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Recent advances of cyanine dyes in tumor theranostics: molecular modification, delivery strategies, and synergistic mechanisms

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The phototheranostic system has garnered significant attention due to its dual functionality of combining imaging and treatment. Moreover, while achieving non-invasive, real-time imaging and precise spatiotemporal controlled treatment, it also maintains low toxicity to normal tissues. Among the phototheranostic systems, cyanine dyes are a kind of ideal near-infrared (NIR) photosensitizer for phototheranostics. However, challenges still remain in terms of photostability, tumor selectivity, and diagnostic and treatment efficiency. This review summarizes advances of cyanine dye-based phototheranostics in tumor diagnosis and treatment over the past five years, with a focus on molecular modifications and nanostructure construction, delivery strategies, and synergistic mechanisms in integrated platforms for enhancing functionality. The review also looks ahead to future opportunities and challenges of cyanine dyes in tumor theranostics.

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1. Introduction

Malignant tumors, characterized by invasive pathology originating from abnormal cell proliferation,¹ possess the ability to infiltrate adjacent tissues and metastasize *via* hematogenous^{2,3} or lymphatic pathways.⁴ As a result, they represent one of the most significant threats to global health.⁵ Clinically, traditional diagnostic and therapeutic approaches are often administered separately, which complicates precise tumor localization, real-time treatment monitoring, and accurate prognosis assessment.⁶ In the era of personalized oncology, researchers are redefining cancer management through integrated theranostics.^{7,8} This precision medicine strategy synergizes diagnostics and therapeutics, allowing real-time monitoring of treatment progression, timely efficacy evaluation, and dynamic adjustment of therapeutic regimens.^{9,10}

With advances in materials science and technology, various theranostic platforms activated by light,^{11,12} ultrasound,¹³ magnetic field^{14,15} or radiation^{16,17} have been developed. Among them, phototherapeutic systems that combine diagnostic imaging, particularly fluorescence and photoacoustic imaging (PAI), with phototherapy have garnered widespread attention for their multifunctional capabilities. In imaging diagnostics,

fluorescence imaging (FLI) not only enables non-invasive, real-time, and high-resolution imaging,⁶ but also simultaneously captures molecular signatures of tumor metabolism and microstructure.¹⁸ Especially, photosensitizers activated by near-infrared (NIR) light can fully leverage the excellent tissue penetration capabilities of the light,^{19,20} enabling diagnosis and treatment of deep-seated tumors. In contrast, PAI detects a phonon after light excitation, exceeding the optical diffusion limit and offering deeper tissue penetration.²¹ In terms of therapy, spatiotemporal control of light enables precise localized treatment, thereby maximizing therapeutic efficacy while minimizing systemic toxicity.²²

An ideal phototherapeutic agent must be able to differentiate tumors from healthy tissues through active or passive targeting. It also needs to generate detectable signals for diagnosis and release cytotoxic payloads for tumor ablation. Among them, cyanine dyes have come into our sight and garnered significant attention. They are a class of structurally tunable compounds composed of nitrogen-containing heterocycles linked by an odd-numbered polymethine chain terminating in a cationic nitrogen atom.⁵ As a family of classical organic fluorescent dyes, cyanine dyes exhibit unique characteristics such as high molar absorption coefficients and narrow absorption/emission bands in the NIR region.^{23,24} Through strategic modifications of the chain length and the introduction of electron-donating or electron-withdrawing substituents, their absorption and emission spectra can be precisely adjusted.^{25–31} Additionally, the structural versatility of cyanine dyes enables flexible molecular engineering, supporting their decades-long biomedical application.^{32–36} A typical clinical validation of this dye category is indocyanine green (ICG), the first NIR fluorescent dye

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approved by the US Food and Drug Administration (FDA).³⁷ In recent years, more and more properties of cyanine dyes have been discovered. Among the most important findings is that cyanine molecules can self-assemble into supramolecular structures such as H-aggregates or J-aggregates in different solutions and at different concentrations.^{38,39} H-aggregates are arranged in parallel between molecules, exhibiting a blue shift in absorption peaks, while J-aggregates adopt a head-to-tail arrangement, showing a red shift in absorption peaks. By modulating the solution concentration, temperature, and solvent properties, the formation of these aggregates can be precisely controlled, enabling specific optical properties in different environments. Notably, cyanine aggregates demonstrate improved photostability and aggregation-induced phototherapy effects, making them highly promising agents for photothermal therapy (PTT) or photodynamic therapy (PDT).³⁸ Despite ongoing challenges in tumor selectivity, theranostic efficiency, and photostability, cyanine dyes continue to be actively investigated even after more than 60 years of use.

The structure characteristics, synthetic methods, optical properties, organic and inorganic nano-encapsulation, and biological applications of cyanine dyes for phototheranostics have been summarized in several reviews.^{40–45} In this review, we focus on the advances of cyanine dyes in tumor theranostics over the past five years, presenting a new perspective that highlights strategies for enhancing tumor targeting and improving diagnostic and therapeutic functionality. Specifically, we emphasize delivery strategies based on biological modification and discuss the underlying mechanisms that enhance diagnostic and therapeutic performance (Fig. 1). The review concludes with an outlook on the opportunities and challenges associated with cyanine dyes in tumor theranostics.

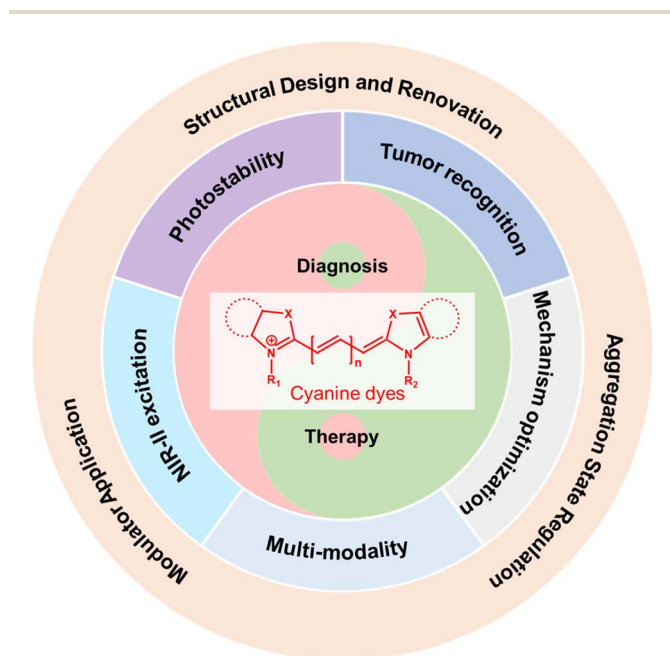


Fig. 1 Scheme of construction strategy for cyanine dye-based theranostics.

2. Tumor targeting and specific response theranostics

Effective tumor site identification and accumulation are prerequisites for the development of integrated theranostic agents. Although cyanine dyes possess inherent tumor-targeting properties, their accumulation efficiency remains insufficient to achieve precise tumor localization. To overcome this limitation, researchers have engineered cyanine dyes through targeted group modifications,^{46,47} supramolecular assembly,⁴⁸ or nanocarrier encapsulation⁴⁹ to enhance their specificity for tumor recognition and accumulation. Additionally, the incorporation of stimulus-responsive annihilation moieties⁵⁰ or regulated dye aggregation states⁵¹ to develop tumor-activated photosensitizers (PS) has greatly improved the precision of lesion-targeted diagnosis and treatment.

2.1. Passive targeting strategy

The pathological features of solid tumors, disrupted vasculature, enlarged endothelial gaps, and impaired lymphatic drainage, are collectively termed the enhanced permeability and retention (EPR) effect. This means that nanoscale drug carriers can more easily enter and remain at tumor sites.⁵² By leveraging the EPR effect, tumor-selective drugs can simultaneously enhance diagnostic and therapeutic efficacy while reducing off-target toxicity. Nanoparticles with an appropriate size and surface charge can effectively evade endocytic clearance and maximize tumor accumulation. Encapsulation can be achieved through diverse approaches, including nanoparticle self-assembly, amphiphilic polymer encapsulation, and biocarrier-based strategies such as coating with serum albumin, tetrahedral framework nucleic acids (tFNAs), or bacterial membranes. These strategies improve probe water solubility and stability, reduce systemic clearance, prolong plasma half-life, and ultimately facilitate the construction of passively targeted nano-theranostic agents.

As a classic supramolecular characteristic of cyanine dyes, J-aggregation drives the spontaneous formation of structurally well-defined nanoparticles with highly arranged molecular packing.^{53,54} This structural feature not only enhances the light-harvesting efficiency^{55–57} and photostability^{58,59} but also endows the dye with a favorable nanoscale size, thereby enabling passive tumor accumulation *via* the EPR effect. Therefore, the rational design of J-aggregates represents an effective strategy in dye chemistry to improve the *in vivo* performance of cyanine-based theranostic systems. Recently, Peng *et al.*⁶⁰ reported a strategy that utilizes the inherent surface charge of a Cyanine PS, 4-((*E*)-3-((*E*)-5-iodo-1,3,3-trimethylindolin-2-ylidene)prop-1-en-1-yl)-1-methylquinolin-1-ium iodide (IDMQ), to induce J-aggregation and drive their spontaneous self-assembly into nanoparticles (Fig. 2A). Leveraging the EPR effect typical of solid tumors, this approach achieved over a 10-fold enhancement in tumor site fluorescence imaging while using only twice the dye dose (Fig. 2B). Furthermore, negligible fluorescence signals were detected in off-target organs such as the colon, lungs, heart, spleen, and liver (Fig. 2C and D).



