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Review

PHOTOTHERMAL NANOMEDICINE-TRIGGERED IMMUNOGENIC CELL DEATH: MOLECULAR MECHANISMS AND SYNERGISTIC IMMUNOTHERAPY STRATEGIES

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Abstract

Photothermal therapy (PTT) leverages light-absorbing nanoparticles (NPs) to convert light energy into localized heat, providing a targeted and minimally invasive approach for tumor ablation. Despite its promise, PTT faces several limitations, chiefly the poor tissue penetration depth and the risk of cancer recurrence due to incomplete tumor eradication. Recent breakthroughs, however, reveal that carefully engineered NPs can trigger immunogenic cell death (ICD) within an optimal thermal range. This process releases a cascade of damage-associated molecular patterns (DAMPs), activating dendritic cells (DCs) and priming tumor-specific T-cell immunity. By converting immunologically "cold" tumors into "hot" ones, this strategy opens the door for synergistic combination therapies with immunotherapy. This review outlines cutting-edge progress across precious-metal, organic, and hybrid photothermal nanomaterials, emphasizing how PTT-triggered ICD works at the molecular level and highlighting key strategies to enhance synergy with other treatments, such as immunotherapy, radiotherapy (RT), and chemotherapy. It also explores future directions and the challenges that remain in improving ICD efficiency, overcoming immunosuppressive tumor microenvironments (TME), and translating these strategies into clinical practice.

Keywords: Photothermal therapy, immunotherapy, antitumor, nanomaterial, immunogenic cell death.

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Introduction

Cancer remains a significant global health challenge. The International Agency for Research on Cancer (IARC), part of the World Health Organization, projects nearly 20 million new cancer diagnoses and 9.74 million cancer-related deaths worldwide in 2022 [1]. By 2050, the number of new cancer cases is expected to exceed 35 million, representing a 77% increase from 2022 [1]. For decades, the primary modalities for cancer treatment have been surgical tumor resection, chemotherapy, and radiotherapy (RT) [2]. However, complete surgical removal is often difficult to achieve, leaving behind tumor remnants that fuel metastasis. RT, although effective, can cause collateral damage to healthy cells and tissues, while chemotherapy, despite its role in reducing cancer mortality, often results in adverse effects, including damage to normal cells, side effects, and the development of drug resistance [3]. These challenges underscore the urgent need for more effective and less toxic therapeutic approaches.

Photothermal therapy (PTT) represents an innovative and minimally invasive treatment option. It relies on light-absorbing agents, known as photothermal agents (PTAs), which accumulate selectively in tumor sites and convert light energy, typically from near-infrared (NIR) radiation, into heat. This localized heating induces targeted destruction of tumor cells. Importantly, the hyperthermic environment generated by PTT also triggers immune responses, including immunogenic cell death (ICD), which further enhances its therapeutic potential [4,5]. What distinguishes PTT from conventional cancer treatments is its precision

targeting, reduced collateral damage to healthy tissues, and its ability to induce a systemic immune response through the release of damage-associated molecular patterns (DAMPs) that activate dendritic cells (DCs) and prime T-cell responses. This combination of direct cytotoxicity and immune activation offers a promising avenue for improving cancer treatment [6].

In the context of PTT, two temperature-regulated paradigms are commonly discussed: mild PTT and conventional high-temperature PTT [7,8]. Mild PTT typically refers to controlled photothermal heating within a moderate temperature window of approximately 42–45°C, which is insufficient for immediate tumor ablation but optimal for inducing ICD through regulated cellular stress, damage-associated molecular pattern release, and immune activation, while minimizing collateral tissue injury and heat shock proteins (HSPs)–mediated thermotolerance [9]. In contrast, conventional high-temperature PTT generally involves temperatures exceeding 45–50°C and primarily relies on rapid thermal ablation of tumor tissue, which, although effective for local tumor destruction, may induce excessive tissue damage and elicit relatively limited or transient antitumor immune responses [7]. Importantly, compared with conventional high-temperature photothermal ablation, mild PTT may partially circumvent excessive HSPs–mediated cytoprotective responses, thereby favoring sustained ICD induction and antitumor immune activation [10,11]. To maximize the benefits of PTT, researchers are exploring strategies that combine it with other therapeutic modalities, such as chemotherapy, RT, photodynamic therapy (PDT), immunotherapy, and gene therapy (GT). These multimodal approaches seek to address treatment resistance and tumor heterogeneity, two of the most significant challenges in cancer therapy.

ICD is a unique form of cell death that not only eliminates cancer cells but also triggers a systemic immune response [12]. In contrast to apoptosis and necrosis, ICD releases specific DAMPs that act as “danger signals,” which are recognized by immune cells [13,14]. This process can enhance antigen presentation, activate DCs, and stimulate a potent immune response against tumor cells. By strategically combining PTT with immunotherapy, it is possible to turn immunologically “cold” tumors into “hot” tumors, thus improving the response to treatment [15,16]. Moreover, by harnessing the immune system’s ability to recognize and attack tumor cells, PTT-induced ICD holds the potential to overcome the limitations of traditional therapies [9,17].

In recent years, several reviews have summarized the development of PTT–based nanomedicine, with a primary focus on material design, photothermal conversion efficiency, or therapeutic efficacy in tumor ablation. Other reviews have highlighted the integration of PTT with immunotherapy or discussed the emerging concept of ICD in cancer treatment. However, a systematic and mechanistically oriented overview that specifically links photothermal nanomedicine–triggered ICD with immune modulation and combination therapeutic strategies remains limited.

In contrast to existing reviews, the present work emphasizes the molecular and immunological mechanisms underlying photothermal-induced ICD, including damage-associated molecular pattern release, antigen presentation, and immune microenvironment remodeling. We will also discuss the synergies between PTT and other treatment modalities, such as immunotherapy, RT, and chemotherapy, as well as the future challenges and directions in this field.

