

Nanoparticle-Enabled Photothermal Therapy Integrated with Gene Delivery, Immunotherapy, and Chemotherapy: A Comprehensive Review

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Abstract: Photothermal therapy (PTT) utilizes near-infrared (NIR)-responsive nanoparticles to induce controlled hyperthermia for tumor ablation and modulation of cellular and microenvironmental processes. Advances in nanomaterial engineering have enabled the integration of PTT with gene therapy, immunotherapy, and chemotherapy, wherein photothermal heating enhances membrane perturbation, accelerates endosomal escape, and initiates thermally triggered release of therapeutic payloads. This review summarizes the photothermal mechanisms of metallic, polymeric, hybrid, and semiconducting nanomaterials and examines how these platforms improve nucleic acid transport, immune activation, and chemotherapeutic performance. In addition, key translational challenges, including NIR penetration limits and thermotolerance, are briefly highlighted. By consolidating mechanistic insights and material-specific strategies, this review outlines current progress and future requirements for advancing clinically translatable PTT-based combination therapies.

Keywords: combination therapy, gene therapy, immunotherapy, chemotherapy, nanoparticles, immunogenic cell death

Introduction

Photothermal therapy (PTT) has emerged as a promising minimally invasive cancer treatment modality that utilizes near-infrared (NIR) light-absorbing agents to generate localized hyperthermia.^{1–3} Upon NIR irradiation, photothermal agents convert optical energy into heat, inducing apoptosis, disrupting tumor vasculature, and modulating the tumor microenvironment.^{4–12} With advances in nanotechnology, nanoparticles (NPs) have become integral to PTT due to their tunable optical properties, high photothermal conversion efficiency, and capacity to integrate imaging or therapeutic functions.^{13–16} These features have enabled PTT to be combined with gene therapy, immunotherapy, and chemotherapy in ways that overcome key limitations of each modality.^{17–19}

Gene therapy aims to regulate or replace aberrant genetic pathways but faces challenges such as inefficient intracellular delivery, endosomal degradation, and cytotoxicity associated with transfection reagents.²⁰ Immunotherapies—including cancer vaccines, immune checkpoint inhibitors, and innate immune agonists—offer durable antitumor responses yet remain constrained by poor antigen presentation and immunosuppressive tumor microenvironments.^{21,22} Chemotherapy remains a clinical mainstay but is hindered by poor tumor selectivity, multidrug resistance, and dose-limiting systemic toxicity.²³

Addressing these challenges requires combination strategies capable of improving therapeutic selectivity and enhancing functional efficacy.

PTT offers several mechanisms that complement these therapeutic modalities. Localized hyperthermia increases membrane fluidity to facilitate cytosolic gene entry, accelerates drug release from thermoresponsive carriers, enhances vascular perfusion, and sensitizes tumor cells to chemotherapeutic agents.^{24–28} In addition, PTT also induces immunogenic cell death (ICD), characterized by the release of damage-associated molecular patterns (DAMPs) such as calreticulin and high mobility group box 1 (HMGB1), which enhance Ag uptake and promote antitumor immunity.²⁹ Unlike photodynamic therapy, which relies on oxygen-dependent reactive oxygen species, PTT generates heat directly and retains efficacy in hypoxic tumor regions.

Despite these advantages, several barriers limit the clinical translation of PTT-based combination therapies. NIR light penetration remains restricted to the millimeter-to-centimeter range depending on wavelength and tissue type, limiting treatment of deep-seated tumors.^{25,30} Photothermal overexposure can induce heat shock protein (HSP)–mediated thermotolerance, reducing treatment responsiveness.³¹ Additional concerns include NP biodistribution, long-term biodegradation, and regulatory requirements for complex multifunctional nanoplatforms.^{32–34} Moreover, differences in tumor anatomy and microenvironmental heterogeneity influence the feasibility of PTT across cancer types.^{34,35}

In this review, we summarize the photothermal mechanisms of various nanomaterials—including metallic, organic/polymeric, hybrid, and emerging Ag₂S-based NPs—and discuss how PTT enhances gene delivery, immunotherapy, and chemotherapy (Figure 1A). We also highlight representative nanoplatforms, current limitations, and future opportunities for improving the precision, safety, and translational relevance of NP-enabled combinatorial PTT (Figure 1B).

Underlying Mechanism on Photothermal Effects of Different NPs

NPs used in PTT convert absorbed NIR light into heat through distinct physicochemical mechanisms. Depending on their composition, structure, and electronic properties, NPs exhibit different photothermal behaviors that determine their efficiency, stability, and suitability for biomedical applications. This section summarizes the representative classes of photothermal nanomaterials—metallic, organic/polymeric, hybrid/composite, and semiconducting nanoparticles—and highlights their corresponding heat-generation mechanisms and practical considerations (Figure 2).

Metallic NPs

Metallic nanoparticles—including gold (Au), silver (Ag), platinum (Pt), and palladium (Pd)—generate heat primarily through localized surface plasmon resonance.^{40–42} Upon NIR irradiation, collective oscillations of conduction electrons lead to efficient light absorption and rapid thermal relaxation.³⁰ Among these, gold nanorods (AuNRs), in particular, offer tunable longitudinal plasmon peaks and strong NIR absorption, making them widely used PTT agents.⁴³ Their photothermal conversion is efficient, but potential concerns include plasmon damping, reshaping under high-intensity laser exposure, and limitations in deeper tissue penetration depending on their absorption wavelength.⁴⁴ Recent advances in AuNR research have further optimized their photothermal performance, demonstrating improved plasmonic stability, enhanced heat conversion efficiency, and tunable aspect ratio control for cancer phototherapy applications.^{45,46}

Silver nanoparticles exhibit comparable plasmonic behavior but suffer from oxidative degradation and higher cytotoxicity, whereas iron oxide nanoparticles offer lower photothermal efficiency but improved biocompatibility and magnetic functionality.^{47–51}

Organic and Polymeric NPs

Organic/polymer-based NPs rely on intramolecular vibrations and π – π stacking interactions to dissipate absorbed energy as heat.³⁵ These systems generally offer favorable biocompatibility and biodegradability compared with metallic nanomaterials. Polydopamine (PDA) NPs are a representative example, characterized by strong broadband NIR absorption, high chemical stability, and versatile surface functionality for cargo loading.^{52,53} Semiconducting polymer nanoparticles and dye-based nanoassemblies offer tunable optical properties but can be limited by photobleaching, aggregation, or reduced irradiation stability over prolonged use.⁵⁴