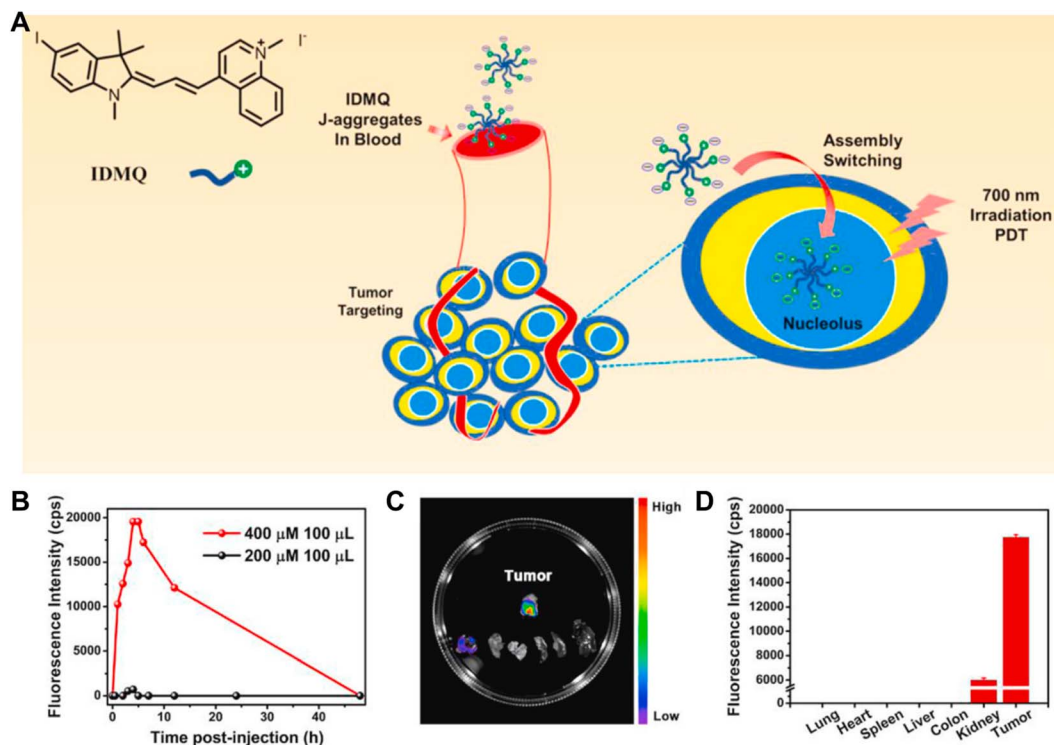


Fig. 2 (A) Chemical structures of free IDMQ and IDMQ J-aggregates and their smart J-aggregates system targeting tumors for PDT. (B) Fluorescence intensity changes of the murine tumor with time. (C) Fluorescence imaging (from top to bottom, left to right: tumor, kidney, colon, lung, heart, spleen, and liver) and (D) fluorescence intensity of various organs at 4 h after IDMQ injection (tail vein injection, 400 μM , 100 μL , 1.73 mg kg^{-1}). Reprinted with permission from ref. 60, copyright 2020 Elsevier.

Albumin, as a major serum protein, has demonstrated considerable potential in drug delivery. Its inherent biocompatibility, low immunogenicity, and natural ability make it an ideal vehicle for drug delivery.^{20,61–63} Yu *et al.*⁶⁴ innovatively proposed an *in vivo* self-assembly of albumin and PS. This approach involved synthesizing a C8 heptamethine cyanine PS featuring dual *N*-alkyl chains with a total carbon chain length of eight atoms. Upon intravenous administration, the compound rapidly and efficiently self-assembled with endogenous serum proteins to form nanoscale dye-albumin complexes. By leveraging endogenous serum transport, the C8 complex achieved markedly prolonged circulation time and enhanced tumor-specific accumulation.

tFNAs are self-assembled from four equimolar concentrations of single-stranded nucleic acids with equal length.^{65,66} Based on this, tFNAs can be precisely controlled in size and geometric shape with a simplified preparation process. More importantly, compared to traditional nucleic acids that are prone to degradation, tFNAs constructed *via* DNA origami technology showed exceptional dispersibility and stability. Additionally, the nanotetrahedral structure endows tFNAs with strong mechanical strength and inherent cell membrane permeability. Thereby, tFNAs can significantly enhance the dispersion and photostability of cyanine dyes in therapeutic and diagnostic applications. Recently, Li *et al.*⁶⁵ utilized this aptamer-tFNA delivery system to deliver Cy5 and achieved its sustained retention in tumors. Besides, Meng *et al.*⁶⁶ employed

tetrads DNA to directly encapsulate hydrophobic cyanine dye IR780 through π - π stacking and electrostatic interactions. This strategy significantly improved water solubility and extended the blood circulation half-life from less than 3 h to 15 h. The tetrads DNA-IR780 complex achieved enhanced tumor accumulation and more efficient phototherapy of tumors.

Bacteria, intrinsically linked to human health and disease pathogenesis, possess the ability to actively sense dynamic environmental signals and migrate toward specific sites. These intrinsic properties establish them as a promising platform for targeted biomedical delivery.⁶⁷ For instance, Wang⁶⁸ employed *Escherichia coli* as a carrier to deliver theranostic agents to chemotherapy-resistant tumors *via* electrostatic adsorption and bioorthogonal click chemistry. This bacterial-drug complex effectively circumvented multidrug resistance mechanisms by evading the efflux pump, offering a novel strategy for chemotherapy-resistant tumors. Beyond their role as passive carriers, the inherent immunogenicity of bacteria also holds great potential for practical applications. With appropriate modification, bacteria can function as immunopotentiators, effectively enhancing the body's immune response and thereby significantly improving the efficacy of anticancer therapies. Sun *et al.*⁶⁹ demonstrated this by exploiting the hypoxia-directed tropism of the *Salmonella* VNP20009 to deliver the photosensitizer N782 to tumor tissue for PDT. The synergistic effect of bacterial immunogenicity and phototherapy effectively triggered the release of tumor antigens. It also downregulated



Table 1 Target functionalized theranostics^a

Target	Cy dyes	Increased fluorescence intensity	Enhanced therapeutic effect	References
The L1 cell adhesion molecule (L1CAM)	Ap-β-gal-Fret	—	—	46
BRD4	PTJQ	—	—	47
Osteosarcoma	Cy7-TCF-PEG-TPPRVPLLTFGS	2.04	—	52
Programmed cell death protein 1	a-PD-1-DBCO	24	—	63
Folate receptor	LET-I-FA	—	—	70
Epidermal growth factor receptor	Pan-Hcy	3.5	7.1	71
Human epidermal growth factor receptor 2	MMAE-Cy5-trastuzumab	—	—	72
	Trastuzumab-mI2XCy-Ac	2	—	73
C-X-C motif chemokine receptor 4	Cy5-1S-FC131	—	—	75
α _v β ₃ -integrin	Cy5.5-c[RGDKLAK]	—	2.82–3.24	76
	IR-PEG-cRGD	4.79	—	79
Man receptor	SeBDP@TPZ-S-S-Cy/Man NPs	~1.6	—	77
Estrogen receptor α	FAPI-Cy7-Cl	4.5	—	80
CD133	CD133Ab-grafted Cy5.5/ PFOB@P-HVs	3	—	81
CD20	aCD20-mAB-P/ P-ibrutinib-Cy3.5	—	—	82
Poly ADP-ribose polymerase	Rib-MHI-148	—	3	83
CD44 receptor	IR783-Fe@MnO ₂ -HA	—	—	84
Mcl-1 protein	Nap	—	—	85
Biotin acceptor	T-BNCy5	—	>9	86
Asialoglycoprotein receptor	PIR NPs	>2.0	—	87
Transferrin receptor	Tf-IRLy NPs	—	2.67 fold	88
Hypoxic	N-V-J	—	—	69
Tumor	LZ-1105@HAm	4.7	—	20
	IR820-TPE@B-Exo	—	—	78

^a “—” date not reported or reported cannot be quantified.

programmed cell death ligand 1 (PD-L1) expression, an immune checkpoint molecule that suppresses T-cell function, thereby alleviating its immunosuppressive effect on T cells. These effects, driven by the combined action of tumor antigen-mediated immune cell recruitment and the relief of T cell immunosuppression, reshaped the tumor microenvironment. The state converted from a “cold tumor” with sparse immune cell infiltration and weak immune response, to a “hot tumor” featuring abundant immune cell infiltration and strong anti-tumor activity. Ultimately, this conversion elicited a systemic anti-tumor immune response.

2.2. Active targeting strategy

Compared with normal tissues, malignant tumors exhibit significant overexpression of tumor-specific receptors on their surfaces (such as folate receptor,⁷⁰ epidermal growth factor receptor,⁷¹ and human epidermal growth factor receptor 2 (ref. 72 and 73)). This phenomenon is driven by epigenetic alterations, which sustain the uncontrolled proliferation, invasion, and survival of tumor cells, as well as their adaptation to the microenvironment. These overexpressed features, characterized by high abundance, surface accessibility, and essential roles in tumor biology, provide an ideal molecular basis for precise tumor identification and active targeting through ligand-receptor recognition. By functionalizing nanocarriers with targeting ligands such as antibodies,^{73,74} peptides,^{75,76}

carbohydrates,⁷⁷ or vitamins,⁷⁸ tumor-specific binding and receptor-mediated endocytosis can be achieved, thereby enhancing theranostic precision and minimizing systemic side effects (Table 1).

2.2.1. Targeting group modification. The structural versatility of cyanine dyes enables the direct integration of targeting moieties into their scaffold, providing a straightforward strategy to confer active targeting for theranostics. This design facilitates specific recognition between the modified dye and receptors overexpressed on tumor cells, leading to preferential accumulation at tumor sites. Consequently, it enhances imaging specificity, improves signal-to-noise ratio, and supports safer, more efficient theranostic integration. Tang *et al.*⁴⁷ exemplified this approach by covalently conjugating JQ-1, a bromodomain protein 4 (BRD4) inhibitor, to a cyanine dye scaffold, thereby achieving selective recognition of BRD4—a key regulator of cell cycle and differentiation that is overexpressed in multiple types of tumor cells. Through specific interaction between the BRD4 inhibitor and the BRD4 bromodomain, the prepared photothermal agent achieved targeted binding, thereby prolonging tumor retention and significantly reducing off-target effects in normal tissues. Chen *et al.*⁸⁹ developed Crizotinib-IR808@BSA nanoparticles for NIR-II imaging-guided chemophototherapy in colorectal cancer. Crizotinib, which targets cellular-mesenchymal epithelial transition factor (c-Met, a tyrosine kinase receptor frequently overexpressed in tumors



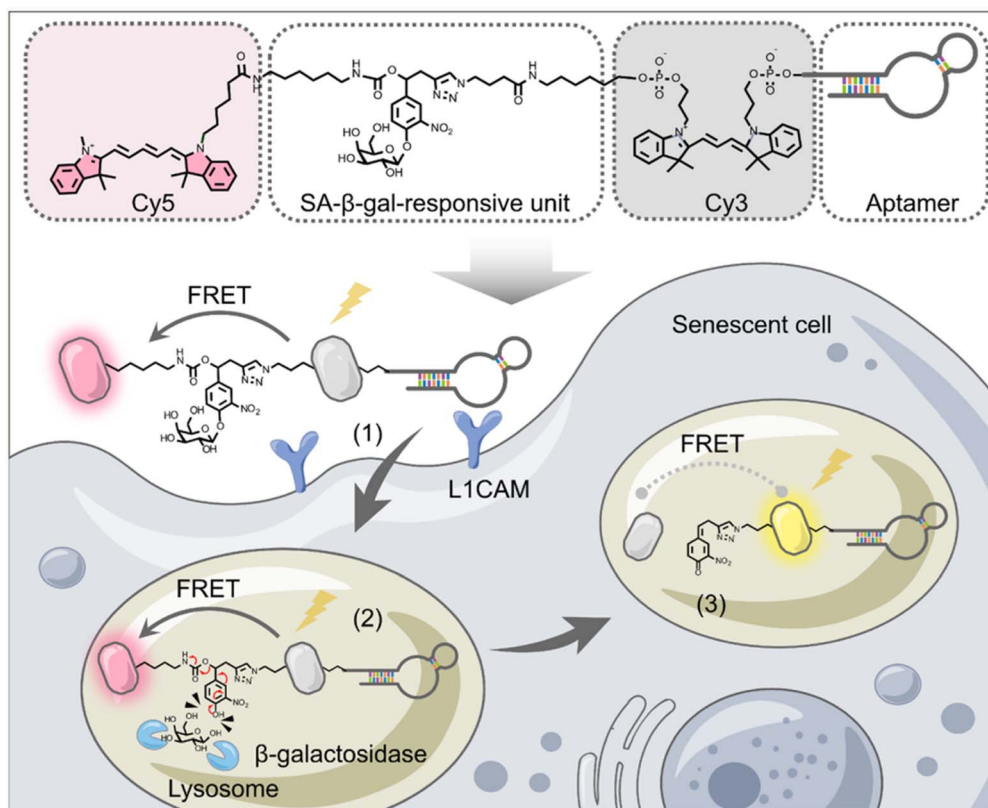


Fig. 3 Schematic illustration of the design of the aptamer conjugate-based ratiometric fluorescent probe and the underlying recognition and responsive mechanisms toward therapy-induced cancer senescence. Reprinted with permission from ref. 46, copyright 2024 American Chemical Society.

