

Nanoagent-Mediated Photothermal Therapy: From Delivery System Design to Synergistic Theranostic Applications

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Abstract: In contemporary medicine, cancer poses a perilous threat to human life, health, and quality of life, remaining a central focus of medical research and clinical practice. Although traditional cancer treatments, such as surgery, chemotherapy, and radiotherapy, have demonstrated some degree of success, they continue to encounter substantial challenges, including incomplete tumor eradication and the occurrence of severe adverse effects. Therefore, there is an urgent need to develop novel cancer treatment strategies characterized by high efficacy, low toxicity, and precise targeting. Photothermal therapy (PTT), as a newly emerging approach, holds considerable promise due to its unique mechanism of action. Upon laser irradiation, PTT utilizes a photothermal agent (PTA) to transform light energy into thermal energy, thereby inducing localized hyperthermia within tumor tissues. This process enables precise ablation of tumor cells while minimizing damage to surrounding healthy tissues. Recent advancements in photothermal agent research have yielded a diverse array of PTAs, and the synergistic integration of PTT with diagnostic and therapeutic techniques has further expanded its therapeutic efficacy and clinical applicability. This paper will provide an overview of the mechanisms underlying PTT, recent progress in photothermal agent development, synergistic theranostic strategies, and combined therapeutic approaches. The aim is to establish a foundation for optimizing PTAs design, elucidating PTT mechanisms, and advancing research on synergistic therapeutic protocols. Ultimately, these endeavors have the potential to result in more effective and safer disease treatments, thereby advancing the translation of photothermal therapy from foundational research to broad clinical application.

Keywords: photothermal therapy, photothermal agents, multimodal imaging theranostics, synergistic therapy, immunotherapy, photodynamic therapy

Introduction

Cancer is a leading global cause of mortality, characterized by the uncontrolled and disorganized proliferation and spread of malignant cells. Its impact substantially surpasses that of common diseases, including cardiovascular disease. In recent years, morbidity and mortality rates have been on the rise, presenting a significant challenge to public health. The complex process of tumor development and progression is influenced by a multitude of interacting factors,¹ each contributing through distinct mechanisms. This complexity, coupled with the difficulty of early detection, poses significant challenges to effective cancer treatment. While the demonstrated importance of genomic variation and epigenetic modifications in cancer development represents a significant advancement with the potential to revolutionize treatment strategies. There are numerous obstacles remain,² such as the development of drug resistance in tumor cells, strong resistance to radiotherapy (RT), and sophisticated mechanisms of immune evasion, which make effective treatment much more challenging. Furthermore, traditional therapies such as surgery, chemotherapy, and RT are limited in their clinical application due to drawbacks such as extensive surgical trauma, prolonged postoperative recovery, poor drug targeting, significant toxicity and side effects, high recurrence rates, and limited efficacy.^{3,4} Modern-era

nanomedicines exhibit great potential in cancer diagnosis and therapy, attributed to their unique design, flexibility and modifiability, enabling targeted delivery and improved biocompatibility.^{5,6} These nanosystems can encapsulate drugs, facilitating combination therapies with chemotherapy, immunotherapy (IT), photothermal therapy (PTT), etc., to reduce systemic toxicity and enhance therapeutic efficacy. Moreover, the enhanced permeability and retention⁷ (EPR) effect in solid tumors promotes nanomedicine accumulation at tumor sites.⁸ Some nanomedicines possess signal-emitting properties (eg, fluorescence) that can be leveraged for both diagnostic and therapeutic purposes,^{9,10} aligning with the principles of precision medicine. Precision medicine aims to develop personalized treatment plans based on individual genes, environment and other differences. The photoacoustic imaging (PAI), magnetic resonance imaging (MRI) and fluorescence imaging (FI),¹¹ as important imaging technologies, provide key support for precision medicine. In recent years, IT, PTT and other treatment modalities have been increasingly used. IT can accurately identify and attack tumor cells or pathogens. And compared with traditional RT and chemotherapy, IT yields less damage to normal tissues and organs of the body, although it may trigger autoimmune responses,^{12,13} and patient responses vary significantly,^{14,15} leading to diverse therapeutic outcomes. PTT is a novel tumor treatment that utilizing specific light wavelengths and photothermal conversion materials to achieve precise heating of specific lesion tissues, with less damage to surrounding normal tissues. This approach often employs fiber optics, lasers, or similar devices for localized irradiation, avoiding open surgery and thus reducing trauma, accelerating recovery, and improving patient quality of life.^{16,17} In comparison to traditional chemotherapy, photothermal therapy demonstrates a reduced likelihood of inducing drug resistance and is associated with fewer adverse effects. Furthermore, when contrasted with radiotherapy, photothermal therapy can be effectively combined with targeted nano-agents to facilitate localized hyperthermia at the tumor site, thereby minimizing the impact on surrounding healthy tissues. However, there are also shortcomings such as limited penetration depth, influence of tissue optical properties, and challenges in precisely controlling thermal damage. Integrating PTT with precision medicine and synergistic therapies has the potential to achieve more effective tumor ablation and significantly improve therapeutic efficacy and prognosis. This review centers on the research advancements of combined diagnostic techniques and therapeutic methods employing photothermal agents (PTAs) and PTT.

Mechanism of Photothermal Therapy

Photothermal therapy (PTT) represents a sophisticated therapeutic approach grounded in the principle of photothermal conversion. This method utilizes materials referred to as photothermal agents (PTAs), which inherently possess the ability to convert absorbed light energy into thermal energy. When exposed to light of specific wavelengths, these agents efficiently facilitate this conversion. Upon accumulation within pathological tissues, the resultant localized thermal energy elevates the tissue temperature, thereby inducing necrosis in tumor cells. PTT¹⁸ is characterized by minimal invasiveness tumor ablation, showing great potential in controlling drug-resistant bacteria¹⁹ and eliminating tumor cells.²⁰ This method utilizes laser irradiation, mainly near-infrared (NIR) light, to deliver energy. NIR light offers greater potential for tumor diagnosis and treatment compared to other wavelengths due to its lower absorption and stronger tissue penetration within the biological window. The NIR spectrum encompasses two primary regions: NIR-I (750–900 nm)²¹ and NIR-II (1000–1700 nm).²² While 700–950 nm NIR light sources are more widely used in PTT treatment, the superior imaging quality and deeper tissue penetration of NIR-II²³ make it a more suitable option for treating deeper-seated tumors.^{24–26} PTT leverages the unique property of PTAs to transform absorbed light energy into heat, thereby inducing cell death in tumors. Upon irradiation, PTAs absorb light energy, exciting electrons from the ground state to a higher energy singlet state.²⁷ Subsequently, these electrons experience internal conversion to attain the lowest excited singlet state. The subsequent de-excitation of electrons to the ground state can occur through three primary pathways: (1) radiative decay via fluorescence emission, (2) non-radiative relaxation, and (3) intersystem crossing, leading to phosphorescence. The photothermal effect is primarily attributed to non-radiative relaxation,²⁸ where excited electrons come back to the ground state while discharging energy as vibrational energy, causing local heating of the surrounding environment. Temperature significantly influences cellular function and viability. Elevated temperatures induce a range of cellular responses, including protein denaturation, membrane disruption, and DNA damage, ultimately leading to cell death. Mild hyperthermia (41°C) accelerates cellular metabolism and blood flow. In the range of 41–48°C,²⁹ protein aggregation occurs, while cell sensitivity to RT and chemotherapy increases. Sustained exposure to temperatures within

this range for more than 60 minutes can cause irreversible cell damage. In contrast, temperatures between 48–60°C induce rapid and severe cell damage within 4–6 minutes due to extensive protein denaturation and DNA damage. When the temperature of the organization exceeds 60°C, protein denaturation and membrane damage cause the cells to die almost instantaneously.³⁰ This temperature-dependent cellular response forms the foundation for PTT in cancer treatment. Photothermal conversion efficiency (PCE) quantifies the capacity of a photothermal agent to convert absorbed light energy into thermal energy. This efficiency is determined by comparing the thermal energy output of the photothermal agent with the amount of light energy absorbed.³¹ The power conversion efficiency (PCE) is influenced by the material's absorbance properties, the alignment of the laser wavelength, the structural design, and the energy scattering characteristics. To enhance the photothermal conversion efficiency,³² it is necessary to increase the photosensitivity of the PTAs, minimize light scattering, and optimize the attenuation of non-radiative relaxation pathways during energy conversion. Table 1 presents the factors influencing PCE and the methods for its improvement.

Advantages of Photothermal Therapy

PTT, as a non-invasive treatment modality, exhibits highly effective and non-invasive properties.^{33,34} For example, compared with traditional antibiotic therapy, PTT demonstrates broad-spectrum antimicrobial activity against various pathogens,¹⁹ with a significantly shorter treatment time (only a few minutes)²⁹ and negligible bacterial resistance. In tumor therapy, it enables precise control of the temperature within the tumor microenvironment by adjusting the dosage of the photothermal agent or the intensity of light, thereby controlling the degree of tumor ablation. In clinical applications, PTT is often employed synergistically with other therapeutic modalities, including IT, photodynamic therapy (PDT), chemotherapy, RT, gene therapy,³⁵ ferroptosis therapy, and others. This synergistic approach enhances selectivity and improves therapeutic efficacy, demonstrating high clinical research value.

Limitations of Photothermal Therapy

Although photothermal therapy has numerous advantages, the following problems remain to be solved.³⁶ Since photothermal therapy needs to be combined with laser irradiation, photothermal therapy may be less suitable for tumors that

Table 1 The Factors and Optimization Methods of Photothermal Conversion Efficiency

Photothermal Conversion Efficiency		
Factors	Light Stability Structural design Light source parameters Absorbance Energy Scattering	
Optimization methods	Enhance sensitivity to light	
	Reduce light scattering effects	Molecular stacking suppresses fluorescence emission through π - π interactions to form J- or H-aggregates.
		Through carefully utilizing the heavy atom effect introduces halogens or enhancing spin-orbit coupling and suppressing fluorescence.
		Through the photo-induced electron transfer effect, electrons are transferred from donor to acceptor after photoexcitation, quenching fluorescence and ROS.
	Enhance non-radiative attenuation	Intramolecular motion accelerates non-radiative attenuation by unimpeded rotation.
		Intra- and intermolecular charge transfer Enhanced non-radiative attenuation by D-A-D structure or distorted intramolecular charge transfer.
	Other pathways	

have spread, and is not conducive to the treatment of deep-seated tumors due to the limitation of light transmittance. Moreover, the optimal temperature of photothermal therapy is yet to be confirmed. Lower temperature is not suitable for killing cancer cells, but high temperature conditions may cause immune cells to gather like the tumor environment with changes such as accelerated blood flow, which in turn will kill normal immune cells, and high temperature may cause certain damage to normal cells or tissues. In the next studies, it is hoped that these problems can be remedied by combining appropriate agents or treatments.

Advances in Photothermal Agents

PTAs are required to have advantages such as high PCE, photostability, good biocompatibility, rapid clearance from the body³⁷ after use, and ease of synthesis and modification. Nanopreparations³⁸ can be directly used as PTAs in PTT, or as drug-delivery systems in combination with other therapies, or as contrast agents for imaging-guided applications. Nanopreparations, with their diverse applications, enhance the potential of photothermal therapy (PTT) by facilitating more precise treatment strategies. This review provides a comprehensive overview of the various types of photothermolysis agents, detailing their advantages, clinical potential, and potential challenges, as outlined in Table 2. Furthermore, Table 3 presents a summary of representative nano-agents, including their synergistic applications with other therapies, mechanisms of action, and therapeutic effects.

Metal Photothermal Agents

Metal photothermal agents constitute a category of photothermal materials derived from metallic compositions.⁶⁰ Metal photothermal agents are capable of absorbing specific wavelengths of light and converting them into thermal energy with high efficiency, thereby facilitating the treatment of various diseases. The fundamental mechanism underlying this process is the Localized Surface Plasmon Resonance (LSPR) effect exhibited by metal nanomaterials. In this section, a series of summary tables have been compiled and are presented in Table 4.

Precious Metal Nanoparticles

The first generation of precious metal materials employed as PTAs primarily includes gold (Au), platinum (Pt), and silver (Ag). These metals effectively capture NIR light, initiating a distinct LSPR effect. These precious metals can be fabricated into metal particles with sizes ranging from 1 to 100 nm, called metal nanoparticles (NPs), through reduction and other methods. When NPs encounter light matching an equally-distributed exciton band, the vibrating electromagnetic field of the light source triggers coordinated vibrations of the free-surface electrons. This leads to the separation of charges relative to the lattice and the creation of an oscillating dipole that aligns with the light's electric field, a phenomenon called LSPR.⁶⁵ LSPR facilitates efficient photothermal conversion in NPs, generating the heat necessary for ablating tumor cells.^{66–68} NPs have advantages including high photothermal conversion rates and imaging

Table 2 Types, Clinical Potential, Advantages and Potential Obstacles of Photothermal Agents

Photothermal Agents	Clinical Potential	Advantages	Potential Obstacles	Common Obstacles
Metal Photothermal Agents	Synergistic therapy combinations, Bio-imaging-guided therapeutic delivery	High thermal efficiency, Easy functional modification	Complex synthesis processes with high cost, Bioaccumulation and toxicity risks	For normal tissue damage due to local overheating, a safe temperature threshold should be defined. The classification of photothermal agents is vague and may be classified as drugs (such as drug carrier system), medical devices (such as laser activation equipment) or combination products, which require multi-center collaborative approval, which is difficult.
Carbon-based Photothermal Agents	Clinical-stage antibacterial and photothermal dual therapy, Chronic Disease-Targeted Therapeutic Platform	High biocompatibility and rapid metabolic clearance, Cost-efficient biodegradable design	Suboptimal PCE, Incomplete long-term toxicity profiles (preclinical-phase limitations)	
Organic Photothermal Agents	Synergistic multimodal therapy integration, Real-time imaging-guided short-term therapeutic platforms	Relatively simple molecular modification, Clear chemical structure, Low toxicity, Easy removability	Low PCE in some cases, Relatively low photostability, Necessitating frequent administration	