The Mechanism of PTT Inducing ICD

PTT operates on the principle that PTAs generate thermal energy when exposed to NIR light, creating localized heating that selectively triggers either apoptosis or necrosis in targeted cells [18]. At around 41°C, the body activates protective mechanisms and synthesizes HSPs to repair mild heat damage [19]. However, at 42°C, the damage becomes irreversible. If the temperature is maintained between 42–46°C for 10 minutes, the cells undergo necrosis. As the temperature rises to 46–52°C, microvascular thrombosis occurs, cutting off the blood supply and causing rapid cell death due to ischemia. Beyond 60°C, proteins denature instantaneously, cell membranes collapse, and cellular death becomes immediate [20,21].

From this, it can be seen that 42°C is the critical threshold for cell fate: below this temperature, cells can still activate protective mechanisms (such as HSPs to repair damage); once the temperature is maintained at 42–46°C for a few minutes, cells enter an irreversible damage or necrosis stage. Notably, within the temperature window characteristic of mild PTT (approximately 42–45°C), this range constitutes the crucial threshold for PTT-triggered ICD [22]. Under thermal stress, cancer cells actively discharge DAMPs, including surface-exposed calreticulin (CRT), secreted high-mobility group box 1(HMGB1), and adenosine triphosphate (ATP), rather than undergoing passive cell death [23]. These signals are recognized by DCs, triggering antitumor immune responses. This process marks the transition from “heat killing” to “immune activation”, forming a synergistic therapeutic effect of PTT-ICD [24].

In addition to these immunogenic events, photothermal stress inevitably activates heat shock responses in tumor cells, particularly the upregulation of HSPs [25,26]. Intracellular HSPs function as molecular chaperones that protect protein homeostasis and may attenuate excessive cell death under high-temperature conditions, thereby partially limiting ICD induction [27]. Conversely, HSPs can also act as immunologically active signals when exposed or released during ICD, contributing to antigen presentation and immune activation [28]. Therefore, the biological outcome of PTT is highly dependent on the balance between thermal damage–induced immunogenic signaling and HSPs-mediated cytoprotective responses [11].

The primary way PTT induces ICD is by using heat stress to prompt tumor cells to emit various "danger signals". These signals then stimulate DCs and trigger T-cell-driven antitumor immune responses [9]. This process can be broken down into four key mechanisms:

Temperature fluctuations and membrane integrity: Within the "moderate high heat" range (approximately 45°C), the cell membrane structure is disrupted, exposing tumor-associated antigens (TAAs) that are picked up by immune cells, initiating targeted immune responses [29]. Studies indicate that post-PTT, alterations in tumor cell membranes lead to the creation of antigen fragments, which are then engulfed and broken down by DCs [30,31]. DAMPs release: A moderate fever can initiate a chain reaction that stresses the endoplasmic reticulum (ER), resulting in a flood of reactive oxygen species (ROS). This triggers CRT to translocate to the outer cell membrane, broadcasting a "come and get me" signal. Meanwhile, ATP is actively pumped out, and HMGB1, along with HSP70/90, leaks into the extracellular space, creating a hallmark DAMPs profile. These molecules act as magnets, drawing in and activating immune cells. They not only enhance the immune system's ability to recognize tumor antigens but also place immune cells on high alert [32]. Antigen cross-presentation: DAMPs bind to DCs surface receptors, including CD91, Toll-like receptors (TLRs), such as Toll-like receptor 4 (TLR4), P2X7, and CD40, triggering DCs maturation. This is marked by the upregulation of CD80 and CD86, as well as the secretion of IL-1β and IL-12 [33]. Consequently, antigen cross-presentation is enhanced, priming naïve $CD8^+$ T cells and boosting the expansion of tumor-specific cytotoxic T lymphocytes (CTLs) [34]. Creating lasting immune memory: T cells that develop immunological memory following PTT-induced ICD can serve as a shield against tumor relapse [35]. These immune "sentinels" spring into action upon detecting recurring tumor cells, reducing the chances of cancer recurrence and giving patients a better shot at long-term survival. Beyond its direct tumor-eradicating effects, PTT essentially supercharges the body's natural cancer-fighting capabilities by triggering ICD (Fig. 1) [9]. This two-pronged approach makes PTT a promising strategy for improving treatment outcomes and preventing tumor recurrences.

Classification and Properties of Photothermal Materials

The effectiveness of PTT depends largely on the performance of PTAs, which efficiently convert absorbed light energy into heat [36]. This rapid thermal conversion generates localized temperature increases in tumor tissues, causing protein degradation, cellular membrane disruption, and ultimately leading to programmed cell death. As a result, PTT offers highly targeted destruction of tumor cells. Research indicated that the efficacy of PTAs was influenced by several factors, including the absorption wavelength, nanoparticle morphology, and surface chemistry [37].

PTAs generally exhibit peak absorption within the NIR spectrum (750–1700 nm), which is further divided into two distinct regions: the first NIR window (NIR-I, 650–950 nm) [15] and the second NIR window (NIR-II, 1000–1700 nm) [38]. Compared with NIR-I light, NIR-II light demonstrates reduced tissue scattering and absorption, enabling significantly deeper penetration in biological tissues and improved signal-to-background ratios, which is advantageous for deep-tissue photothermal applications [39]. The performance of PTT is also influenced by the size of the PTAs. Larger NPs (exceeding 200 nm) generally exhibit superior photothermal conversion efficiency and extended circulation times in the bloodstream [40]. However, they face limitations in tissue penetration and cellular uptake. In contrast, smaller PTAs (approximately 50–100 nm) penetrate tumors more effectively, enhance cellular absorption, and exhibit slower immune system clearance [41]. Therefore, optimizing PTAs' design to strike the right balance between size, biocompatibility, stability, and minimal toxicity is critical for maximizing therapeutic efficacy [42].

Based on their chemical composition and photothermal mechanisms, PTAs can be systematically classified into five categories: precious metal-based, carbon-based, organic small molecule/polymer-based, inorganic non-metal-based, and other PTAs (Fig. 2).

Each category has distinct characteristics in terms of absorption wavelength, photostability, biocompatibility, and functionalization potential, offering a rich material foundation and strategic choices for developing next-generation precision PTT platforms. The representative materials, along with their advantages and disadvantages, are summarized in Table 1.

