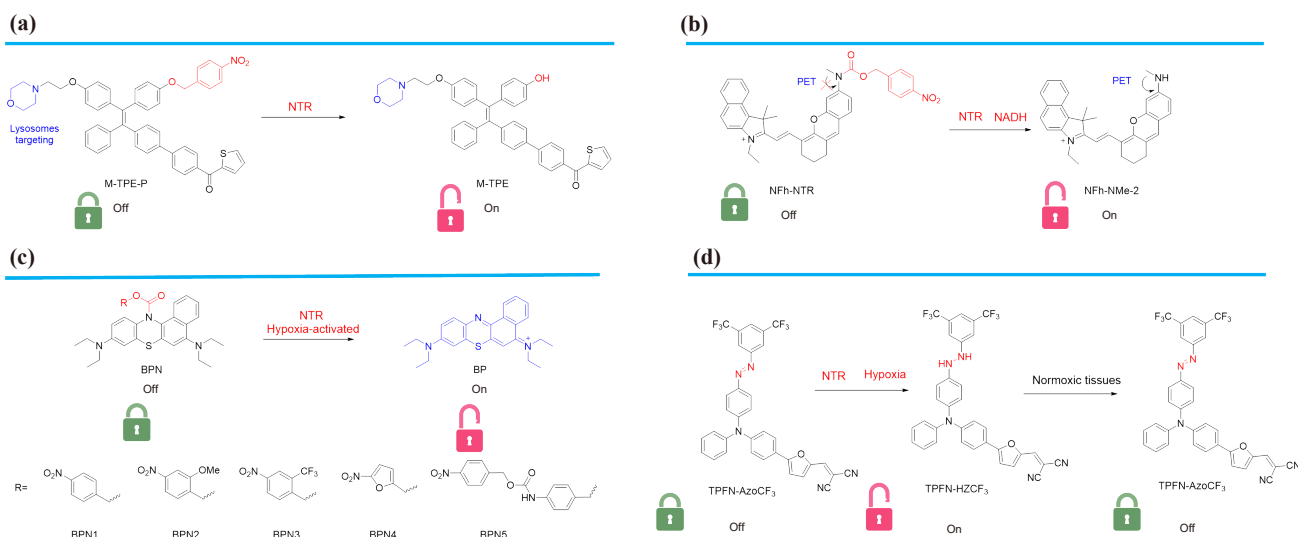


Figure 4 **a.** Chemical structures of photosensitizers M-TPE-P and M-TPE and NTR-activatable PDT [78]. Reproduced with permission. **b.** Chemical structures of NFh-NTR and NFh-NMe-2, and the NTR/NADH-mediated structure conversion [79]. **c.** Schematic illustration of hypoxia-responsive Pro-I-PSs BPN specifically eradicating hypoxic tumors through monopulse laser activation [80]. **d.** Description of the design principle of reversible anoxic-normoxic reactivity type I photosensitizer TPFN-AzoCF₃ [81].

4b) [79]. The inactive prodrug NFh-NTR exhibited minimal ¹O₂ generation, with a fluorescence quantum yield of 1%. However, upon NTR activation, the nitro group in PBN was reduced into the amino group, and unimolecular photosensitizer NFh-NMe-2 was released; thus, the fluorescence emission and the ¹O₂ generation were recovered, owing to the PET effect to facilitate the charge separation state and triplet state generation. Additionally, transient absorption spectroscopy verified exclusive triplet state formation via spin-orbit charge transfer intersystem crossing (SOCT-ISC), ensuring biological inertness in normoxic tissues. Under the 808 nm laser excitation, photosensitizer NFh-NMe-2 was restored to efficiently produce ¹O₂ to destroy tumor cells.

Through covalently conjugating type I photosensitizer benzo-phenothiazine (BP) with different nitroaromatic moieties, a family of hypoxia-activatable pre-photosensitizer BPN was synthesized for fluorescence and photoacoustic imaging-guided oxygen-independent PDT (Figure 4c) [80]. The NTR-specific reduction of totally caged photosensitizer BPN's nitro moiety initiated the controlled release of the active photosensitizer BP, effectively converting the initially photo-inert precursor into a highly potent photosensitizer with remarkable tumor selectivity. BPN's well-caged molecular architecture ensured the complete suppression of photodynamic activity in healthy tissues while enabling rapid activation within hypoxic tumor regions. This activation process simultaneously produced distinctive fluorescence and photoacoustic signals for imaging. When exposed to single-pulse laser irradiation, the activated photosensitizer BP exhibited oxygen-independent type I photodynamic action to produce cytotoxic superoxide and hydroxyl radicals. *In vivo* models demonstrate enhanced ROS generation in hypoxic tumors, with levels reaching 3.2 times those observed under normoxic conditions. Pharmacokinetic evaluation further revealed a favorable blood circulation profile, with a plasma half-life of (8.2±0.7) h, maintaining effective concentration even at 24 h post-injection. This integrated approach of hypoxia-responsive

activation coupled with oxygen-independent type I PDT achieved superior tumor growth suppression of 78% in preclinical studies, dramatically outperforming conventional oxygen-dependent photosensitizers that showed only 35% inhibition.

