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Photothermal and Photodynamic Nanotherapies: Synergistic Approaches for Cancer Ablation and Immune Activation

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ABSTRACT

Photothermal therapy (PTT) and photodynamic therapy (PDT) are minimally invasive, light-activated treatment modalities that have gained considerable attention in oncology due to their spatial precision, reduced systemic toxicity, and compatibility with nanotechnology. Individually, PTT employs photoabsorbing agents to convert near-infrared (NIR) light into localized heat, inducing cancer cell death, while PDT generates reactive oxygen species (ROS) through photosensitizers under light activation, leading to oxidative damage and apoptosis. However, their standalone applications often suffer from limited tissue penetration, hypoxia-induced resistance, and incomplete tumor eradication. Emerging nanotechnology-enabled platforms offer a promising solution through the synergistic integration of PTT and PDT into a single nanotherapeutic system. This combinatorial strategy amplifies therapeutic efficacy via complementary mechanisms: enhanced tumor destruction, vasculature disruption, and immunogenic cell death (ICD), which primes antitumor immunity. Moreover, these dual-modal platforms can be engineered for tumor-specific targeting, real-time imaging, and controlled drug release. This review presents a comprehensive overview of the fundamental mechanisms of PTT and PDT, the design and functionalization of nanocarriers for synergistic therapy, and recent advances in preclinical and clinical studies. Special emphasis is placed on the role of PTT/PDT-induced immune activation and its integration with checkpoint blockade therapies. Finally, the challenges and prospects for clinical translation are critically discussed, highlighting the potential of photothermal–photodynamic nanotherapy as a next-generation oncological strategy.

Keywords: Photothermal therapy, Photodynamic therapy, Nanoparticles, Cancer immunotherapy, Synergistic cancer therapy

INTRODUCTION

Cancer continues to be one of the leading causes of mortality worldwide, with increasing incidence and mortality rates attributed to population aging, environmental factors, lifestyle changes, and genetic predispositions[1–4]. Despite advances in early diagnosis and targeted therapies, conventional treatment modalities such as surgery, chemotherapy, and radiotherapy remain the backbone of cancer management. However, these approaches are often plagued by significant limitations[5, 6]. Chemotherapy, while systemic, frequently results in off-target toxicity, immune suppression, and the development of multidrug resistance (MDR), compromising long-term efficacy. Radiation therapy, though localized, may damage surrounding healthy tissues and is often ineffective against metastatic lesions. These challenges underscore the urgent need for novel, selective, and minimally invasive therapeutic strategies that can offer spatiotemporal precision with reduced systemic toxicity[7–9].

In this context, light-activated therapies, namely photothermal therapy (PTT) and photodynamic therapy (PDT), have emerged as promising alternatives[10, 11]. These modalities harness the power of specific wavelengths of light in combination with exogenous agents to initiate tumor cell death through heat generation (PTT) or reactive oxygen species (ROS) production (PDT). A notable advantage of these therapies is their ability to localize therapeutic action to illuminated regions, thereby reducing collateral damage to surrounding healthy tissue. Moreover, light dosage, intensity, and duration can be finely tuned to modulate treatment outcomes, offering personalized therapeutic options[12, 13].

Photothermal therapy operates on the principle of converting light energy, typically in the near-infrared (NIR) range (650–950 nm), into heat through photothermal agents (PTAs), leading to localized hyperthermia and tumor cell death[14]. Photodynamic therapy, in contrast, relies on photosensitizers (PSs) that, upon light activation in the presence of oxygen, generate cytotoxic ROS that damage cellular components. Despite their

individual strengths, both PTT and PDT face distinct limitations. PTT may induce non-uniform heating and incomplete ablation, while PDT is highly dependent on oxygen availability and light penetration, limiting its effectiveness in hypoxic and deep-seated tumors[15, 16].

To overcome these drawbacks and improve therapeutic outcomes, researchers have explored the combination of PTT and PDT within a unified nanotechnology-based platform. Nanoparticles offer a versatile platform for the co-delivery of PTAs and PSs, enhancing tumor specificity through the enhanced permeability and retention (EPR) effect and facilitating controlled release at the tumor site[17, 18]. Additionally, nanoparticles can be engineered to respond to tumor-specific stimuli such as pH, redox potential, or enzymatic activity, further enhancing their selectivity and reducing off-target effects[18].