Table 3 Nanopreparations as Photothermal Agents

Nanopreparations	Advantages	Combinational Application	Tumor Targeting Mechanism	The in vitro/vivo Efficiency	References
mPt@PDA-RGD NPs	High PCE, Good biocompatibility	PTT	It generates sufficient heat to disrupt the actin cytoskeleton of SKOV-3 cells and suppress the motility of tumor cells.	Effectively inhibiting the migration of SKOV-3 cells.	[39]
C-CPE-AuNP	Specifically targeted on claudin expressing cells, Less side effects	PTT	Through the specific binding of C-CPE to claudin proteins, it activates the gold nanoparticles, generates heat, causes perforation of the cell membrane, and leads to cell death.	Ability to significantly reduce the survival of tumor cells expressing claudin protein to less than 30%.	[40]
RGD-CuS-Cy5.5	Good photothermal effect, High CT imaging ability	CT imaging, PTT	It selectively enters MKN-45 gastric cancer cells through $\alpha v \beta 3$ -mediated endocytosis and initiates an efficient PTT process, thereby killing tumor cells.	It has a significant photothermal treatment effect, with a PCE of 51%.	[41]
PEG-dBSA-RuS1.7NCs	Longer body circulation time, More prominent tumor targeting	PTT	High temperature at the tumor site, causes apoptosis or necrosis, achieving ablation of the tumor.	Significantly reduced the level of cell proliferation.	[42]
RBC-AuNCs	Long cycle half-life	PTT	Local high temperatures are generated under NIR laser irradiation, leading to thermal ablation of tumor cells.	Effectively inhibit tumor growth	[43]
MoOx@M-SN38	Enhance the anti-tumor immunity	PTT, IT	Rapid warming destroys DNA and protein, activates cGAS-STING pathway, triggers the innate immune response, and induces the production of type I interferon to enhance adaptive antitumor immunity.	Effective inhibition of primary tumors and lung metastasis.	[44]
M/Fe-CDs	Water solubility and biocompatibility were both good	PTT, IT	M / Fe-CDs generate local high temperatures with 808-nm NIR light that to kill tumor cells.	Significant photothermproperty, with PCE of 30.1%.	[45]
GO-Austar@rHSA-FA@IR780	Excellent phototoxicity, Good targeting	PTT	High temperature at the tumor site leads to thermal ablation of tumor cells.	Significant phototoxicity, the percentage of total apoptosis in MGC-803 cells reached 70.9%.	[46]
FA-CD/PPy-NPs	Good photothermal stability	Imaging, PTT	It can specifically identify and track cancer cells. Under NIR irradiation, it produces local high temperature to kill tumor cells.	Efficient PCE ($\eta = 40.80 \pm 1.54\%$) and significantly reduced the survival rate of HeLa cells to $25.02 \pm 1.85\%$.	[47]
PPy@MIL-100(Fe) NCs	Good biocompatibility, Highly efficient PCE	PTT, chemotherapy	Its shell gradually decomposes to release the drug, and after NIR irradiation, it can produce local high temperatures, which can be targeted to kill cancer cells.	Efficient PCE, with 40%.	[48]
PMo@CCM	Ability to inhibit distal tumor growth	PTT, CDT	It depletes GSH in the tumor microenvironment, produces ROS in a manner similar to the Fenton reaction, and enhances cytotoxicity.	Significantly enhanced immune response to distal tumors.	[49]
ICG-MOF-SS-AUNP12	Good photothermal effect, Good biocompatibility	PTT, IT	The release of AUNP-12, blocking the PD-1 / PD-L1 pathway, to activate the immune response, and is combined with the photothermal effect to directly kill tumor cells.	Effective inhibition of tumor metastasis and recurrence.	[50]
HAuNS	Good photothermal effect	PTT, IT	It cause the tumor local temperature to increase, causing the thermal ablation of the tumor cells.	It effectively eliminated most of the primary tumors and significantly inhibited the growth of distant tumors.	[51]

(Continued)

Table 3 (Continued).

Nanopreparations	Advantages	Combinational Application	Tumor Targeting Mechanism	The in vitro/vivo Efficiency	References
SCNT-PS/siRNA	Excellent temperature sensitivity and photothermal properties	PTT, GT	It triggers the release of siRNA by the phase transition of temperature-sensitive lipids, silences specific genes and inhibits the growth of tumor cells.	With significant antitumor activity, after laser irradiation, caused $76.2 \pm 4.4\%$ of HeLa cell death.	[52]
MnO ₂ -SOR-Ce6@PDA-PEG-FA	Ability to control drug release and overcome drug resistance	PTT, PDT, Chemotherapy, Ferroptosis therapy	PEG-FA binds specifically to FA-FR and is endocytosed into cancer cells. Sorafenib is then released to block tumor proliferation signaling, and Ce6 generates ROS. Then the GPX4/SLC7A11 pathway was inhibited and induces ferroptosis, leading to tumor death.	Significantly reduced the migration and invasion ability of tumor cells.	[53]
CM CTNPs@OVA	Trigger ferroptosis, Immune activation ability	PTT, IT, Ferroptosis therapy	Through the continuous release of copper ions, it triggers the Fenton reaction and depletes GSH, initiates ferroptosis, releases DAMPs, promotes the maturation and activation of DCs, and thus induces ICD.	Significant tumor suppression rate, with the CM CTNPs @ OVA + NIR group as high as $97.48 \pm 0.61\%$.	[54]
PBNP	Simple synthesis, Stable under acidic pH conditions	PTT, IT	It is capable of reversing immunosuppression, activating endogenous immune cells and enhancing the antitumor response.	With a significant therapeutic efficiency, 55.5% of the mice treated with photothermal immunotherapy were still alive after 100 days.	[55]
MnFe ₂ O ₄	Good photothermal stability	PTT, IT, MRI	Stimulates the maturation of DCs and increased the expression of M1 type-associated cytokines, while decreasing the expression of M2 type-associated cytokines and attenuated immunosuppression.	Effectively inhibit primary tumor growth and prevent lung metastasis.	[56]
BiNPs	Ability to suppress radiation-induced corrosion	PTT, RT	It interacts with X-rays to promote the generation of ROS, consumes GSH, then, with the help of GO, inhibit radiation-induced corrosion, and combines with PTT to kill tumor cells.	The PCE reaches 29.63% and effectively suppresses radiation-induced corrosion.	[57]
HUC-PEG	Good colloidal stability and cell-targeting capability	PTT, PDT	It can produce more ¹ O ₂ and local hyperheat to kill tumor cells.	PCE up to 41%.	[58]
AuNRd@P-DOX/ICG/ISIS132	GLUT-targeting, pH-responsive drug release, Highly biocompatible	PTT, PDT, GT, Chemotherapy	Specific targeting of GLUT5, gold nanorods as a photothermophore, ICG as a photosensitizer, DOX acting through chemotherapy, and ISIS132 inhibiting cancer cells from developing drug resistance.	Significant mortality in MCF-7 cells (IC50=3.11 µg/mL), low toxicity in normal cells analyzed by MTT analyses.	[59]

Table 4 Representative Metal Photothermal Agents

Category	Preparation	Disease	Application prospect	Improved methods	References
Precious metal nanoparticles	SFT-Au	Colorectal cancer	It can achieve precision targeted therapy for tumor cells and can be combined with other therapies.	In combination with immunotherapy or chemotherapy to overcome tumor resistance and improve overall efficacy.	[61]
	mPt@PDA-RGDNP	Oophoroma	It is used for the treatment of tumors with high expression of $\alpha X\beta 3$ and can utilize X-ray imaging for guidance.	It can introduce biodegradable carriers to facilitate the removal of nanoparticles after treatment.	[39]
	Mesoporous Platinum Nanoparticles	Neuroblastoma	It can be combined with other therapies to play a synergistic effect.	Degradable carriers can be added to accelerate metabolism to reduce long-term toxicity.	[62]
Metal sulfides and oxides	RGD-CuS-Cy5.5	Lymph node metastasis in gastric cancer	It can be combined with other therapies to play a synergistic effect.	The better biocompatible polymers or bioactive molecules are introduced to reduce the immune response and improve the biocompatibility.	[41]
	PEG-dBSA-RuS _{1.7} NCs	Mammary cancer	It can be combined with image guidance to achieve accurate treatment.	Conduct chronic toxicity experiments and explore surface modifications to further reduce nonspecific accumulation.	[42]
	BP@Mn-NC	Drug-resistant bacterial infections	Can overcome bacterial drug resistance and can be used to treat drug-resistant bacterial infections.	BP nanosheets are prone to oxidation and can develop antioxidant coatings or optimize synthesis processes to improve stability.	[63]
Biomimetic metal nanostructures	RBC-AuNCs	Mammary cancer	The hollow porous structure can load the drug, be combined with the photothermal triggered release to realize the chemotherapy-photothermal combination therapy.	Large sizes and cubic rigid structures may cause residues that can improve distribution by reducing the AuNCs core size or adopting flexible carriers.	[43]
	MoOx@M-SN38	Mammary cancer	It can combine with other therapies to play a synergistic effect.	M2 macrophages or Treg cells in the tumor microenvironment may weaken the immune effect, which can be combined with immune checkpoint inhibitors to further relieve immune suppression.	[44]
	I7-DMAG/MPNPs@PM	Mammary cancer	MPNPs have the function of photoacoustic imaging simultaneously, which can realize the integration of diagnosis and treatment.	The low drug loading rate could optimize the mesoporous structure of MPNPs or adopt a co-loading strategy.	[64]

capabilities, which provide a basis for mild and effective non-invasive cancer diagnosis and treatment. Compared to traditional chemotherapeutic drugs, NPs demonstrate fewer adverse reactions and improved targeting. Furthermore, their absorption spectra are mainly dependent on size and adjustable factors such as the aspect ratio, which can be defined as the wavelength at which light energy is absorbed.⁶⁹ Unique optical properties, coupled with chemical inertness, high biocompatibility, and low toxicity, make metallic nanoparticles suitable as raw materials for PTAs or biochemical sensors. These distinctive properties render metal nanoparticles ideal for use as raw materials in PTAs⁷⁰ or biochemical sensors.⁷¹

The particle shape of NPs significantly influences their absorption wavelengths. Consequently, NPs exhibit diverse shapes, including nanospheres, nanorods, nanocages, nanocubes, and others, each suitable for specific applications. The influence of the shape and structure of NP on the optical absorption and conversion efficiency of materials was investigated. Utilizing identical surface modifications, three common gold nanoparticles (AuNPs)⁷² were developed: gold nanorods, gold nanorods and gold nanostars.^{73,74} The findings demonstrated that several types of AuNPs could effectively convert 808 nm NIR laser light energy into heat energy via LSPR. However, among these, gold nanostars exhibited the highest efficiency in converting light energy into thermal energy. Among precious metal photothermal materials, gold nanoparticles are some of the most widely utilized. Building upon these observations, for Plasmonic Nanoparticles (PNPs) capable of generating LSPR, researchers used simple harmonic resonance theory analysis incorporating defect-induced attenuation, and found that the attenuation arising from defects introduced into PNPs could effectively reduce optical scattering, thereby significantly enhancing energy conversion efficiency. The study further indicated that at larger scales (Au, Ag > 100 nm), the attenuation effect resulting from introduced defects in nanoparticles could greatly enhance the properties of light absorption and photothermal effect in the materials.

NPs have been shown to be useful in clinical applications, such as antimicrobial⁷⁵ and anticancer therapies. They can kill cancer cells and reduce tumor mass upon irradiation with biocompatible NIR lasers. NPs can serve as PTAs, targeting tumor cells for ablation through PTT. Besides, they can function as contrast agents⁷⁶ for improved diagnosis, sensitizers for RT,^{77,78} and tools to differentiate cancer cell populations by conjugating them with antibodies.⁷⁹ Furthermore, combining NPs with IT and chemotherapy has shown promising synergistic treatment effects, which have undergone extensive research in recent years.⁸⁰ For example, synthetic silver nanomaterials can significantly inhibit HIV-1 infection.^{81,82}

In cancer treatment, Zhang et al developed a multifunctional metal nanoplatform, termed SFT-Au, that synergistically combined starvation therapy with physiological calcification.⁶¹ This platform comprised gold nanoparticles functionalized with salivary acid (SA), folic acid (FA),⁸³ and triphenylphosphine (TPP) as targeting moieties. This system exhibited efficient light absorption and photosensitization, and demonstrated the effective integration of SA, FA, and TPP onto a single platform through PTT evaluation. By leveraging the ability of FA and TPP to target tumor cells and the ability of SFT-Au to target Ca^{2+} (abundant in tumor cell mitochondria), coupled with the excellent light-trapping and photothermal properties of SFT-Au, the platform establishes a precise tumor mitochondria-targeted calcification system, enhancing the efficacy of “starvation therapy”. The results are summarized in the be more specific. SFT-Au was found to promote Ca^{2+} chelation and trigger calcification, further amplified by a thermal agent at 808 nm optical radiation, resulting in persistent photodamage. A recent study has introduced a novel multifunctional nanomaterial, synthesized via glycol chitosan-assisted in situ formation of gold-coated PLGA nanoshells (AuPLGA-NS). This material integrates the biodegradability of PLGA with the near-infrared (NIR) photothermal properties of gold nanoshells and the imaging capabilities of X-ray/CT. Experimental results demonstrated that AuPLGA-NS exhibits substantial photothermal conversion efficiency when subjected to 808 nm laser irradiation, achieving an 80% mortality rate in MCF-7 breast cancer cells cultured in vitro after just 4 minutes of exposure. Additionally, its X-ray attenuation performance was found to be comparable to that of conventional iodine-based contrast agents, underscoring its potential utility as an imaging contrast medium. Biocompatibility assessments indicated that the material does not exhibit significant toxicity towards normal cells.⁸⁴ This study substantiates the potential of this easily synthesized multifunctional nanosystem to concurrently facilitate photothermal therapy and image guidance, thereby offering a promising strategy for the integrated diagnosis and treatment of cancer. Similarly, Zou and Ma et al engineered a versatile Pt-based nanoplatform aimed at PTT with targeting capabilities, incorporating Arg-Gly-Asp peptide (RGD) combined polydopamine-altered Pt nanoparticles,

designated as mPt@PDA-RGDNPs.³⁹ Initially, K_2PtCl_4 and hexadecyltrimethylammonium bromide (CTAB) were fully reacted, followed by the addition of ascorbic acid to the reaction system. Upon reaction completion, anhydrous ethanol was utilized to remove excess CTAB, yielding an aqueous solution of mPtNPs. Subsequently, mPtNPs and PDA were reacted in a tris-HCl buffer to synthesize mPt@PDANPs. Finally, mPt@PDA-RGDNPs were obtained by reacting mPt@PDANPs with RGD in the tris-HCl buffer. The mPt@PDA-RGDNPs synthesized through this method exhibited high PCE under 808 nm NIR laser irradiation⁸⁵ and demonstrated good biocompatibility. The specific interaction between RGD and the overexpressed $\alpha\beta_3$ integrins on SKOV-3 cells conferred targeting and migration inhibition capabilities. Cell scratch tests indicated that the photothermal impact of mPt@PDA-RGDNPs efficiently restricted the migration of SKOV-3 cells. Overall, mPt@PDA-RGDNPs exhibited significant potential in achieving targeted photothermal ablation of tumors and inhibiting the migration of cancer cells. On the platinum nanopatform, Zhang, Zhao et al explored the utilization and possible mechanisms of Mesoporous Platinum Nanoparticles (MPNs)⁶² combined with the drug chlorosartan in PTT, utilizing neuroblastoma as a model system. Their findings demonstrated that chlorosartan-induced fibroblast ablation enhanced MPN penetration into the tumor, facilitated MPN deposition within tumor cells, thus boosting the effectiveness of PTT when it comes to eliminating tumor cells. Furthermore, this nanopatform exhibited a synergistic effect in activating immune cells, thereby inducing immunogenic cell death. This strategic approach holds significant promise for the in vivo treatment of neuroblastoma.