and critical for tumorigenesis), was covalently conjugated to the near-infrared dye IR808. Further bovine serum albumin (BSA) encapsulation was employed to enhance optical stability and water solubility. Benefiting from the combined effect of passive and active targeting, the nanoparticles exhibited a blood half-life of 24.23 minutes, representing an over 8-fold increase compared to free ICG (180 seconds). The system achieved a high tumor inhibition rate of 96% and enabled high-contrast NIR-II imaging of tumor vasculature, with a signal-to-background ratio of 1.29.

Aptamers are short-stranded oligonucleotides typically composed of 20 to 100 nucleotides, featuring a unique tertiary structure that enables them to specifically recognize target biomarkers. Therefore, designing drugs with specific aptamers as tumor-targeting moieties holds great potential for enhancing tumor recognition efficiency. Based on this, Liu *et al.*⁴⁶ developed an aptamer conjugate-based ratiometric cyanine probe for precise imaging of therapy induced cancer senescence, by leveraging the aptamer-mediated L1CAM recognition. As shown in Fig. 3, this aptamer-modified probe can precisely identify and internalize senescent cancer cells. Subsequently, the elimination of Förster resonance energy transfer between two cyanine dyes induced by lysosomal senescence-associated β -galactosidase (SA- β -gal) triggers ratiometric fluorescence changes, enabling precise localization and high-contrast imaging of senescent cells.

Antibodies are immunoglobulins capable of specific antigen binding. By leveraging this selective recognition, monoclonal antibodies (mAbs) can be conjugated with diagnostic or therapeutic payloads to form antibody–drug conjugates (ADCs).^{73,74} ADCs harness the high affinity and precision of mAbs for tumor-associated antigens, enabling targeted localization of drug cargoes within cancer cells and promoting their selective accumulation. Moreover, through tumor-microenvironment-responsive release mechanisms, systemic toxicity to healthy tissues can be minimized.⁹⁰ When challenges such as labeling efficiency and cargo aggregation are effectively addressed, ADCs can substantially enhance the precision of tumor eradication guided by diagnostic imaging.⁷¹

2.2.2. Biocarrier encapsulation. Beyond direct conjugation of targeting groups to photosensitizers, encapsulating probes within ligand-functionalized nanocarriers offers an alternative and effective targeting strategy. This method combines passive and active targeting mechanisms to improve the delivery of theranostic agents to tumors. Various synthetic nanocarriers, including targeted micelles, liposomes, and inorganic nanoparticles, have been shown to extend blood circulation half-life and enhance tumor accumulation in numerous studies.^{81,88} Nevertheless, as exogenous materials, most synthetic nanocarriers remain prone to rapid immune clearance, which still limits their overall accumulation efficiency in tumors. In stark contrast, biologically derived carriers, including certain



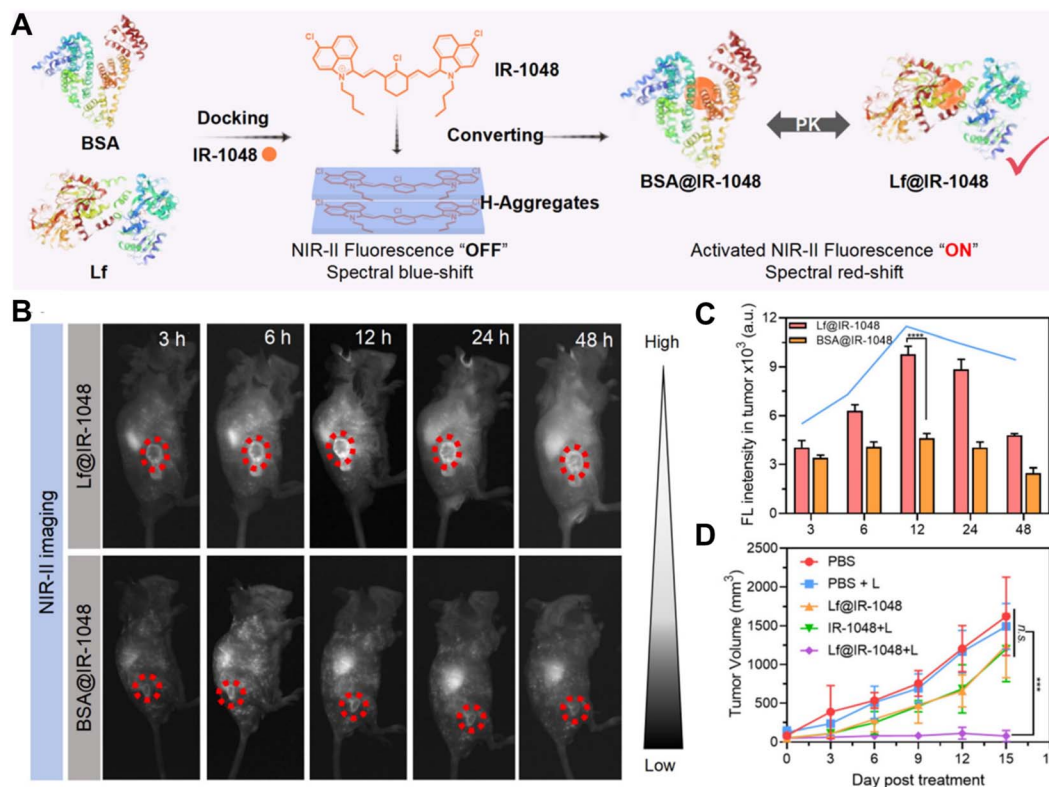


Fig. 4 (A) The synthesis process of Lf with BSA proteins hitchhiking IR-1048. (B) Time-dependent *in vivo* NIR-II fluorescence imaging of CT26 tumor-bearing mice after the intravenous injection of BSA@IR-1048 and Lf@IR-1048 (IR-1048: 2 mg kg⁻¹) under excitation wavelength of 980 nm. (C) Corresponding fluorescence intensity of tumor sites at different time points. (D) Tumor growth curve of mice with various treatments. Reprinted with permission from ref. 92, copyright 2024 Ivyspring.

proteins, cell membranes, and exosome camouflage, offer distinct advantages for targeted drug delivery. Their biomimetic nature not only endows them with improved biocompatibility and enhanced immune escape capability, but also provides them with tumor targeting ability.⁹¹

Protein-based carriers enable the delivery of therapeutic cargo by virtue of their excellent biocompatibility and low immunogenicity. Moreover, protein-dye interactions can modulate fluorophore conformation and aggregation, suppress non-radiative transitions from molecular rotation and vibration, and thereby tune dye photophysical properties. Compared to serum proteins, which mediate passive targeting *via* the EPR effect, active targeting proteins demonstrate greater advantages in both tumor targeting and molecular optical properties regulation. Jiang *et al.*⁹² pioneered the application of physiological lactoferrin (Lf) for theranostic delivery (Fig. 4A). A systematic comparison between Lf and BSA conjugates with the NIR-II dye IR-1048 revealed the critical advantages of the Lf system. Structurally, Lf@IR-1048 demonstrated a stronger binding affinity (-10.83 kcal mol⁻¹) than its BSA counterpart, leading to a >100% enhancement in NIR-II fluorescence brightness (Fig. 4B and C). Mechanistically, unlike the passive accumulation of BSA@IR-1048, Lf@IR-1048 achieved active targeting *via* receptor-mediated endocytosis, which is driven by the specific recognition of Lf receptors overexpressed on tumor

cells. Functionally, this significantly enhanced tumor accumulation enabled Lf@IR-1048 to achieve 94.8% tumor growth inhibition under NIR-II phototherapy, representing a substantial improvement over control groups (Fig. 4D).

Biologically derived carriers, particularly exosomes⁷⁸ and cell membranes,^{20,93} offered superior biocompatibility and immune evasion capabilities compared to synthetic counterparts. Crucially, the retained biomolecular components, such as exosomal integrins and tumor cell membrane homotypic binding proteins, enable active targeted recognition.⁹⁴ This dual functionality synergistically enhances lesion-specific accumulation while avoiding immune clearance.⁹⁵ Huang *et al.*²⁰ exemplified this paradigm by employing tumor cell membrane-encapsulated theranostic agents (Fig. 5A). Assembly of cyanine dye-serum albumin complexes and subsequent tumor-derived membrane coating yielded biomimetic nanoparticles with a 3.0-fold longer plasma half-life (1.92 h *vs.* 0.63 h for free dye) (Fig. 5B), attributed to membrane-mediated immune evasion. Leveraging homotypic targeting, the agent demonstrated significantly enhanced tumor accumulation, with photoacoustic and fluorescent signals increasing by 1.7-fold and 4.7-fold, respectively (Fig. 5C and D). Consequently, under 808 nm irradiation, robust photothermal efficacy was achieved, resulting in 100% tumor inhibition and complete tumor ablation compared to the control group (Fig. 5E).