Through the covalent conjugation of type I photosensitizer TPFN with hypoxia-responsive switch aryl azobenzene AzoCF₃, hypoxia-activatable photosensitizer TPFN-AzoCF₃ was synthesized with quenched photosensitization pre- and post-PDT (Figure 4d) [81]. The TPFN moiety was constructed with a D- π -A architecture, where triphenylamine (TPA) served as the electron donor, furan and carbon-carbon double bonds as the π -conjugation bridge, and dicyanovinyl groups as electron acceptors, enabling efficient ISC and electron transfer capabilities for type I PDT. The aryl azobenzene switch was incorporated with a reversible, responsive mechanism. Under normoxic conditions, the azobenzene moiety remained in its E-configuration, where rapid E-Z photoisomerization effectively quenched the excited state of TPFN and quenched almost all the ROS production (98%) compared to the activated form, allowing photosensitizer TPFN-AzoCF₃ to remain non-toxic in normal tissues pre, post, and during the PDT treatment. Under hypoxia, the azobenzene group was reduced to its corresponding hydrazine derivative mediated by endogenous NTRs, restoring the efficient ROS generation of hydroxyl and superoxide radicals of photosensitizer TPFN. *In vivo* evaluation revealed that TPFN-AzoCF₃ NPs remained completely inactive in normoxic tissues, with no detectable phototoxicity observed. Upon accumulation in hypoxic tumor regions, selective activation of TPFN produced substantial therapeutic effects, demonstrating 71% tumor growth inhibition in xenograft models.

2.3 Glutathione-activatable organic photosensitizers

GSH, frequently overexpressed in cancer cells, helps maintain redox balance by neutralizing ROS. Although this is beneficial

under normal conditions, excessive GSH in tumor cells, particularly in lung cancer, diminishes ROS levels, impairing PDT and promoting therapy resistance. Since GSH primarily reacts with disulfide bonds, strategies targeting these bonds are highly effective. Monitoring and modulating GSH levels during PDT can provide insights into tumor oxidative status while improving therapeutic efficacy by suppressing the tumor's antioxidant defenses.

GSH-responsive NIR photosensitizer TBPPN with AIE effect was developed for GSH level monitoring and fluorescence imaging-guided enhanced PDT for lung cancer (Figure 5a) [82]. An AIE-active photosensitizer, TBPPN, was constructed using TPA as the electron donor and benzothiadiazole (BTD) as the acceptor, exhibiting twisted intramolecular charge transfer (TICT) for enhanced ROS generation. Simultaneously, 2,4-dinitrobenzene (DNB) was incorporated as the trigger group to enable fluorescence turn-on and GSH depletion for enhanced PDT efficacy. A positive charge is conferred to TBPPN by the pyridinium group, which optimizes its hydrophilicity and cellular permeability with improved GSH response. *In vitro* studies demonstrated TBPPN's dual functionality of real-time GSH monitoring with GSH-depletion-enhanced PDT efficacy and subcellular targeting in A549 cells. Subsequent *in vivo* evaluation confirmed significant tumor growth inhibition, positioning TBPPN as a promising theragnostic platform for lung cancer.

Nile Blue and its S- or Se-substituted derivatives serve as efficient NIR photosensitizers with remarkable type I PDT efficacy under hypoxia through enhanced electron-transfer-mediated ROS generation [102]. Through a disulfide bond to covalently conjugate the S-substituted Nile Blue photosensitizer and chemotherapy drug nitrogen mustard, an innovative GSH-responsive prodrug, NBSCEA, was designed for fluorescence

imaging-guided combinational chemotherapy and PDT (Figure 5b) [83]. NBSCEA was coated with amphiphilic DSPE-PEG₂₀₀₀ to fabricate NBSCEA@D NPs to improve the chemo-drug delivery efficiency and protect the photosensitizer NBSCEA from being activated prematurely. In normal tissues, NBSCEA maintained an inactive state through ICT-induced fluorescence quenching and PDT deactivation, thereby minimizing off-target effects on healthy tissues. Upon accumulation in the tumor, overexpressed intracellular GSH cleaved the disulfide bonds in NBSCEA, resulting in the controlled release of the active components of nitrogen mustard and the photosensitizer NBS-NH. The unimolecular photosensitizer NBS-NH demonstrated light-triggered ROS generation capability upon 660 nm irradiation, while the concurrently released nitrogen mustard exerted complementary cytotoxic effects. This dual-action mechanism enabled selective tumor cell eradication through combinational chemotherapy and PDT, with spatial control ensured by the tumor-specific GSH activation. The tumor-selective activation mechanism of NBSCEA@D NPs was further validated through *in vivo* phototheranostic studies. Fluorescence imaging confirmed the excellent tumor-targeting capability and high tumor-to-background contrast of NBSCEA@D NPs.