One of the most intriguing outcomes of combining PTT and PDT is the induction of immunogenic cell death (ICD). Unlike conventional apoptosis, ICD triggers the release of tumor-associated antigens (TAAs) and damage-associated molecular patterns (DAMPs), which can stimulate dendritic cells (DCs) and promote T-cell–mediated systemic antitumor immunity[19]. This opens new avenues for integrating PTT/PDT with immunotherapeutic strategies such as immune checkpoint inhibitors or cancer vaccines, thereby converting "cold" tumors into "hot" ones that are more responsive to immune attack[20].

This review aims to provide a comprehensive analysis of the mechanistic principles underlying PTT and PDT, the rationale for their synergistic combination, and the design of nanomaterials that facilitate dual-modal therapy. We also highlight the immunological implications of this combinatorial approach, drawing attention to its potential in enhancing not only localized tumor ablation but also long-term systemic immune surveillance. Preclinical successes and early clinical studies are examined, alongside current challenges such as light penetration depth, phototoxicity, and nanoparticle biocompatibility. Finally, we discuss the future direction of this rapidly evolving field, with emphasis on personalized nanomedicine, image-guided therapy, and theranostic integration.

2. Mechanistic Basis of PTT and PDT

Photothermal Therapy (PTT) is a form of light-triggered therapy that exploits the conversion of light energy into thermal energy to induce localized hyperthermia[21, 22]. This approach primarily utilizes photothermal agents (PTAs) that exhibit strong absorption in the near-infrared (NIR) region, which penetrates tissue more deeply than visible light. Upon NIR irradiation, PTAs absorb the photons and dissipate the energy as heat, raising the temperature of the surrounding environment to cytotoxic levels, typically in the range of 42–48 °C. This thermal insult can disrupt cellular membranes, denature proteins, and induce cell death via apoptosis or necrosis, depending on the intensity and duration of heating[23].

The most widely studied PTAs include gold-based nanomaterials (e.g., gold nanorods, nanoshells, and nanostars), carbon-based materials (e.g., graphene oxide and carbon nanotubes), and transition metal-based nanoparticles (e.g., copper sulfide and palladium nanoparticles). These materials offer favorable photothermal conversion efficiency, tunable optical properties, and high biocompatibility. Moreover, their surfaces can be functionalized with targeting ligands (e.g., antibodies, peptides) to enhance tumor specificity. PTT also benefits from real-time thermal monitoring and can be precisely controlled by adjusting laser power and exposure time.

Photodynamic Therapy (PDT), in contrast, relies on the light-triggered activation of photosensitizers (PSs) in the presence of molecular oxygen to produce reactive oxygen species (ROS), particularly singlet oxygen (^1O_2)[24]. These ROS interact with cellular components such as lipids, proteins, and nucleic acids, leading to oxidative stress and cell death. PDT-induced damage often involves the mitochondria and lysosomes, triggering apoptosis through caspase activation or autophagy. Importantly, PDT can also disrupt tumor vasculature and induce inflammatory responses, contributing to its therapeutic effects[25].

Photosensitizers used in PDT include porphyrins, phthalocyanines, chlorins, and newer synthetic dyes, many of which have been approved or are in clinical trials. These agents can accumulate preferentially in tumor cells due to differences in cellular metabolism and vascular permeability[26]. However, one major limitation of PDT is its dependency on oxygen, which poses challenges in hypoxic tumor environments where ROS generation is compromised. Furthermore, the limited penetration depth of visible light restricts PDT's application to superficial or endoscopically accessible tumors[26, 27].

While PTT and PDT are effective as standalone therapies, they are not without limitations. PTT may result in incomplete ablation, particularly at the tumor margins where heat diffusion is insufficient[28, 29]. Moreover, repeated PTT applications can lead to heat shock protein (HSP) upregulation, conferring thermotolerance and reducing therapeutic efficacy. PDT, on the other hand, is often ineffective in deeply seated or hypoxic tumors due to poor light penetration and limited oxygen supply.