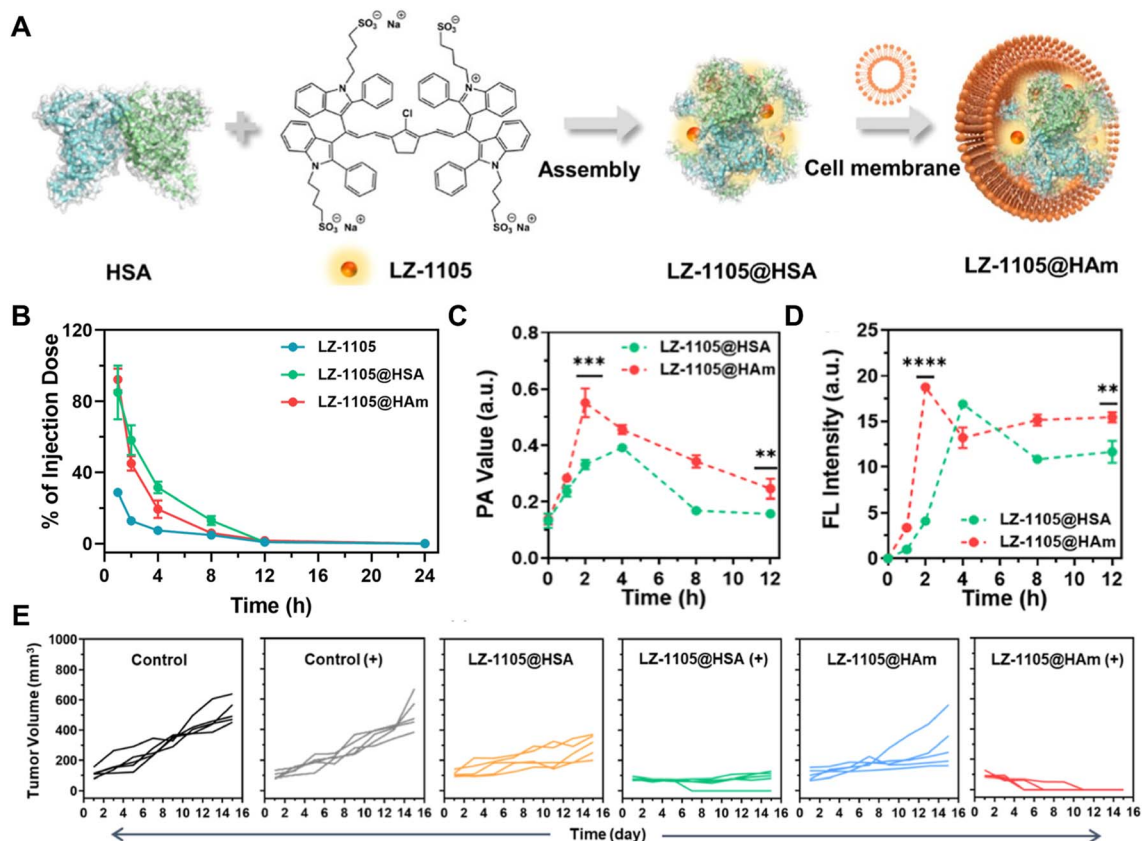


Fig. 5 (A) Preparation of homologous cell membrane-coated albumin-energized NIR-II cyanine dye (LZ-1105@HAM). (B) Pharmacokinetic curves of total LZ-1105 in blood from the mice. (C and D) Time-dependent PA (C) and FL (D) intensity. (E) Tumor growth curves of the mouse after different treatments. Reprinted with permission from ref. 20, copyright 2025 American Chemical Society.

2.3. Tumor microenvironment responsive theranostics

The development of targeted theranostic agents aimed to improve the diagnostic accuracy and therapeutic efficiency of drugs. However, a series of challenges persists, including non-specific recognition during diagnosis⁹⁶ and phototoxicity in normal tissues caused by constitutively active agents.⁹⁷ To address these challenges, activatable theranostic agents have been developed that leverage distinctive tumor microenvironmental features, such as hypoxia,^{32,49,98–100} acidity,^{70,85,101,102} and overexpressed enzymes.^{46,50,51,73,96} These agents remain biologically inert during systemic circulation, and are selectively activated only upon exposure to tumor-specific stimuli, enabling

precise imaging and therapeutic functions. Cyanine dyes exemplify this approach through two responsive activation mechanisms. The first approach involves conjugating them to tumor microenvironment-sensitive quenching groups *via* stimuli-cleavable linkers (*e.g.*, enzyme-, pH-, glutathione-, or ROS-responsive bonds). This design restrains their photoactivity until tumor-specific stimuli trigger linker cleavage or structural rearrangement, thereby recovering fluorescence and phototherapeutic function (Fig. 6). Based on this paradigm, diverse activatable photosensitizers responsive to various tumor microenvironmental cues have been developed (Table 2).

The second approach leverages their inherent aggregation-induced quenching in aqueous environments. In this case,

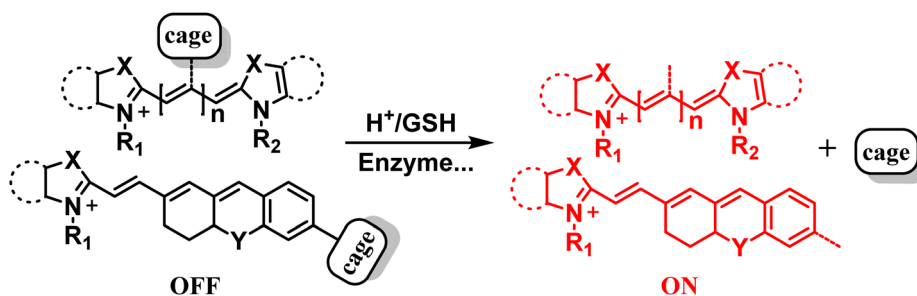


Fig. 6 Commonly used design strategies in constructing activatable cyanine dye-based theranostics.



Table 2 Tumor microenvironment-activated photosensitizers^a

Stimuli	Responsive moiety	Cy dyes	Effect	References
Hypoxia	Azo bond	HDIM	—	32
	Nitrobenzene	CNO	—	49
	Nitrobenzene	BPN2	11.7-Fold FL	98
	Nitrobenzene	CyI-Cbl-NTR	Photocytotoxicity index 3.29	99
β -Galactosidase	β -Galactose	Ap- β -gal-Fret	Signal change 3-fold	46
Aldehyde dehydrogenase	Xenobiotic aldehyde	PS-CHO	—	50
Granzyme B (GraB)	Ile-Glu-Pro-Asp	Cy5.5-CBT-dimer	3.1-Fold FL enhancement	51
pH	Tertiary amine group	LET-I-FA	Ratio of FLT/N = 2.5	70
			PA ratio of PAT/N = 4	
	Tertiary amines	FPZ	PCE up to 69.96%	101
	Tertiary amines	Cy-Nap	—	85
Esterase	Molecular rearrangement	Cy-TPA	Signal-to-background ratio 6.4	102
		Ab-mI2XCy-Ac	$\tau_{1/2}$ 3.7-fold slower	73
Alkaline phosphatase (ALP)	Phosphate group	ALPIN-6I	Over 2000-fold enrichment	96
Glutathione	2,4-Dinitrobenzenesulfonate (DNBS)	Cyl-DNBS	6-Fold inhibition	97
	Quinone	Cy-Res	80-Fold FL enhancement	105
	3,5-bis(Trifluoromethyl)benzenethiol	CyI-S-diCF3	—	106
ROS	Thioketal linkage (TK)	DON-TK-BM	$\tau_{1/2}$ 31.8 min	103
Oxidized BSA	3,5-Dioxocyclohexanecarboxylic acid (DHCA)	DIR	\approx 28-fold to background	104

^a “—” date not reported or reported cannot be quantified.

disrupting their aggregated state using tumor-specific stimuli can also achieve responsive “on-off” switching for imaging and therapeutic applications. Lee *et al.*¹⁰⁷ engineered ammonium octasulfate anions as an intraluminal precipitant to construct liposomes with Cy5.5 encapsulation efficiency approaching 100%. Sulfonate-induced nano-precipitation confined Cy5.5 within self-quenched H-aggregates, achieving 98% fluorescence quenching. Upon liposomal disintegration, the complete dye was released and disaggregated from aggregates, restoring and enhancing fluorescence intensity by 60-100-fold (Fig. 7).

Liang *et al.*⁵¹ synthesized enzyme-responsive chimeric nanoparticles *via* a reduction-instructed 2-cyanobenzothiazole (CBT)-Cys click condensation reaction (Fig. 8A). The resulting cyclic dimer CY5.5-CBT-Dimer spontaneously assembled into nanoparticles (Cy5.5-CBT-NPs) *via* hydrophobic interactions and π - π stacking, forming H-aggregates and inducing double fluorescence quenching through exciton coupling. However, after cell internalization, granzyme B (GraB) rapidly hydrolyzed the nanoparticle scaffold, triggering its disassembly and subsequent fluorescence activation (3.1-fold enhancement *in vivo*) (Fig. 8B). Since GraB activity was directly correlated with cytotoxic T lymphocyte (CTL) effector function in immune-mediated tumor killing, these nanoparticles could also serve as a real-time reporter of CTL activity. In a mouse model bearing B16-OVA melanoma, fluorescence activation of nanoparticle synchronously occurred with enhanced tumor infiltration of CD8⁺ CTL during S-(2-boronoethyl)-L-cysteine hydrochloride-mediated tumor immunotherapy (Fig. 8C).

3. Strategies to enhance diagnostic and therapeutic capabilities

The preceding sections have outlined numerous strategies to enhance the targeting precision and stimulus-responsive switching of theranostic agents. These strategies primarily focused on improving targeting recognition capabilities, with limited attention given to critical limiting factors such as biological stability and tissue penetration depth.¹⁰⁸ This section will focus on the latest advances across four interconnected domains: molecular stabilization strategies, construction of NIR-II probes, engineered architectures with amplified theranostic outputs, and multimodal synergistic platforms with integrated complementary diagnostic and therapeutic modalities.

3.1. Molecular stability enhancement

The photostability of cyanine dyes is critically important, as it directly impacts the reliability, accuracy, and quality of data obtained from imaging and detection. Traditional cyanine dyes exhibit poor chemostability and photostability, which worsen as the polymethine chain lengthens. On one hand, the low steric hindrance around the polymethine chain makes it susceptible to attack by nucleophiles. On the other hand, the dense electron distribution along the chain renders it vulnerable to oxidants. In particular, singlet oxygen (¹O₂) generated by photoexcitation of the dye can oxidize the electron-rich polymethane chain,