Methylene blue (MB) with an excitation wavelength of 660 nm and an emission wavelength of 690 nm, is also a well-recognized clinical dye for lymph node localization in surgery, diagnosis of breast and head and neck cancer, and root canal PDT [32]. Through attaching photosensitizer MB to chemo-drug CPT via a disulfide bond, a composite photosensitizer MB-SS-CPT was developed for GSH-activatable PDT (Figure 5c) [84]. MB-SS-CPT showed excellent fluorescence response and selectivity in the detection of GSH, and demonstrated good fluorescence imaging capabilities upon GSH activation in breast cancer cells and

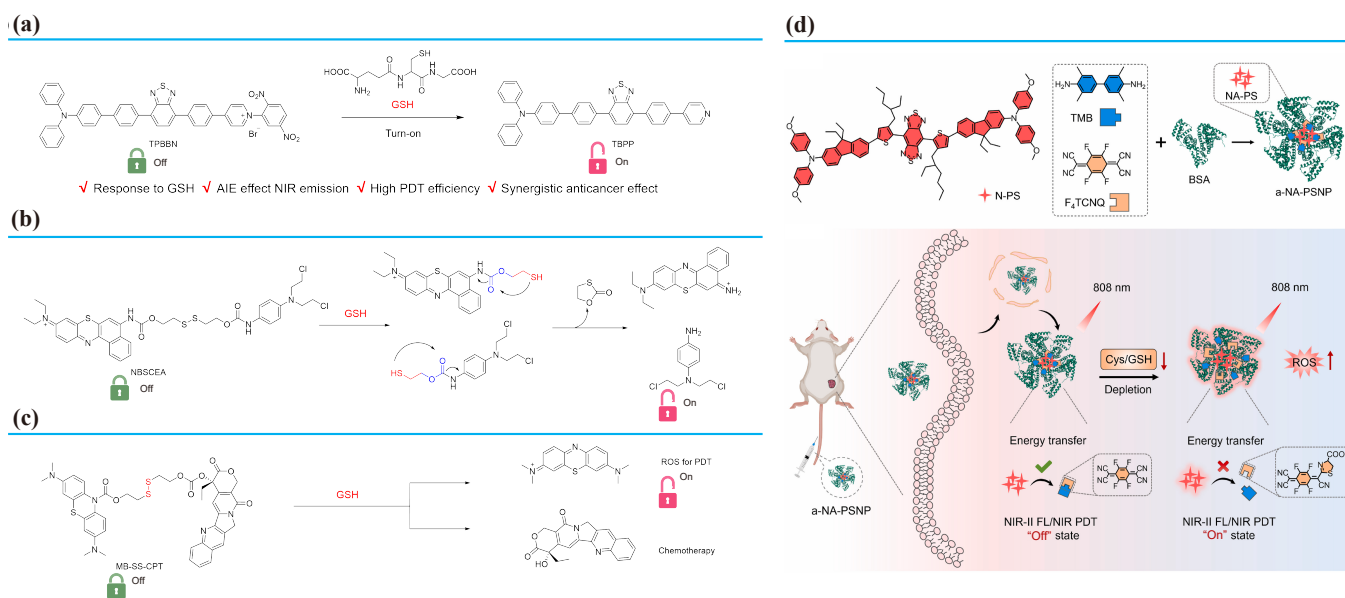


Figure 5 a. Structure and schematic diagram of GSH-responsive photosensitizer TBPPN for cancer therapy [82]. b. The principle and process of the preparation of NBSCEA@D and NBSCEA@D are activated by GSH for cancer therapy [83]. c. Structure and schematic diagram of GSH-responsive photosensitizer MB-SS-CPT for cancer therapy [84]. d. Schematic diagram of the a-NA-PSNP structure; when FL and a-NA-PSNP accumulate at the tumor site, their photosensitivity will be activated due to the Cysteine (Cys)/GSH produced by tumor cells, thereby effectively imaging and ablating the tumor, achieving precise and efficient PDT [85].

esophageal cancer cells. More importantly, the performance of MB-SS-CPT in fluorescence imaging and PDT was comparable to that of pure MB, demonstrating its application potential in these areas. Because both MB and CPT were approved clinical drugs, MB-SS-CPT demonstrated strong competitiveness in clinical translation.

Charge transfer complexes (CTCs) emerge through electron donor-acceptor interactions, facilitating electron delocalization that induces a significant absorption redshift. Precise modulation of the donor's HOMO and acceptor's LUMO energy levels enables the development of efficient NIR-II absorbing CTC for photothermal therapy (PTT) and PDT [103]. Through incorporating AIE photosensitizer with CTC within bovine serum albumin (BSA), Cys/GSH-activatable NIR nanophotosensitizer a-NA-PSNP was developed for 808 nm laser-triggered NIR-II fluorescence imaging and PDT (Figure 5d) [85]. Due to the hydrophobic cavity of BSA, it was employed as a carrier matrix to stabilize both the AIE-active N-PS dye aggregates and CTC. Specifically, 3,3',5,5'-tetramethylbenzidine (TMB) and 2,3,5,6-tetrafluoro-7,7,8,8-tetracyanoquinodimethane (F_4TCNQ) were integrated as electron donor-acceptor pairs to form CTC, which effectively quenched both NIR-II fluorescence and ROS generation of N-PS photosensitizer in physiological conditions. This CTC-mediated quenching mechanism ensured systemic safety by maintaining nanophotosensitizer a-NA-PSNP in an inactive state during circulation. However, in the TME, elevated thiol concentrations triggered the conversion of F_4TCNQ to mono-thiol derivatives, disrupting CTC and restoring both NIR-II fluorescence ($\Phi_F=2.32\%$) for imaging and ROS production ($\Phi_A=4.47\%$) for targeted PDT. Importantly, the nanophotosensitizer a-NA-PSNP demonstrated self-amplifying PDT effects through GSH depletion, further enhancing treatment efficacy with high therapeutic precision.