Gold nanophotothermal agents are currently undergoing clinical trials. Notably, Ardeshtir R. Rastinehad et al have reported preliminary findings from a trial involving gold-silica nanoshells (GSN). In this study, photothermal therapy was integrated with MRI-ultrasound imaging, and patients were monitored at various intervals post-procedure. The results demonstrated a 94% success rate for GSN in the photothermal ablation of tumors, with the feasibility and safety of the approach also being confirmed.⁸⁶

Clearance of drugs from the body is an issue that requires special attention. This is closely related to the side effects or toxicity of the drug. Biodegradable drugs show big advantages. Aravind Kumar Rengan et al developed a biodegradable liposomal gold nanoparticles (Lipos Au NPs) for tumor photothermal therapy. In vitro and in vivo studies show that Lipos Au NPs significantly inhibit cancer cell growth. Biodistribution analysis showed that the nanoparticles were metabolized by the liver and kidneys and largely cleared within 14 days.⁸⁷ The PDPC NPs developed by Tejaswini Appidi et al are also biodegradable nano-formulations for photothermal therapy. The therapeutic efficacy was verified.⁸⁸ These systems combine efficient photothermal conversion, biodegradability and real-time bioluminescence monitoring, which provides a new idea for precision tumor therapy.

Metal Sulfides and Oxides

Metal sulfides or oxides are less costly than precious metals and can also be used for PTT.^{89,90} For example, MoS_2 is a representative two-dimensional transition metal dichalcogenide,⁹¹ exhibiting significant potential in the act of eradicating bacteria owing to its intrinsic antimicrobial properties, encompassing contact killing, PDT, and PTT.¹⁹ Furthermore, MoS_2 is readily prepared with high PCE and low cost. However, metal sulfides or oxides typically exhibit negligible fluorescence and lack inherent tumor-targeting capabilities, hampering rapid real-time FI and exact localization of both primary tumors and lymph node metastases.⁹² To address these limitations, their combination with NIR organic dyes, such as Cy5.5, can be used for fluorescence dual-mode imaging therapy. For example, Shi et al developed RGD-CuS-Cy5.5,⁹³ a CuS nanoparticle-based platform, for synergistic fluorescence/PTT applications.⁴¹ These nanoparticles effectively serve dual functions: FI and targeted PTT therapy for metastatic gastric tumor cells within lymph nodes. In vivo studies demonstrated that 808 nm laser irradiation, guided by RGD-CuS-Cy5.5-mediated FI, facilitated the targeted PTT-induced destruction of gastric cancer cells in lymph nodes while causing minimal systemic toxicity.

Complex nanostructures based on metal sulfides have been reported, such as ruthenium sulfide as core nanoclusters (NCs) constructed by Lu and Huang et al. Ruthenium sulfide nanodots (OA-RuS_{1.7}NDs) encapsulated by oleic acid were initially prepared and subsequently coated with denatured bovine serum albumin (dBSA)⁹⁴ and polyethylene glycol (PEG) to obtain PEG-dBSA-RuS_{1.7}NCs.⁴² These nanostructures exhibited excellent light-to-heat conversion capabilities and possessed an optimal diameter and a near-neutral surface charge (approximately 0 mV). These characteristics contributed to prolonged in vivo circulation times and enhanced tumor targeting. Leveraging these advantages, PEG-

dBSA-RuS_{1.7}NCs could effectively target and ablate cancer cells under NIR irradiation. Metal oxides, such as manganese dioxide (MnO₂), also offer potential for PTT. Wang, Wu et al developed a nanocomposite, BP@Mn-NC,⁶³ comprising Black Phosphorus (BP) and Manganese Nanozymes (Mn-NZ) that exhibiting both photothermal and catalytic properties. The integration of Mn-NZ conferred glucose oxidase- and peroxidase-like activities to BP@Mn-NC, facilitating the generation of Reactive Oxygen Species (ROS).⁹⁵ These ROS cause lipid peroxidation and the build-up of malondialdehyde in the bacterial cell membrane. This process disrupted the exposed and vulnerable respiratory chain complex of the bacterial cell membrane, leading to a decline in intracellular Adenosine Triphosphate (ATP) levels and a concomitant loss of normal function in ATP-dependent bacterial heat shock proteins. Consequently, mild PTT mediated by BP@Mn-NC effectively eradicated multidrug-resistant bacterial infections by specifically impairing bacterial heat resistance.

Biomimetic Metal Nanostructures

Metallic nanostructures, while exhibiting potential in cancer therapy, often lack active targeting capabilities and primarily rely on the passive EPR⁹⁶ effect to accumulate at tumor sites. To address these limitations, researchers have drawn inspiration from biomimicry, employing biologically active cell membranes to encapsulate nanoparticles. This approach offers several advantages over traditional nanomedicines, including prolonged circulation time within the body, enhanced targeting and aggregation within the tumor region, and improved biosafety and biocompatibility.⁹⁷ Common sources for these cell membranes include red blood cells, platelets, and tumor cells. Cell-derived membranes, when used to coat nanoparticles, effectively camouflage them from immune recognition, thereby extending their blood circulation time. This process involves the complete transfer of natural markers, typically found on the source cell's membrane or extracellular vesicles, onto the surface of the chosen nanomaterial. The integration of gold nanoparticles (GNPs) with biofilms demonstrates significant potential within the field of drug delivery systems, especially when such integration can further optimize therapeutic effects.

Coating with erythrocyte membranes has been demonstrated to extend the drug's half-life within the body, thereby enhancing its therapeutic efficacy.⁹⁸ In a recent study, it was found that by delicately binding natural Red Blood Cell (RBC) membranes⁹⁹ to the outer surface of Polyvinylpyrrolidone-noble metal nanocomposites (PVP-AuNCs),¹⁰⁰ Piao and Wang et al successfully fabricated erythrocyte-derived loaded noble metal nanocomplexes (RBC-AuNCs).⁴³ This innovative strategy not only preserved the biological activity and pharmacological properties of AuNCs but also enhanced their biocompatibility and improved their localization ability, thus showing more significant effects during the treatment of diverse diseases. The construction of RBC-AuNCs not only successfully facilitated the integration of nanomaterials with biological systems but also opened up innovative avenues for the development of efficient and safe biomedical applications. Notably, RBC-AuNCs could be constructed with tumor cell membranes possessing cell adhesion molecules homologous to the tumor cells,¹⁰¹ which promoted the aggregation of cancer cells and enables targeted delivery of the drug to tumor cells.

Liu, Wu, et al reported a novel nanostructure, MoOx@M-SN38, where molybdenum oxide (MoOx) nanoparticles were coated with egg yolk phospholipids and subsequently encapsulated in tumor cell membranes. This nanostructure was further loaded with 7-ethyl-10-hydroxycamptothecin (SN38). In vivo studies demonstrated that MoOx@M-SN38⁴⁴ nanosheets effectively inhibited primary tumor growth and lung metastases compared to monotherapy. Notably, these novel nanosheets enabled the synergistic combination of PTT and chemotherapy,¹⁰² significantly enhancing anti-tumor immunity. Building upon this concept, researchers have explored the use of platelet membranes for drug delivery.¹⁰³ Platelet membranes are now understood to possess unique properties, including the ability to reduce drug immune rejection, exhibit specific adsorption to tumors and damaged blood vessels, and facilitate drug accumulation at the lesion site. Leveraging these advantages, Zhao, Li, et al built a biomimetic platform for tumour treatment. This platform comprised Mesoporous Platinum Nanoparticles (MPNPs) loaded with 17-Dimethylaminoethylamino-17-Demethoxygeldanamycin (17-DMAG),¹⁰⁴ a heat shock protein (HSP) inhibitor,¹⁰⁵ and subsequently encapsulated in a platelet membrane (PM) coating, resulting in the 17-DMAG/MPNPs@PM nanostructure.⁶⁴ In vitro and in vivo studies demonstrated that 17-DMAG/MPNPs@PM exhibited efficient tumor accumulation and effectively inhibited tumor cell growth.

Carbon-Based Photothermal Agents

Carbon-based¹⁰⁶ nanostructures, including graphene oxide, nanotubes, and carbon nanodots, have arisen as promising prospects¹⁰⁷ for applications in the biomedical field, particularly in PTT and PDT.^{108,109} These nanostructures exhibit unique properties that enable precise heat generation within the treatment area and the generation of tunable ROS,¹¹⁰ facilitating highly efficient tumor cell elimination. Furthermore, their distinctive effects on bacteria and specific optical properties make them valuable tools in antibacterial applications, effectively mitigating the development of drug-resistant pathways.^{111,112}

Carbon Nanotubes

Carbon Nanotubes (CNTs) are allotropes of carbon, formed by single or multiple layers of graphite flakes curled around a central axis at a certain helix angle.^{52,113} A single-walled carbon nanotube (SWNT) is characterized as a cylindrical structure composed of a single layer of carbon atoms organized in a hexagonal lattice.¹¹⁴ Multi-walled carbon nanotubes (MWCNTs) are characterized by their multi-layered nested structures.¹¹⁵ CNTs are characterized by high mechanical strength, and based on this property, there are now cases of animal experiments in which CNTs have been successfully utilized to achieve functional restoration of force-transmitting connective tissues (such as bone).¹¹⁶ Owing to the extensive surface area that they possess, strong chemical stability, and rich electronic polycyclic aromatic structure, CNTs exhibit excellent drug-carrying capacity, and a variety of drug molecules, antibodies, and nucleic acids can be attached or linked to carbon nanotubes.^{117,118} These molecular entities can be adhered to the surface of CNTs by means of non-covalent interactions (such as π - π stacking or van der Waals forces),^{118,119} or directly attached using covalent bonding methods, enhancing their stability and durability.¹²⁰ CNTs can effectively transport these molecular payloads to target cells, safeguarding therapeutic molecules from metabolic alterations during transit. Consequently, CNTs emerge as promising carriers for the intracellular delivery of nucleic acids,¹²¹ proteins,¹²² and drug molecules,¹²³ establishing a foundation for CNTs to synergize PTT with gene therapy. However, CNTs have smooth surfaces, and to load their surfaces with a certain composition, they need to undergo some treatment first to make their surfaces rough.¹²⁴ Furthermore, CNTs exhibit the advantageous capability of readily crossing the blood-brain barrier.¹²⁵ This characteristic renders them particularly suitable for the treatment of encephalopathy, offering enhanced efficacy compared to drugs with limited blood-brain barrier penetration. The high PCE of CNTs has driven their utilization in the development of PTAs. Carbon nanotubes are capable of efficiently combining chemotherapy and PTT to enhance anti-tumour effects. In addition to their therapeutic potential, CNTs serve as exceptional diagnostic tools, endowed with photoacoustic, fluorescence, and Raman imaging capabilities.^{126,127} As a result, CNTs have been thoroughly studied for numerous biomedical applications, serving as a potential treatment alternative for carcinoma. SWNTs¹²⁸ are one of the particularly promising candidates for PTT, demonstrating strong absorption in the NIR region (700–1100 nm).¹²⁹ Because biological systems display high translucency at this wavelength, SWNTs can be efficiently utilized for thermal excitation within living cells. This NIR wavelength can induce thermal stimulation by disrupting protein function and compromising the plasma membrane, leading to cell destruction. In this respect, SWNTs promote tumor ablation when the temperature reaches above 40 °C,^{52,118} while normal cells are typically resistant to this treatment. The local ablation effect based on CNTs overcomes the challenges of uneven tumor heating and the risk of tumor cell dissemination along the needle tract associated with invasive techniques like radiofrequency ablation. Zhou and Liu et al developed a SWNT-based thermo-sensitive hydrogel (SWNT-GEL) for treating xenografted gastric cancer in mice. Interestingly, SWNT-GEL could deliver the drug Doxorubicin (DOX) directly to the tumor site, enabling in situ anticancer effects. Concurrently, NIR light could penetrate the tissue to stimulate the SWNTs located at the tumor site, thereby providing thermal therapy. The DOX release profile demonstrated sustained drug delivery, with more than 20% released on the first day of injection and cumulative release reaching approximately 96% by day 28. In addition, after intratumoral injection of SWNT-GEL, NIR irradiation significantly reduced tumor growth rate in mice compared to the control group without NIR (156% vs 261%) after 28 days of treatment, suggesting sustained tumor remission under NIR irradiation.^{60,130} To further enhance PCE, MWCNTs characterized by nested columnar structures with diameters ranging from a few nanometers to a few micrometers, have been investigated. MWCNTs offer several advantages, including the capacity to load more drugs and absorb more NIR radiation than SWNTs, making them an ideal platform for combined chemo-thermal therapy.¹³¹

Oudjedi et al developed a photothermal agent utilizing gold nanorod (GNR)-modified MWCNTs (MWCNTs-GNRs).¹³² The LSPR property of GNRs enhanced light absorption¹³³ in the NIR region,¹³⁴ while the high PCE of MWCNTs facilitated efficient dispersion of heat into the surrounding environment. By synthesizing plasma MWCNTs-GNRs¹³⁵ as PTAs, researchers achieved superior local absorption¹³⁶ and heat conversion¹³⁷ compared to bare carbon nanotubes, resulting in more effective thermal ablation of cancer cells than some carbon-metal-based PTAs.¹³⁸ A similar MWCNT-based photothermal nanosystem is mTHPC/MWCNT, a complex of m-tetrahydroxyphenyl chlorin (mTHPC) and MWCNTs, developed by Marangon et al. The researchers confirmed its photothermal activity and demonstrated its low cytotoxicity and potency in promoting tumor cell apoptosis.¹³⁹

Carbon Dots

Carbon Dots (CDs) correspond to carbon-based materials typically less than 10 nm in size and are usually composed of carbon, oxygen, and hydrogen. There are currently four main types of carbon quantum dots: graphene quantum dots, carbon nanodots, and carbonized polymer dots.^{140,141} CDs exhibit a number of outstanding properties, including good stability, high electrical conductivity, photo-induced photothermal conversion, tunable fluorescence, excellent photostability, very low cytotoxicity, and high biocompatibility.^{142,143} Intrinsic photosensitivity¹⁴⁴ is also one of the core properties of CDs. The prominence of this trait stems from their unique chemical composition and surface modifications, enabling efficient and stable photoexcitation within the visible and NIR spectral intervals. Under photoexcitation, carbon dots not only facilitate a diverse array of photochemical reactions, such as electron and energy transfer, and photothermal conversion, but also exhibit a rich spectrum of photophysical properties through complex processes like inter-system crossing. These attributes have resulted in a large number of application potentials in the field of medical sciences.