Combining PTT and PDT in a single treatment strategy offers a powerful solution to these challenges. The heat generated by PTT can improve tumor oxygenation by increasing blood flow, potentially enhancing PDT efficacy. Likewise, PDT-induced vascular damage may increase local retention of PTAs, improving PTT outcomes[30]. This synergy can be further amplified using nanotechnology-based platforms that co-encapsulate PTAs and PSs, enabling synchronized activation upon light exposure. Such dual-modal nanomedicine not only ensures more complete tumor destruction but also facilitates the induction of immunogenic cell death, thereby bridging local ablation with systemic immune activation[30, 31].

The mechanistic foundation of PTT and PDT highlights their complementary modes of action. Leveraging their synergistic effects through nanotechnology-enhanced delivery systems offers a highly promising approach for precise, efficient, and immune-activating cancer therapy.

3. Design Strategies for Synergistic Nanoplatforms

The successful integration of photothermal therapy (PTT) and photodynamic therapy (PDT) into a single nanoplatform requires deliberate and sophisticated design strategies. The goal is to co-deliver photothermal agents (PTAs) and photosensitizers (PSs) in a manner that ensures stability, bioavailability, tumor specificity, and responsiveness to the unique characteristics of the tumor microenvironment[32]. These platforms must also possess excellent pharmacokinetic profiles, biocompatibility, and be capable of performing multiple functions, including imaging, drug delivery, and therapeutic action. Several innovative nanocarrier designs have emerged to fulfill these requirements.

a. Core–Shell Structures:

Core–shell nanostructures are among the most commonly used designs for combining PTT and PDT functionalities. In this architecture, one therapeutic agent is encapsulated in or constitutes the core, while the other forms or is conjugated to the shell[33]. For instance, gold nanorods, known for their excellent near-infrared (NIR) photothermal conversion, often serve as the core for PTT. The shell, typically made of silica or polymer, is functionalized with photosensitizers such as chlorin e6 or porphyrins, enabling PDT upon light irradiation[34]. This spatial compartmentalization offers several advantages: it prevents premature degradation of the therapeutic agents, enables sequential or simultaneous activation under specific wavelengths, and allows fine-tuning of particle size, shape, and surface charge to optimize biodistribution and tumor penetration. Moreover, this design allows for the incorporation of targeting ligands, enhancing cellular uptake and specificity.

b. Hybrid Nanoparticles:

Hybrid nanoparticles incorporate multiple therapeutic functionalities into a single material system. Materials like black phosphorus, graphene oxide, carbon dots, and metal–organic frameworks (MOFs) exhibit both photothermal and photodynamic properties[35]. These materials simplify design complexity by eliminating the need to load separate PTAs and PSs, thus reducing synthesis steps and potential stability issues. MOFs, in particular, offer tunable porosity and large surface areas, making them ideal for drug loading and co-delivery. Moreover, some MOFs possess inherent catalytic activities that can generate reactive oxygen species (ROS) without external photosensitizers, enhancing PDT effects[36, 37]. Hybrid nanoplatforms are particularly attractive due to their potential for activation under a single NIR wavelength, thereby reducing light source complexity and tissue damage during therapy.

c. Stimuli-Responsive Systems:

Smart nanoparticles that respond to tumor-specific stimuli such as acidic pH, elevated glutathione (GSH) levels, or overexpressed enzymes (e.g., MMPs, cathepsins) allow for controlled and site-specific release of therapeutic agents. pH-responsive linkers like hydrazone or cis-aconityl groups can be used to tether PSs or PTAs to the nanocarrier, enabling their release in the acidic tumor microenvironment[38, 39]. Similarly, disulfide bonds cleaved by high intracellular GSH concentrations facilitate the intracellular release of the payload. This targeted release mechanism not only enhances therapeutic efficacy but also reduces systemic toxicity and minimizes adverse effects on healthy tissues. Some advanced designs also incorporate thermoresponsive materials that trigger drug release upon PTT-induced hyperthermia, creating a feedback loop that amplifies treatment effects.[39]

d. Imaging-Guided Therapy:

Incorporating imaging functionalities into nanoplatforms allows real-time monitoring of nanoparticle distribution, accumulation, drug release, and therapeutic response. Imaging modalities such as fluorescence imaging, magnetic resonance imaging (MRI), photoacoustic imaging, and computed tomography (CT) can be integrated into the nanocarrier via the inclusion of contrast agents, fluorescent dyes, or metallic cores[40]. This enables theranostic applications, where diagnosis and therapy are simultaneously performed. Real-time imaging ensures accurate irradiation of the tumor site, minimizes off-target exposure, and facilitates personalized treatment adjustments based on biodistribution profiles[40].