Boron-dipyrromethene (BODIPY) fluorophores exhibit excellent optical properties, including high fluorescence quantum yields, large molar absorption coefficients, and remarkable stability, making them attractive for biomedical applications [104–106]. Through incorporating dinitrobenzene sulfonate (DNBS) as a GSH-responsive quenching moiety, NIR BODIPY-based fluorescent probe Pro-Dye was developed for tumor PDT [86]. With the functionalization of the DNBS group, the fluorescence of Pro-Dye was initially suppressed through ICT. Upon exposure to elevated concentrations of GSH (2–10 mM), the DNBS moiety underwent nucleophilic aromatic substitution, releasing the active BODIPY fluorophore and restoring NIR emission with 33-fold enhancement. The activation process demonstrated high selectivity, with minimal fluorescence observed in normal cells (HUVECs) and GSH-depleted 4T1 cells (pretreated with L-buthionine sulfoximine (BSO)). *In vivo* evaluation confirmed tumor-specific accumulation of Pro-Dye NPs, achieving a tumor-to-background ratio of 8.3:1 compared to conventional, always-on probes. Furthermore, the GSH-activation mechanism was further verified by an 82% reduction in fluorescence intensity in BSO-pretreated tumors.

2.4 H_2O_2 -activatable organic photosensitizers

ROs, particularly H_2O_2 , are natural byproducts of cellular

aerobic metabolism that exhibit unique biological properties due to their uncharged nature and moderate reactivity, including an extended half-life and capacity for long-distance intracellular diffusion, enabling H_2O_2 to function as a key signaling molecule regulating diverse cellular processes ranging from proliferation and apoptosis to inflammatory responses [107]. While in cancer biology, malignant cells demonstrate significantly elevated H_2O_2 generation due to hyperactive metabolic demands and mitochondrial dysfunction, with this oxidative stress further exacerbated by impaired antioxidant defense systems, resulting in pathological H_2O_2 accumulation that establishes a biochemical hallmark of malignancy exploitable for targeted therapeutic interventions.

An H_2O_2 -activatable theranostic prodrug, PBE-AMF, was synthesized by conjugating amonafide (AMF) to a phenylboronate ester (PBE) trigger (Figure 6a) [87]. When the prodrug PBE-AMF encountered H_2O_2 (50–100 $\mu\text{mol/L}$), the fluorescent AMF molecules were released by oxidative cleavage of the PBE moiety. This activation process demonstrated concentration-dependent kinetics, with maximal therapeutic efficacy observed in high- H_2O_2 MDA-MB-231 breast cancer cells. The liberated AMF exerted dual functionality through simultaneously inducing DNA damage and restoring fluorescence signals for treatment monitoring. Moreover, prodrug PBA-AMF was synthesized through the replacement of PBE with phenylboronic acid (PBA), exhibiting enhanced stability and tumor-selective accumulation via sialic acid receptor-mediated uptake. The design capitalizes on tumor-selective H_2O_2 elevation while incorporating real-time treatment monitoring capabilities through the AMF fluorophore's intrinsic optical properties.

Through the incorporation of diphenylamine as an electron donor and a bromine atom to endow a heavy atom effect, type I photosensitizer DCzIBr was developed with improved NIR emission for enhanced PDT (Figure 6b) [88]. DCzIBr was co-encapsulated with bis[2,4,5-trichloro-6-(pentylloxycarbonyl) phenyl] oxalate (CPPO) with amphiphilic F-127 to form DCzIBr-C NPs, which could be selectively activated in the TME with H_2O_2 concentrations of 50–100 $\mu\text{mol/L}$. Upon reaction with H_2O_2 to oxidatively decompose CPPO, the photosensitive moiety DCzIBr was subsequently excited via chemically initiated electron exchange luminescence (CIEEL). This process generated sustained NIR fluorescence emission and continuous $O_2^{\cdot-}$ production without requiring external light irradiation. *In vivo* experiments achieved a tumor growth inhibition rate of 75%, which came from the optimized molecular structure for efficient type I ROS generation, H_2O_2 -responsive activation, and energy-matched components enabling light-free operation through chemiexcitation.