Within the context of PDT and PTT, CDs demonstrate unique dual-functionality, with unprecedented potential and extensive applications in cancer treatment and microbial infections.¹⁴⁵ In response to the simplified functionalized surface properties exhibited by CDs, their efficient combination with photosensitizers (PSs) has demonstrated significant synergistic effects in the combination therapy of PDT and PTT.¹⁴⁶ The synthesis of Mannose-grafted Fe-doped Carbon Dots (M/Fe-CDs) was reported in a study by Ye and Zhang et al⁴⁵ whereby M/Fe-CDs exhibited excellent photothermal properties, with a PCE significantly elevated to 30.1% compared to unmodified CDs. They also possessed good water solubility and biocompatibility. It has been demonstrated that M/Fe-CDs can achieve localized heating and killing of tumor cells under 808 nm NIR light irradiation. In addition to their excellent photothermal properties, M/Fe-CDs can be utilized in conjunction with IT. M/Fe-CDs are capable of binding CpG-oligodeoxynucleotides (CpG-ODN) via electrostatic interactions and transporting them into the cytoplasmic region of Dendritic Cells (DCs), significantly increasing CD80/86 expression on the surface of DCs. Therefore, M/Fe-CDs represent a multifunctional nanoplatform that synergizes PTT and IT. In addition to CDs synthesized from chemical materials, there are also CDs synthesized from natural materials. For instance, Liu and Cui et al synthesized fluorescent CDs from cinnamon fruit, exhibiting excellent photothermal properties and negligible toxicity. Their bright green fluorescence is conducive to bio-imaging. Experiments have demonstrated that these CDs can successfully and efficiently induce Hela cell death under 808 nm NIR irradiation.¹⁴⁷ Zhang, Yang, et al have developed an advanced nanoplatform utilizing copper-nitrogen coordinated carbon dots (Cu-N-CDs) for targeted tumor therapy through hyaluronic acid modification. This material exhibits valence state switching in response to the glutathione-rich microenvironment, leading to dynamic modulation of its photophysical properties: the Cu²⁺ state predominantly facilitates photothermal therapy (PTT), while the Cu⁺ state enhances fluorescence imaging in conjunction with photodynamic therapy (PDT). The study demonstrated, through multimodal characterization, that a single laser irradiation can simultaneously achieve a combined PTT/PDT effect. Furthermore, residual tumors can be precisely targeted using Cu⁺-state fluorescence for complementary PDT-mediated eradication. This system is both biocompatible and responsive to the tumor microenvironment, offering a novel strategy for multimodal precision therapy of solid tumors.¹⁴⁸

Graphene Oxide

Graphene is closely related to carbon nanotubes, and graphene and its derivatives, including Graphene oxide (GO) and reduced graphene oxide (rGO), have been extensively explored as PTT reagents. GO offers a potential new approach to

treating cancer by assisting in the precise transfer of genetic components and therapeutic chemicals to the tumor region.¹⁴⁹ GO possesses exceptional properties, being the thinnest and strongest material discovered to date,¹⁵⁰ with excellent electrical and thermal conductivity. Its unique single-atom-thick, two-dimensional structure renders it an ideal scaffold for composite nanomaterials. Carbon-based materials, such as graphene oxide (GO), are considered promising substrates for metal ions due to their high surface area and uniform pore size, which provide a basis for further modification.¹⁵¹ The multi-layered and porous structure of GO endows it with a specific adsorption capacity, making it advantageous for addressing environmental pollution challenges.¹⁵² The advantages of GO nanostructures encompass encapsulating genes or drugs to protect them from degradation and enhancing cellular uptake, besides enhancing pharmacokinetics and bioavailability through concentrating therapeutic substances in a specific tumor region. Its excellent photothermal properties and ability to generate ROS can effectively convert NIR light into heat to selectively ablate cancer cells. Based on GO's phototherapeutic capabilities, the combined application of GO nanoparticles with PDT and PTT has demonstrated significant potential in inhibiting tumor growth.¹⁵³ The successful tumor eradication observed with GO nanoparticles is largely attributed to their internalization via the primary endocytosis pathway, ensuring precise delivery to the target site. Along with their potential medical utilizations, GO nanoparticles show promising prospects as vaccine candidates because of their capacity to trigger both cellular and innate immunity.¹⁴⁹

These nanoparticles can also be used to detect, diagnose, and eradicate cancer. Gao and Pei et al synthesized GO-Austar@rHSA-FA@IR780 through a multi-step process: firstly, large-molecule GO was synthesized and then processed to obtain small-molecule GO. Subsequently, Au was modified to yield GO-Austar, which despite not improving targeting or PCE, was further modified with Reduced Human Serum Albumin-FA coupling (rHSA-FA) to enhance targeting and encapsulate IR780. In vitro experiments demonstrated excellent biocompatibility with MGC-803 cells and potent phototoxicity. In vivo studies revealed significant tumor growth inhibition and near-complete tumor elimination.⁴⁶

In the field of antibacterial applications, Wu and Deng et al synthesized GO/Ag₂S via chemical precipitation in a weak alkaline environment. GO/Ag₂S exhibited excellent photothermal conversion properties and considerable antibacterial potency against *Staphylococcus aureus* and *Escherichia coli*. It disrupted bacterial membrane integrity and inhibits bacterial growth through various mechanisms.^{154,155} Ma and Qi et al prepared GO-PEG-NH₂ for sterilization therapy. The positively charged amino group enabled GO-PEG-NH₂ to selectively kill supracellular bacteria in the presence of cells, demonstrating superior efficacy in mammalian cells. Furthermore, it exhibited good photostability and effective photothermal ablation under 808 nm NIR light irradiation with low cytotoxicity.¹⁵⁶

Organic Photothermal Agents

Semiconductor Polymer Nanoparticles

Semiconductor polymer nanoparticles (SPNs) are novel optical organic nanomaterials derived from Semiconductor Polymers (SPs),¹⁵⁷ including polyaniline (PANI), polypyrrole (PPy) and quinoxaline. SPs offer several advantages for PTT, such as excellent optical properties, good photostability, large absorption coefficients, and facile surface functionalization. Importantly, the absence of metal ions in SPNs contributes to their good biocompatibility, low toxicity, and biodegradability.^{158,159} The optical properties of SPNs are primarily determined by the precursor SP and can be modulated by altering the molecular structure of the SP. Leveraging these properties, chemiluminescence and NIR fluorescence of SPNs have been explored for tumor visualization and detection of physiological indicators and biomarkers following photoacoustic imaging.^{160,161} Furthermore, SPNs can effectively respond to NIR light, generating localized heat and ROS for both PTT and PDT.¹⁶² By capitalizing on these superior PTT and PDT effects, SPNs can precisely modulate biological activities,¹⁶³ such as neuronal activation and gene transfection.¹⁶⁴ The integration of other therapeutic components into SPNs facilitates the development of combined phototherapy cancer treatments with significantly enhanced therapeutic efficacy.

PANI is a material renowned for its exceptional electrical properties and commendable stability, with a relatively straightforward synthesis process. It finds applications across various domains, including photothermal therapy and chemical sensing. However, a notable limitation of PANI is its poor solubility, which can lead to reduced bioavailability. Nevertheless, the properties of PANI can be substantially enhanced through chemical modifications, such as protonation doping¹⁶⁵ or integration with other substances. Such modifications not only optimize its properties but also enable PANI

to exhibit anticancer and antimicrobial effects.¹⁶⁶ PANI is the first organic PTAs demonstrated to have pH-responsive properties,¹⁶⁷ exhibits an extensive array of diagnostic and curative applications. For example, researchers have developed Polyaniline Nanoparticles (PANPs) modified by F127.¹⁶⁸ These nanoparticles exhibited a high molar extinction coefficient ($8.95 \times 10^8 \text{ M}^{-1} \text{ cm}^{-1}$), achieving a PCE of 48.5%. In vivo tumor ablation studies under 808 nm NIR irradiation demonstrated efficacy comparable to other methods, while low toxicity was confirmed through tissue and hematology experiments. Research on polypyrrole has also been extensive, with innovative methods developed to synthesize Polypyrrole Nanosheets (PPy NSs). Xie and Xu et al utilized Manganese Dioxide Nanosheets (MnO_2 NSs) as both the oxidizing agent and a self-sacrificial template, enabling the rapid synthesis of PPy NSs within minutes.^{169,170} PPy NSs exhibited strong NIR-II absorption with a PCE of 66.01% under 1064 nm NIR-II light irradiation and possessed PA imaging capabilities, allowing for synergistic PA imaging and PTT for both diagnosis and treatment. Furthermore, Zhu and Gao et al reported a multifunctional thiazole-fused quinoxaline imide semiconducting polymer (PQIA-BDTP).¹⁷¹ PQIA-BDTP demonstrated a high PCE of 72.6% under 1064 nm NIR light irradiation. In vivo and in vitro experiments demonstrated the significant anti-tumor effect of PQIA-BDTP in combination with PTT, while also confirming its biocompatibility.

Conjugated Polymer Nanoparticles

Conjugated Polymer Nanoparticles (CPNs) are a subtype of SPNs. CPNs constructed upon π -extended conjugated systems exhibit significant advantages in cell-penetrating nanoparticles, including very high fluorescence brightness, extremely low cytotoxicity, excellent photostability, efficient ROS generation capability, and high PCE.¹⁷² These combined properties endow π -extended CPNs with the potential to serve as efficient therapeutic and diagnostic tools. CPNs can be utilized as drug-carrying systems,¹⁷³ contrast agents,¹⁷⁴ and PTAs concurrently, demonstrating numerous applications within the biomedical domain. In addition, the distinct light-gathering and energy-effective transport properties of CPNs enable their conversion into intelligent functional nanocomposites with significantly enhanced properties. Given these numerous features and the availability of simple and efficient preparation and isolation processes, the rapid development of CPNs and their hybrids within the medical community has been propelled to become a key player in leading cutting-edge research, with notable achievements observed in several specialized fields. As efficient photothermal conversion materials, CPN-based organic photothermal materials hold significant promise for NIR-II applications with good deep tissue penetration and low scattering properties.^{175,176} The D- π -A- π -D type conjugated small molecules synthesized with¹⁷⁷ fluorene as the donor unit can achieve NIR-II absorption by simply replacing one atom within the molecule.¹⁷⁸ Moreover, the assembly of these molecules into nanoparticles exhibits good photothermal stability and high PCE, which has been confirmed to demonstrate high efficiency for tumor treatment in both in vitro and in vivo experiments. CPNs are also suitable for NIR-I applications. Some researchers successfully synthesized Diketopyrrolopyrrole-Borondipyrromethene (DPP-BDP), a conjugated polymer with NIR-I absorption properties, through an innovative cross-coupling reaction. Utilizing Pluronic F127 as a stabilizer and functionalizing the polymer with folic acid enabled the creation of a targeted photothermolysis agent. Subsequent formation into conjugated polymer nanoparticles with uniform particle size resulted in a photothermolysis agent capable of achieving a PCE of 38.9% and a tumor reduction of 99.2%.¹⁷⁹

Organic Small Molecule Dyes

Organic Small Molecule Dyes (OSMDs) are organic photothermal materials^{180,181} that can be used as PTAs,¹⁸² with the advantages of low toxicity along with excellent biocompatibility.¹⁸³ When irradiated with NIR light, OSMDs produce heat via the PTT effect and also generate ROS¹⁸¹ via the PDT effect, acting as PS.^{184–186} The combined synergy of PTT and ROS treatment boosts cancer cell destruction and improves therapeutic outcomes.¹⁸⁷ Notably, a novel organic small-molecule photothermal material demonstrated a PCE exceeding 72.7% under 808 nm laser irradiation.¹⁸⁸ OSMDs include anthocyanine-based dyes (such as Indocyanine Green, ICG), IR series, porphyrins, boron dipyrrole dyes, rhodamine dyes, and others. These small molecules hold significant promise for clinical antimicrobial PTT applications. For instance, Diketopyrrolopyrrole (DPP) exhibits excellent photophysical properties, photostability, and structural tunability. Consequently, PTT agents based on DPP derivatives have found widespread use in PTT and have garnered

considerable attention for FI and PAI diagnostics.^{189–191} Furthermore, ICG has been approved by the Food and Drug Administration (FDA) for over fifty years for medical imaging and the treatment of patients with internal contamination from cesium or thallium exposure. In a clinical trial, ICG was used in the treatment of periodontitis with PTT, which induced minimal bacterial resistance and less cytotoxicity to oral cells than chlorhexidine gel.¹⁹² IR780 is an appropriate candidate for utilization as a photothermal agent. Upon loading nanosystems with IR780, they demonstrate fluorescence properties. This characteristic facilitates the integration with fluorescence imaging, thereby enhancing the efficacy of the therapeutic system.^{88,193} However, these PTAs possess certain intrinsic limitations. For instance, they may have a low PCE, exhibit poor stability, show hydrophobic characteristics and fast removal rate. It has been reported that although the PCE of OSMDs was lower than that of metallic agents, they could be immobilized on metallic or nonmetallic materials. This approach not only enhanced OSMD stability but also improved the overall PCE, enabling synergistic exploitation of OSMDs' PCE and ROS generation.¹⁹⁴ For instance, Biomimetic cell membrane-coated polymer vesicles were created by binding cetyltrimethylammonium bromide, ICG, and polycaprolactone onto the surface of hydrophobic gold nanorods, achieving self-assembly in aqueous solution. The increased stability of vesicles facilitated synergistic roles for PTT and PDT in prostate cancer treatment. This method enhanced ICG loading while maintaining ICG fluorescence and activity. In comparison with free ICG or Au nanorods, this material exhibited superior stability, PCE (up to 47.7 °C), and effects of photodynamic action, significantly inhibiting tumor growth. For the IR series of organic dyes, Yang and Xu et al synthesized PPy(Fe)-IR820-BSA¹⁹⁵ by polymerizing PPy nanoparticles using Fe³⁺ as an oxidant, followed by Bovine Serum Albumin (BSA) coating and IR820 loading. Fe³⁺ acted as a Chemodynamic Therapy (CDT) agent, PPy and IR820 as photothermite, and IR820 produced toxic ROS under NIR irradiation, acting as PDT. These nanoparticles were demonstrated to promote immunogenic cell death. A class of anthocyanin dyes, similar to IR820 but with higher PCE, namely the naphthylimide-modified anthocyanin dye ML880, featured a stronger electron-leaving domain due to the naphthamide modification. Jin and Cheng et al constructed a PDT/PTT/CDT multimodal synergistic nanoplatform by loading both ML880 and desired chemotherapeutic agents into ROS-responsive Mesoporous Organosilicon (RMON), significantly inhibiting tumor growth.¹⁹⁶ For another organic small molecule dye, porphyrin, researchers prepared a combined anthocyanin-porphyrin nanoparticle demonstrating good efficacy in PTT treatment of prostate cancer. Rhodamine and semicarboxyanine derivatives (RC) also exhibited strong NIR absorption. The nanoparticles RC-BSANPs, prepared by combining RC with BSA, effectively eliminated tumors via the PTT mechanism under 915 nm NIR irradiation.¹⁹⁷

Metal-Organic Frameworks

Metal-organic Frameworks (MOFs) belong to a novel class of crystalline materials characterized by periodic and internally porous structures. They are primarily constructed from metal atoms, metal clusters, and organic ligands (such as azoles, porphyrins, and carboxylates)¹⁹⁸ containing oxygen or nitrogen donor atoms, which coordinate with a variety of metals including Fe, Ca, Mg, and Zn. As crystalline materials assembled from metal nodes and organic ligands, MOFs display a multitude of distinctive benefits. These include a large specific surface area, high porosity, an adjustable pore size, a high drug-loading capacity, good biocompatibility, and the potential for surface modification. MOFs are porous nanoreactors. It also has good adsorption capacity to adsorb pollutants.¹⁹⁹ MOFs also have excellent thermal stability and can be used as photocatalysts.^{200,201} Furthermore, their porosity can be harnessed to encapsulate a diverse range of materials, such as pharmaceuticals, targeting agents, or imaging probes. This porous structure enables the controlled release of therapeutic agents and the design of stimulus-responsive systems that can be activated by light, pH, and other external stimuli.^{202–204} Therefore, MOFs serve as versatile multifunctional therapeutic platforms, finding widespread applications in catalysis, gas adsorption, energy storage, and drug delivery. They represent ideal platforms for the design of drug delivery systems, demonstrating significant potential for the development of cancer therapies.