Precious Metal-based Nanomaterials

Precious metal-based nanomaterials (AuNMs), particularly gold nanoparticles (AuNPs), are widely employed in PTT for antitumor treatment due to their low toxicity, tunable optical properties, high specific surface area, excellent conductivity, large extinction coefficient, and strong chemical stability [43,50]. Gold-based PTAs, a subclass of AuNMs, are particularly notable for their remarkable light absorption capabilities. Their light intensities can exceed those of organic dye molecules by over a thousandfold. A distinguishing feature of AuNMs is their localized surface plasmon resonance (LSPR), which significantly enhances light absorption and scattering, making them highly efficient for photothermal conversion [44]. The absorption peak's wavelength and intensity can be precisely controlled by modifying the size and shape of the gold NPs, offering a versatile platform for optimized PTT performance [45].

AuNMs exist in various shapes, including gold nanorods (AuNRs) [46], gold nanostars [47], gold nanocages (GNCs) [48], and their spherical derivatives [49], each offering distinct advantages in terms of pho-

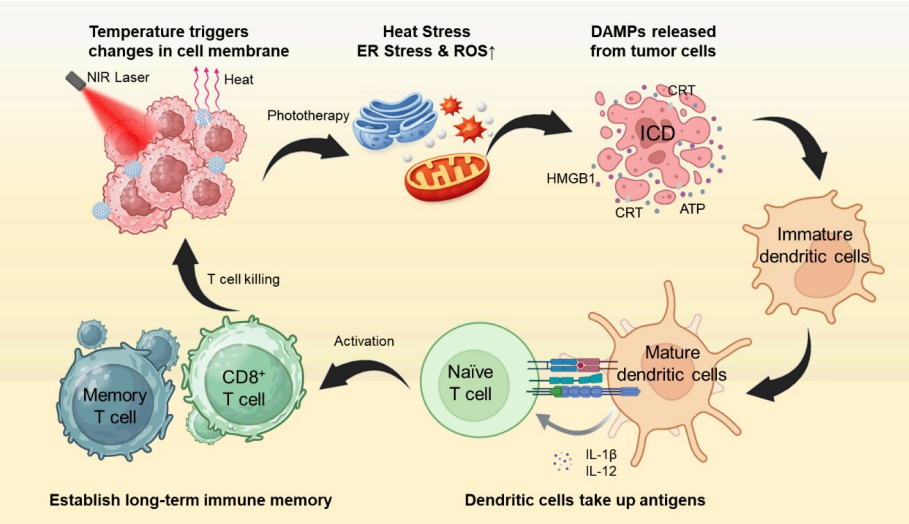

Fig. 1. Mechanism of ICD induced by PTT. Heat stress generated by PTT triggers ER stress and elevates ROS levels in tumor cells, leading to the release of DAMPs. These DAMPs activate pattern recognition receptors on DCs, promoting their maturation and subsequent activation of $CD8^+$ T cells. This cascade initiates tumor-targeted immune responses and establishes long-lasting antitumor immune memory. Figure created using PowerPoint, with elements from Biorender (www.biorender.com), used with permission.

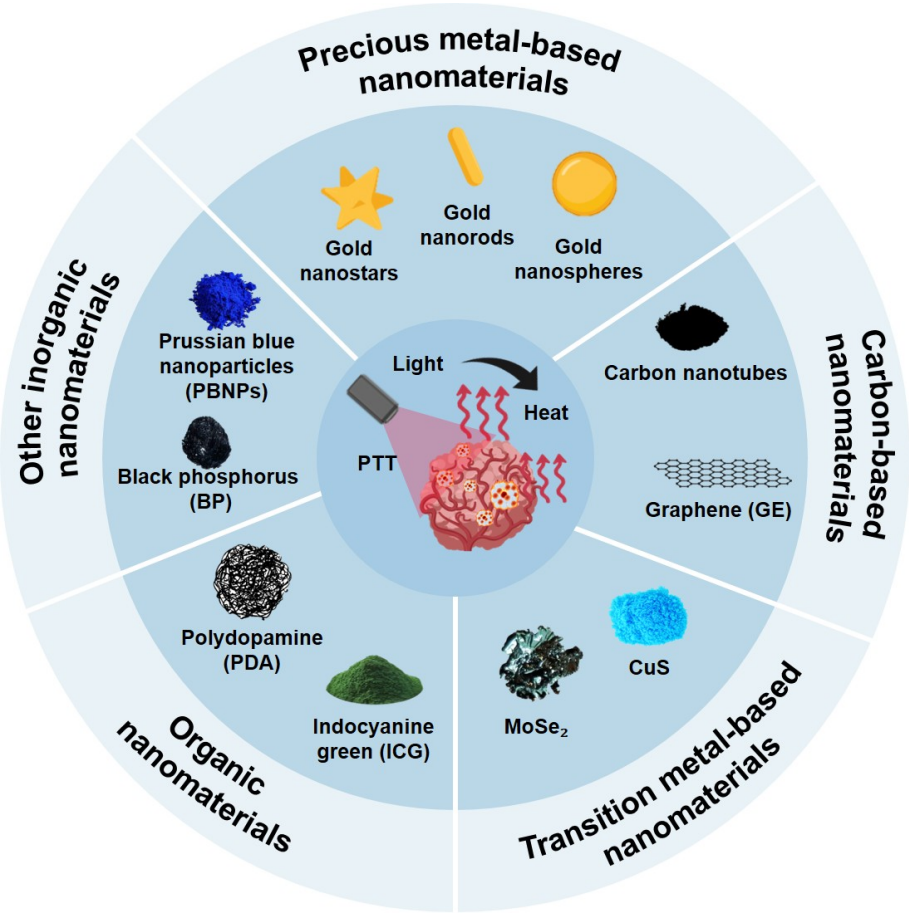

Fig. 2. The main types of photothermal conversion nanomaterials. PTAs serve as energy converters in PTT, efficiently transforming absorbed light energy into thermal energy to enable selective ablation of diseased tissues. Figure created using PowerPoint, with elements from Biorender (www.biorender.com), used with permission.