The thioketal (TK) unit is a ROS-responsive group, and it has been widely embedded into the polymers for controllable drug delivery. Jiang et al. [89] designed a ROS-activatable heterodimeric prodrug-loaded enzyme assembly as a nanophotosensitizer NTP@GOx, for self-boosting programmable release of multiple therapeutic agents for combinational tumor therapy (Figure 4c). Through covalently conjugating the phenothiazinium photosensitizer NBS and the chemotherapeutic drug paclitaxel with the TK unit to prepare the prodrug NBS-TK-PTX, it was further bound with the glucose oxidase for the fabrication of ROS-activatable nanophotosensitizer NTP@GOx.

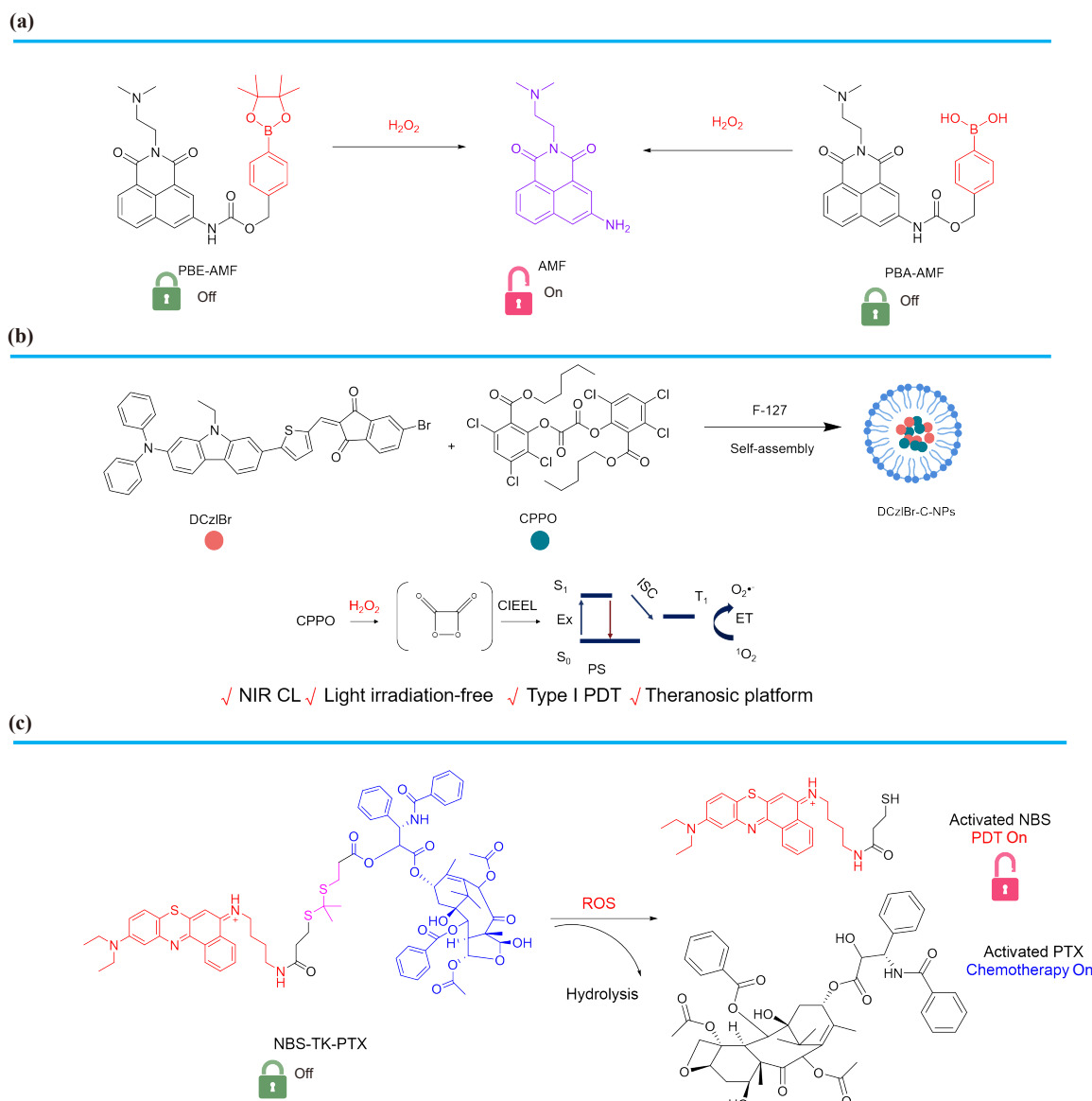


Figure 6 **a.** AMF-based H_2O_2 -activatable pre-treatment drug designed to identify and eradicate cancer cells with high H_2O_2 levels [87]. **b.** Preparation of DCzIBr-C NPs and mechanism of PDT [88]. **c.** ROS-activatable heterodimer prodrug NBS-TK-PTX that can self-amplify and programmably release multiple tumor therapeutic drugs [89].

Upon accumulation in the tumor tissues, nanophotosensitizer NTP@GOx was first decomposed after reacting with the weak acid to release GOx, which could subsequently consume glucose and generate acid in turn to promote the dissociation of NTP@GOx. Meanwhile, after breaking the TK linker with overexpressed H_2O_2 , as released prodrug NBS-TK-PTX, which could be activated to release the chemodrug PTX for chemotherapy and photosensitizer NBS for type I PDT. This smart, activatable heterodimeric Prodrug-Enzyme nanoassembly provided insight for multimodal synergistic cancer therapy.