In sum, these sophisticated design strategies enable synergistic and targeted delivery of PTT and PDT agents, thereby overcoming the limitations of conventional monotherapies. These multifunctional nanoplatforms improve drug solubility, circulation half-life, and tumor accumulation while offering opportunities for precise control over therapeutic actions[41]. As research progresses, next-generation platforms are likely to further incorporate artificial intelligence-guided designs, multi-organ delivery capabilities, and patient-specific customization, marking a significant leap forward in cancer nanomedicine.

4. Synergistic Antitumor Effects and Immune Activation

The therapeutic synergy achieved by combining photothermal therapy (PTT) and photodynamic therapy (PDT) lies in the ability of these modalities to complement and amplify each other's effects. Both PTT and PDT independently induce tumor cell death through different mechanisms PTT via hyperthermia-induced denaturation of cellular proteins and membrane disruption, and PDT via the generation of cytotoxic reactive oxygen species (ROS) that damage cellular components[42]. When combined in a single nanoplatform and

appropriately activated, they exhibit enhanced antitumor efficacy, deeper tissue penetration, improved selectivity, and crucially, the ability to stimulate systemic antitumor immunity[42].

The primary mechanism underlying this synergy is the mutual reinforcement between PTT and PDT. PTT-induced hyperthermia increases tumor vascular permeability and local blood flow, thereby improving oxygenation levels within the tumor microenvironment[43]. Since PDT efficacy relies on the presence of molecular oxygen to produce ROS, this PTT-mediated enhancement of oxygen supply significantly augments PDT performance. Conversely, PDT-induced damage to tumor vasculature can trap nanoparticles at the tumor site, enhancing the accumulation and retention of nanocarriers for prolonged PTT action. These feedback mechanisms create a therapeutic loop where each treatment amplifies the other's effects, resulting in complete tumor ablation and a lower risk of recurrence[43, 44].

Beyond local tumor ablation, the PTT/PDT combination therapy is notable for its ability to elicit immunogenic cell death (ICD). Unlike apoptotic cell death, which typically leads to immune tolerance, ICD is characterized by the release of damage-associated molecular patterns (DAMPs) such as calreticulin, ATP, and high-mobility group box 1 (HMGB1)[45]. These molecules act as danger signals, recruiting dendritic cells (DCs) and facilitating their maturation. Mature DCs then process and present tumor-associated antigens to naïve T cells, leading to the activation and expansion of tumor-specific cytotoxic T lymphocytes (CTLs). These CTLs can travel throughout the body and attack metastatic tumor cells, thereby transforming a localized treatment into a systemic antitumor response[46].

Recent research has focused on harnessing this immune-stimulating potential by combining PTT/PDT with immune checkpoint inhibitors (ICIs) such as anti-PD-1 and anti-CTLA-4 antibodies[47]. These ICIs release the brakes on T cell activation, allowing for a more robust and sustained immune response. In preclinical models, this combination has shown significant improvement in tumor rejection, prevention of metastasis, and the establishment of long-term immune memory, providing durable protection against tumor recurrence[47]. In particular, the use of nanocarriers to co-deliver PSs, PTAs, and immunomodulatory agents (e.g., CpG oligonucleotides, STING agonists, or TLR agonists like R848) further enhances the immunotherapeutic potential of the platform. These immunoadjuvants help reprogram the immunosuppressive tumor microenvironment into an immunostimulatory one, promoting T cell infiltration and activity.

Moreover, the combination therapy also has the potential to overcome challenges associated with tumor heterogeneity and immune evasion[48]. By inducing a broad immune response targeting multiple tumor antigens released during ICD, the therapy reduces the risk of immune escape and enhances the efficacy of cancer immunotherapy in non-immunogenic or "cold" tumors.

Summarily, the integration of PTT and PDT offers a multifaceted approach to cancer treatment that goes beyond cytotoxicity to include robust immune activation. Through enhanced tumor ablation, immunogenic cell death, and synergistic interaction with immune checkpoint inhibitors, PTT/PDT combination therapies represent a promising strategy for both local tumor control and systemic anticancer immunity. Future developments are likely to focus on optimizing dosing regimens, refining nanocarrier designs, and integrating real-time imaging and immunomonitoring to maximize therapeutic outcomes.