Table 1. Typical basic nanomaterials for PTT induced ICD.

Category	Nanomaterials	Advantage	Disadvantage	References
Precious metal-based nanomaterials	Gold (Au), silver (Ag), platinum (Pt), palladium (Pd) based nanomaterials	Low toxicity, adjustable optical properties and shape, high specific surface area, high conductivity, high extinction coefficient, and strong chemical stability.	Easy to melt under light irradiation.	[43–50]
Carbon-based nanomaterials	Graphene, carbon nanotubes, graphene oxide, etc	Has strong absorption ability for NIR light.	Long-term toxicity and systemic toxicity require further research.	[51–54]
Transition metal-based nanomaterials	Metal sulfide (CuS, FeS), metal oxide (ZnO, CuO)	Has adjuvant activity.	High cost, unable to produce on a large scale	[55,56]
Organic NIR dye	Indocyanine green (ICG), IR780, IR808	Excellent water solubility, biocompatibility, and multifunctionality, suitable for simultaneous use as PTAs and drug carriers	The immune dose and toxicity of it as an immune adjuvant need further research.	[57,58]
Natural melanin	Polydopamine (PDA)	High photothermal conversion efficiency.	The dimensions require modification.	[59]
Other inorganic nanomaterials	Prussian blue nanoparticles (PBNPs)	Stable photothermal properties, simple preparation, low cost, and easy functionalization.	The efficiency of its photothermal conversion is suboptimal.	[60–62]
	Black phosphorus (BP)	High photothermal conversion performance.	Water instability, photobleaching characteristics, photodegradation, thermal degradation, extremely short cycle life, and easy binding with lipoproteins	[63]

tothermal efficiency and application. Among these, AuNRs are particularly prominent due to their narrow LSPR absorption peak, higher monodispersity, and smaller half-peak width, which enhance their photothermal effects[64]. For instance, Xie *et al.* [46] developed hybrid core-shell nanorods by coating a cuprous oxide (Cu_2O) shell on the surface of AuNRs, resulting in AuNRs@Cu_2ONRs (ACNRs). These hybrid nanorods exhibit excellent near-infrared II (NIR-II) photothermal performance, increase intracellular copper concentration, and induce severe copper-dependent cell death, which in turn activates ICD in tumor cells. By utilizing the photothermal conversion capabilities of AuNRs, it is possible to convert immunologically "cold" tumors into "hot" tumors through ICD, thereby enhancing the efficacy of immunotherapy. In another study, Tang *et al.* [65] employed a photothermal genome editing approach using supramolecular cationic AuNRs as delivery vehicles for CRISPR/Cas9 to target PD-L1. When exposed to 1064 nm laser light, the AuNRs efficiently absorb NIR-II radiation and convert it into mild heat, which triggers Cas9 gene expression targeting PD-L1, initiating ICD and enhancing the antitumor immune response.

Gold nanostars possess a highly branched, anisotropic structure, with their NIR absorption stemming from plasmonic hybridization between the core and sharp protrusions [66,67]. Researchers can fine-tune the absorption wavelength by carefully adjusting the tip dimensions—both length and thickness play crucial roles in this optical tuning [68]. Notably, studies have demonstrated remarkable tumor suppression when combining AuNS-mediated PTT with tumor-targeting exosomes (TDSP Exos) derived from cancerous cells, showcasing a potent synergistic effect against malignancies [69]. However, the heat generated by PTT may melt the gold nanostars into nanospheres [67,70], so researchers further coated them with polyethylene glycol-modified liposomes (LP) [47] or silica [71] to improve the stability of the particles.

In contrast to other gold NPs, GNCs and gold nanospheres stand out as excellent candidates for photothermal conversion and drug delivery, thanks to their distinctive hollow porous architecture and high photothermal conversion efficiency [72,73]. Nonetheless, the hollow nature of GNCs can pose challenges, such as possible drug leakage and compromised stability when used as drug carriers [74]. To overcome this challenge, Li *et al.* [48] utilized a thermosensitive liposome-encapsulated GNCs drug-loading platform, which was loaded with the immune adjuvant maleimide. Laser-triggered GNCs enhance local hyperthermia, accompanied by thermoresponsive maleimide release and glutathione (GSH) consumption, leading to up-regulation of ROS levels and tumor cell apoptosis. It also promotes the release of subsequent DAMPs, enhancing photothermal-induced ICD.

In terms of clinical translation, GNPs offer key ad-

vantages: they can control light absorption peaks through shape and size, exhibit high photothermal conversion efficiency, and have been used in clinical studies with no major safety concerns [75]. A literature review shows over 20 clinical trials using GNPs as drug carriers or PTT platforms, with no significant safety issues [76]. For example, in a prostate cancer study, gold-silicon nanoshells achieved selective thermal ablation under NIR laser irradiation without severe complications [75]. However, challenges remain, such as *in vivo* circulation time, nanoparticle retention in the hepatosplenic system, and unclear long-term clearance pathways [75]. Future research should focus on improving biocompatibility, biodegradability, and therapeutic efficacy to facilitate the transition from "material platform" to "clinical application".

Carbon-based Nanomaterials

Carbon-based materials such as carbon nanotubes (CNTs), graphene (GE), graphene oxide (GO), and carbon quantum dots (CQDs) possess unique three-dimensional porous architectures and remarkable surface texturing [54]. These materials excel at absorbing NIR radiation and converting it into thermal energy, effectively destroying cancerous cells [53]. Notably, mesoporous carbon nanomaterials (MCNs) and other similar carbon-based NPs have gained significant attention as nanocarriers for drug delivery due to their exceptional surface area-to-volume ratios and straightforward surface functionalization capabilities [51,52].