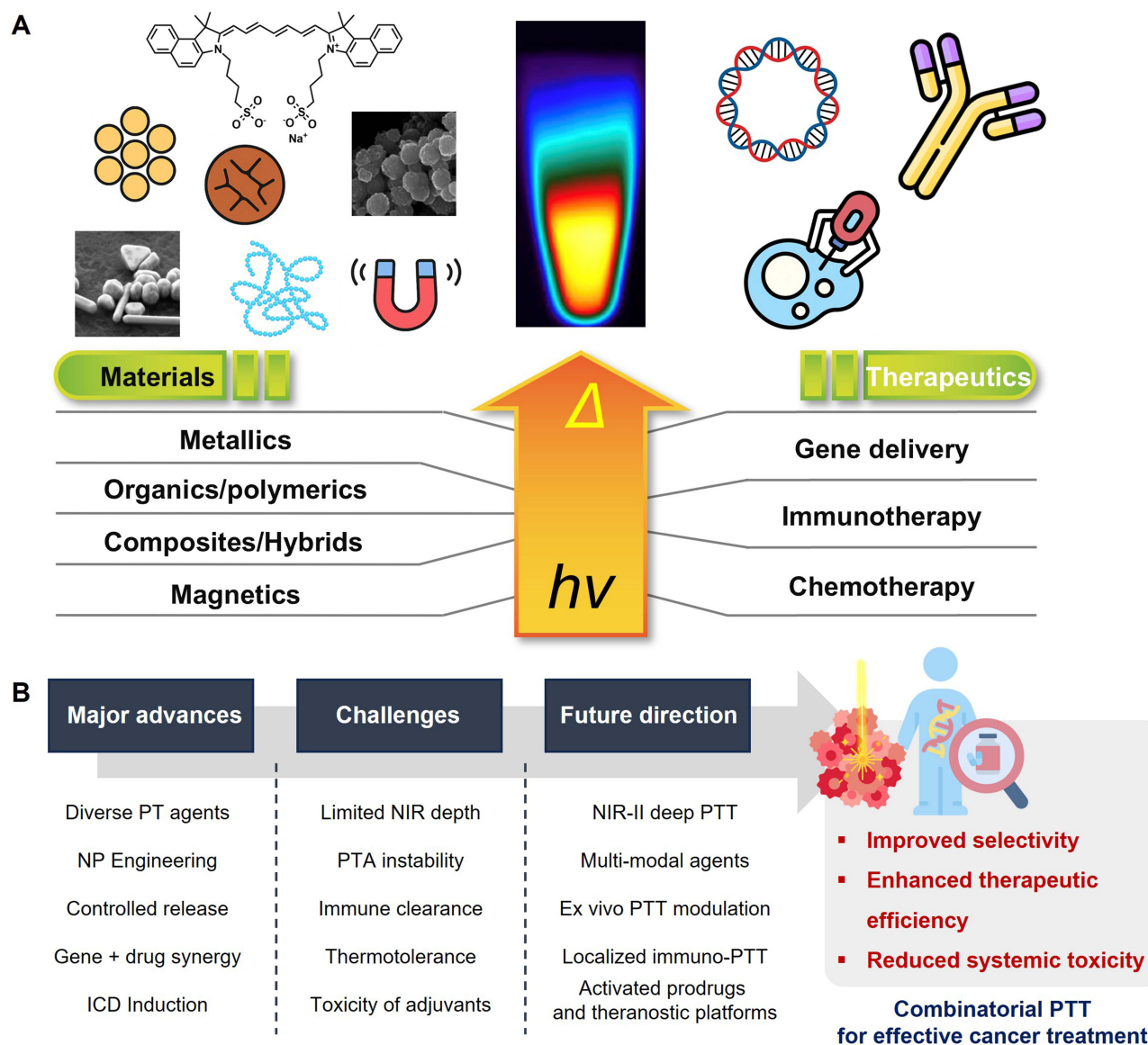


Figure 1 Schematic overview of PTT as a nanomaterial-enabled platform for combinatorial cancer treatment. **(A)** A variety of nanomaterials—including metallic, polymeric, hybrid, and magnetic systems—can be engineered for efficient PT conversion under light irradiation ($h\nu$). **(B)** Schematics illustrating the major advances, challenges, and future directions of combinatorial PTT-based agents for effective cancer treatment. Created by the authors.

Composite and Hybrid NPs

Composite/hybrid NPs integrate metal, polymer, or inorganic components to achieve enhanced photothermal properties and multifunctionality. Black phosphorus (BP) nanosheets (BPNS) can form synergistic hybrid structures with metals, enhancing their properties for PTT. The authors introduced BP-Au-thiosugar NSs (BATNS) composites to enhance stability and anticancer efficiency. Importantly, Au-thiosugar coating mitigated rapid oxidation and degradation of BPNS, which made them stable under laser irradiation. Also, BATNS (BP-Au-thiosugar NSs) offer better photon absorption and heat conversion than BPNS due to the shrinking bandgap (0.97 eV), allowing to convert more photon energy into heat, which was evidenced by the significantly enhanced ablation efficiency in an NIR-irradiated Hep1-6 cells. Additionally, BATNS-mediated PT promoted robust infiltration of tumor-killing NK cells without affecting T- or B-cell populations, thereby enhancing tumor necrosis with hypoxia markers, ultimately improving mouse survival rate.⁵⁵

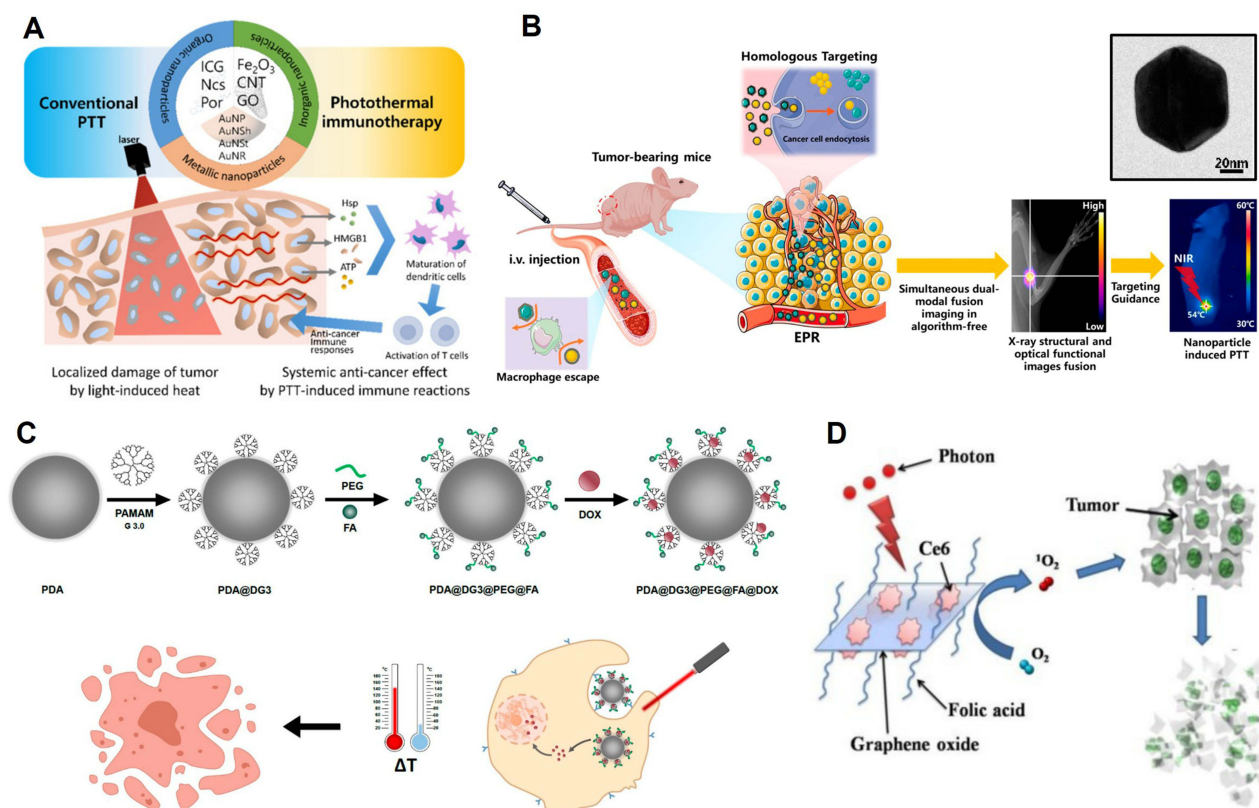


Figure 2 NP-based PTT. **(A)** A schematic diagram of NPs for PTT, where conventional PTT targets cancer cell death, while PTT enhances immune responses for a systemic effect.³⁶ Copyright MDPI 2022. **(B)** Application of cancer cell membrane-coated AuNPs for PTT application.³⁷ Copyright MDPI 2020. Inset image shows morphology of AuNPs. **(C)** Dual chemo- and PTT-assisted synergistic cancer therapy using functionalized polydopamine.³⁸ Copyright MDPI 2021. **(D)** Graphene oxide-based composite PTT probe for tumor ablation.³⁹ Copyright Ivyspring International Publisher 2011. All Figures were reproduced with permission.

Ag₂S -Based Semiconducting Nanomaterials

Ag₂S NPs represent an emerging class of semiconducting photothermal agents distinguished by their narrow bandgap (~1.0–1.1 eV), which enables strong NIR-I and NIR-II absorption and intrinsic NIR-II fluorescence. This dual optical behavior facilitates both photothermal heating and deep-tissue imaging.^{56–58} Unlike metallic Ag NPs, Ag₂S exhibits higher chemical stability and substantially lower cytotoxicity, improving its suitability for in vivo theranostics. Ag₂S can be incorporated into multifunctional structures—including Ag₂S@SiO₂, Ag₂S@PDA, polymeric micelles, and Ag₂S–photosensitizer hybrids—allowing simultaneous PTT, chemotherapy, or photodynamic therapy.^{58,59}

Despite these advantages, Ag₂S-based platforms remain relatively underexplored compared to traditional PTT agents such as gold nanorods. Key challenges include synthetic complexity, insufficient biodegradation data, and a lack of standardized protocols for photothermal characterization and NIR-II imaging. Nevertheless, their combined photothermal and fluorescent capabilities highlight Ag₂S as promising candidate for next-generation combinational PTT systems.