MOFs with azoles as organic ligands include Zeolitic Imidazolate Frameworks (ZIFs), which consist of a transition metal coordinated to an imidazole-based linker (eg, 2-methylimidazole). ZIF-8, for example, comprises Zn as a metal node coordinated to 2-methylimidazole via two nitrogen atoms, exhibiting a sodalite topology. ZIF-8 and its biocomposites have shown promise in various biomedical applications, including biosensing, cancer and bacterial therapy, wound healing, and biocatalysis.²⁰⁵ Cancer therapy utilizing ZIF-8-based materials can be achieved through diverse strategies

such as drug delivery, PTT, PDT, CDT, starvation therapy, and gene therapy. Notably, the encapsulation of indocyanine green within ZIF-8 significantly enhanced photostability, thereby improving PTT efficacy. Similarly, ZIF-8 nanostructures encapsulating Hollow Silver Sulfide (HAg₂S), forming HAg₂S/ZIF-8 structures, might be additionally modified using hyaluronic acid to target the CD44 receptor overexpressed in cancer cells. In this study, this nanoplatform was further functionalized to encapsulate azithromycin hydrochloride, enabling the synergistic combination of PTT and CDT for enhanced therapeutic outcomes.²⁰⁶

Zhang and Yuan designed and synthesized a porphyrin-cored, Cu²⁺-doped MOF, namely PCN-224(Cu), and subsequently modified its surface with Polydopamine (PDA) to obtain PCN-224(Cu)@PDA (PCP).²⁰⁷ This porphyrin-based organic ligand was then incorporated into a multifunctional nanocomposite hydrogel through dynamic Schiff base bonding between oxidized sodium alginate and methyl chitosan. This resulted in injectable and self-repairing hydrogels. Within this system, Cu²⁺ within the MOF was converted to Cu⁺ by reacting with glutathione, thereby reducing the antioxidant activity of tumors and enhancing CDT effects. The Cu²⁺/Cu⁺ redox couple induced a Fenton-like reaction within tumor cells, generating highly toxic hydroxyl radicals. Simultaneously, PDA enabled efficient photothermal conversion for PTT under NIR irradiation. Moreover, the porphyrin core acted as a photosensitizer, generating ROS for effective PDT. This injectable, self-healing hydrogel served as a versatile platform for in situ delivery of PCP to the tumor site, followed by cellular endocytosis. This approach facilitated precise and synergistic CDT-PDT-PTT therapy.

Unlike the aforementioned ligands, carboxylic acids have also been employed in MOF synthesis. For instance, Hao and Liu et al synthesized MOF nanoparticles using amino-terephthalic acid as a ligand and Zr⁴⁺ as a metal ion.²⁰⁸ Subsequently, the NH₂ group was modified to N₃ using an azide-transferring reagent. Through a click chemistry reaction without copper, DBCO disulfide bond-functionalized PD-1/PD-L1²⁰⁹ encapsulating AUNP-12 was covalently incorporated into the MOF nanoparticles. The nanoparticles were then loaded with the PTAs ICG to successfully obtain ICG-MOF-SS-AUNP12²¹⁰ nanoparticles with uniform and stable size.⁵⁰ These nanoparticles displayed the release of PD-1/PD-L1 blockers triggered by GSH and demonstrated a powerful photothermal effect be able to effectively killing cancer cells. By 808 nm NIR irradiation, ICG-MOF-SS-AUNP12 successfully facilitated the maturation of DCs and initiated the immune response.

Multimodal Imaging Theranostics

Numerous photothermal agents possess bio-imaging capabilities, and the comprehensive utilization of this property could significantly enhance the optimization and application of photothermal therapy. Therapeutic diagnostic probes, which integrate diagnostic functions with therapeutic efficacy, represent a promising class of tools for cancer treatment. A close and indispensable relationship exists between diagnosis and treatment. Integrated diagnostics, achieved through the fusion of multidisciplinary technologies, enable comprehensive and accurate diagnosis, characterization, and monitoring of disease efficacy. This integrated approach is crucial for enhancing the quality of medical care and facilitating patient recovery.^{16,211,212} The synergistic application of PTT and imaging techniques is shown in Figure 1.

Photoacoustic Imaging

Photoacoustic Imaging (PAI) represents a new-fangled biomedical imaging technique. It capitalizes on the photoacoustic effect, integrating the high-contrast feature of optical imaging with the deep-tissue-penetrating ability of ultrasound imaging. In PAI, a brief laser pulse irradiates biological tissue, inducing light absorption and subsequent thermoelastic expansion. This expansion generates ultrasound waves (ie, photoacoustic signals).^{213,214} These signals are detected by ultrasound transducers, and subsequent signal processing and image reconstruction algorithms generate images that reflect the optical absorption properties of the tissue. PAI exhibits high resolution,²¹⁵ exceptional contrast, and non-invasive nature, with applications in diverse fields such as tumor detection, vascular imaging, and brain function mapping. As a non-ionizing imaging technique, PAI surpasses traditional optical imaging by mitigating the significant light scattering that limits deep tissue penetration, as acoustic waves experience far less scattering.²¹⁶ PAI represents an innovative imaging technique achieving deep tissue penetration while maintaining high spatial resolution,²¹⁷ demonstrating significant potential for real-time, in vivo monitoring of biological processes. To enhance therapeutic efficacy, minimize side effects, and reduce the risk of overdose, accurately setting the therapeutic window and monitoring

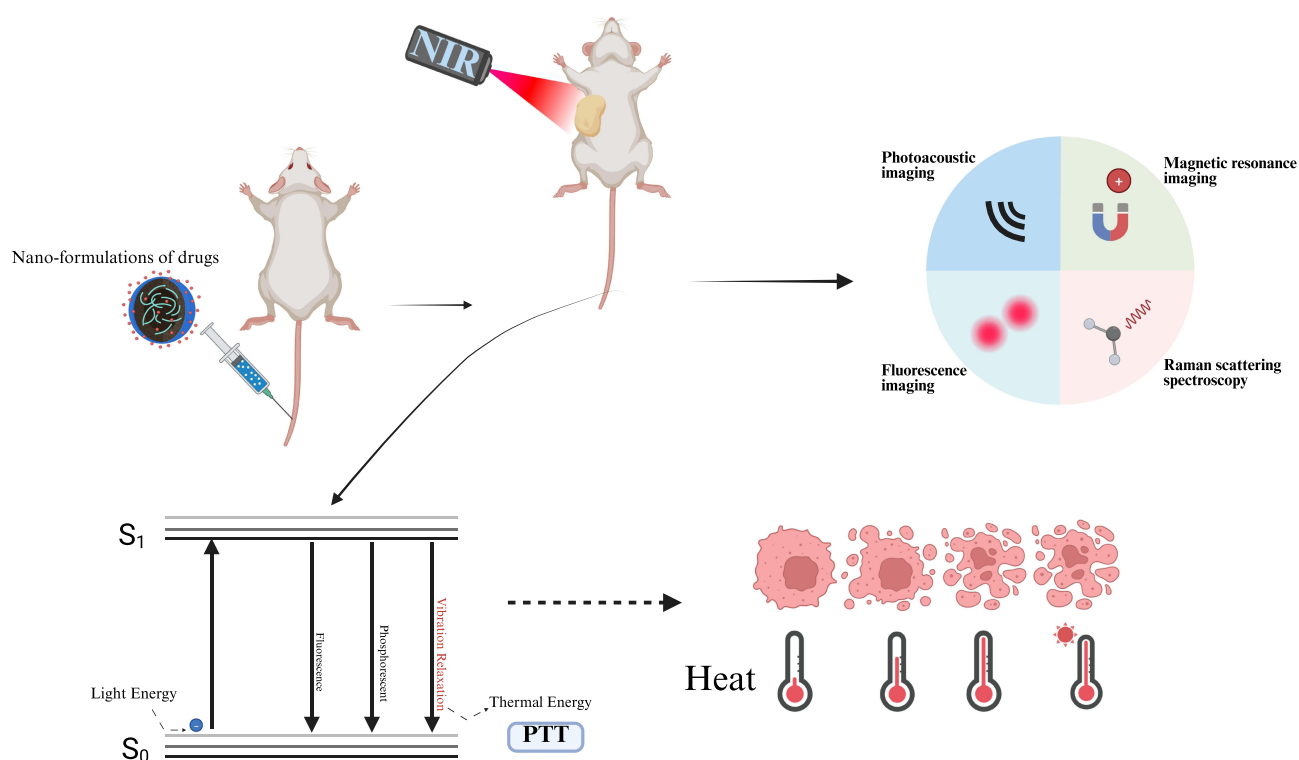


Figure 1 Schematic diagram of PTT-imaging theranostics (Created in BioRender. shang, y. (2025) <https://BioRender.com/dbx88p9>).

therapeutic efficacy through imaging and diagnostic tools is crucial. Consequently, the design of PTT photothermal agents should adhere to PAI principles,²¹⁸ aiming to improve overall treatment effectiveness, safety, and precision.²¹¹ In the context of physically assisted interferometry, PNP are widely utilized. Their unique properties trigger substantial light-matter interactions, ensuring that nanoparticle absorption efficiency significantly surpasses that of dye molecules, facilitating efficient photoacoustic signal generation. These signals originate from the activation of endogenous molecules within living cells or the release of exogenous contrast agents.²¹⁹ The optimal excitation light wavelength²²⁰ can be selected based on nanoparticle size, geometry, and constituent components. For instance, Antimony (Sb) semimetallic nanomaterials exhibit high efficiency as PAI and PTT agents.²²¹ Sb Nanorods (Sb NPs) can be synthesized using a mixture of 1-octadecane and oleylamine as a solvent.²²² Aqueous dispersions of polyethylene glycolized Sb NPs demonstrate high-intensity light absorption across UV to NIR wavelengths, enabling their function as PTAs for 808 nm NIR light, achieving a PCE of 41% without significant toxicity. In vivo experiments revealed that injecting this reagent into tumors produced a strong photoacoustic signal upon NIR irradiation, confirming its suitability as a NIR PAI reagent. Similar multimodal nanoplatforms based on metallic nanomaterials include AuNCs/Se, comprising gold nanocages (AuNCs) coated with selenium-modified Chitosan Shells (CS) and modified with iRGD for targeted delivery. Fang et al further developed AuNCs/DOX@Se-iRGD by loading the platform with the chemotherapeutic drug DOX, creating a CDT/PTT/PAI multimodal antitumor nanoplatform.^{223,224}

Magnetic Resonance Imaging

Magnetic resonance imaging (MRI), as a non-invasive imaging technique,²²⁵ is favored for its ability to perform precise imaging and track various pathological changes, especially in diseases such as cancer. Its principle of operation relies on the phenomenon of relaxation of protons within tissues,^{226,227} a process significantly influenced by the unique properties of the chemical environment of matter.²²⁸ MRI probes are divided into two main types: MRI contrast agents based on T2-weighting and MRI contrast agents based on T1-weighting. In T2-weighted MRI imaging, the contrast agent achieves this effect by modulating the transverse relaxation time of the tissue. Specifically, the contrast agent increases the

transverse relaxivity (r_2) of the tissue, which results in the region appearing darker on T2-weighted images. This technique facilitates clearer identification and contrast of different tissue characteristics, particularly crucial for the diagnosis and evaluation of certain pathological states. In contrast, T1-weighted MRI contrast agents substantially enhance image brightness by adjusting the longitudinal relaxivity (r_1) of the tissue.⁷⁶ Both contrast agents possess distinct advantages in clinical use and are suitable for different imaging needs and diagnostic goals. Achieving contrast in MRI applications with nanosystems following intravenous injection hinges on their ability to significantly enhance the plasmonic relaxation properties of specific tissues relative to surrounding tissues. This concept also applies to the design of photothermal media within PTT. By integrating MRI contrast agent functionality, PTT achieves highly effective thermal therapy and enables precise image monitoring.^{229,230} For example, Mo and Qiu et al synthesized polydopamine-manganese dioxide-IR780 iodide, integrating the tumor therapeutic diagnostic function of IR780, the photothermal conversion ability of IR780, and the property of Mn to promote T1-weighting in MRI, and the preparation reduced the biotoxicity of IR780 and enhanced the PTT effect. And the component MnO_2 can reverse the hypoxic environment in the tumor environment and facilitate the occurrence of PDT.²³¹

A research team implemented an innovative strategy to load manganese carbonyls at the core of hollow mesoporous copper sulfide nanoparticles, aiming to develop a composite material with both MRI contrast enhancement and photothermal effects. This design not only significantly improved the efficiency of the PTT process but also enabled real-time MRI images to monitor the treatment process, thus supporting more precise and customized treatment strategies.²³² He et al reported the preparation of a novel core-shell hollow copper sulfate-metal-organic framework HCuS@MIL-100 .^{233,234} HCuSNPs were first synthesized, and then MIL-100 was coated on the outer layer of HCuSNPs to form HCuS@MIL-100 , which showed good photothermal effect under 1064 nm NIR-II light irradiation and excellent biocompatibility, showing strong T_2 MRI capability. The biomimetic photothermite mentioned above is also widely used in PTT/MRI dual-mode synergy. Zhang et al combined a photothermite gold nanobipyramid (AuNBP) with MRI-capable MnO_2 to prepare a core/shell structure (Au@MnO_2), and then modified the surface of Au@MnO_2 with plasma membranes (PMs) of homologous cancer cells that have targeting capabilities. $\text{Au@MnO}_2\text{@PM}$ (AMP)²³⁵ was obtained to achieve tumor targeting. It was experimentally demonstrated that AMP possessed multimodal imaging functions, such as computed tomography, photothermography, and MRI, and showed significant PTT efficacy in both in vivo and in vitro experiments.