However, when paired with single-wavelength lasers, the broad absorption spectrum of these materials often remains underutilized, which limits their photothermal conversion efficiency and therapeutic outcomes. To address this limitation, one research group developed an innovative strategy by coating MCNs with a layer of lanthanide oxysulfide upconversion material (Y_2O_2S: Yb^{3+}, Er^{3+}). This coating allows the conversion of 980 nm irradiation into visible light, broadening the absorption range of the core MCNs. As a result, the photothermal efficiency of the MCNs was significantly improved, from 59.48% to 82.86%, demonstrating precise tumor targeting and substantial photothermal therapeutic effects against both subcutaneous and ocular melanomas [77]. Meanwhile, another research group engineered a versatile, metal-free carbon-based nanoplatform that integrates PTT with PDT. This approach addresses key challenges such as biocompatibility issues, insufficient light stability, and the need for multiple illumination sources typically associated with metallic components [78].

In terms of clinical relevance, although large-scale human trials of carbon-based nanomaterials remain limited, their low metal residue, customizable structure, and compatibility with multimodal therapies position them as promising candidates for future clinical applications [79]. However, significant challenges persist, including issues with uneven *in vivo* distribution, restricted tumor penetration depth, and unclear biological clearance mechanisms following functionalization [20]. To address these obstacles, future research should prioritize optimizing the biodegradability of carbon-based nanomaterials, enhancing their tumor penetration efficiency, and rigorously assessing their safety and tolerability in early-phase clinical trials. These efforts are essential to ensure their successful translation from preclinical studies to clinical use.

Transition Metal-based Nanomaterials

Transition metal nanomaterials outperform molecular light absorbers as photothermal converters due to their plasmonic characteristics and exceptional optical and thermal stability. These properties position them as ideal materials for cancer therapy and diagnostics [55]. Compared to organic dye NPs, transition metal-based NPs exhibit a larger absorption cross-section, as they possess stronger surface plasmon resonance effects and higher photothermal conversion efficiency than other PTAs [56].

Among these materials, copper sulfide (CuS) NPs are widely utilized in cancer treatment due to their unique optical properties, low production cost, low cytotoxicity, and small size [80]. Zhang *et al.* [81] incorporated CuS NPs into mesoporous silica nanoparticles (MSN), and the CuS NPs effectively converted light energy into heat under NIR light irradiation, demonstrating strong photothermal performance and high photothermal conversion efficiency.

In addition to CuS, other transition metal chalcogenides, oxides, and their multi-component composite systems also exhibit excellent photothermal conversion capabilities in the NIR window due to their rich d–d energy level transitions and LSPR effects [82]. Wu *et al.* [83] developed an innovative iron-based ternary sulfide compound, $AgFeS_2$, which integrates PTT, Fenton chemistry driven by iron ions (which induces ferroptosis), and ICD activation into a single platform. This multifaceted approach exhibited remarkable antitumor efficacy and robust immune activation in triple-negative breast cancer (TNBC) models, highlighting the therapeutic synergy of this triple-action strategy.

Transition metal-based nanomaterials, such as CuS and $MoSe_2$, have gained widespread use in PTT and chemodynamic therapy (CDT). In recent years, $MoSe_2$ has garnered significant attention due to its excellent photothermal conversion efficiency and stability [84]. In preclinical studies, CuS-based NPs have demonstrated strong photothermal effects coupled with low cytotoxicity, and they are being investigated in advanced preclinical studies with translational potential [85]. However, despite the promising antitumor efficacy of materials like CuS, challenges remain in their clinical application, including potential toxicity to critical organs such as the liver and kidneys, as well as concerns about long-term stability in humans [86]. Additionally, while $MoSe_2$ holds promise, its biodegradability

and tumor targeting capabilities require further optimization [87]. To address these limitations, researchers are exploring safer and more effective drug delivery platforms to enhance clinical translation.

Organic Nanomaterials

Organic NIR Dye

While inorganic PTAs often exhibit extensive absorption capabilities, remarkable efficiency in photothermal conversion, and excellent chemical stability, their lack of biodegradability and potential long-term toxicity present significant challenges for clinical application [88]. In contrast, organic PTAs maintain high photothermal conversion performance while offering superior biocompatibility and metabolic safety, thus providing broader clinical potential [57]. Among organic PTAs, ICG has garnered considerable attention due to its well-established pharmacological profile and tunable optical characteristics. ICG, a type of anthocyanin, demonstrates strong light absorption in the NIR spectrum while ensuring clinical-grade safety. It serves triple roles in providing NIR fluorescence, PTT, and PDT [58].

However, ICG faces certain drawbacks, including instability in water, susceptibility to photobleaching, photodegradability, and thermal degradation [89,90], along with a very brief circulation time and a tendency to bind to lipoproteins. These factors contribute to rapid clearance *in vivo*, limiting its clinical use [91]. To address these challenges, researchers have employed various strategies such as encapsulating ICG in liposome-encapsulated ICG J-aggregates [92], PLGA-lipid hybrid NPs [93], or silica shells [94]. These modifications help isolate ICG from water, enhancing its chemical and photothermal stability and significantly improving its therapeutic effectiveness.

Natural Melanin With PDA

PDA, a conjugated polymer, exhibits significant absorption in the NIR spectrum, possesses excellent biocompatibility, and offers straightforward integration with various materials to facilitate multifunctionality [59]. Due to these advantages, Gu *et al.* [95] utilized PDA NPs as a scaffold, gradually integrating MnO_2 and metformin onto their surfaces. Upon exposure to NIR irradiation, PDA rapidly elevates in temperature, initiating ICD. This not only promotes localized tumor destruction but also triggers the "vaccine effect" associated with ICD under NIR exposure.

In a separate study, Sun *et al.* [96] constructed NIR-responsive hollow PDA carriers (HPDA-OPC/DTA-1), which combine photothermal heating with the controlled release of the antioxidant OPC and the GITR agonist DTA-1. These two drugs synergistically eliminate ROS and deplete regulatory T cells (Tregs), thereby alleviating immune suppression, enhancing DCs maturation, and triggering ICD. As a result, they achieved a 6.75-fold reduction in tumor volume and a survival rate exceeding 80%. This approach provides a closed-loop strategy for the combination of PTT and immunotherapy, offering a promising treatment for pancreatic ductal adenocarcinoma.