Furthermore, a dual-key organic photosensitizer BX-B was designed for PDT [108]. Both H_2O_2 and viscosity were employed to co-activate photosensitizer BX-B for PDT and PTT, when exposed to a 600 nm laser (1.0 W/cm^2). Besides, after co-activation, two fluorescence bands in the NIR-I region, peaked at 810 nm, and NIR-II region, peaked at 945 nm, came out, which

could be used for fluorescence imaging to monitor the phototherapeutic efficacy in real-time.

2.5 Enzyme-activatable organic photosensitizers

Enzyme-activatable photosensitizers (EAPs) leverage tumor-over-expressed enzymes (e.g., MMPs, cathepsins, β -glucosidase) for targeted PDT [109]. These photosensitizers remain inert until specific enzymatic cleavage (e.g., MMP-2 hydrolyzing GPLGVR peptides) releases active photosensitizers, enabling tumor-selective ROS generation.

Alkaline phosphatase (ALP) is a phosphatase that can significantly hydrolyze phosphate groups. It is reported to be overexpressed in lung cancer, cervical cancer, and other tumor cells. Using the enzyme's substrate specificity, a series of NIR Photosensitizers has been designed and synthesized for tumor

phototheranostics. Through decorating an ALP-cleavable phosphate group and a hydrophilic moiety onto the iodine-substituted semi-cyanine dye, ALP-activatable photosensitizer ALPIN-6I was developed for tumor PDT (Figure 7a) [90]. The ALP-responsive phosphate group could trigger sequential transformations beginning with enzymatic hydrolysis that induced an over 100-fold increase in hydrophobicity. This was followed by quinone methide-mediated protein conjugation, demonstrating binding efficiency exceeding 90% for enhanced cellular retention, ultimately restoring photosensitization capability with a $^1\text{O}_2$ quantum yield of 0.42. This activation cascade demonstrated exceptional specificity for ALP-overexpressed tumors, showing more than 2,000-fold enhancement that enabled simultaneous imaging and PDT. The innovative “1-to-3” design paradigm successfully integrated enzymatic activation with multiple synergistic mechanisms to achieve targeted tumor theranostics.

To overcome the limited tissue penetration depth of conventional PDT, an ALP-activatable NIR hemi-cyanine photosensitizer NFh-ALP was developed for 808 nm laser-triggered frequency upconversion luminescence guided PDT (Figure 7b) [91]. The molecular design incorporated a phosphate group at the hydroxyl position of NFh-Br₁₁, creating an enzyme-responsive prodrug NFh-ALP that remained biologically inert until ALP-mediated hydrolysis to release the active photosensitizer NFh-Br₁₁. This innovative approach combined deep tissue penetration capability with tumor-specific activation, as the phosphate group served as both an ALP recognition site and a solubility modulator, ensuring selective activation only in ALP-overexpressing TME. The activated NFh-Br₁₁ demonstrated enhanced $^1\text{O}_2$ generation and potent tumor cell apoptosis induction while maintaining

minimal off-target effects in normal tissues. The NFh-ALP design represented a significant advancement in precision theranostics by simultaneously addressing the critical challenges of tissue penetration depth, tumor selectivity, and PDT efficacy.

Cys proteases, including cathepsin B, are lysosomal enzymes involved in protein degradation. In cancer, their overexpression promotes tumor invasion and metastasis through extracellular matrix remodeling. This elevated activity has been exploited to develop tumor-activatable photosensitizers for targeted PDT. Through functionalization of hypocrellin B with Cys-reactive acryloyl groups, an L-Cys-responsive photosensitizer was designed for 660 nm-triggered PDT [92]. After reaction with Cys, the acryloyl group was cut to release the active form of hypocrellin B photosensitizer, restoring its highly efficient photosensitization ability, demonstrating selective and significant cytotoxicity to HeLa and A549 cells overexpressing Cys after light irradiation at low micromolar concentrations.

2.6 Others

Tumor tissues exhibit significantly elevated peroxynitrite (ONOO^-) levels compared to their normal counterparts. The metabolic activity of tumor cells, coupled with a chronic inflammatory microenvironment, disrupted antioxidant defenses and abnormal vascular networks, creating conditions favoring ROS and reactive nitrogen species generation. These pathological alterations are further exacerbated by hypoxia-induced changes in enzyme expression profiles and immune cell infiltration, collectively driving increased production of superoxide anions and nitric oxide. The subsequent rapid reaction between these two