Fluorescence Imaging

Fluorescence Imaging (FI) refers to the phenomenon where a fluorescent substance emits light with different colors or intensities when irradiated with light, and this emission ceases quickly upon cessation of irradiation. Artificial design can be carried out for exogenous fluorescent probes to exhibit unique fluorescence in the UV, visible, or NIR spectrum. Furthermore, their fluorescent properties, including excitation and emission wavelengths, are highly sensitive to their local environment (polarity, viscosity, etc.). FI offers several advantages, such as high sensitivity and temporal resolution, low cost, and excellent safety, making it widely used in clinical settings. Some nanoprobes employed in FI exhibit good photothermal conductivity, enabling their use as PTAs in PTT. Through targeted processing and modification, these PTAs can be specifically directed towards certain tumor cells.²³⁶ The integration of FI with PTT/PDT can reveal tumor location in real time, which has great potential in early diagnosis and precision treatment of cancer. Moreover, combining FI with drug delivery facilitates the development of dual-function systems for both diagnosis and therapy.^{237,238} However, conventional FI in the visible and NIR-I regions can be susceptible to interference from tissue scattering and autofluorescence, leading to reduced imaging resolution and high false-positive rates.²³⁹ Deeper tissue penetration, lower autofluorescence background, and reduced light absorption and scattering in biological tissues make NIR-II FI a promising solution to these challenges. Integrating NIR-II FI with PTT and PDT can notably enhance the precision of cancer therapeutic diagnostics. Simultaneously, it reduces the harm inflicted on healthy tissues to the greatest extent possible. However, due to the principle of energy conservation, the two energy dissipation modes of PTT (non-radiative decay) and FI (radiative decay) are inherently in conflict.²⁴⁰ Therefore, a primary objective in FI-guided PTT is to develop methods that effectively balance the photothermal effect with fluorescence. IR-780, an anthocyanin dye, exemplifies an agent possessing both fluorescence emission and photothermal conversion properties, facilitating real-time monitoring of tumor sites.²⁴¹ Although IR-780 offers improved therapeutic efficacy, its high toxicity at elevated

doses restricts its further application as a PTT agent. IR-825 exhibits two absorption peaks at 600 nm and 820 nm, a characteristic that is favorable for mitigating this issue. Upon excitation with a 600 nm laser, fluorescence emission occurred at approximately 650 nm with a fluorescence quantum yield (Φ) of 42%.²⁴² Conversely, when stimulated by the 820 nm laser, Φ decreased markedly, while the PCE increased significantly. Dual excitation wavelengths enabled energy dispersion, thereby reducing the degree of energy concentration at a specific wavelength. Furthermore, this approach could partially compensate for the limitations inherent in single-wavelength excitation, leading to a more comprehensive and homogeneous excitation effect. This, in turn, diminished the risk of localized high-energy accumulation and associated toxicity. Leveraging this unique property of IR-825, researchers developed a dual-excitation light-induced therapeutic and diagnostic agent capable of both FI-guided and simultaneous PTT. This innovative agent showed efficient thermal ablation within a mouse breast cancer model.²⁴³ Wang, Xu, and their research team have engineered a biomimetic nanodelivery system, designated as M-HMnO₂@ICG NP, tailored for multimodal imaging-guided therapy targeting cervical cancer. Within the tumor microenvironment, the degradation of the carrier particles releases indocyanine green (ICG), which facilitates the self-generation of oxygen for PDT and reduces glutathione levels, thereby enhancing therapeutic efficacy through the combined effects of CDT and PDT. Furthermore, ICG contributes to synergistic PDT/PTT. Manganese ions (Mn²⁺) function as contrast agents for magnetic resonance imaging, while ICG is employed for photothermal and fluorescence imaging. The M-HMnO₂@ICG system demonstrates efficient tumor site accumulation, exhibiting promising therapeutic efficacy and biocompatibility. This approach represents an innovative strategy for the synergistic treatment of cervical cancer.²⁴⁴

Raman Spectroscopy

Raman spectroscopy is an imaging technique that relies on the inelastic scattering of incident light caused by molecular vibrations, rotations, and other energy level transitions, enabling “fingerprint” identification.²⁴⁵ The frequency difference between the scattered and incident light corresponds to the energy level differences in molecular vibrations or rotations. By analyzing the frequency and intensity of Raman scattered light, valuable insights into molecular structure and chemical bonding can be obtained. Raman scattering can be utilized for diagnosing and monitoring diseases, such as employing serum Raman spectroscopy to detect the presence of cancer cells in a patient’s body, thereby providing a preliminary diagnosis. Surface-enhanced Raman scattering, which is based on Localized Surface Plasmon Resonance (LSPR), occurs near metal ions and further amplifies the Raman spectra.²⁴⁶ Wang, Sun, et al developed a hyaluronic acid-modified, doxorubicin-loaded gold nanoframework (AuNF). This AuNF exhibits strong absorbance in the near-infrared II region, facilitates photothermal therapy (PTT), and generates a robust photoacoustic signal. The LSPR effect of gold enhances the capabilities of AuNF.²⁴⁷

Synergistic Therapy

When PTT technology is applied within a tissue, its effectiveness may be affected by a decrease in light intensity.²⁴⁸ PTT-treated tumor tissues exhibit inhomogeneous heat distribution and significant hypoxia, hindering complete tumor cell eradication through a single therapeutic approach. Consequently, synergistic therapies¹¹² have emerged as an effective strategy to address these challenges.²⁴⁹ Secondly, a significant advantage of combinatorial therapies lies in their ability to effectively reduce the occurrence of side effects. By combining multiple therapies, the dosage of individual therapies can be reduced without significantly affecting the overall therapeutic efficacy. For example, the heat energy produced by the photothermal effect is capable of augmenting the therapeutic effectiveness of some anti-cancer medications. Furthermore, heat generation induced by NIR radiation can not only cause damage to malignant cells but also significantly enhance the efficacy of other therapeutic modalities, serving as the foundation for the realization of photothermal synergistic therapies. Photothermal synergistic therapy operates through a variety of mechanisms, including but not limited to: photo-controlled drug release, photothermal-enhanced enzyme activation, photothermal-regulated gene expression, photothermal-stimulated immune response, and photothermal-promoted chemical reactions. These mechanisms work synergistically with the aim of optimizing therapeutic effects and enhancing the precision and efficiency of biomedical interventions.²⁵⁰ The synergistic effects of different therapies and PTT are shown in [Figure 2](#). A statistical

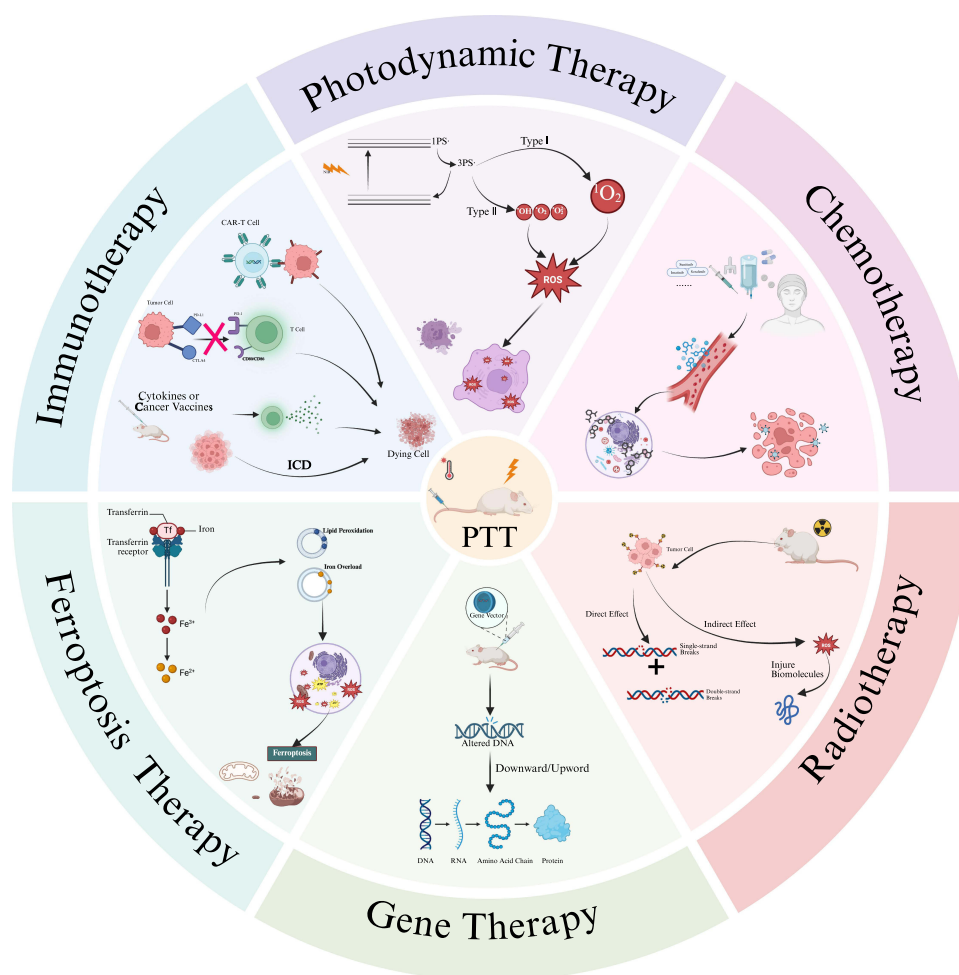


Figure 2 Synergy of different therapies with PTT (Created in BioRender: shang, y. (2025) <https://BioRender.com/9ze5nbo>).

study was conducted regarding the efficacy of synergistic therapies. Several cases are summarized in Figure 3. This highlights the fact that the efficacy of synergistic therapies is significantly better than that of monotherapies.

Immunotherapy

Immunotherapy (IT)²⁵³ is an approach that depends on the patient's native immune system for combating cancer, demonstrating a higher level of safety and efficacy compared to traditional treatments.²⁵⁴ Immunotherapy operates through four primary mechanisms: enhancing antigen recognition, initiating an immune response, diminishing immune escape, and alleviating immunosuppression. These mechanisms are illustrated in Figure 4. To activate and enhance the effects of IT, a range of strategies have been widely adopted, including but not limited to checkpoint blockade therapy (ICB),^{255,256} adoptive T-cell transfer, as well as the application of emerging technologies such as chimeric antigen receptor T-cell (CAR-T)²⁵⁷ therapy and cancer vaccines.^{258–261} The combined application of PTT and IT has demonstrated remarkable potential and effectiveness in the field of cancer therapy.²⁶² Through this combination, PTT not only directly destroys tumor cells. It also releases specific tumor antigens in situ within them, thereby activating the body's specific anti-tumor immune response against these antigens.^{263,264} This process enables patients to rely on their own immune system to eliminate diffuse lesions that are not covered by laser irradiation, effectively preventing tumor recurrence. Meanwhile, as an immune adjuvant, PTAs effectively promotes the activation of the immune system and further enhances the ability to recognize and attack tumors. This synergistic effect not only improves treatment efficiency but also significantly enhances the safety of the treatment and the long-term survival rate of patients. A team of researchers designed an innovative microneedle delivery system that incorporated sulfhydryl-modified Au nanorods

with the immune checkpoint inhibitor anti-PD-1 peptide, aiming to achieve precise drug release and enhance immune response.^{265,266} With its superior mechanical properties, the microneedle system enabled accurate transdermal drug delivery. Upon insertion into human skin, it released anti-PD-1 peptides and gold nanorods. These components enhanced the cytotoxic T-lymphocyte-mediated destruction of tumor cells. When exposed to NIR radiation, the system generated heat, facilitating PTT for tumor elimination. Notably, this microneedle delivery system significantly enhanced the immune response and prolonged the survival of mice. Bionic-type nano-delivery systems have also demonstrated significant potential in IT synergistic with PTT. Ma and Li et al⁴⁹ constructed a Prussian blue variant of PMo@CCM doped with Molybdenum (Mo) and coated with cancer cell membranes (CCMs). This system could activate the immune system through a combination of PTT and CDT, inducing immunogenic cell death and promoting antigen presentation.²⁶⁷

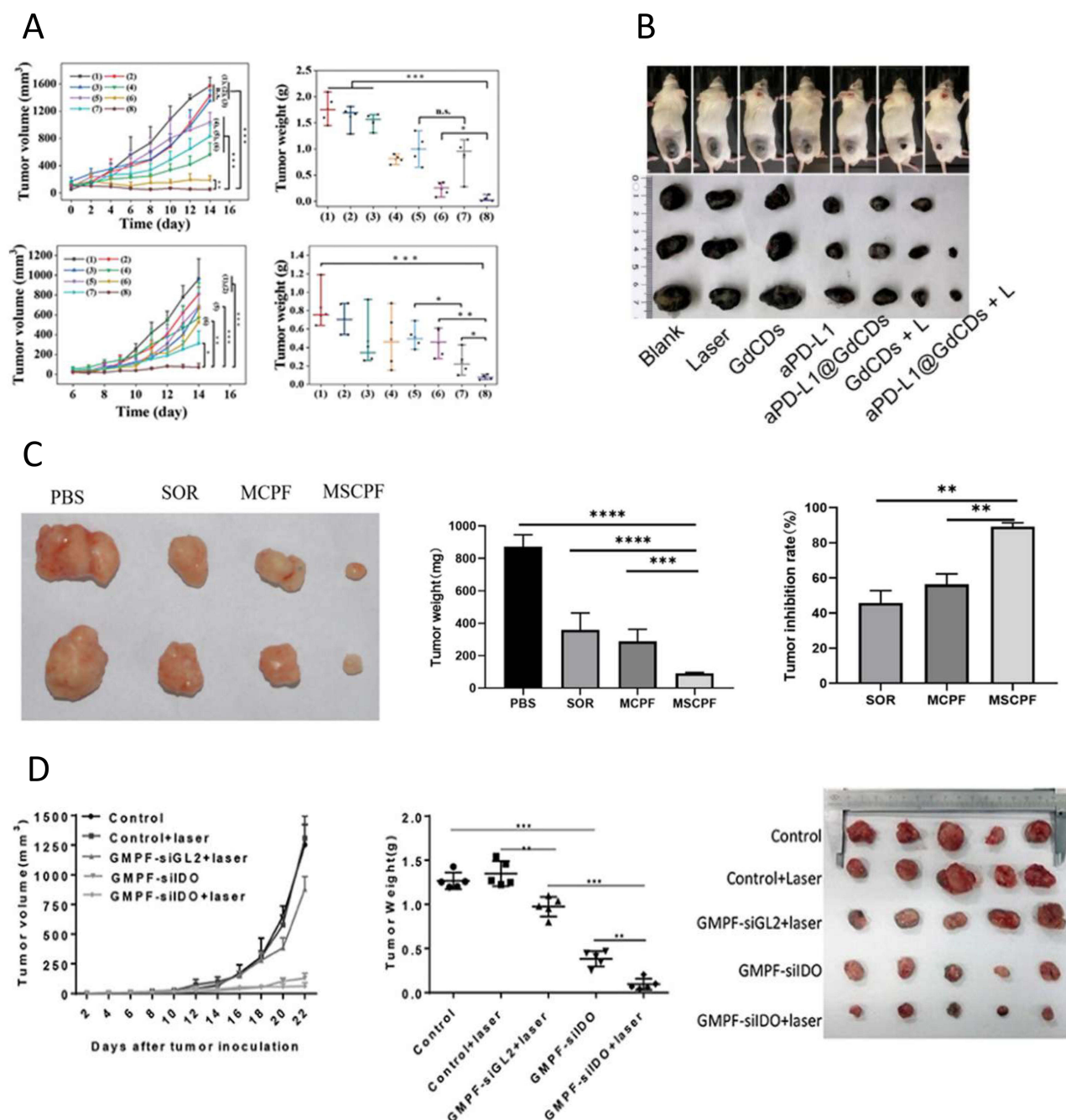


Figure 3 Continued.