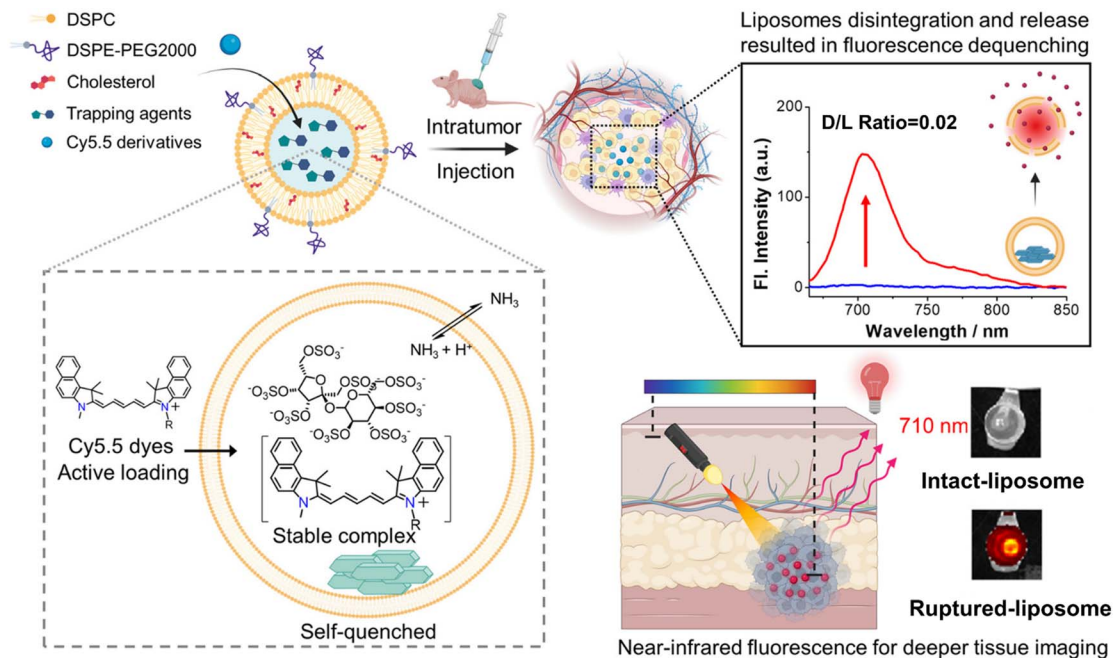


Fig. 7 Schematic illustration of the self-quenched Cy5.5-loaded liposomes for significant fluorescence enhancement with an excellent signal-to-noise ratio. Reprinted with permission from ref. 107, copyright 2024 Royal Society of Chemistry.

inducing irreversible photodegradation and consequent fluorescence reduction.^{40,109}

Structure modification or utilizing them in a protective chemical environment are effective strategies for enhancing cyanine photostability. Introducing a five- or six-membered ring into the central position of heptamethine cyanine dyes, or introducing electron-deficient units into the cyanine framework to alter electron distribution, are two strategies to improve photostability.^{40,110} Furthermore, introducing steric hindrance groups can also reinforce structural integrity by limiting nucleophilic attack. Smith's group pioneered molecular constraint strategies to stabilize cyanine dyes by isolating intermolecular interactions.^{108,111–113} Their recent "double-constrained" molecular design addressed the vulnerability of the C4'-O-aryl bond in traditional cyanine to nucleophilic attack (Fig. 9A).¹⁰⁸ Specifically, this structure shielded the C4'-O-aryl bond through steric shielding, thereby protecting it from attack by biological nucleophiles. Additionally, the dye molecules maintained a distance of approximately 9 Å, thereby avoiding π -stacking-induced fluorescence quenching. The dye maintained structural integrity for 10 hours (Fig. 9B) when co-incubated with nucleophilic GSH (1 mM, room temperature), showing excellent stability compared to the unmodified control group. When it was conjugated to antibodies, the "double-constrained" design also prevented surface dye aggregation (Fig. 9C), achieving sustained tumor-to-background ratios exceeding 8 in murine xenografts at 72 h post-injection (Fig. 9D and E).

Protein- or nucleic acid-mediated structural stabilization and regulation could significantly enhance the photostability of cyanine dyes in aqueous solutions.¹¹⁴ Additionally, regulating

the aggregation state of the dyes, particularly the formation of J-aggregates^{107,115} can further modulate stability¹¹⁶ through exciton delocalized energy dissipation and oxygen scavenging effects. Cyanine molecules in the J-aggregate adopt an ordered head-to-tail arrangement with a slip-stacked conformation, forming a one-dimensional coherent exciton band. This configuration enables rapid exciton delocalization and non-radiative relaxation. As a result, the generation of $^1\text{O}_2$ is suppressed, fundamentally inhibiting excited-state-induced photooxidative degradation. In addition, the dense and ordered supramolecular stacking of J-aggregates effectively impedes the penetration of reactive species such as oxygen and solvent molecules. This minimizes the contact area between the dye and oxygen, further suppressing photooxidation. Through these two synergistic mechanisms, the rates of photobleaching and photodegradation of phthalocyanine dyes are substantially reduced, thereby enhancing their photostability. Peng *et al.*¹¹⁷ developed J-aggregates (C5T-ET) through electrostatic co-assembly of cationic C5TNa and anionic Cy-Et to promote intermolecular close packing and induce intermolecular charge transfer (ICT). This strategy triggered ultrafast energy transfer, reducing the excited state lifetimes from hundreds of picoseconds (≈ 400 ps) to tens of picoseconds (≈ 22 ps). In addition, photodegradation was suppressed under 730 nm laser irradiation (0.1 W cm^{-2}), thereby enhancing the photostability of the dyes.

3.2. Constructing NIR II theranostics agents

As near-infrared fluorophores, cyanine dyes offer superior tissue penetration depth compared to visible-light fluorescent dyes. However, the excitation wavelengths of most cyanine dyes



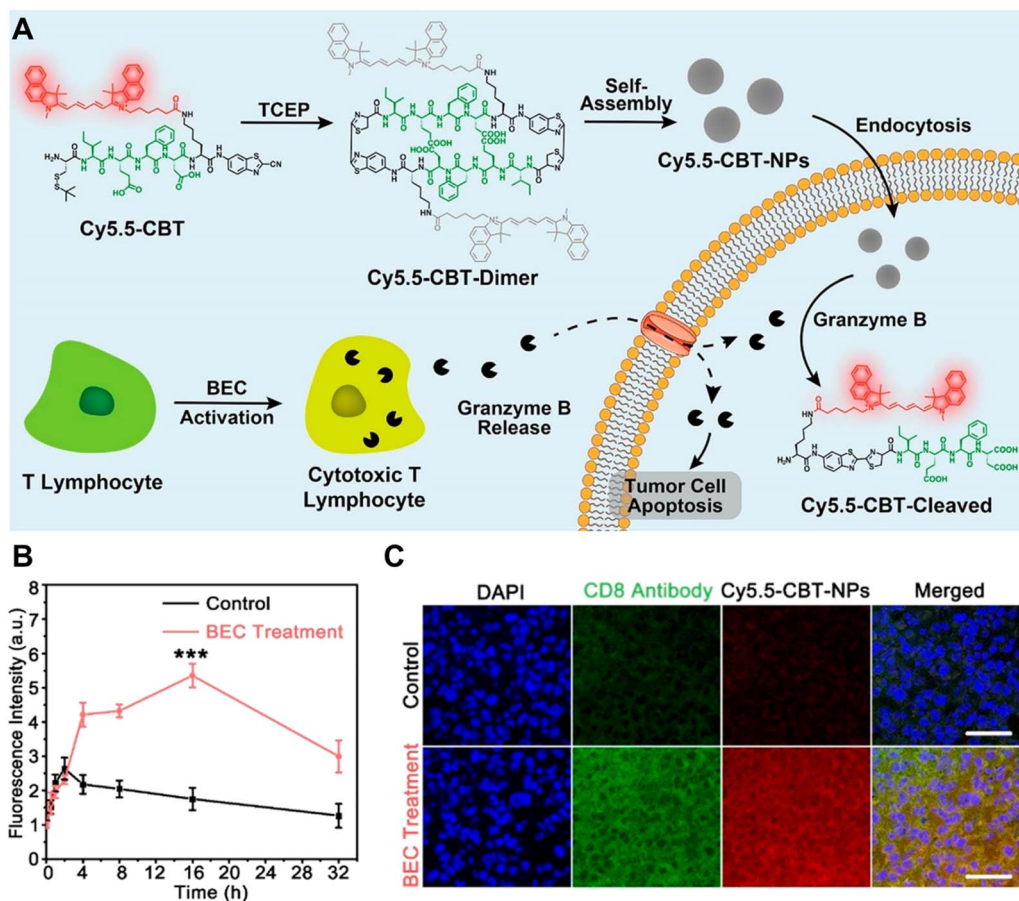


Fig. 8 (A) Schematic illustration of fluorescence-“dual quenched” Cy5.5-CBT-NPs preparation and cartoon representation of using Cy5.5-CBT-NPs to image the tumoricidal activity of cytotoxic T lymphocytes. (B) Time-dependent fluorescence intensity of the tumor after pretreatment with saline and Cy5.5-CBT-NPs. (C) Confocal fluorescence microscopy images of CD8 staining of tumor tissues. Reprinted with permission from ref. 51, copyright 2022 American Chemical Society.

fall within the NIR-I region (700–950 nm), which limits their *in vivo* applications due to the restricted tissue penetration depth of such excitation light. NIR-II (1000–1700 nm) radiation enables deeper tissue penetration compared to NIR-I light,¹¹⁸ thereby enhancing imaging resolution, contrast, and therapeutic efficacy.¹¹⁹ More importantly, biological tissues exhibit higher biological tolerance to NIR-II wavelengths. For example, the maximum permissible exposure for skin at 1064 nm (NIR-II, 1.0 W cm⁻²) is three times that at 808 nm (NIR-I, 0.33 W cm⁻²).¹²⁰ This expanded safety threshold enables NIR-II irradiation to utilize higher excitation power densities. Therefore, developing cyanine-based photosensitizers tailored for the NIR-II wavelength band represents a strategic approach to advance phototheranostic technologies.

Extending π -conjugation and incorporating strong donor/acceptor groups represent effective approaches to achieve a bathochromic shift in cyanine dyes, as they enhance the charge-transfer character and lower the HOMO–LUMO energy gap. Based on this principle, Wang group¹²¹ introduced an electron-donating methoxyphenyl group at the terminal position of the cyanine dye, yielding YN-Glu. This modification expanded the conjugated system and increased the electron density of the dye molecule, thus extending the emission

wavelength up to 1300 nm. Zhang *et al.*¹²² synthesized a series of NIR-II heptamethine cyanines, NIR-ACs, through a simple ectopic substitution of the electron-donating amino group in Flav7 (Fig. 10A). This modification achieved the HOMO–LUMO separation and significantly extended the wavelength of symmetrical cyanine into the NIR-II region (Fig. 10B).

Modulating the aggregation state of cyanine dyes, particularly by alleviating H-aggregate or promoting J-aggregate formation, offers another effective strategy to redshift their absorption into the NIR-II window. The orderly arrangement facilitates constructive coupling of transition dipoles, leading to red-shifted absorption wavelengths with increased molar extinction coefficients, and altered fluorescence properties.¹²⁰ Lin and colleagues¹²³ developed a metal ion-assisted strategy to assemble cyanine dye IR1064 by exploiting the coordination interactions between them. Introducing different metal ions into the IR-1064 solution effectively regulated molecular arrangement through ion-specific coordination interaction. Notably, gadolinium ions (Gd³⁺) effectively alleviated π – π stacking of H-aggregates between dye molecules, thereby promoting the formation of stable nano-assemblies in aqueous media. The maximum excitation and emission wavelengths of these nano-assemblies were 962 nm and 1098 nm, respectively.