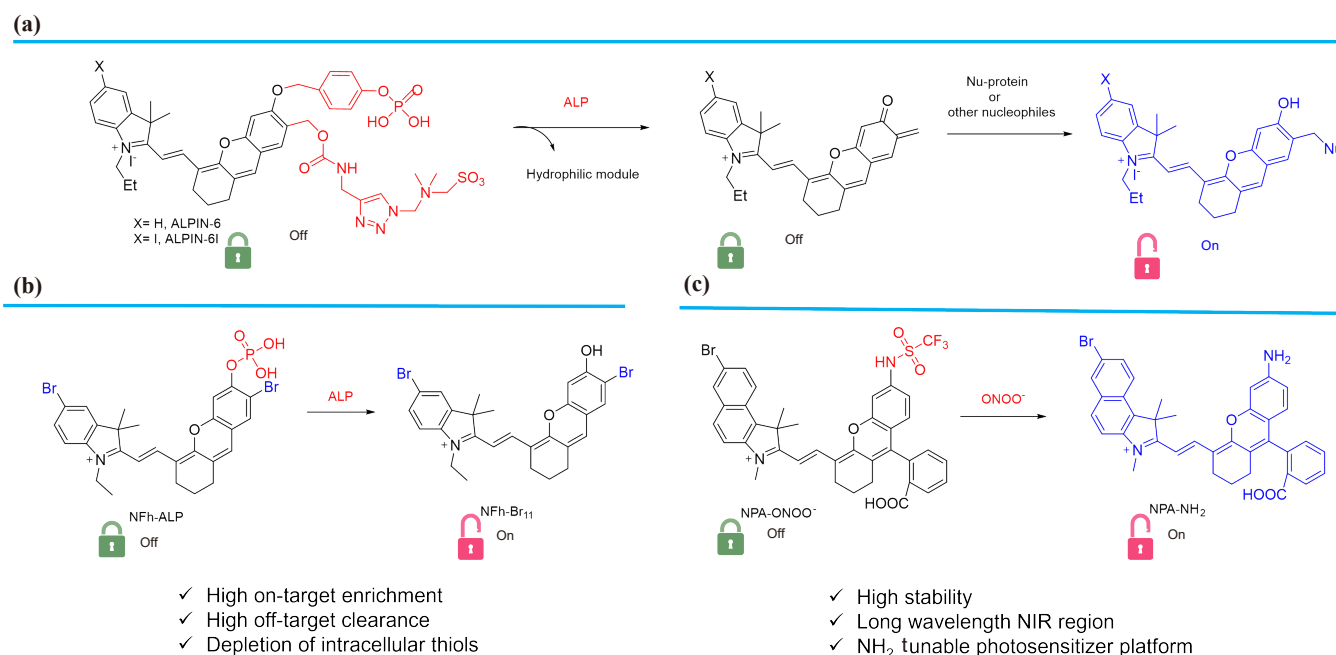


Figure 7 a. Schematic diagram of ALP-activatable NIR fluorescent probe or photosensitizer based on “1–3” multi-effect design. The chemical structure of ALPIN-6 and ALPIN-6I, and the activation and immobilization promoted by ALP are proposed. The mechanism by which ALPIN-6I is activated as a photosensitizer for PDT to treat ALP-overexpressing tumor cells was proposed [90]. b. Chemical structures of NFh-ALP and NFh-Br₁₁, and the ALP-mediated structure conversion [91]. c. Schematic diagram of ONOO^- -activatable photosensitizers treating mammary tumors in mice with PDT [93].

reactive species leads to substantial ONOO[−] accumulation within the tumor niche. This elevated ONOO[−] burden exerts multifaceted effects, directly impacting tumor cell behavior while simultaneously modifying the surrounding stromal microenvironment. Through mechanisms involving protein nitration, lipid peroxidation, and redox signaling modulation, peroxynitrite not only contributes to genomic instability and malignant progression but also facilitates the establishment of an immunosuppressive tumor milieu, ultimately accelerating tumor development and metastatic dissemination.

Through employing trifluoromethyl sulfonamide as the ONOO[−] recognition site, peroxynitrite-activatable photosensitizer NPA-ONOO[−] was developed for fluorescence imaging and breast cancer PDT (Figure 7c) [93]. Upon introducing the ONOO[−]-sensitive group trifluoromethyl sulfonamide onto the photosensitizer NIR-NH₂-Ben, well-caged photosensitizer NPA-ONOO[−] was synthesized with good mitochondria-targeting performance. Upon accumulation in the tumor cells with subsequent 660 nm photoirradiation, ONOO[−] could recognize the trifluoromethyl sulfonamide group and react to produce the active photosensitizer NIR-NH₂-Ben, which then emitted abundant fluorescence for imaging and generated sufficient ¹O₂ to inhibit the tumor growth of the 4T1 tumor-bearing mouse model.

Abnormal production of hydrogen sulfide (H₂S) poses significant health risks. Under 660 nm visible laser irradiation with 50 mW/cm² for 3 min, ZNNPs@FA undergo nucleophilic substitution reaction with H₂S for NIR conversion and ratiometric photoacoustic, which caused the generation of ROS for PDT. The ZNNPs@FA effectively deplete mitochondrial H₂S in tumor cells, leading to a significant reduction in ATP levels and severe mitochondrial dysfunction [46]. Notably, this photosensitizer system also demonstrated potent suppression of colorectal tumor growth in murine models.