PTT Contribution with Gene Delivery to Cancer Treatment

The properties of the cell membrane (eg, stiffness, melting temperature), where genes or drugs, need to penetrate, can be changed based on wavelength, intensity, or duration of NIR-I (650–950 nm) and NIR-II (1000–1700 nm) laser windows within a specific wavelength depending on the disease site, including tumor depth and area.⁶⁰ It is commonly exploited using metallic nanostructures (eg, AuNRs, Au nanoshells), organic and polymer-based photothermal dyes (eg, ICG, semiconducting polymers), or hybrid platforms that integrate inorganic cores with organic coatings. The photothermal conversion efficiency, absorption cross-section, biodegradability, and thermal stability of these agent classes vary considerably, influencing both performance and translational potential. At the cellular level, the photothermal heat generated under NIR irradiation, modulates the fluidity of cell membranes composed of phospholipids, proteins, etc,

for transient regulation purposes using photothermal heat generated by laser irradiation. Based on these phenomena, the photothermal heat could possibly alter the permeability of the cell membrane or create pores temporally, enabling the direct delivery of genes and drugs of interest to the cytosol rather than the endocytosis pathway. Heat-induced signaling further activates pathways involving HSPs and, under certain regimes, can trigger ICD, providing an additional mechanistic basis for synergy with gene therapy, immunotherapy, and chemotherapeutic agents. Similarly, in terms of the use of the polymer properties, the release rate of the payload can be controlled by changing the conformation of polymer-based NPs, which are light- and thermal-sensitive materials, after laser irradiation.^{61,62} Thus, in this section, cancer treatment using genes delivery will be discussed through the application of PTT (Figure 3).

Cell Membrane Modulation for Gene Delivery with Photothermal Effects

Positively charged liposomes, such as lipofectamine and Mirus, are typically used as a commercially available method for gene delivery. It has a high transfection efficiency regardless of the size and shape of nucleic acids, such as siRNA, mRNA, and plasmid DNA, in numerous cell types.^{63,64} However, when nucleic acids are delivered to primary cultured cells or neurons using general transfection agents, transfection efficiency and cell viability are frequently lower than anticipated.⁶⁵ To use a PTT for nucleic acid delivery, it should be considered in terms of power density per area, duration of laser irradiation, and desirable wavelengths of light. Oh et al and Hosseinpour et al focused on the permeability change of the cell membrane by photothermal heat to deliver genes. The former group used an 808 nm diode laser with different types of cells, such as primary culture fibroblasts (D551), hepatocytes, and Jurkat cells, which are known to be difficult to deliver genes into cells to deliver commercially available lipofectamine and plasmid DNA complexes. To generate a photothermal effect, mPEGylated AuNRs were used, and the laser was irradiated for 30 min, which was sufficient for mPEGylated GNR to stay only outside of the cells. The transfection efficiency of primary cultured fibroblasts, Jurkat cells, and hepatocytes was enhanced 2.72-, 7.19-, and 2.54-fold.⁶⁶ Another research group of Hosseinpour et al applied various wavelengths such as 445, 685, 810, or 970 nm for 2 h by using a diode laser on preosteoblast MC3T3 cells to improve cationic lipids to transfect ability. When the cells were irradiated with 810 nm at 12 J and 970 nm at 6 J, the proportion of GFP-positive cells significantly increased compared with Lipofectamine alone, reaching approximately 72% and 71%, respectively.⁶⁷

The other groups focused on making transient pores on the cell membrane to allow impermeable dye to get into the cells. Based on this strategy, the light-triggered self-assembled nanobombs (NBs) gene transfection system was developed (Figure 4A). Iron oxide consists of NB cores, which play a key role as a photothermal component to generate water

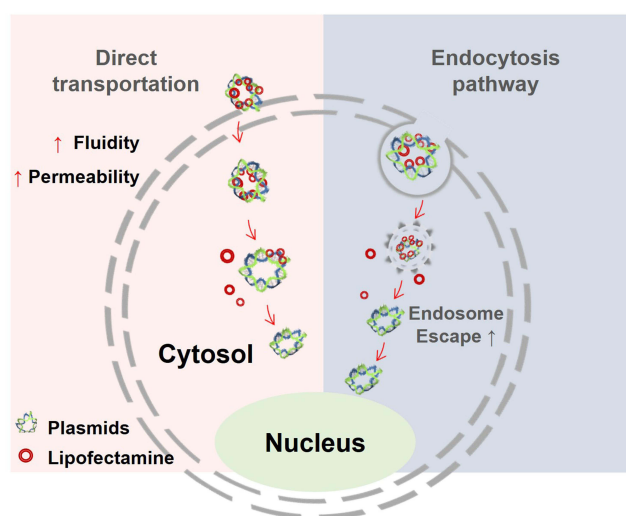


Figure 3 Schematic illustration of the intracellular trafficking pathways of plasmid–lipofectamine complexes. The figure depicts two major pathways by which plasmid–lipofectamine complexes enter the cytosol: Direct transportation across the plasma membrane (left) and Endocytosis-mediated internalization (right). Red directional arrows (→) indicate the movement of plasmid–lipofectamine complexes along each intracellular trafficking route. Red upward arrows (↑) denote an increase in specific cellular processes, including membrane fluidity, membrane permeability, and endosomal escape efficiency. Created by the authors.