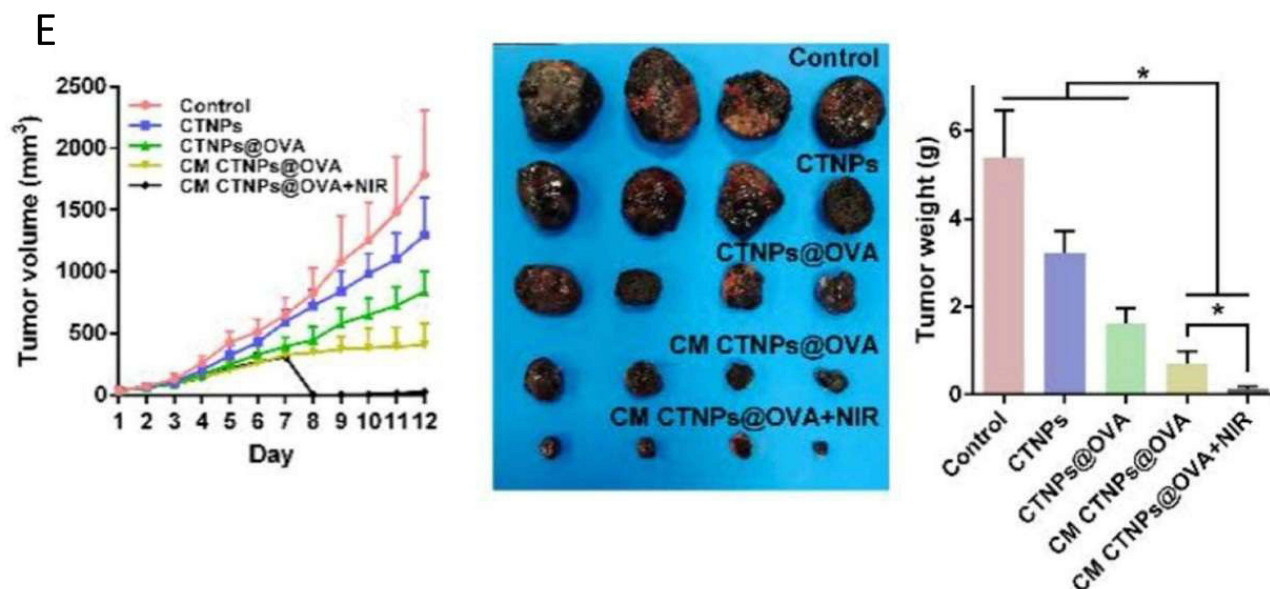


Figure 3 Synergistic therapy statistics. (A) The Integrated Impact of Synergistic PTT, IT and CDT Employing PMo@CCM. Reprinted with permission from *Advanced Functional Materials*. 2024; 34(41):2402692. Ma S, Li D, Jia X, Xu W, Ding G, He J et al. Homologous tumor targeting molybdenum-doped prussian blue for enhancing immunotherapy via PTT/CDT and remodeled tumor immune microenvironment. Copyright © 2024 John Wiley and Sons.⁴⁹; (B) The Integrated Impact of Synergistic PTT, PDT, and ICB Employing aPD-L1@GdCDs. Reprinted with permission from *Journal of Colloid and Interface Science*. 2025; 678:1088–1103. Fan Y, Zhang R, Shi J, Tian F, Zhang Y, Zhang L et al. Mild near-infrared laser-triggered photo-immunotherapy potentiates immune checkpoint blockade via an all-in-one theranostic nanoplatfrom. Copyright © 2025 with permission from Elsevier.²⁵¹; (C) The Integrated Impact of Synergistic PTT, Chemotherapy and Ferroptosis Employing MnO₂-SOR-Ce6@PDA-PEG-FA. Reprinted with permission from *Nanoscale Research Letters*. 2022; 17(1). Wang CG, Cheng XL, Peng H, Zhang YW. NIR-Triggered and ROS-Boosted Nanoplatfrom for Enhanced Chemo/PDT/PTT Synergistic Therapy of Sorafenib in Hepatocellular Carcinoma. Copyright © 2022 Springer Nature. Creative Commons.⁵³; (D) The Integrated Impact of Synergistic PTT, GT and IT Employing GMPF-silIDO. Reprinted with permission from *Frontiers in Immunology*. 2020; 11:968. Zhang Y, Feng Y, Huang Y, Wang Y, Qiu L, Liu Y et al. Tumor-targeted gene silencing IDO synergizes PTT-induced apoptosis and enhances anti-tumor immunity. Copyright © 2020 Zhang, Feng, Huang, Wang, Qiu, Liu, Peng, Li, Kuang, Shi, Shi, Chen, Joshi, Wang, Yuan and Min. Creative Commons.²⁵²; (E) The Integrated Impact of Synergistic PTT, Ferroptosis and IT Employing CMCTNPs@OVA. Reprinted with permission from *Materials Today Chemistry*. 2023; 27:101308. Fang T, Ma S, Wei Y, Yang J, Zhang J, Shen Q. Catalytic immunotherapy-photothermal therapy combination for melanoma by ferroptosis-activating vaccine based on artificial nanoenzyme. Copyright © 2023 Elsevier.⁵⁴ Based on the research data presented, it can be concluded that the therapeutic efficacy of the synergistic treatment group is significantly superior to that of the single treatment group.

Modification with anti-programmed cell death Protein-1 (PD-1) could effectively modulate the tumor immunosuppressive microenvironment, further enhancing the efficacy of IT. Building upon ICB strategies, Fan, Zhang, et al designed and synthesized anti-PD-L1-modified gadolinium-doped carbon dots (aPD-L1@GdCDs), which integrate PTT, PDT, and ICB. This composite material exhibits potential for multimodal imaging applications. In vivo experimental results demonstrated that aPD-L1@GdCDs significantly enhance immune cell activity and exhibit pronounced cytotoxic effects against tumor cells, while causing no discernible damage to normal tissues. The biosafety of this system has been successfully validated.²⁵¹

Photodynamic Therapy

Photodynamic therapy (PDT) is a treatment approach that makes use of photosensitizers and lasers to selectively destroy cancer cells.²⁶⁸ It is a localized therapy where ROS production is induced by the photosensitizer. The Photosensitizer (PS), enriched at the tumor site, is excited to an excited state by laser irradiation. PDT comprises three core elements: light, PS, and O₂.²⁶⁹ When activated at specific NIR wavelengths, the presence of PS leads to oxygen depletion, which in turn triggers a large amount of ROS. These highly oxidative species effectively destroy tumor cells and inhibit their further proliferation. During the PDT process, the photosensitizer is first incorporated into the target area, followed by exposing to light of a particular wavelength that matches the photosensitizer's absorption spectrum. After irradiation, two types of redox reactions, type I and type II, are initiated.²⁷⁰ Type I ROS generation mainly involves electron transfer within the PS, producing superoxide anion radicals (O₂^{•-}), hydrogen peroxide (H₂O₂), and hydroxyl radicals (OH[•]).²⁷¹ Type II ROS primarily consists of singlet oxygen (¹O₂) generated via energy transfer from oxygen.²⁶⁸ Several studies have demonstrated that OH[•] exhibit the highest cytotoxicity against cancer among free radical oxides. The core process

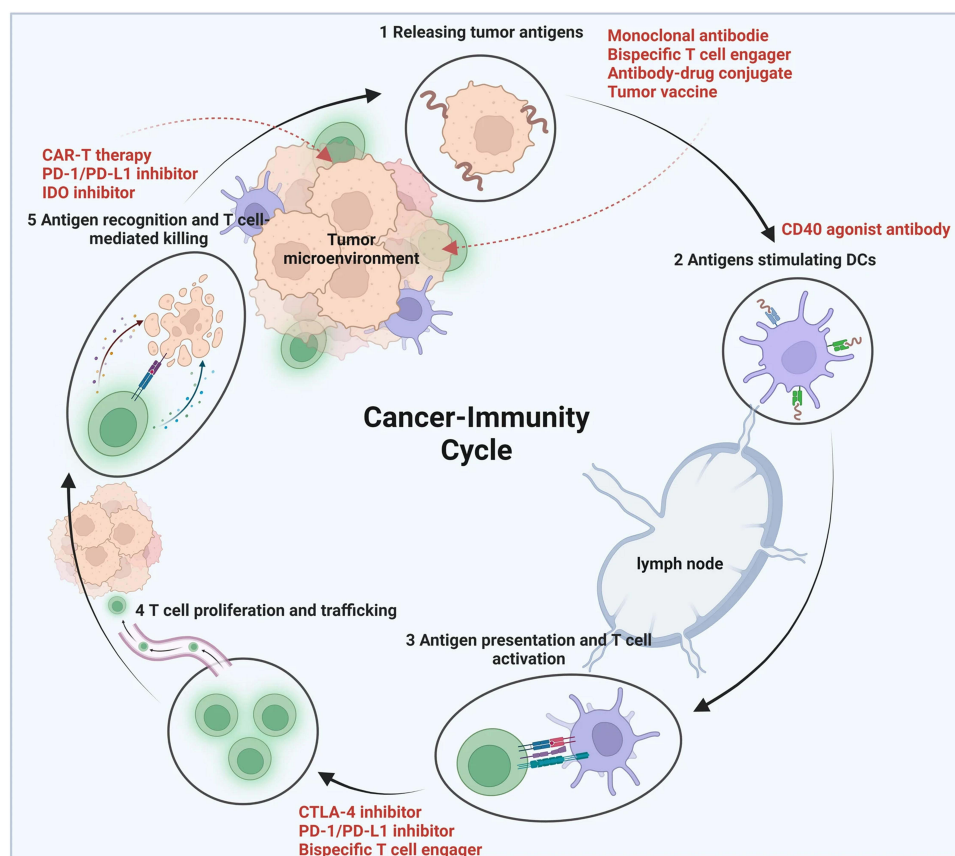


Figure 4 The main process of immunotherapy. Reprinted with permission from *Signal Transduction and Targeted Therapy*. 2023; 8(1):306. Tang, L, Huang, Z, Mei, H. et al. Immunotherapy in hematologic malignancies: achievements, challenges and future prospects. Copyright © 2023 Springer Nature. Creative Commons.²⁵³

involves photons exciting PS from its ground state to a singlet excited state ($^1\text{PS}^*$). This singlet state undergoes intersystem crossing to a triplet state ($^3\text{PS}^*$), which then either interacts with an oxygen molecule to generate $^1\text{O}_2$ or reacts with substances in the body to generate free radicals, including H_2O_2 and O_2^- , which triggers the generation of ROS. The basic mechanism of Type I and Type II photodynamic therapy is shown in the following Figure 5. ROS have a vital part in the redox control of ion channels, transcriptional regulators, and protein phosphorylation processes. When maintaining steady levels, ROS are able to function as messengers for the regulation of physiological activities.^{272,273}

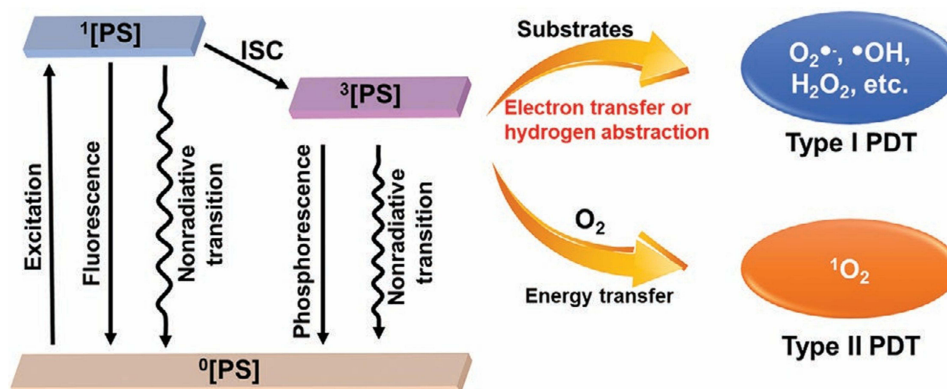


Figure 5 Schematic illustration for the basic process of type I and type II PDT. Reprinted with permission from *Small*. 2021; 17(31):2006742. Dapeng Chen, Qian Xu, Wenjun Wang et al. Type I Photosensitizers Revitalizing Photodynamic Oncotherapy. Copyright © 2021 John Wiley and Sons.²⁷⁸

However, excess ROS can have toxic effects,²⁷⁴ causing to cell death and tissue dysfunction.²⁷⁵ Scientists have been inspired by this effect to utilize ROS for cancer cell destruction. Many compounds, such as arsenic oxides, platinum drugs, and paclitaxel, exert their anticancer effects by promoting cellular ROS production.²⁷⁶ Both PTT and PDT are advanced non-invasive medical treatments that play an important role in the treatment of cancer and other diseases.^{16,277} Combining these technologies not only significantly enhanced the photothermal enhancement effect of PDT but also triggered synergistic mechanisms. This strategy promoted blood circulation in the tumor region, increasing the local oxygen supply and significantly enhancing PDT's therapeutic efficacy. This integrated application not only expands the range of therapeutic tools but also provides a new way to improve the success rate of cancer treatment.

Zhang and Ma et al developed multifunctional metal-organic nanocomposite nanoparticles—Fe-TCPP@CS NPs—whose excellent properties arise from the utilization of chitosan (CS) as the outer layer. This successful integration of chitosan facilitated a triple therapeutic approach: targeted delivery, PDT, and PTT, demonstrating significant potential for biomedical applications. A stable Fe-TCPP core structure was achieved through the formation of a coordination complex between Tetrakis (4-carboxyphenyl) porphyrin (TCPP) and Fe^{3+} ions. This core not only provided the basis for low-temperature photothermal therapeutic technology but also enhanced efficient $^1\text{O}_2$ generation capacity by reducing spontaneous aggregation of porphyrin molecules. Upon light irradiation, these nanoparticles exhibited excellent ROS generation capacity and PCE, synergistically achieving highly efficient inhibition and eradication of a wide range of bacteria, such as *Staphylococcus aureus* and *Escherichia coli*. This groundbreaking achievement not only validated the remarkable potential of Fe-TCPP@CS NPs as a highly effective and comprehensive antimicrobial agent but also established a novel and innovative approach to antimicrobial therapy. And the researchers evaluated their biosafety by cytocompatibility and hemolytic activity, which proved that Fe-TCPP@CS NPs have low toxicity to normal cells without laser irradiation, and the percentage of cytolysis is negligible.²⁷⁹

There are also many cases in the fight against cancer, such as Au@MOF, have been developed. Cai and Zhao et al took advantage of the carboxylic acid groups present on the surface of gold nanorods (AuNRs) to fabricate Au@MOF core-shell hybrids via a step-by-step metal-porphyrin metal self-assembly process.²⁸⁰ In Au@MOF, AuNRs facilitate photothermal conversion, while metal nodes, such as $\text{Fe}_3\text{O}(\text{OAc})_6(\text{H}_2\text{O})^{3+}$ clusters within the MOF, catalyze the decomposition of H_2O_2 into O_2 to modulate the hypoxic tumor environment. Furthermore, porphyrin ligands convert O_2^- into $^1\text{O}_2$ under light conditions, synergistically promoting PDT.²⁸⁰ Experimental data confirmed that Au@MOF exhibited negligible biotoxicity and excellent biocompatibility, effectively killing cancer cells and significantly inhibiting tumor growth. Moreover, the surface of Au@MOF could be further modified, such as with folic acid, to enhance tumor targeting, thereby reducing toxicity and side effects. PDT/PTT bimodal nanoparticles were also synthesized without the use of metal nodes, relying solely on organic components. Sha and Deng et al synthesized BDP-BTNPs by modifying the benzene ring of Boron-dipyrroliidylmethylene (BODIPY) with poly ethylene glycol (PEG) chains to improve biocompatibility and hydrophilicity. Subsequently, a Donor-acceptor-donor (D-A-D) structured molecule, BDP-BT, was synthesized employing BODIPY as the donor and benzothiadiazole as the acceptor. Amphiphilic BDP-BT spontaneously formed corresponding nanoparticles (BDP-BTNPs) through π - π stacking and hydrophilic interactions. The results demonstrated that BDP-BTNPs effectively generated ROS and ablated tumor cells through local thermotherapy.²⁸¹

Chemotherapy

Chemotherapy²⁸² usually combines one or more adjuvant drugs to eradicate cancer cells, with these drugs distributed across various tissues and organs to achieve systemic therapy. However, chemotherapy faces several limitations,²⁸³ including the accelerated development of drug resistance, non-selective systemic distribution of antitumor drugs, inadequate drug concentration at the target site, and significant toxic side effects, which together result in serious therapeutic challenges including interference with normal cell proliferation and damage to healthy tissues and organs.