5. Clinical Translation and Challenges

Despite the substantial promise demonstrated by photothermal therapy (PTT) and photodynamic therapy (PDT) nanoplatforms in preclinical models, translating these technologies into clinical practice faces significant hurdles[49]. One of the major limitations is the restricted tissue penetration of near-infrared (NIR) light, which affects the ability to effectively treat deep-seated tumors. Conventional NIR-I (650–950 nm) light can only penetrate a few centimeters into tissues. To address this, researchers are investigating strategies such as interstitial fiber-optic light delivery, where light is administered directly into the tumor core, and the use of the second NIR window (NIR-II, 1000–1700 nm), which offers deeper penetration and higher resolution[50].

Another critical challenge is nanoparticle clearance and long-term toxicity. Many nanocarriers tend to accumulate in the liver, spleen, or kidneys, potentially leading to off-target effects or long-term toxicity. Moreover, incomplete clearance from the body raises safety concerns, especially with repeated administrations[51, 52]. Therefore, rigorous biocompatibility testing, biodegradability analysis, and pharmacokinetic profiling are essential to gain regulatory approval.

Tumor heterogeneity also complicates clinical translation[51]. Differences in vascular permeability, interstitial pressure, oxygen levels, and immune cell infiltration across tumor types and within individual tumors can result in inconsistent therapeutic responses. Consequently, strategies that account for the tumor microenvironment and integrate real-time feedback systems are needed. Regulatory and manufacturing issues further delay clinical application. The multifunctional and often complex design of these nanoplatforms poses challenges in quality control, scalability, and batch-to-batch reproducibility. These intricacies increase the time and cost associated with clinical trials and approval pathways[53].

Nonetheless, ongoing research has led to the development of several dual-functional PTT/PDT nanotherapeutics that have reached preclinical and early-phase clinical trials, showing encouraging safety and efficacy profiles. These advances highlight the significant potential for future clinical integration with appropriate optimizations.

6. Future Perspectives

The future of photothermal–photodynamic nanotherapy lies in its convergence with precision medicine and personalized oncology. Rather than relying on one-size-fits-all treatments, future approaches will tailor therapies based on individual patient profiles, including tumor genetics, immune responses, and microenvironmental factors such as hypoxia or acidity. This personalization will be facilitated by advances in bioinformatics and artificial intelligence (AI), which can predict optimal treatment strategies and nanoparticle formulations using patient-specific data. Moreover, smart nanomaterials are being developed that can dynamically respond to specific biological cues such as pH, enzyme expression, or reactive oxygen species, enhancing selective activation and reducing systemic toxicity. Modular and biodegradable nanoplatforms are particularly attractive for their tunability and improved safety profiles. Simultaneously, non-invasive *imaging-guided systems*, such as fluorescence, photoacoustic, or MRI-based techniques, will play a crucial role in real-time monitoring of nanoparticle biodistribution, tumor accumulation, and therapeutic response. Another exciting prospect is the use of patient-derived 3D tumor organoids and microfluidic tumor-on-a-chip platforms for pre-treatment screening. These models can recapitulate tumor heterogeneity, enabling optimization of light dosimetry, timing of administration, and nanoparticle design before clinical application. Such technologies may significantly reduce failure rates in human trials. Furthermore, *combination strategies*, particularly with immune checkpoint inhibitors, CAR-T cells, or cancer vaccines, could augment the immunogenic cell death (ICD) effects triggered by PTT/PDT, transforming localized ablation into systemic anti-tumor immunity. Ultimately, the successful translation of PTT/PDT nanotherapies will rely on multidisciplinary collaboration among oncologists, materials scientists, immunologists, and regulatory experts. Continued investment in translational research, robust clinical validation, and standardized regulatory frameworks will be essential in bringing this transformative therapeutic modality from bench to bedside.

CONCLUSION

Photothermal and photodynamic nanotherapies offer a potent synergistic approach for effective cancer ablation and immune activation. Through rational nanoparticle design and integration with immunotherapeutic strategies, this dual-modality treatment holds great promise for eradicating tumors, preventing metastasis, and inducing long-term antitumor immunity. While challenges remain, the continued evolution of nanotechnology and precision medicine will undoubtedly shape the future of photonic cancer therapies.

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