Other Inorganic Nanomaterials

In contrast to nanomaterials based on precious metals, Prussian blue nanoparticles (PBNPs) exhibit superior photothermal conversion efficiency and enhanced cycling stability, allowing them to rapidly increase local temperatures to an optimal treatment range [60]. Their synthesis is straightforward, and both their morphology and size are easily controlled, making them ideal for various applications in diagnosis, treatment, and drug delivery [61]. However, PBNPs tend to accumulate in normal organs when administered systemically, leading to liver toxicity [62]. Despite this, PBNPs-mediated PTT can induce ICD, release TAAs and DAMPs, generate in situ tumor vaccination effects, and trigger TAAs-specific immune responses against various solid tumors [97]. For example, Yin *et al.* [98] engineered PBNPs with a mesoporous structure, which exhibited excellent spectral absorption performance, enabling efficient photothermal conversion in the 808 nm NIR region. Under 808 nm laser irradiation, the material can rapidly increase the local temperature of the tumor to 60°C within 5 minutes, with a high photothermal conversion efficiency of 44.17%. The photothermal induction enhances ICD by releasing CpG in response to the photothermal reaction, thereby achieving photothermal-immune synergy.

BP nanosheets, recognized as a promising candidate among emerging two-dimensional nanomaterials, have garnered significant interest in the biomedical field due to their impressive efficiency in photothermal conversion, extensive surface area relative to their volume, favorable biocompatibility, and remarkable biodegradability [63]. Zhong *et al.* [99] developed a photothermal immunotherapy system based on an injectable hydrogel (BP@Gel-CD[SA] hydrogel). This system harnesses the photothermal and photodynamic properties of BP nanosheets (BPNSs) to generate hyperthermic damage and ROS-induced apoptosis in cancer cells. Additionally, the interaction between the host and guest molecules in the BP@Gel-CD[SA] hydrogel nanocapsules effectively activates the cGAS-STING pathway, triggers ICD, and collaboratively enhances the infiltration of immune cells.

In a study by Zhou *et al.* [100], BP nanosheets and decitabine were further encapsulated within myeloid-derived suppressor cell (MDSC) membrane vesicles to construct the BP@Decitabine@MDSCs (BDM) nanomedicine system. This system enables membrane-mediated active targeting, leading to high accumulation of BP within solid tumors. Subsequently, BP nanosheets exploit their photothermal and photodynamic properties to induce thermal effects and mitochondrial damage, thereby enhancing antitumor immunity mediated by ICD.

PTT Induced ICD Treatment Strategies

Rationale and Advantages of PTT-induced ICD-based Combination Strategies

Although PTT has demonstrated promising antitumor effects using nanoparticle-based PTAs, several challenges remain [101–103]. One major limitation is the restricted penetration depth of NIR light, which complicates the treatment of deep-seated or metastatic tumors and may result in incomplete tumor ablation, thereby compromising therapeutic efficacy [104]. In addition, high-temperature photothermal treatments may cause collateral damage to adjacent healthy tissues, leading to adverse effects such as inflammation and pain; although careful control of irradiation temperature and duration can partially mitigate these issues, complete avoidance of tissue injury remains challenging [103,105]. Moreover, the *in vivo* degradation or aggregation of certain PTAs raises concerns regarding their structural stability and sustained photothermal conversion efficiency [106].

Importantly, while PTT can induce ICD and promote the release of TAAs and DAMPs, these immunogenic signals alone are often insufficient to elicit durable systemic antitumor immune responses or prevent tumor recurrence. In this context, PTT-induced ICD provides a mechanistic bridge between localized photothermal tumor ablation and broader therapeutic enhancement, thereby offering a strong rationale for combination strategies. To enhance the intuitiveness and systematic understanding of these multimodal approaches, Fig. 3 provides a comparative schematic overview of the shared ICD foundation and the distinct synergistic mechanisms underlying different PTT-induced ICD combination strategies.

To overcome the limitations of PTT monotherapy and further amplify therapeutic efficacy, PTT-induced ICD has been extensively integrated with multimodal treatment strategies, including immunotherapy [107], RT [108], chemotherapy [109], PDT [110], and starvation therapy [111]. Representative nanoparticle-based systems integrating PTT with diverse therapeutic approaches and their corresponding functional principles are summarized in Table 2.

PTT Induced ICD Combined With Immunotherapies

Based on the above rationale, this section focuses on recent advances in combining PTT-induced ICD with immunotherapeutic strategies. Immunotherapy, a novel approach to cancer treatment, is gaining significant traction in the medical community. Essentially, it works by strengthening the immune system so that it can recognize and eliminate cancer cells on its own. However, single-agent tumor immunotherapy has notable limitations and must be combined with other antitumor strategies to achieve optimal results [105]. Local PTT can rapidly reduce tumor burden, creating an "antigen exposure" window that primes the immune system. Meanwhile, immunotherapy works to alleviate immune suppression in the TME, enhance T-cell activity, or block immune checkpoints, significantly amplifying and prolonging the immune system's ability to recognize and destroy tumor cells. This results in a "local-systemic" synergistic enhancement of the antitumor immune response [117].

PTT Induced ICD Combined With Immune Checkpoint Inhibitors

Immune checkpoint blockers (ICBs) counteract immune suppression induced by immune checkpoints by inhibiting molecules like CTLA-4, PD-1, or the immune checkpoint ligand PD-L1. This process reactivates immune cells, enabling them to perform their antitumor functions [118]. Currently, the use of immune checkpoint inhibitors as a therapeutic approach against tumors has become a prominent treatment option for various cancers, including non-small cell lung cancer, metastatic melanoma, renal cell carcinoma, and bladder cancer [119]. The combination of PTT and ICBs can overcome the limitations of monotherapy, forming an integrated "imaging-ablation-immune activation" strategy [105]. Du *et al*. [107] engineered an innovative multifunctional nanotherapeutic agent, ICG@Tf-DTPA-Gd (Fig. 4**A**), which demonstrates remarkable photothermal capabilities. The synergistic effects of mild PTT-induced ICD coupled with PD-L1 checkpoint blockade significantly promote DCs maturation and cytotoxic T-cell infiltration into tumor sites, leading to a substantial reduction in primary tumor burden. As shown in Fig. 4**B–C**, tumor progression curves clearly demonstrate that the combination of mild PTT with anti-PD-L1 therapy effectively curbs tumor growth. This approach not only initiates a robust adaptive immune response but also converts immunologically "cold" TNBC into immunogenic "hot" tumors, thereby unlocking the full potential of anti-PD-L1 therapeutic intervention.