The integration of PTT and chemotherapy has shown a synergistic impact,²⁸⁴ significantly enhancing the control of tumor metastasis, leading to more precisely targeted therapeutic strategies while reducing the harm inflicted on healthy tissues. Recent research has focused on the design of innovative nanosystems aimed at improving the productivity and meticulousness of therapeutic agent delivery. For instance, researchers have developed a photoresponsive drug carrier composed of amorphous carbon-coated rGO sheets with mesoporous silica, exhibiting a unique nanocookie structure.²⁸⁵

This design endowed the carrier with a photothermal effect, enabling it to effectively release the drug upon NIR light irradiation while generating significant heat, thereby introducing an efficient therapeutic strategy for drug delivery. With its superior biocompatibility and efficient cellular uptake, the material achieved effective clearance of subcutaneous tumors within fourteen days after five minutes of NIR light irradiation without causing distant tissue damage, demonstrating its excellent potential as a platform for chemotherapy and PTT co-administration. For chemotherapeutic agents such as Sorafenib (SOR), a first-line therapeutic agent for advanced hepatocellular carcinoma (HCC), the effectiveness is frequently restricted by drug resistance and adverse effects. To address this, Zeng and Zhang et al constructed a multifunctional nano-platform, MnO_2 -SOR-Ce6@PDA-PEG-FA (MSCPF), which improved the targeting and efficacy of SOR.⁵³ The synthesis involved loading SOR into MnO_2 NPs, followed by the sequential addition of chlorine 6 (Ce6), PDA, and HS-PEG-FA to form MSCPF. This platform utilized MnO_2 as a photothermal agent and Ce6 as a photosensitizer, enabling it to generate excess ROS to alleviate tumor hypoxia, enhance SOR accumulation in tumor cells, and induce ferroptosis through the inactivation of Glutathione Peroxidase 4 (GPX4) and Solute Carrier Family 7 Member 11 (SLC7A11), as well as the inhibition of P-glycoprotein expression. These synergistic pathways significantly enhanced the antitumor efficacy of SOR. The experimental results (shown in Figure 5) indicated that the MSCPF group of the synergistic treatment strategy was significantly better than the SOR group. Similarly, Yang and Zhang et al developed a calcium carbonate-based pH and NIR dual-responsive nanoparticle, DOX-CuS@ CaCO_3 @PL-PEG (DCCP), which co-loaded DOX and CuS nanoparticles into CaCO_3 and modified the surface with PEG. DCCP enabled the combined application of PTT, CDT, chemotherapy, and Ca^{2+} overloading, offering controlled drug release and improved chemotherapy efficiency.¹⁰²

Radiotherapy

Radiotherapy (RT)²⁸⁶ plays a pivotal role in clinical oncology, its mechanism relying on the generation of localized ionizing radiation²⁸⁷ to eradicate cancer cells.²⁸⁸ This modality is indispensable for patients with surgically inoperable tumors, those with incomplete initial resection, and those experiencing disease recurrence.²⁸⁹ Notably, RT trigger immunogenic cell death under specific circumstances, thereby stimulating systemic immunotherapeutic responses. In addition, local irradiation not only eradicates the treated tumor but also exerts significant therapeutic effects beyond the irradiated site.²⁹⁰ However, the efficacy of RT is significantly hindered by several factors: inherent tumor radioresistance, hypoxic tumor microenvironments, and substantial systemic and local toxicities. Consequently, there is a pressing necessity to create novel therapeutic strategies that reduce harm to normal tissues to the greatest extent possible while optimizing antitumor impacts. Analogous to the working principle of PDT, the efficacy of radiation therapy is significantly dependent on the oxygen concentration within the tumor. Fortunately, scientists have innovatively researched Oxygen-Independent Radiodynamic Therapy, which combining radiation therapy with novel sensitizers.²⁹¹ Oxygen-Independent Radiodynamic Therapy overcomes the limitations of conventional RT and PDT.

Elements such as gold and Bismuth (Bi) exhibit potential as radiosensitizers.^{292,293} Yu and Li et al synthesized ultramicrogranular Bismuth Nanoparticles (BiNPs) for combined PTT and radiation therapy. These BiNPs were prepared by reducing Bi ions to BiNPs through heating oleylamine in a nitrogen atmosphere. These nanoparticles were then transferred to aqueous media by encapsulating them with 1,2-distearoyl-sn-glycero-3-phosphoethanolamine-N-[methoxy (polyethylene glycol)] (DSPE-PEG) and further functionalized with a specific peptide chain (CGNKRTRGC, ie, LyP-1) to enable targeted delivery to tumor sites. Upon irradiation with a 1064 nm laser, the BiNPs exhibited strong light absorption, leading to efficient photothermal conversion and generating heat. In addition, BiNPs acted as radiosensitizers, enhancing the efficacy of RT. The study demonstrated that while individual therapeutic strategies only temporarily delayed tumor growth, the combination of PTT and RT effectively halted tumor progression.²⁹⁴ In another study, Hu and Tian et al synthesized AuNCs embedded within a PDA matrix and modified with Arg-Gly-Asp (RGD) peptides for targeted PTT/RT of non-small cell lung cancer (NSCLC). AuNCs were synthesized by reducing HAuCl₄ with dopamine, followed by PDA coating to form a protective shell. Subsequent modification with RGD peptides imparted tumor-targeting capabilities to the AuNC/PDA-RGD nanostructures, enhancing their cellular uptake. These nanostructures exhibited excellent colloidal stability, low cytotoxicity, and synergistic therapeutic efficacy when combined with PTT and RT compared to monotherapy.²⁹⁵

Gene Therapy

Gene Therapy (GT) has demonstrated significant promise in the treatment of numerous disorders through the down-regulation of the expression of particular genes.²⁹⁶ The advancement of gene vectors has substantially promoted the extensive clinical utilization of nucleic acid substances (mRNA, siRNA, etc.).^{297,298} Both GT and PTT, as effective complements to conventional chemotherapy and RT, have shown great potential with their non-invasive nature and reduced side effects.^{299,300} However, the therapeutic efficacy of monotherapies is limited. GT often exhibits slow response rates and is constrained by rapid enzymatic degradation and low intracellular uptake. In contrast, PTT is mainly limited to the ablative treatment of localized tumors. Among the approaches integrating photothermal and physical tumor therapy, the fusion of photothermal gene nanocarriers shows significant advantages. These nanocarriers act as effective gene delivery vehicles, forming stable bonds with negatively charged gene fragments, thereby enhancing the stable accumulation of genes in serum and tumor sites. GT promotes the efficacy of PTT by enhancing the cellular sensitivity to heat, which in turn provides GT performance enhancement by optimizing the process of gene transfer, deconvolution, and expression. This integrated approach presents a unique opportunity for cancer therapy, characterized by rapid response and high efficacy.

Electrostatic attraction was employed to integrate heat shock protein 70 (HSP70)-regulated genes into Ferrocene-based dendritic polymers (DSPs), resulting in the formation of stable nanocomplexes.²⁹⁷ Upon NIR light irradiation, DSPs induced localized hyperthermia, promoting the conversion of heat shock factors from their monomeric to trimeric state. Subsequently, these trimers made their way to the nucleus, attached themselves to heat shock elements, and initiated the transcription of target genes.³⁰¹ The transgene expression capacity under NIR activation was evaluated in HeLa cell lines by employing enhanced green fluorescent protein with luciferase as a biomarker. NIR laser irradiation significantly enhanced gene transcription and expression, as evidenced by increased fluorescence signal intensity. Notably, while Zhao et al reported nanoplateforms utilizing RNA-based regulation, other studies have explored the use of Peptide Lipid (PL) and Sucrose Laurate (SL)-coated SCNTs and MCNTs as bifunctional transport systems (SCNT-PS and MCNT-PS) with excellent temperature sensitivity and photothermal properties.⁵² These CNT/siRNA systems could inhibit tumor growth by silencing survivin expression and exerting a photothermal effect upon NIR irradiation, with SCNT-PS/siRNA demonstrating high anti-tumor efficacy. Similarly, Zhang and Feng et al developed GMPF-siIDO,²⁵² a gold nanorod (GNR)-based platform modified with tumor-targeting FA and Indoleamine-2,3-dioxygenase (IDO)-specific siRNA. This system combined PTT with GT and IT, enabling tumor cell ablation, silencing of IDO gene expression, and enhancement of the body's immune response, thereby significantly improving therapeutic efficacy.

Ferroptosis Therapy

Iron, an essential element for human life, plays a crucial role in numerous physiological processes. However, abnormal iron metabolism can lead to disturbances in these activities. Ferroptosis is a regulated cell death process characterized by Fe²⁺-catalyzed lipid peroxidation, resulting in elevated levels of lipid peroxides³⁰² and iron overload.³⁰³ This process leads to increased ROS production and oxidative stress, ultimately causing cell damage and death.³⁰⁴ Genes involved in iron and lipid metabolism can regulate ferroptosis by regulating iron overload and lipid peroxidation through direct or indirect pathways.³⁰⁵ Glutathione (GSH), a key antioxidant, plays a crucial role in combating lipid peroxidation.^{306,307} As a cofactor for GPX4, GSH facilitates the conversion of toxic lipid peroxides to less harmful alcohols.^{308,309} While not directly involved in lipid peroxide reduction, GPX4 plays a vital role in inhibiting lipid peroxidation by maintaining the reduced state of selenocysteine residues within its active site.^{310,311} Cysteine, a rate-limiting precursor for GSH synthesis, requires extracellular cystine uptake for intracellular cysteine production. SLC7A11, a cystine transporter protein, thus plays a crucial role in ferroptosis.^{312,313} Studies have shown that multiple genes and drugs can regulate ferroptosis by targeting GPX4, GSH, or SLC7A11.³¹⁴ Morphological features of ferroptotic cells include aberrant mitochondria with reduced or lost cristae and membrane condensation. Mechanistically, ferroptosis differs from classical cell death pathways, often relying on oxidized phospholipids containing polyunsaturated fatty acids. Notably, mesenchymal and dedifferentiated cancer cells, which are frequently resistant to apoptosis and traditional therapies, display a high level of susceptibility to ferroptosis. This highlights the potential of ferroptosis as a promising therapeutic approach, especially

for cancers that are difficult to treat. Researchers fabricated multifunctional PDA-coated Manganese Sulfide (MnS) nanoclusters. The polyhydroxyl structure of PDA facilitated enhanced hydration of pH-responsive MnS nanoclusters through hydrogen bonding, significantly increasing the spin-lattice relaxation rate from 5.76 to 19.33 $\text{mM}^{-1}\cdot\text{s}^{-1}$ at pH 5.5, thereby improving their efficacy as MRI contrast agents for tumor visualization.¹⁶⁹ In addition, PDA conferred excellent biocompatibility and PCE to the MnS nanoclusters for PTT. Notably, the acidic tumor microenvironment triggered the release of H_2S from MnS nanoclusters, efficiently suppressing mitochondrial respiration and the generation of ATP. This consequently downregulated the expression of heat shock proteins, mitigating tumor cell resistance to photothermal stimulation and enhancing PTT efficacy. Concurrently, the liberated Mn^{2+} ions demonstrated strong peroxidase-like and glutathione oxidase-like activities, synergistically provoking ferroptosis and apoptosis in tumor cells. These findings demonstrate the potential of this multifunctional nano-platform for synergistic MRI-guided ferroptosis-mediated PTT in cancer therapy. These findings demonstrate the potential of combining ferroptosis therapy with PTT as a novel approach for addressing refractory cancers. Deng and Zhang et al¹⁵ developed a nanoplatform (MP@PI) that exemplified this synergistic strategy. MP@PI, composed of MOFs modified with PDA and IR820 and loaded with Piperonyl Longumine (PL), leveraged MOFs as an iron source and PL as a source of H_2O_2 to induce ferroptosis. Concurrently, the iron source contributed to pyroptosis. PDA, responding to pH changes and depleting GSH, reduced GPX4 levels, further promoting ferroptosis. The photosensitizer IR820 generated heat upon NIR light irradiation, enhancing both ferroptosis and pyroptosis. In addition, MP@PI stimulated immune responses, augmenting anti-tumor efficacy. Similarly, Fang and Ma et al⁵⁴ synthesized CMCTNPs@OVA, a catalytic immunotherapeutic ferroptosis-activated vaccine, which combined ferroptosis, IT, and PTT. This platform utilized copper telluride nanoparticles, mimicking peroxidase to deplete GPX4, and incorporates Ovalbumin (OVA) as an exogenous antigen. The photothermal effect of copper telluride enhanced PTT efficacy, while Cu^{2+} released initiates ferroptosis. Furthermore, ferroptosis, in conjunction with PTT, induced ICD, emanating damage-related molecular patterns to facilitate dendritic cell maturation and the recruitment of T-cells. The results demonstrated the efficacy of CM CTNPs@OVA in treating melanoma, highlighting the potential of this combined strategy for combating cancer. The researchers verified that CM CTNPs@OVA did not induce any abnormal damage to normal tissues, and its biosafety was confirmed through the examination of pathological tissue sections.

Summary and Outlook

This review comprehensively examines PTT, encompassing its underlying mechanism, the developmental landscape of PTAs, and the advancements in PTT-based diagnostic and therapeutic strategies. Research on PTAs, including metal-based, carbon-based, and organic-based materials, alongside their diverse nanoformulations, are introduced. Recognizing PTAs as the cornerstone of PTT, the rational design of these agents leverages the inherent advantages of the nanomedicine,³¹⁶ facilitating enhanced diagnosis and treatment. This includes advancements in FI, PAI, and MRI-guided PTT, enabling real-time tumor visualization during surgery and paving the way for complete tumor eradication. Furthermore, synergistic approaches combining PTT with chemotherapy, RT, PDT, gene therapy, and ferroptosis therapy are explored. These combinatorial strategies aim to capitalize on the complementary strengths of each modality, thereby improving therapeutic efficacy, enhancing patient quality of life, and demonstrating promising clinical translation potential. While preclinical and clinical studies have shown encouraging results in treating breast, lung, and prostate cancers, further optimization of PTAs remains crucial. Photothermal therapy still faces difficulties in clinical translation and is not conducive to deeper levels of treatment. And developing nanoformulations with superior PCE, facile synthesis and application, and compatibility with synergistic therapies is essential. Moreover, innovative combined treatment strategies are necessary to address current clinical limitations and ultimately achieve the goal of effective tumor eradication. Future advancements in photothermal therapy research should establish systematic integration with existing scientific foundations, with prioritized investigation focusing on three pivotal aspects: (1) innovative development of photothermal conversion agents, (2) synergistic therapeutic modalities combining multiple treatment approaches, and (3) real-time imaging-guided intervention systems. Crucially, greater emphasis must be placed on accelerating clinical translation through standardized preclinical evaluation protocols and multidisciplinary collaboration, thereby expediting practical applications to advance cancer treatment paradigms.

Author Contributions

All authors have made significant contributions to the reported work, whether in conceptualization, execution, literature review, statistical analysis, data interpretation, writing, or any combination of these elements. All authors participated in drafting, revising, or critically reviewing the article and gave final approval of the version to be published. All authors have agreed on the journal to which the article will be submitted and agreed to accept responsibility for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this work.

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