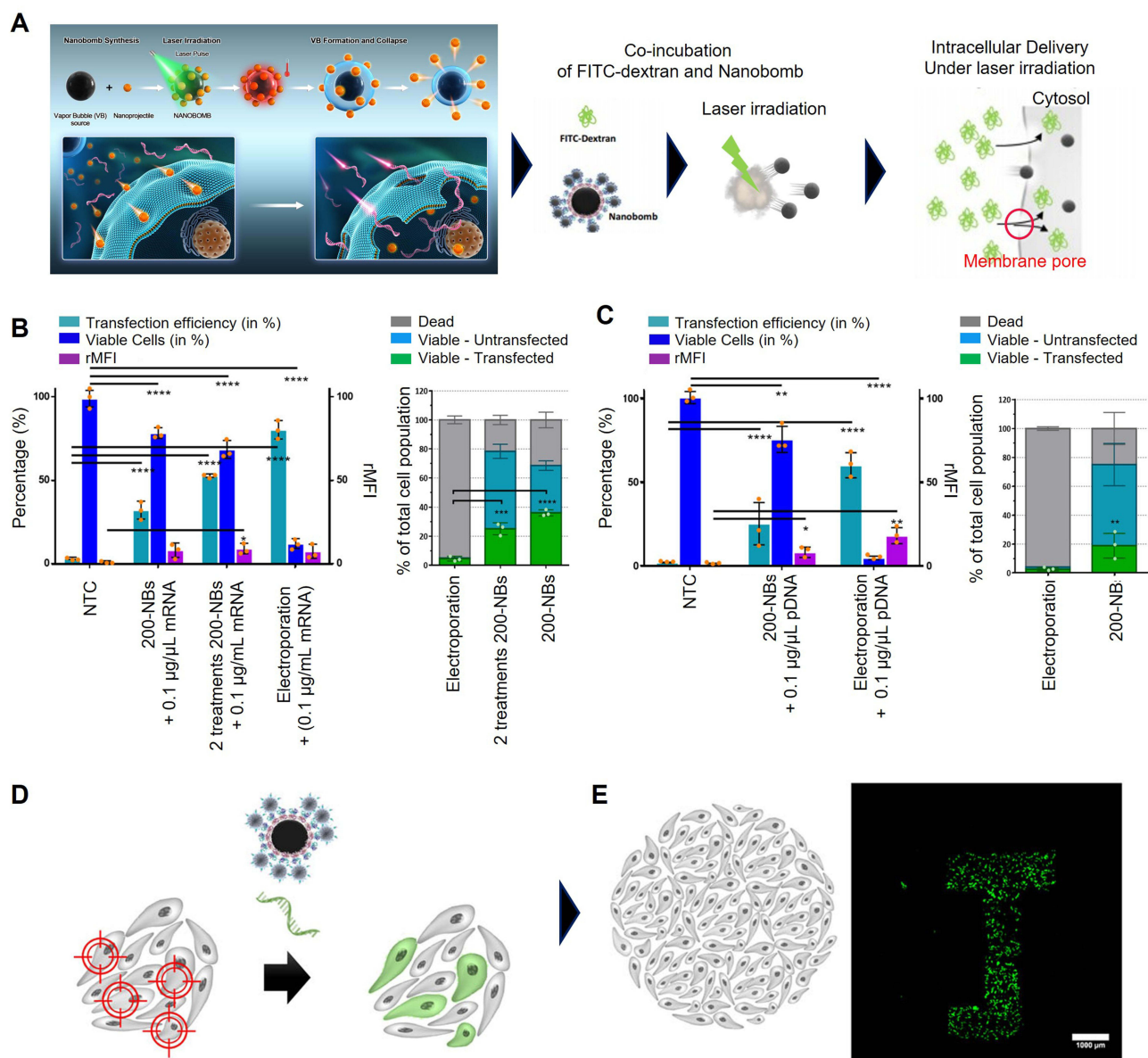


Figure 4 Gene delivery strategy with optically triggered nanobombs. **(A)** the working principle of nanobombs upon irradiation with an intense laser pulse (left) and cytosolic delivery of macromolecules by laser-activated NBs (right). **(B)** Transfection experiment proceeded with HeLa cells as adherent cells. **(C)** Transfection experiment proceeded with Jurkat cells as suspension cells (* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$, **** $p < 0.0001$). **(D)** The strategy of spatial-selective NB mediated mRNA delivery. **(E)** Confocal images after transfection in HeLa cells for selective expression of proteins of interest. Scale bar = 1000 μm.⁶⁸ Copyright Springer Nature Publisher 2022. All Figures were reproduced with permission.

vapor bubbles when a 561-pulse laser is applied. Compared to electroporation and photoporation by using mRNA and plasmid DNA (Figure 4B), light-triggered NB-mediated photoporation results in a 5.5–7.6-fold increase in transfected cells compared with electroporation, while maintaining higher cell viability. Figure 4C shows parallel results for plasmid DNA, confirming that NB-assisted delivery outperforms both electroporation and repeated irradiation in terms of transfection rate and safety. Based on this result, they applied this strategy to spatial-selective eGFP-mRNA transfection in HeLa cells. As illustrated by the representative fluorescence images (Figure 4D and E), the delivery of genetic material resulted in efficient intracellular expression. Collectively, these data highlight the potential of nanobomb-assisted photoporation as a highly efficient, biosafe, and tunable platform for gene transfection.⁶⁸ In another strategy, crystalline magnetic carbon NPs (CMCNPs) were introduced to accelerate plasmids into cancer cells under a localized magnetic field and photothermal effect by irradiation of NIR laser simultaneously since CMCNPs showed strong absorption in NIR

region and magnetic properties. It was allowed to be an effective localized heating and magnetic field in the target area for delivering impermeable dye as a drug and plasmids.⁶⁹

NP Modulation for Gene Delivery with Photothermal Effects

As shown in Table 1, some research groups used photothermal heat to stimulate a light-sensitive protein such as heat shock protein instead of modulating the properties of the cells. Nakatsuji et al sought to regulate gene expression by 780 nm NIR pulse laser.⁷⁰ They synthesized DOTAP functionalized AuNRs with HSP promoter-driven vectors and then incubated them in HEK293T cells for 24 h (Figure 5A and B). In order to activate HSP promoters, a 780-nm NIR pulse laser was irradiated for 10s; this transfection condition showed less irradiation time than intracellular carbon nanohorns (0.5 W/cm² continuous, 30 min), silica-gold nanoshells and hollow gold NPs (2 W/cm² continuous, 15 min) and then transfection efficiency using AuNP functionalized with various cationic coating was quantified (Figure 5C). Flow cytometry analysis demonstrated that DOTAP- and lipofectamine-based formulations produced the highest levels of

Table 1 The Strategy and Effect of Gene Delivery by PT Heat

Type of Cells	Laser Specification	PT NPs	Vector/Delivered Material	Therapeutic Outcomes	Ref
Primary cultured human fibroblast (D551), Jurkat cell, Hepatocytes	808 nm, 4.0 mW/cm ² , 30 min	Pegylated GNR	Lipofectamine/ Plasmid DNA encoding EGFP	- Enhances the transient change of permeability of the cell membrane by the PT heat of GNPs - Increase transfection efficiency was increased under the laser irradiation	[66]
Pre-osteoblast MC3T3	445, 685, 810, or 970 nm, 104.64 mW/cm ² , 2 h	Laser alone	Lipofectamine/ Plasmid DNA encoding EGFP	Enhanced transfection efficiency of lipofectamine and plasmid DNA complexes through 810 nm at 12 J and 970 nm lasers at 6 J over wavelength with 445 nm and 685 nm	[67]
HEK293T	780 nm, 150 - 900 W/cm ²	GNR, oleate, 1,2-dioleoyl-3-trimethylammonium-propane (DOTAP)	Plasmid DNA encoding heat shock protein (pHSP) with eGFP	Facilitate the activation of HSP promoters by photothermal heat of DOTAP-GNPs with less irradiation time than intracellular carbon nanohorns, silica-gold nanoshells, and hollow gold NPs.	[70]
Hela, Jurkat	561 nm, 0.84 W/cm ² , 5 ns	Iron oxide	Light-triggered self-assembled nanobombs with a PT core particle/ mRNA/ plasmid DNA encoding eGFP	Increase biosafety of NBs to deliver pDNA and mRNA in adherent and non-adherent cells compared to electroporation.	[68]
Human prostate cancer (PC3), human fibroblast sarcoma (HT1080)	720 and 800 nm, 40 mW, 0–20 s	Crystalline magnetic carbon NPs (CMCNPs)	Impermeable dye, plasmids encoding light-sensitive proteins	Generate PT heat and magnetic field by CMCNPs in localized region of interest and these properties allowed impermeable dye and naked plasmids to penetrate cell membrane efficiently	[69]
HSC (oral), MCF-7, Huh7.5	808 nm, 5.8 W/cm ² , 2 min	GNRs	Lipofectamine/ siRNA	Induce enhanced apoptosis by inhibiting expression level of heat shock protein 70 using siRNA which is down-regulated HSP70	[71]

Notes: PTT Parameters Such as Light Source, Output Power (mW or W), Wavelength (nm), Energy Density (J), and Irradiation Time (h, min, s).