The team led by Jia has developed an advanced photosensitizer, ICG-Z_{PD-L1}, which integrates the capabilities of PTT and ICBs. They successfully tethered this innovative molecule to ICG, creating a specialized ICG-Z_{PD-L1} probe aimed at PD-L1. This probe not only halts the spread of primary tumors but also induces apoptosis within them, thereby enhancing the body's antitumor immune response. Moreover, it amplifies the immunotherapy impact of ZPD-L1 on metastatic tumors, demonstrating a "2 plus 2 equals 5" effect [120]. In another study, a research team developed a tumor-targeted liposome system carrying PD-L1 inhibitors (BMS-1) and ICD inducers (IR780 and OXA) (FOIB@Lip). Results from laser irradiation treatment with the FOIB@Lip (+) group showed a significant delay in the development of secondary tumors, achieving a tumor inhibition rate of 95.6%, significantly higher than other single-treatment groups. The combination of PTT-induced ICD and PD-L1 inhibitors effectively enhances cancer immunotherapy and inhibits tumor regen-

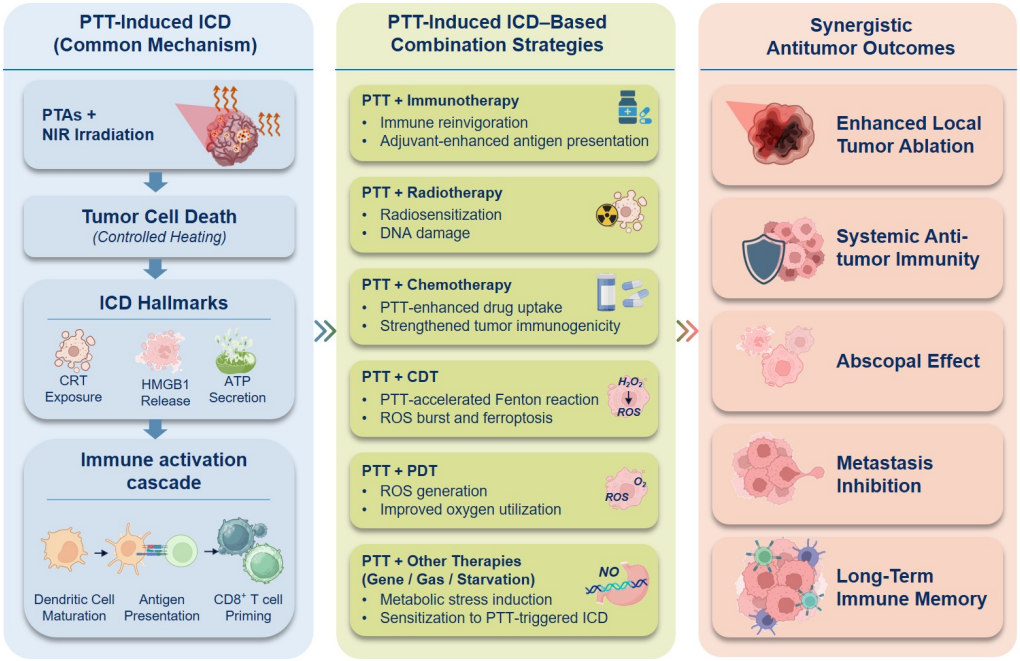

Fig. 3. Schematic comparison of PTT–induced ICD–based combination strategies. PTT triggers ICD through controlled hyperthermia, leading to the release of DAMPs, DCs maturation, and T-cell activation. Based on this common immunogenic foundation, different combination strategies—including immunotherapy, RT, chemotherapy, CDT, PDT, and other emerging modalities—synergistically amplify antitumor immune responses through distinct but complementary mechanisms. These interactions collectively enhance local tumor ablation, induce systemic immunity, suppress metastasis, and establish long-term immune memory. Figure created using PowerPoint, with elements from Biorender (www.biorender.com), used with permission.

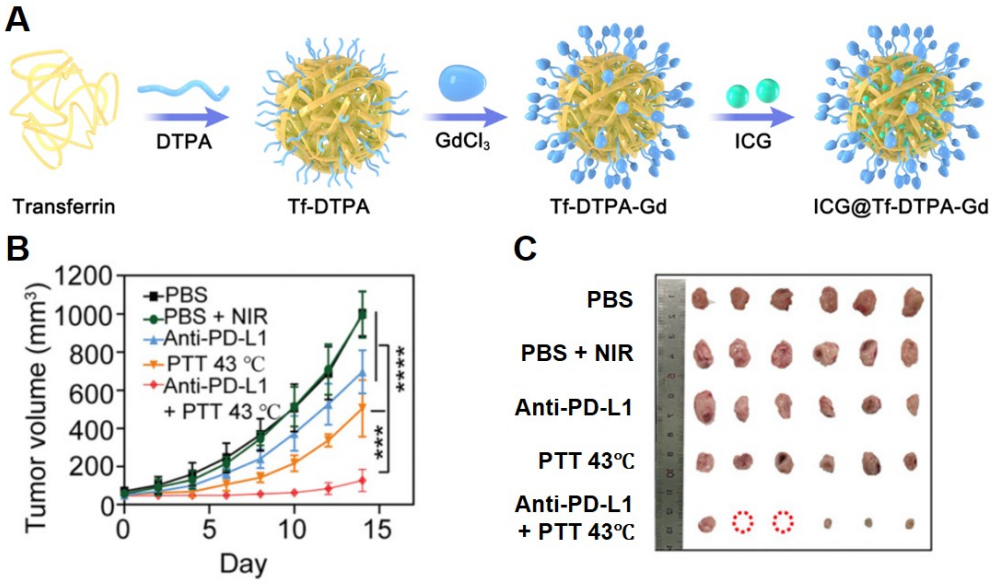

Fig. 4. The synthetic route of the ICG@Tf-DTPA-Gd NPs and their antitumor effect of ICD combined with ICBs induced by PTT. (**A**) Preparation of ICG@Tf-DTPA-Gd NPs, (**B**) the tumor volume, and (**C**) tumor images after treatment [107]. Copyright 2025, Journal of Materials Chemistry B.