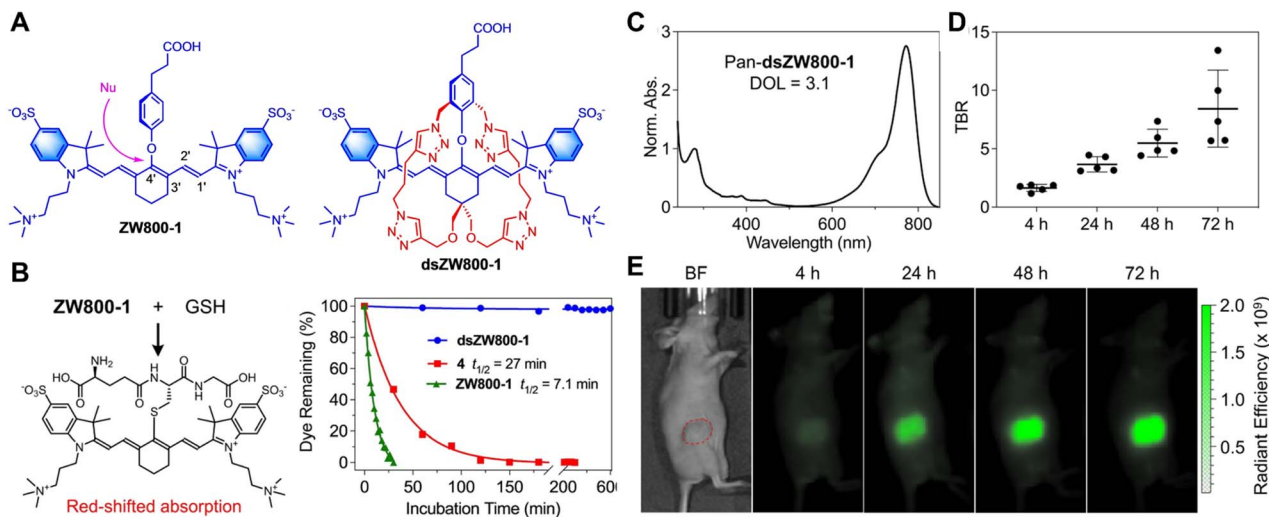


Fig. 9 (A) Introducing shielding arms to improve the stability of cyanine dyes. Nu: nucleophile. (B) Reaction of ZW800-1 with glutathione (GSH) to give a product with red-shifted absorption maxima band and comparison of dye stabilities in pH 7.4 PBS buffer with 1 mM GSH, room temperature. (C) Normalized absorption spectrum of Pan-dsZW800-1 (Degree of labeling, DOL = 3.1) in pH 7.2 PBS at room temperature. (D) Tumor-to-background ratio (TBR) from *in vivo* NIR-I imaging (ex: 745 ± 15 nm, em: 800 ± 10 nm) of JIMT-1 tumor-bearing mice ($N = 5$) after intravenous injection of Pan-dsZW800-1 (50 μg dose) and imaging at 4, 24, 48, and 72 h post-injection. (E) Representative *in vivo* NIR-I fluorescence images of the JIMT-1 tumor-bearing mice. Reprinted with permission from ref. 108, copyright 2023 Wiley.

3.3. Multimodal collaborative diagnosis and treatment

Phototherapy offers significant advantages such as minimal side effects and precise spatiotemporal control, yet its efficiency

in single-modality applications remains limited. To overcome this challenge, a key research focus has been the development of phototherapeutic agents that integrate multimodal imaging with synergistic treatment modalities.

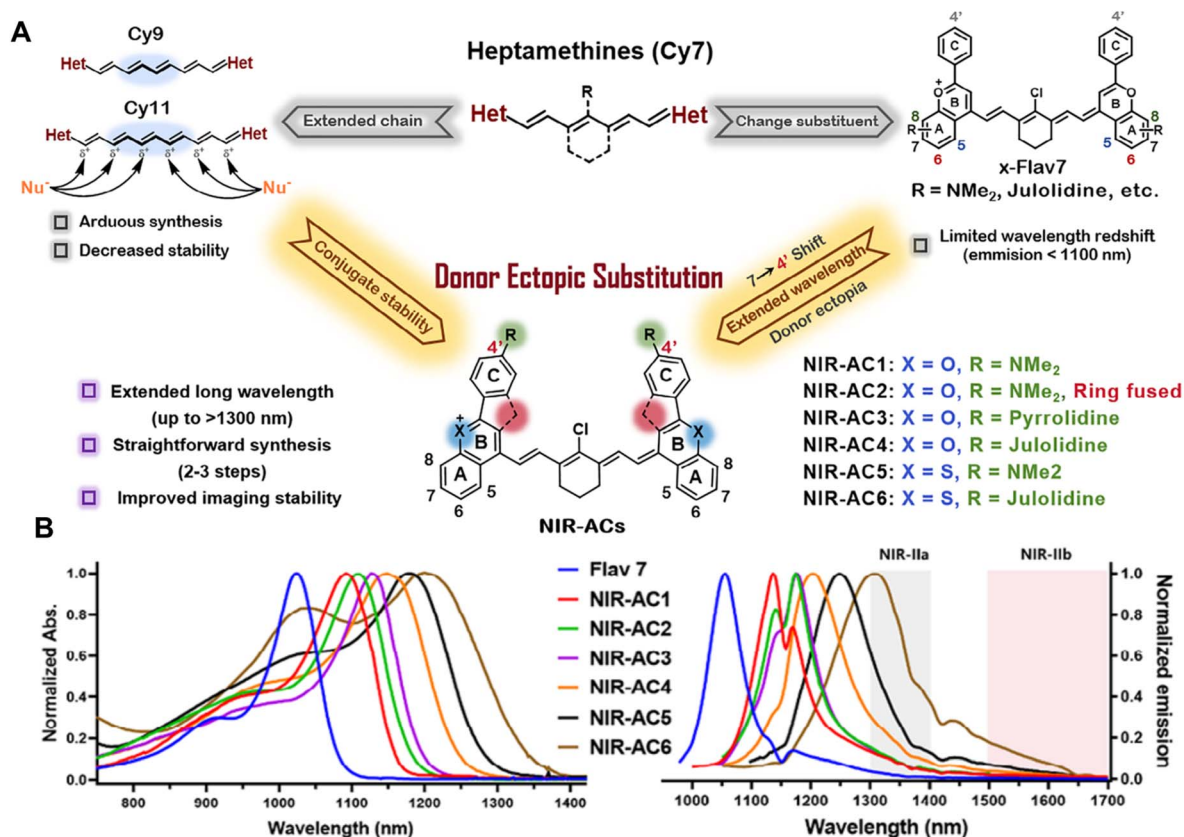


Fig. 10 (A) Donor ectopic substitution strategy guidance for constructing long-wavelength stable NIR-ACs dyes. (B) Absorption and emission spectra of Flav7 and NIR-ACs in DCM. Reprinted with permission from ref. 122, copyright 2025 Wiley.



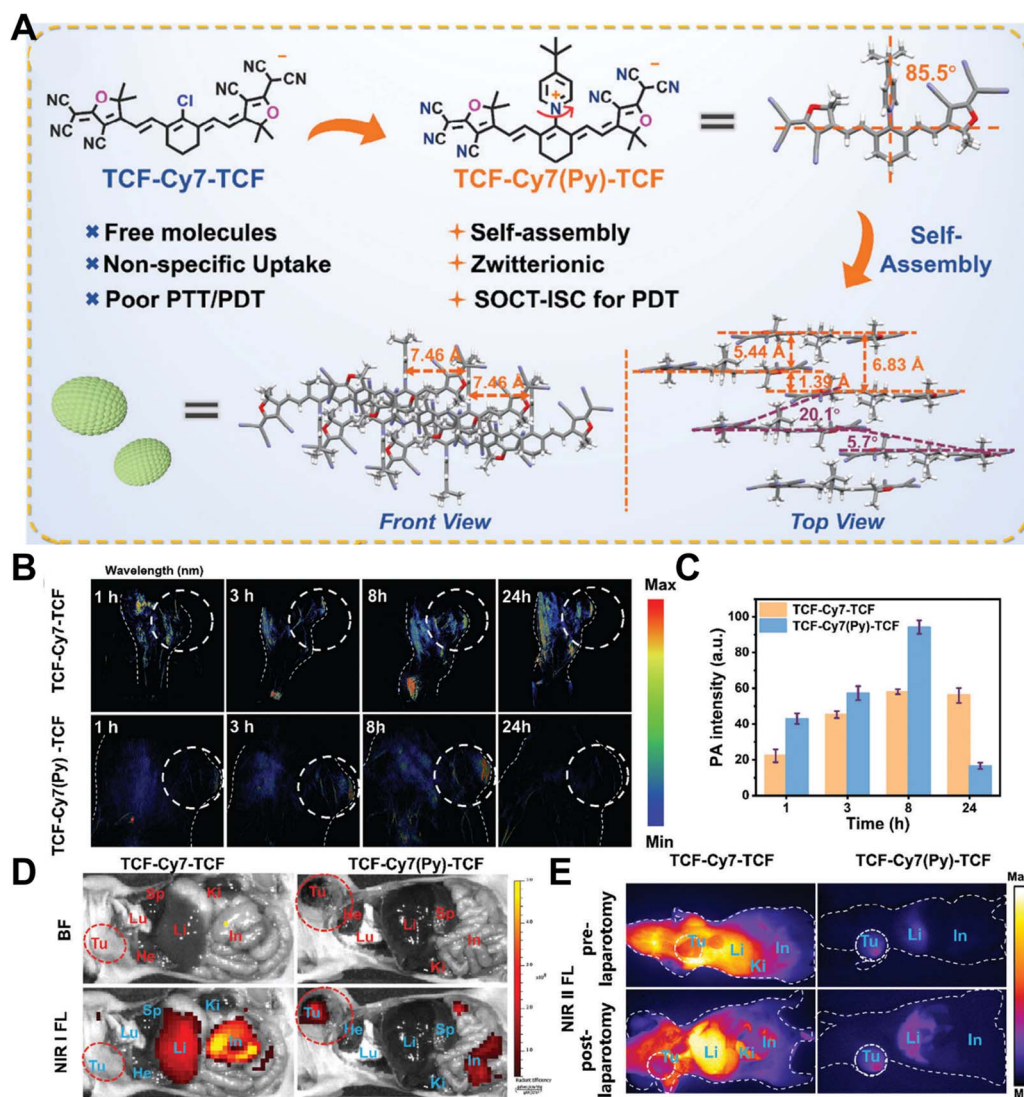


Fig. 11 (A) Schematic illustration of the self-assembly and stacking patterns of TCF-Cy7(Py)-TCF. (B) Time-dependent PAI of TCF-Cy7-TCF or TCF-Cy7(Py)-TCF in 4T1 tumor-bearing mice. The dashed circle indicates the tumor. (C) Relative PA intensities of tumor sites based on the quantitative analysis of (B). (D) NIR-I fluorescence images of surgically exposed tissues/organs before and after laparotomy. He: Heart; Li: liver; Sp: spleen; Lu: lung; Ki: kidney; In: intestine; Tu: tumor; FL: fluorescence; BF: bright field. Reprinted with permission from ref. 129, copyright 2024 Wiley.