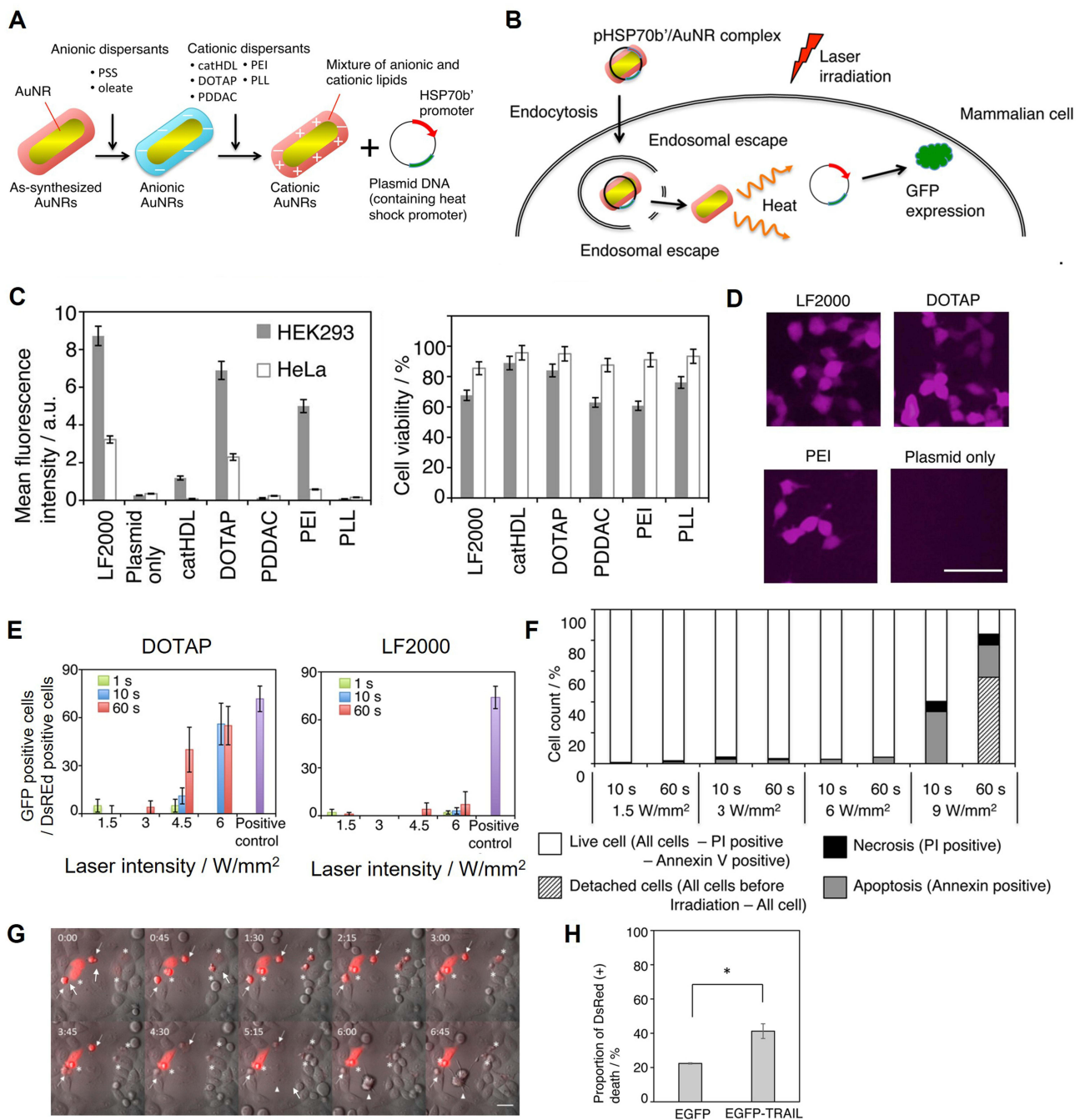


Figure 5 Gene delivery strategy with functionalized AuNPs and plasmid DNA. **(A)** Design of the complex with functionalized AuNPs and plasmid. **(B)** Schematic of PT induction of protein expression delivered by AuNPs. **(C)** Transfection efficiency by the formulation of AuNP with PT effect was determined by flow cytometry. **(D)** Fluorescence images of HEK293T cells treated with cationic AuNPs/plasmid DNA corresponded to flow cytometry data. Scale bar = 100 μm. **(E)** Transfection efficiency for DOTAP-AuNPs (left) and lipofectamine 2000 (lipo 2k) (right) to investigate optimal condition of laser power and irradiation time. **(F)** Investigation of phototoxicity by intracellular PT heating. **(G)** Time-lapse images of 45 minute internal of pHSP70-TRAIL transfected cells. Arrows indicate DsRed positive cells that had died before start of time lapse imaging. Asterisks display DsRed positive cells that die during time lapse imaging. Arrowhead shows DsRed negative cell that dies during time lapse imaging. Scale bar = 40 μm. **(H)** Quantification data of DsRed positive cells (*p < 0.05).⁷⁰ Copyright Springer Nature Publisher 2017. All Figures were reproduced with permission.

GFP expression in both HEK293 and HeLa cells. These results correspond to the fluorescence microscopy images (Figure 5D). Because promoter activation is tightly linked to photothermal input, they further optimized irradiation parameters by altering laser power and exposure time (Figure 5E). Given the potential risks associated with intracellular heating, they assessed photothermal cytotoxicity using flow cytometry (Figure 5F). To evaluate functional protein expression driven by photothermal induction, they monitored apoptosis in cells transfected with a pHSP70-TRAIL

plasmid. Time-lapse imaging revealed dynamic cell death events among DsRed-positive cells following irradiation (Figure 5G). Some cells were already apoptotic prior to imaging, while others underwent apoptosis during the observation period, indicating active TRAIL expression. Quantitative analysis confirmed a significant increase in the proportion of apoptotic DsRed-positive cells compared with controls (Figure 5H).⁷⁰ Ali et al have made a new strategy to enhance apoptosis by plasmonic PTT over necrosis because necrosis causes inflammation, known to induce metastasis and cancer growth. This group found that inhibition of HSP 70 was related to an increase in apoptosis.⁷¹

Through the use of NPs and the photothermal effect, nucleic acids such as plasmid DNA, siRNA, mRNA, and cationic lipid complexes can be delivered into the cytosol by endocytosis pathways. In the cases, photothermal effect was utilized to promote the escape of NPs from endosome or lysosome.

Unlike this strategy for gene delivery, the method of temporarily forming a pore in the cell membrane and another method of regulating the fluidity of the membrane while generating photothermal heat by irradiating laser onto NPs utilized the melting point of the phospholipids, comprising the cell membrane between -20°C and 60°C .⁷² This photothermal heat is also known to accelerate the endosomal escape of nucleic acids that have entered the cell via the endocytosis pathway. Both methods have the advantage of being applicable to adherent and nonadherent cells, despite the limited in vivo access due to the limitations of the laser's tissue penetration depth ($< 50\text{ mm}$ for NIR lasers) and are being actively researched for ex vivo cell modulation. These methods have the advantage of being applicable to both cell types to deliver nucleic acid of interest, despite the limited in vivo access due to the limitations of the tissue penetration depth of the laser ($< 1.0\text{ }\mu\text{m}$ for NIR lasers) and are being actively researched for ex vivo cell modulation.

PTT Contribution with Drug Delivery to Cancer Treatment

Combining PTT with drug delivery systems allows heat-dependent activation of therapeutic agents at tumor sites, improving intratumoral penetration and release kinetics, and tumor-specific accumulation while minimizing off-target exposure.^{73–75} Controlled hyperthermia alters vascular permeability, softens extracellular structures, and sensitizes tumor cells to pharmacological agents. Through these mechanisms, photothermal heating enhances the performance of both immunotherapy and chemotherapy. This section outlines how PTT interacts with immunogenic adjuvants and chemotherapeutic drugs to produce synergistic anticancer effects.

NP-Mediated Photothermal Immunotherapy

Integrating PTT with immunotherapy leverages localized hyperthermia to enhance antigen release, dendritic cell activation, and overall immune priming within the tumor microenvironment.⁷⁶ This combined approach builds upon the established modes of immunotherapy—including checkpoint inhibitors, adoptive cell therapies, and vaccines—while addressing key barriers such as insufficient antigen presentation and immune suppression.^{77–80} PTT-induced ICD releases DAMPs, including HMGB1, ATP, and HSPs, which promote dendritic cell (DC) maturation and antigen presentation.^{81–86} Photothermal nanomaterials further facilitate targeted delivery of immunostimulatory molecules and enable spatio-temporal control over immune activation. These synergistic interactions have been demonstrated across a range of NPs that improve cytotoxic T-cell responses and inhibit both primary and metastatic tumors. This process is essential for initiating a robust and specific anti-tumor immune response (Figure 6). The localized hyperthermia induced by PTT creates an immunostimulatory microenvironment conducive to immune cell activation.^{87,88} Following cancer cell death, the released cancer antigens, pro-inflammatory cytokines, and other factors are captured by DCs, which then present the antigens to T cells via major histocompatibility complex (MHC) class I and II molecules.⁸⁹ This interaction leads to T cell activation, with activated T cells migrating to and infiltrating the tumor site.⁹⁰ The T cells specifically recognize and bind to cancer cells through the interaction between T cell receptors and antigen-captured MHC class I molecules, leading to the targeted destruction of tumor cells by cytotoxic T lymphocytes.⁹¹ However, cancer antigens alone are insufficient to induce a potent immune response. When used in conjunction with immunogenic adjuvants, these antigens can further enhance or prolong antigen-specific immune responses.^{92,93}

The most effective immune adjuvants used in PTT-immunotherapy include toll-like receptor (TLR) agonists, which activate DCs and promote tumor-specific T cell responses.^{94–100} Although systemic administration of these agonists can cause immune-related toxicities, nanoparticle carriers enable localized delivery to the tumor microenvironment, thereby