Despite the significant advances of TME-activated strategies in enabling selective PDT, a fundamental challenge remains unresolved in the general design of activatable photosensitizers: cross-reactivity among different stimuli, which substantially undermines targeting specificity. For instance, boronic ester- or pinacol boronate-based photosensitizers are widely exploited as H₂O₂-responsive systems, while o-phenylenediamine motifs are commonly employed for ONOO[−] detection and activation. However, both approaches suffer from poor chemoselectivity. Boronic ester-derived probes, in addition to reacting with H₂O₂, are also highly susceptible to nucleophilic substitution and oxidative cleavage in the presence of elevated ONOO[−], resulting in unintended activation, false-positive readouts, and off-target phototoxicity. Conversely, ONOO[−]-sensitive scaffolds may exhibit compromised stability under excessive ROS stress, thereby limiting their reliability. This lack of precise selectivity is particularly concerning in the TME, where H₂O₂ and ONOO[−] are frequently co-upregulated and heterogeneously distributed. Such overlap severely complicates the accurate recognition of individual biomarkers, diminishes the fidelity of molecular activation, and ultimately constrains the precision of PDT. Therefore, overcoming cross-reactivity to achieve orthogonal and unambiguous stimulus-response behavior represents a critical bottleneck for the clinical translation of activatable photosensitizers.

3. Conclusion and future perspectives

This review systematically summarizes recent advances in TME-activatable organic photosensitizers for precision PDT. By exploiting unique TME features of acidic pH, hypoxia, elevated GSH/ROS, and enzyme overexpression, these smart photosensitizers achieve tumor-specific activation while minimizing off-target effects. Various molecular design strategies have been developed through employing TME features as bio-targets for stimuli-responsive photosensitizers. These activatable photosensitizers are also integrated for combined therapies, demonstrating enhanced therapeutic efficacy and reduced side effects in preclinical studies. While significant progress has been made, further optimization of activation specificity, photophysical properties, and biocompatibility is needed for clinical translation. Overall, TME-activatable photosensitizers represent a promising approach for targeted cancer therapy, offering new opportunities for precision medicine.

(1) To develop smart photosensitizers through artificial intelligence by integrating molecular design optimization strategies [110]. Utilizing deep generative models and reinforcement learning, AI enables precise modulation of key photophysical properties, including absorption wavelength, singlet oxygen quantum yield, and biological compatibility. A pivotal direction lies in leveraging these computational approaches to rationally design photosensitizers excitable by longer-wavelength light (e.g., within the NIR-II window), which remains underexplored yet is critical for achieving deeper tissue penetration. These AI-driven strategies accelerate the de novo creation of novel photodynamic agents with tailored functionalities, moving beyond conventional trial-and-error methods. For instance, generative adversarial networks have been employed to design porphyrin derivatives with optimized absorption profiles [111], while reinforcement learning frameworks facilitate adaptive treatment planning. By integrating predictive modeling of photophysical behavior and physiological environments, AI offers a transformative platform for developing next-generation photosensitizers with enhanced penetration and therapeutic precision.

(2) To develop next-generation TME-responsive systems exhibiting enhanced specificity through dual-key or cascade activation mechanisms. Future photosensitizer architectures should be precisely engineered to respond to multiple characteristic TME features, such as the concurrent presence of acidic pH, elevated GSH, specific enzymes, or abnormal metabolite levels, in a logic-gated manner. Only when two or more stimuli are detected simultaneously will the photosensitizer undergo full activation, thereby drastically reducing off-target effects and maximizing tumor-selective therapeutic action. This approach moves beyond conventional single-key systems, which are prone to cross-reactivity and false activation in non-malignant pathological tissues. Recent pioneering work, including the development of a dual lock-and-key photosensitizer responsive to both GSH and pH, has demonstrated the feasibility and enhanced precision of such strategies [112].

(3) To advance the clinical translation of photodynamic therapy through an integrated approach combining large animal models, organ-on-a-chip systems, and detailed pharmacokinetic studies. While mouse models offer initial insights, their predictive value for human outcomes remains limited. Organ-on-a-chip [113]

platforms provide a human-relevant microenvironment to study photosensitizer penetration and activation under controlled conditions. Large animal models, particularly pigs [114], enable a comprehensive assessment of systemic pharmacokinetics, specifically circulation half-life, biodistribution, and metabolic clearance, thereby bridging a critical gap between conventional preclinical studies and clinical applications. Together, these approaches form a multi-level validation framework that enhances the predictive power of translational research and supports the rational development of clinically effective photodynamic therapies.

Compliance and ethics The author(s) declare that they have no conflict of interest.

Authors' contributions Shu Qin: conceptualization, formal analysis, investigation, writing – original draft. Yurong Liu: investigation, writing – original draft, writing – review and editing. Jinjun Shao: funding acquisition, writing – original draft, writing – review and editing. Zewei Luo: writing – original draft, writing – review and editing. Peng Chen: writing – original draft, writing – review and editing. Peng Huang: funding acquisition, writing – original draft, writing – review and editing. Xiaochen Dong: funding acquisition, writing – original draft, writing – review and editing.

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