3.3.1. Multimodal imaging. Multimodal diagnosis integrates complementary imaging methods, including FLI, PAI, magnetic resonance imaging (MRI), ultrasound imaging, positron emission tomography (PET), and others. Compared with single-modality optical methods, multimodal diagnostic techniques enable comprehensive disease characterization and significantly improve diagnostic accuracy by multidimensional characterization of tissue properties, physiological functions, and pathological changes.^{25,124} These modalities function synergistically: optical imaging offers structural data at cellular resolution, and MRI excels in providing soft-tissue contrast and delineating anatomical structures. At the same time, PET quantifies metabolic activity to enable early lesion detection.¹²⁴ Importantly, deep-penetrating techniques such as CT, MRI, PET, and PAI^{123–126} complement FLI, thereby effectively

overcoming the inherent penetration-depth limitations of fluorescence signals.

Cyanine dyes possess a distinctive dual functionality: they are not only effective for FLI, but can also be engineered into excellent photothermal converters for PAI.^{127,128} The photothermal conversion efficiency is primarily determined by the absorption coefficient and photothermal conversion ability of dyes, without the need for molecular redesign.²⁵ Utilizing this mechanism, Zhou *et al.*¹²⁴ constructed an orthogonal charge-transfer dyad, tricyanofuran (TCF)-containing heptamethine cyanine (TCF-Cy7(Py)-TCF), by introducing a cationic pyridine group at the *meso*-position of an anionic heptamethine cyanine dye (TCF-Cy7-TCF) (Fig. 11A). The TCF and the pyridine conferred excellent crystallization properties on TCF-CY(Py)-TCF and enhanced its photothermal conversion efficiency



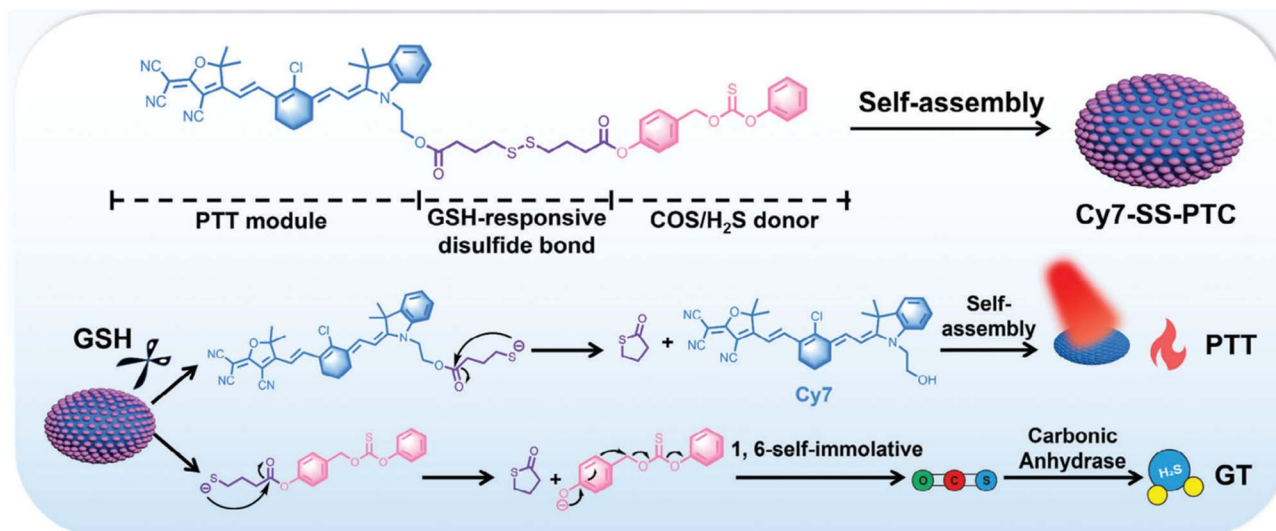


Fig. 12 Molecular structure and H₂S release mechanism of Cy7-SS-PTC NPs, and the schematic illustration of H₂S-assisted synergistic tumor photothermal therapy. Reprinted with permission from ref. 135, copyright 2025 Wiley.

from 7.78% to 55.06%, which was beneficial for exhibiting excellent PAI signals. This engineered nanoplatform achieved a high signal-to-noise ratio for tumor PAI/FLI imaging within the NIR window and demonstrated significant phototherapy efficacy after target accumulation (Fig. 11B–E).

3.3.2. Synergistic treatment. The inherent complexity of cancer, characterized by pathological diversity, metastasis, and high recurrence rates, renders single-modality treatment insufficient in clinical practice. Despite benefits such as NIR excitation, low phototoxicity, and multiple antitumor mechanisms, cyanine-dye-based phototherapy remains constrained by tumor heterogeneity and metastatic potential. Therefore, integrating phototherapy with other treatment modalities such as chemotherapy,^{49,130} radiotherapy,^{131–133} gas therapy,^{134,135} and immunotherapy^{32,63} represents a promising strategy to enhance therapeutic efficacy through complementary mechanisms.

(a) Chemo-phototherapy. Chemotherapy remains the cornerstone of clinical tumor management. The engineered integration of chemotherapy and phototherapy has emerged as a promising strategy to address the challenges posed by malignant tumors.¹³⁶ Cyanine dye-based chemo-phototherapy nanoplatforms offer distinct advantages, including spatiotemporally controlled drug release, reduced systemic dosage, mitigated drug resistance, and synergistic therapeutic effects.

In addition to traditional covalent drug–dye conjugates^{130,137–140} and co-encapsulation systems,^{49,141} emerging dye–drug co-assembly strategy^{48,142,143} represents an advanced design paradigm for such synergistic agents. The cyanine dye–drug co-assembly employs supramolecular recognition mechanisms, such as hydrogen bonding, π – π stacking, and electrostatic interactions, to drive the spontaneous formation of nanodrugs. This approach not only enhances therapeutic payload concentration but also optimizes key pharmaceutical properties through synergic effects, ultimately improving drug stability, solubility, and bioavailability. Crucially, the

spatiotemporally synchronized release of diagnostic and therapeutic agents from these nanotheranostics enables precise tumor targeting and synergic treatment.

(b) Synergistic photo/gas therapy. Tumor heterogeneity may lead to uneven distribution of dyes within tumors, combined with reduced light transmission capacity and heat loss caused by blood perfusion. These factors collectively weaken the efficacy of phototherapy, resulting in incomplete tumor clearance, ultimately contributing to recurrence and metastasis. Gaseous molecules such as nitric oxide (NO), carbon monoxide (CO), and hydrogen sulfide (H₂S) diffuse rapidly within tumors and possess intrinsic physiological functions,¹³⁵ effectively complementing the limitations of photosensitizers. For instance, CO and H₂S can reduce inflammation through the mitogen-activated protein kinase (MAPK) pathway. In contrast, NO reacts with superoxide anion radicals ($\cdot\text{O}_2^-$) to form peroxynitrite (ONOO⁻), which can activate matrix metalloproteinases (MMPs) to degrade collagen and disrupt the extracellular matrix (ECM) barrier, thereby enhancing intratumoral accumulation. Notably, H₂S exhibits a concentration-dependent effect in tumors: low concentrations promote tumorigenesis by inducing angiogenesis, inhibiting apoptosis, enhancing mitochondrial metabolism, and accelerating the cell cycle; in contrast, high concentrations exert cytotoxic effects through mitochondrial respiration inhibition, adenosine triphosphate (ATP) synthesis disruption, and heat shock protein (HSP) expression downregulation.

Gas-phototheranostic agents are typically developed by either integrating gas-donor moieties into the structure of cyanine dyes^{134,135,144} or by co-assembling such moieties with dye molecules.^{145,146} Zhou *et al.*¹³⁵ conjugated the photosensitizer Cy7 with the H₂S donor phenylthiocarbonate (PTC) through a disulfide linkage, fabricating carrier-free nanoparticles (Cy7-SS-PTC; Fig. 12). Within the tumor microenvironment, overexpressed GSH triggered a cleavage of the disulfide bond, thus



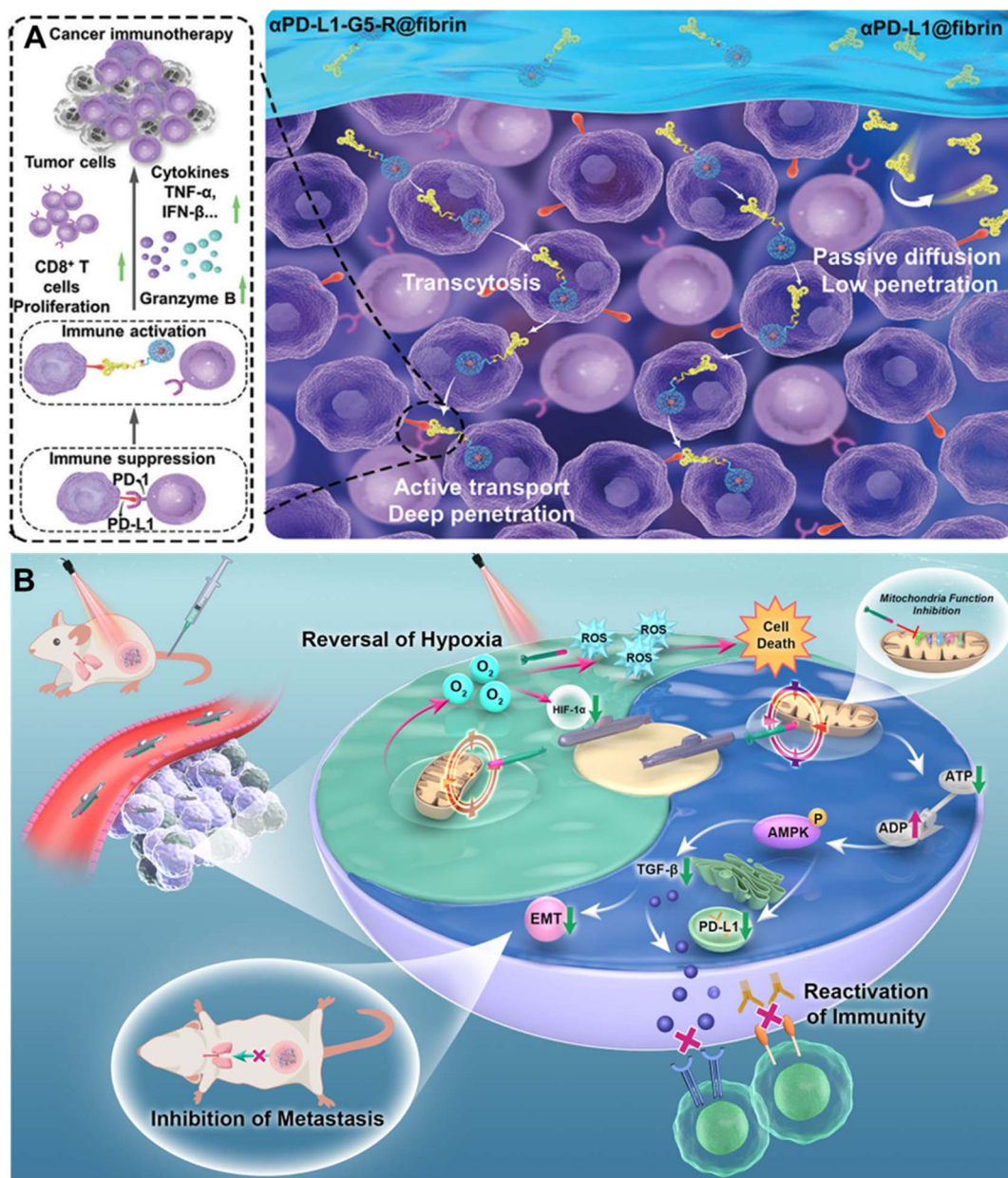


Fig. 13 (A) Illustration of Cy5 nanodots α PD-L1 conjugates (Cy5 nanodots- α PD-L1 conjugates) loaded in fibrin gels (α PD-L1-G5-R@fibrin). Reprinted with permission from ref. 150, copyright 2023 Wiley. (B) Preparation process of MHI-TMX@ALB nanoparticles and the mechanisms for enhancing photoimmunotherapy via highly efficient TGF- β and PD-L1 dual-depression. Reprinted with permission from ref. 151, copyright 2024 American Chemical Society.