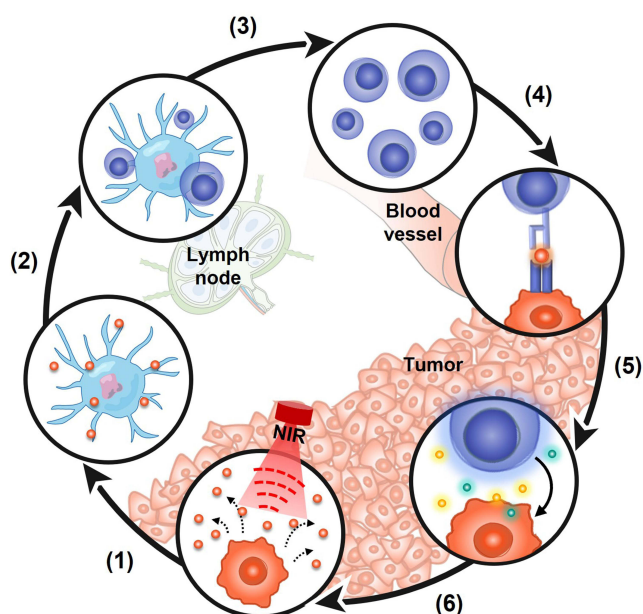


Figure 6 Schematic representation of nanomaterial-based photoimmunotherapy. The anti-cancer immune response follows a cyclic and self-propagating process, leading to the accumulation of immune-stimulatory molecules that enhance and amplify T cell responses. This cycle consists of six key stages: (1) Release of apoptotic bodies containing cancer antigens, (2) Presentation of cancer antigens by dendritic cells (DCs), (3) Activation of DCs and T cells, (4) Migration of activated T cells to the tumor site, (5) Recognition of cancer cells by T cells, and (6) Elimination of cancer cells. Created by the authors.

improving safety and immunomodulatory precision. Though these mechanisms, PTT-based combinations can enhance ICD, DC maturation, and antigen presentation, offering a strong rationale for integrating PTT with immunotherapy. Table 2 summarizes the approach and impacts of immunotherapy using hyperthermia. Zhan et al developed an

Table 2 The Approach and Impacts of Immunotherapy Thorough Using Hyperthermia Involve Adjusting Various Parameters for PTT, Including Laser Power Output, Wavelength, and Duration of Laser Irradiation

Type of Cells	Laser Specification	PT NPs	Delivered Material	Therapeutic Outcomes	Ref
4T1	NIR-II laser, 1 W/cm ² , 6 min	Dopamine hydrochloride self-polymerized into polydopamine	cGAMP	Significant treatment of both primary and distant tumors, with nearly complete restraint of metastasis to the liver and lungs in a mouse model.	[85]
CT26 and 4T1	808 nm, 1 W/cm ² , 5 min	Gold nanorod	LPS-free <i>E.coli</i> lysate and FimH	Prevention of cancer metastasis and recurrence through antigen-specific T cell activation.	[86]
B16F10	808 nm, 0.1 W/cm ² , 5 min	ICG loaded PLGA	Melanoma cytomembrane and attenuated <i>Salmonella</i> outer membrane vesicles	Demonstrates anti-tumor synergy, combining local elimination and sustained inhibition, and shows potential as a cancer vaccine.	[88]
B16F10	808 nm, 0.5 W/cm ² , 5 min	Mesoporous polydopamine NPs	R837	Effective inhibition of tumor growth through thermal ablation-induced apoptosis and generation of cytotoxic T lymphocytes.	[92]
CT26	808 nm, 2.0 W/cm ² , 5 min	Dopamine hydrochloride self-polymerized into polydopamine	CpG	Inhibition of tumor growth, regulation of the tumor microenvironment from immunosuppressive to immunogenic, and stimulation of systemic antitumor immune responses in vivo.	[95]

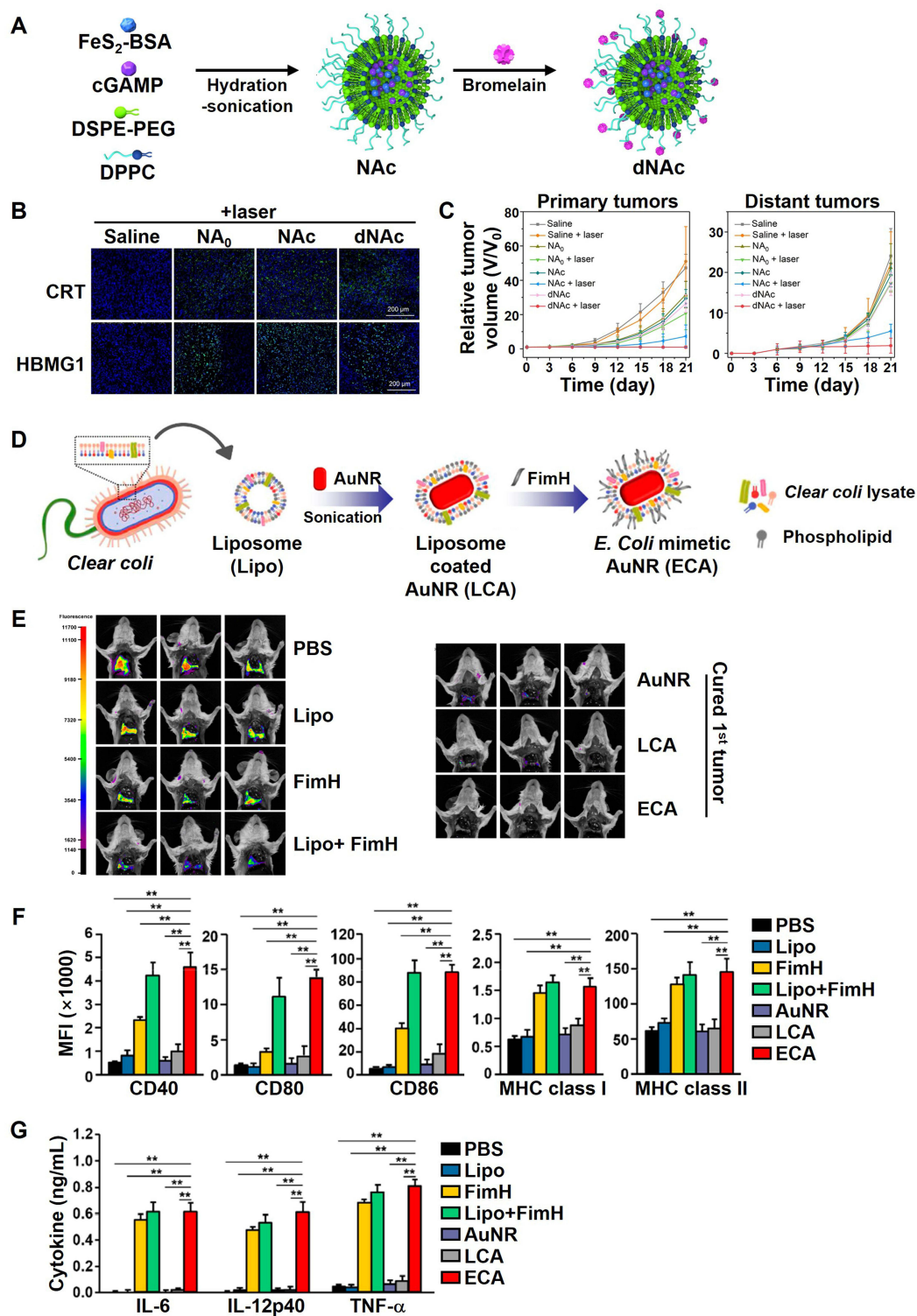


Figure 7 Photothermal-enhanced immunotherapy. **(A)** Conceptual illustration depicting the preparation of extracellular matrix (ECM)-degrading photothermal nanoagonist (dNac), generated through a hydration–sonication procedure followed by surface functionalization for combined chemodynamic and immune modulation. **(B)** Representative immunofluorescence images of 4T1 cancer cells showing calreticulin (CRT) and HMGB1 exposure after treatment with NA₀, NAc or dNac in presence of 100 μ M H₂O₂, followed by NIR-II laser irradiation (1 W/cm², 6 min). **(C)** Growth curves of primary and distant tumors after administration of NA₀, NAc, or dNac, with or without NIR-II laser exposure (1 W/cm², 10 min).⁸⁵ Copyright 2022, John Wiley and Sons. **(D)** Schematic overview of E. coli-mimetic gold nanorod (ECA) formation via liposome coating and FimH functionalization. **(E)** iRFP signal in the lungs of mice on day 14 after the secondary tumor challenge, demonstrating metastatic suppression. **(F)** Flow cytometry analysis of dendritic cell surface markers in tumor-draining lymph nodes (tdLNs). **(G)** Quantification of IFN- γ and T-bet mRNA expression levels in tdLNs (** p < 0.01).⁸⁶ Copyright 2022, American Chemical Society. All Figures were reproduced with permission.

extracellular matrix (ECM)-degrading nanoagonist (dNAc) composed of NIR-II-absorbing ferrous sulfide (FeS₂) NPs and the SITNG agonist cyclic guanosine monophosphate–adenosine monophosphate (cyclic GMP-AMP, cGAMP) within thermoresponsive liposomes (Figure 7A).⁸⁵ To enhance tumor infiltration, the surface of dNAc was functionalized with bromelain, an enzyme that degrades ECM. Upon exposure to an NIR-II laser (1064 nm), dNAc released cGAMP and induced ICD, as shown by calreticulin (CRT) and HMGB1 release (Figure 7B). In vivo studies demonstrated that dNAc treatment significantly robustly inhibit and distant tumors, highlighting the robust systemic immune activation (Figure 7C).

Hwang et al synthesized an ECA composed of lipopolysaccharides-free clear Escherichia coli (E. coli) lysate and phospholipid-coated AuNRs, conjugated with FimH, a bacterial surface adhesin protein from E. coli (Figure 7D).⁸⁶ Under NIR irradiation, ECA effectively inhibited tumor growth and significantly prevented secondary pulmonary metastasis (Figure 7E). This approach not only induces direct tumor cell death but also promotes dendritic cell activation in tumor-draining lymph nodes, stimulating antigen-specific T cell immunity and offering protection against secondary tumor challenges (Figure 7F and G).

Notably, PTT-immunotherapy has demonstrated efficacy not only in preventing the progression of primary tumor but also in suppressing metastatic spread and reducing recurrence risk. By inducing ICD and activating adaptive immune responses, combination therapies offer a compelling strategy for treating both primary and metastatic cancers.^{98,101,102}

Collectively, these studies demonstrate that photothermal immunotherapy can potentiate antigen release, dendritic cell maturation, and T-cell-mediated tumor clearance through heat-amplified immunomodulation. Nonetheless, its therapeutic consistency remains influenced by heterogeneous heat distribution, tumor-specific immune suppression, and limited NIR penetration. Further optimization of photothermal dosing, nanomaterial design, and integration with clinically validated immunotherapies—including immune checkpoint blockade—will be required to translate these synergistic effects into reproducible and durable clinical outcomes.

NP-Based Chemo-Photothermal Combination Therapy

When combined with chemotherapeutic agents, PTT provides localized heating that improves drug delivery, accelerates drug release from temperature-responsive carriers, and enhances tumor cell susceptibility to cytotoxic effects.^{103–105}

Table 3 T Strategies and Outcomes of Chemotherapeutic Drugs Combined with Hyperthermia, Including Various PTT Parameters (Laser Power Density, Wavelength, and Irradiation Duration)

Cell Type	Laser Specification	PT NPs	Chemotherapeutic Agents	Therapeutic Outcomes	Ref
MDA-MB-231	805 nm, 1.6 W/cm ² , 10 min	Composite scaffolds of biodegradable black phosphorus nanosheets and gold nanorods	Doxorubicin	- Synergistically kills breast cancer cells in the early stage and induces chemotherapy effects in the late stage. - Supports hMSC proliferation for tissue regeneration after complete drug release.	[106]
4T1	665 nm, 0.6 W/cm ² , 5 min	Phospholipid-micelle	Mitoxantrone	- Efficient accumulation at tumor sites post-intravenous injection. - Downregulates HSP70 expression, reducing tumor thermoresistance and enhancing mild-PHT efficacy.	[107]
4T1	808 nm, 3.97 W/cm ² , 5 min	Platinum NPs	Paclitaxel	- Releases paclitaxel in a redox environment and scavenges ROS to induce tumor cell death. - Exhibits a strong anti-tumor effect and remodels the TME.	[108]

(Continued)

Table 3 (Continued).

Cell Type	Laser Specification	PT NPs	Chemotherapeutic Agents	Therapeutic Outcomes	Ref
4T1	808 nm, 0.8 W/cm ² , 5 min	PDA(DOX) nanoplatform	Doxorubicin	- Effectively inhibits tumor growth in 4T1 tumor-bearing mice. - Reduces DOX-induced cardiotoxicity in electrocardiogram and echocardiogram assessments.	[110]
HeLa, 4T1	808 nm, 0.5 W/cm ² , 8 min	Cy-S-S-Cbl	Chlorambucil	- Releases Cbl (alkylating agent) upon elevated GSH levels in cancer cells, inducing DNA damage. - PT effect from Cy-NH ₂ downregulates HSP70, enhancing therapy efficacy.	[115]

Photothermal nanomaterials—including gold nanorods, black phosphorus nanosheets, platinum nanoparticles, poly-dopamine, and carbon-based platforms—act as both drug carriers and heat-generating agents, enabling coordinated delivery and activation (Table 3).^{106–114}

For example, Chen et al developed mitoxantrone (MTO)-micelles that integrate MTO with mild PTT for improved treatment of triple-negative breast cancer (Figure 8A).¹⁰⁷ Following tumor accumulation via enhanced permeability and retention (EPR) effect, NIR irradiation produced mild hyperthermia that triggered MTO release and reduce HSP70 expression (Figure 8B). The combination of MTO-micelles and laser treatment exhibited significant antitumor effects compared to single treatments, highlighting the potential of chemo-PTT as an effective therapy for TNBC (Figure 8C).

Another innovative approach by Zou et al involved a glutathione (GSH)-activated prodrug, Cy-S-S-Cbl, which coupled a photothermal agent (Cy7) with an alkylating agent (cobalamin, Cbl) (Figure 8D).¹¹⁵

In the high-GSH tumor microenvironment, the disulfide bond is cleaved to yield Cy-NH₂ and the active alkylating species. Cy-NH₂ demonstrated higher photothermal conversion, while the released alkylating drug induces DNA damage; together, these processes further downregulated HSP70 expression and reduce cancer cell thermotolerance (Figure 8E and F). As a result, combined chemo-PTT produced stronger tumor inhibition than either modality alone (Figure 8G).

These systems illustrate how heat-triggered drug activation and photothermal sensitization create a synergistic therapeutic response capable of overcoming drug resistance and improving intratumoral drug.^{116–126}

However, their translation remains limited by variability in thermal dosing, incomplete data on nanoparticle clearance and long-term toxicity, tumor heterogeneity, and the lack of standardized irradiation parameters across studies. Future progress will require harmonized photothermal protocols, systematic evaluation of chronic safety, and development of deeper-penetrating NIR-responsive nanomaterials to enable reliable efficacy in clinically relevant tumor models.