initiating a cascade release of both Cy7 and H₂S. Under 808 nm laser irradiation, Cy7 simultaneously generates fluorescence and photoacoustic signals while generating photothermal effects, enabling integrated tumor theranostics. Concurrently, the released H₂S disrupts mitochondrial respiration, inhibits ATP synthesis, and downregulates HSP70 expression, thereby synergistically enhancing the photothermal efficacy and achieving an 88% tumor suppression rate.

(c) *Photoimmunotherapy*. The essence of phototherapy in activating antitumor immune responses is inducing immunogenic cell death.^{147–149} However, immunosuppressive solid tumors formed an “immune brake” mechanism through the

overexpression of checkpoint molecules (such as PD-L1 and cytotoxic T lymphocyte-associated antigen-4), infiltration of regulatory T cells, and secretion of immunosuppressive cytokines (such as transforming growth factor- β (TGF- β) and interleukin-10). This will ultimately weaken the immune response triggered by phototherapy. Therefore, integrating immune checkpoint inhibitors (ICIs) has become one of the most important strategies to reverse immune suppression. By selectively blocking T cell inhibitory signals, ICIs can amplify the immune activation induced by phototherapy, transforming local ablation into systemic immune surveillance. Zhou *et al.*¹⁵⁰ constructed a nanostructure by conjugating Cy5-labeled



polylysine dendrimers with surface-anchored anti-PD-L1 (α PD-L1) through a copper-free click reaction (Fig. 13A). The nanostructure facilitated global α PD-L1 delivery into tumors through adsorption-mediated endocytosis, which enhanced checkpoint blockade efficacy, reduced tumor recurrence rates, and significantly prolonged mouse survival.

In addition, Zhang *et al.*³² conjugated a cyanine photosensitizer with a PD-1 inhibitor to actively recognize and block PD-1/PD-L1 binding between T cells and tumor cells. By this strategy, they effectively reversed the immunosuppressive microenvironment and prevented tumor cell immune evasion. In the hypoxic tumor microenvironment, cyanine dyes were activated, which then induced tumor cell pyroptosis *via* highly efficient PDT and further remodeled the immune microenvironment. This dual-action strategy, combining light-induced pyroptosis and PD-1 blockade, initiated a sequential cascade reaction of “immune activation – tumor microenvironment reprogramming – escape prevention”, thereby achieving potent tumor immunotherapy.

Beyond exogenous checkpoint inhibitors, downregulating tumor PD-L1 expression through metabolic reprogramming represents a promising approach for converting tumors from low immunogenicity to high immunogenicity.^{48,133,151} Shen¹⁵¹ developed an albumin-based nanocarrier loaded with the cyanine dye MHI-148 that conjugated with tamoxifen, a clinically approved mitochondrial metabolism modulator (Fig. 13B). This nanoplateform simultaneously reversed tumor hypoxia and suppressed PD-L1/TGF- β expression through tamoxifen-mediated metabolic reprogramming, thereby enhancing T-cell infiltration and inhibiting 4T1 tumor lung metastasis. This synergistic epigenetic and metabolic reprogramming alleviates dual immunosuppression, enabling highly efficient fluorescence-guided PDT.

3.4. Optimizing photodynamic mechanisms

PDT serves as a core anti-tumor mechanism of cyanine dyes. Its fundamental principle lies in the synergistic effect of photosensitizers, light, and tissue oxygen to generate ROS.¹⁵² Excessive ROS can further induce apoptosis or necrosis in tumor cells while causing negligible damage to surrounding normal tissues. To date, numerous studies have systematically elucidated the core mechanisms of PDT.^{153,154} Among these, Kozlikova *et al.*¹⁵⁵ noted that the photodynamic activity of dyes is closely related to their ability to generate singlet oxygen and their aggregation state. Furthermore, the type of PDT directly determines its tumor-killing potency and its adaptability to the hypoxic tumor microenvironment.

The type of PDT is primarily determined by the mechanism of ROS generation and can be classified into Type I and Type II. Type II PDT involves energy transfer from the photosensitizer to oxygen, producing $^1\text{O}_2$. Type I PDT generates ROS (such as $\cdot\text{O}_2^-$, hydroxyl radicals ($\cdot\text{OH}$), and hydrogen peroxide) through electron transfer with surrounding water and oxygen. Crucially, heteropolar reactions and the Haber-Weiss/Fenton cycle enable efficient generation of $\cdot\text{O}_2^-$ and $\cdot\text{OH}$ even under severe hypoxic conditions, with significantly lower oxygen dependence at the

target site.^{86,156} Therefore, Type I PDT demonstrates superior efficacy against hypoxic solid tumors. In type I PDT, ROS generation relies on electron transfer, in which the formation of a charge-separated state (CSS) within the PS is a critical step. A common strategy for achieving efficient charge separation involves constructing an electron donor–acceptor molecular system.^{157,158} Prolonging the lifetime of the CSS is crucial to provide sufficient time for electron transfer, which drives research into molecular structural modulation. By inserting bridging groups between the donor and acceptor moieties, charge recombination can be effectively suppressed, thereby stabilizing the CSS. Additionally, transformation from local to non-local CSS through symmetry-breaking charge separation during molecular self-assembly can generate reactive anionic and cationic free radicals. Based on this principle, Fan *et al.*^{159,160} designed a series of *meso*-modified, heavy-atom-free NIR photosensitizers that could self-assemble into nanoparticles in aqueous media. Through light-induced cascade charge transfer processes, these photosensitizers generated substantial $\cdot\text{OH}$ for highly efficient phototherapy of hypoxic tumors.

Compared to the rapid energy transfer characteristic of Type II PDT, the electron transfer process in Type I PDT is relatively slower. Extending the triplet excited state (T_1) lifetime of photosensitizers thus represents another key strategy for improving electron transfer efficiency. This can be achieved through dye structural design and by adjusting the spatial arrangement of intramolecular electron donors and acceptors.¹⁶¹ Guided by this approach, Guo⁸⁶ introduced a naphthyl imide group as an electron acceptor at the *meso* position of a Cy5 electron donor scaffold. In the resulting molecular structure, the acceptor and the Cy5 donor adopt a nearly perfect orthogonal geometry with high structural rigidity. Upon forming an intracellular sandwich-like π – π stacking assembly between the *N*-benzyl and naphthalimide units, this system not only extended T_1 lifetime (up to 389 μs), but also significantly boosts $\cdot\text{O}_2^-$ generation. Remarkably, after a single *in vivo* PDT treatment, the tumor was almost completely eradicated.

4. Conclusions and outlooks

As readily engineerable NIR fluorophores, cyanine dyes hold significant promise for integrated cancer theranostics. This review systematically outlines strategies for cyanine dye modulation, encompassing both direct molecular modifications and nanostructure construction, to achieve precise tumor targeting, high-fidelity imaging, and efficient tumor ablation. As a light-activated theranostic platform, cyanine dyes pose challenges, including photochemical instability, limited excitation wavelength, and suboptimal treatment efficiency. Strategic molecular and supramolecular engineering, particularly structural modification and aggregate regulation, can red-shift excitation profiles. This spectral extension substantially enhances photostability while elevating diagnostic sensitivity and therapeutic potency.

In terms of diagnosis, the integration of optical diagnosis with complementary imaging modalities (*e.g.*, CT, MRI) enables



the development of synergistic systems. These systems combine high spatiotemporal resolution, molecular sensitivity, and deep-tissue penetration to overcome the inherent limitations of standalone optical techniques. In therapeutic applications, multimodal combination therapy, which integrates phototherapy with chemotherapy, gas therapy, and immunotherapy, can effectively address monotherapy's critical obstacles, including oxygen dependency, tumor recurrence, and metastasis. Although cyanine dye-based phototheranostics have been well developed for tumor treatment, several challenges remain in advancing their practical use.

(1) Pharmacokinetic and biodistribution challenges. Despite demonstrating excellent spatiotemporal controllability, biosafety, and tumor-targeting capabilities *in vivo* through structural optimization, cyanine dye-based theranostics still face significant obstacles in dynamic distribution. Real-time dynamic biodistribution mapping remains technically challenging, hindering the precise correlation between agent localization and therapeutic efficacy. Additionally, tumor heterogeneity frequently leads to uneven intratumoral distribution, generating treatment blind spots that cannot be detected by current imaging modalities. To overcome these limitations, it is necessary to integrate multimodal analytical techniques. By combining real-time imaging with mass spectrometry and computational modeling, *in vivo* distribution and metabolic behavior, key requirements for clinical translation, can be comprehensively simulated and analyzed.

(2) AI-enabled molecular design. The rapid evolution of artificial intelligence, particularly machine learning algorithms, offers transformative potential for accelerating development cycles. Computational approaches can predictively optimize cyanine dye structures and self-assembly configurations, enabling rational design of next-generation agents. This paradigm shift will revolutionize both synthesis protocols and performance evaluation, allowing high-throughput virtual screening of photophysical properties, tumor-targeting efficiency, and metabolic stability before experimental validation.

(3) Synthesis scalability barriers. Current synthetic routes for structurally sophisticated cyanine dyes involve labour-intensive, multi-step processes with suboptimal reaction yields. These complexities, particularly for dyes requiring precise stereochemistry or polycyclic architectures, severely constrain large-scale production. Streamlining synthetic protocols through catalytic innovation, continuous-flow chemistry, and an automated purification system is needed to improve reaction efficiency and yield. Such process intensification will facilitate clinical-grade manufacturing while reducing production costs.

Conflicts of interest

There are no conflicts to declare.

Data availability

No primary research results, software, or code have been included, and no new data were generated or analysed as part of this review.

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