Conclusion and Perspectives

While PTT shows promising prospects through its integration with gene therapy, immunotherapy, and chemotherapy, this review presents the potential for PTT's clinical application and critically evaluates its current limitations. Even though the paucity of consistent experimental outcomes based on NP designs and irradiation parameters complicates direct comparison between studies, NP-enabled PTT has progressed from a heat-based tumor ablation method to a multifunctional platform. In this review, we hereby present wavelength-dependent cellular and molecular responses to PTT and correlation with quantifiable optical parameters in comparison with a recent review,¹²⁷ which mainly addressed the condition and their effect of PTT in cancer treatment. Through localized hyperthermia, PTT increases membrane permeability, promotes endosomal escape, triggers thermally responsive drug release, and induces immunogenic cell death—mechanisms that collectively improve the performance of co-administered therapeutics. Emerging NIR-II-responsive materials, including Ag₂S-based semiconductors, further expand the potential of PTT by offering deeper light penetration and integrated imaging capability. Despite these advances, several hurdles limit clinical

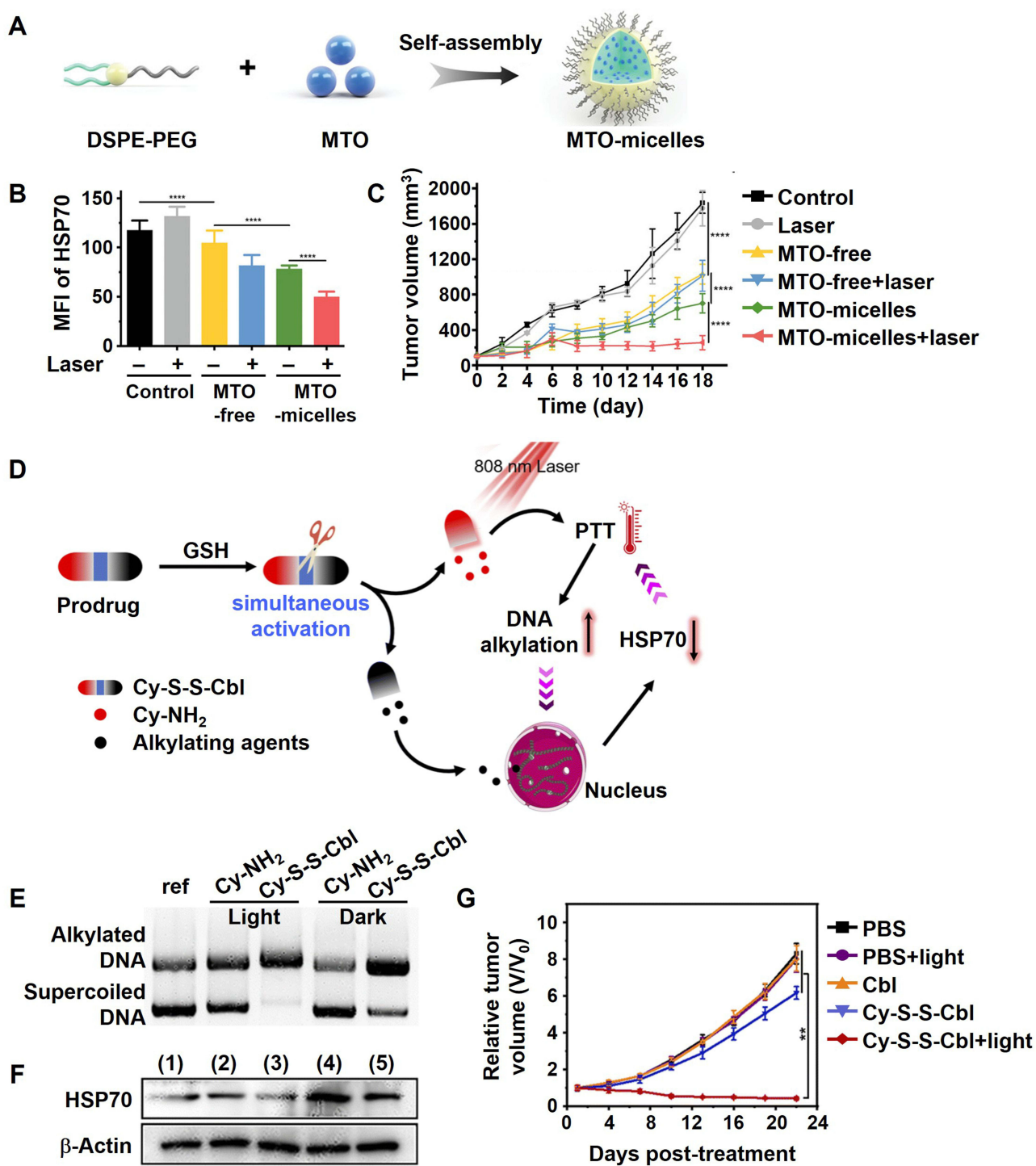


Figure 8 Combining Chemotherapy and Immunotherapy for synergistic cancer therapy. **(A)** Schematic diagram of self-assembled mitoxantrone (MTO)-micelles engineered to deliver MTO in combination with mild-photothermal heating for enhanced therapy in triple-negative breast cancer (TNBC). **(B)** Quantification of HSP70 expression levels in 4T1 cells following various micelle- or laser-based treatments. **(C)** Tumor growth curves in mice receiving mild photothermal chemotherapy using either MTO-free or MTO-loaded micelles (**** $p < 0.0001$).¹⁰⁷ Copyright 2023, Wiley-VCH GmbH. **(D)** Schematic depiction of a glutathione (GSH)-activated Cy-S-S-Cbl prodrug system that able simultaneous activation of photothermal and alkylation functions. **(E)** Agarose gel electrophoresis showing plasmid DNA (pBR322) after incubation with Cy-S-S-Cbl or Cy-NH₂ (50 μM) at 37°C for 4 h in 10 mM GSH, with or without NIR light. **(F)** Western blot analysis of HSP70 expression in HeLa cells under treatments: (1) PBS, (2) PBS + 808 nm light, (3) Cy-S-S-Cbl, (4) Cy-NH₂ + NIR light, and (5) Cy-S-S-Cbl + NIR light. **(G)** Relative tumor growth in HeLa tumor-bearing mice across different treatment groups (** $p < 0.01$).¹¹⁵ Copyright 2023, Royal Society of Chemistry. All Figures were reproduced with permission.

translation. NIR penetration depth restricts treatment of deep-seated tumors; thermal overexposure may induce HSP-mediated thermotolerance; and long-term biodistribution, biodegradation, and immunotoxicity of nanomaterials remain insufficiently characterized. Moreover, inconsistencies in laser parameters, thermal dosimetry, and treatment protocols hinder reproducibility and complicate cross-study comparison. Additionally, the therapeutic efficacy of PTT-based combinations is highly dependent on tumor anatomy and microenvironmental heterogeneity.

Future progress will benefit from the development of photothermal agents with enhanced optical efficiency and improved tissue penetration—particularly biomimetic and NIR-II-responsive materials—together with standardized laser irradiation parameters and thermal-dosing protocols and more systematic long-term safety evaluations. Mechanistic integration of PTT with clinically validated modalities—such as immune checkpoint inhibitors, nucleic acid therapeutics, or multimodal imaging-guided systems—may yield more reproducible and durable responses. As these translational challenges are addressed, combinatorial PTT has the potential to evolve into a more selective and adaptable treatment framework that complements and extends the capabilities of current cancer therapies.

What's New in This

A comparison of the present study with existing reviews on photothermal therapy reveals several novel points. The initial point unveils a mechanism-centered, indicator-based framework that establishes a correlation between optical parameters and cellular and molecular responses. The subsequent point concerns the most detailed synthesis to date of PTT-enabled gene delivery mechanisms, encompassing nanobomb-mediated photoporation. The third point pertains to the formulation of a unified mechanistic map that elucidates the manner in which PTT synergizes with gene therapy, immunotherapy, and chemotherapy. The fourth point is an updated and translation-oriented assessment of emerging NIR-II photothermal agents. The fifth point involves a comparative analysis of nanoparticle families aligned with heat-biology interactions rather than material categories alone. The final point reveals that a critical appraisal of current limitations—such as dosimetry inconsistency, thermotolerance, toxicity, and intratumoral heterogeneity—clarifies challenges that must be addressed for clinical translation.

Abbreviations

PTT, Photothermal therapy; NIR, near-infrared; NPs, nanoparticles; ICD, immunogenic cell death; DAMPs, damage-associated molecular patterns; HMGB1, High mobility group box 1; HSP, heat shock protein; AuNRs, gold nanorods; PDA, Polydopamine; BP, Black phosphorus; BPNS, BP nanosheets; BATNS, BP-Au-thiosugar NSs; NBs, nanobombs; DC, dendritic cell; MCH, major histocompatibility complex; TLR, toll-like receptor; ECM, extracellular matrix; cGAMP, cyclic guanosine monophosphate-adenosine monophosphate; CTR, calreticulin; *E. coli*, *Escherichia coli*; MTO, mitoxantrone; GSH, glutathione.

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Disclosure

The authors report no conflicts of interest in this work.

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