Table 2. Representative NPs of PTT are integrated with diverse therapeutic approaches and functional principles.

Common Combination Mode	Classification	Nanomaterials	Tumor Type	Laser	Mechanism and Characteristics	References
PTT induced ICD combined with immunotherapies	PTT induced ICD combined with immune checkpoint blockers (ICBs)	ICG@Tf-DTPA-Gd	TNBC	808 nm	PTT ablation releases tumor antigens and induces a 'hot' immune microenvironment. Following the reversal of immune suppression, checkpoint inhibitors further activate T cells, thereby achieving a local-systemic synergistic antitumor immune response.	[107]
	PTT induced ICD combined with immune adjuvants	BP@Gel-CD[SA] hydrogel	Lung cancer	808 nm	PTT ablation delivers antigens and danger signals, while immunological adjuvants capture and amplify these signals. Together, they promote antigen presentation and T-cell activation, thereby achieving "*in situ* vaccine"-style immunotherapy.	[99]
PTT induced ICD combined with RT		ZrC-NP	TNBC	808 nm	PTT-induced thermophysical sensitization to RT causes DNA double-strand breaks and inhibits their repair, while RT amplifies PTT-induced ICD and TAA release. The spatiotemporal synergy between these two processes reshapes the immune microenvironment, achieving a cascade of antitumor effects.	[108]
PTT induced ICD combined with chemotherapies		PEIGCP(Z)/mPEG@PTX@IR783 (PPI)	TNBC	808 nm	PPI promotes tumor ablation and induces ICD, activates antitumor immunity, and enhances tumor cell responsiveness to chemotherapy drug PTX, significantly inhibits tumor growth, and achieves synergistic antitumor effects.	[109]
PTT induced ICD combined with CDT		Au-MBP NP	TNBC	808 nm	PTT thermodynamics accelerates CDT Fenton chemistry, wherein CDT continuously supplies ROS and drives ferroptosis. These two processes form a closed-loop feedback system, synergistically amplifying oxidative stress and triggering a "thermo-chemical-ferroptosis" cascade of antitumor effects.	[112]
PTT induced ICD combined with PDT		PTQ-TPA3	Pancreatic cancer	808 nm	Photothermal-induced hyperaeration and photodynamic ROS production act as mutual amplifiers, synergistically triggering a thermo-oxidative-ferroptotic cascade to achieve dual-mode energy-oxygen closed-loop antitumor efficacy from a single light source.	[110]

Table 2. Continued.

Common Combination Mode	Classification	Nano-materials	Tumor Type	Laser	Mechanism and Characteristics	References
PTT induced ICD combined with other therapies	PTT induced ICD combined with GT	AR@PSS@PCM	Melanoma	1064 nm	PTT provides a heat-triggered switch and ablation tumor, while GT immediately downregulates heat tolerance and encodes therapeutic molecules. Together, they form a thermo-genetic positive feedback loop, enabling highly efficient gene-immune synergistic antitumor effects driven by low-dose photothermal energy.	[65]
	PTT induced ICD combined with gas therapy	CPM NPs	TNBC	1064 nm	Gas therapy can enhance the therapeutic effect of PTT, inhibit the proliferation of tumor cells, and achieve a synergistic effect.	[113]
	PTT induced ICD combined with starvation therapy	AuPtAg- glucose oxidase (Gox)	TNBC	1064 nm	The starvation therapy systemically cuts off glucose supply to tumors, inducing an energy crisis. PTT then delivers low-power localized "thermal" ablation, further inhibiting glycolytic enzyme activity and blocking HSPs' protection. This dual depletion of ATP and antioxidant capacity significantly amplifies tumor cell apoptosis/ferroptosis while activating ICD, efficiently suppressing deep-seated tumors and blocking recurrence and metastasis.	[111]
Multimodal therapies based on PTT induced ICD	PTT combined with immunotherapy and PDT	HA-BP	TNBC	808+ 635 nm	PTT works in synergy with other therapies, utilizing multiple mechanisms to enhance efficacy, reduce the incidence of drug resistance, and minimize side effects.	[114]
	PTT combined with immunotherapy and chemotherapy	HA/Lipo@MTO @IMQ	TNBC	650 nm		[115]
	PTT combined with PDT and chemotherapy	Fe_3O_4/g-C_3N_4@PPy-DOX	Hepatoblastoma	638 nm		[116]

eration and metastasis [121].

PTT Induced ICD Combined With Immune Adjuvants

Immune adjuvants serve as non-specific immunological boosters that primarily enhance the body's defensive mechanisms, thereby amplifying the immune response to antigens. Concurrently, TAAs produced locally through PTT can initiate an immune cascade when supported by adjuvant immunotherapy [122].

The combination of PTT-induced ICD and immune adjuvants can effectively treat tumor metastasis, regulate the immunosuppressive TME, and promote bone regeneration while eliminating tumors. Zhong *et al.* [99] developed an injectable BPNS hydrogel composite system (BP@Gel-CD[SA]) (Fig. 5**A**), which incorporates the immune adjuvant STING agonist (SA). Under NIR irradiation, SA synergizes with the photothermal and photodynamic effects of BP nanosheets (BPNS), inducing ICD in tumor cells, activating the cGAS-STING pathway, and significantly enhancing immune cell infiltration. This approach achieves complete local tumor ablation in bone-metastatic lung cancer mice, suppresses distant lesions, and simultaneously promotes bone defect regeneration, thereby improving bone strength (Fig. 5**B**).

A different team ingeniously integrated ICG, a TLR4 activator photosensitizer, with another photosensitizer and Monophosphoryl lipid A (MPLA) into the core of PEG-PLGA nanocarriers, further modifying their surface with

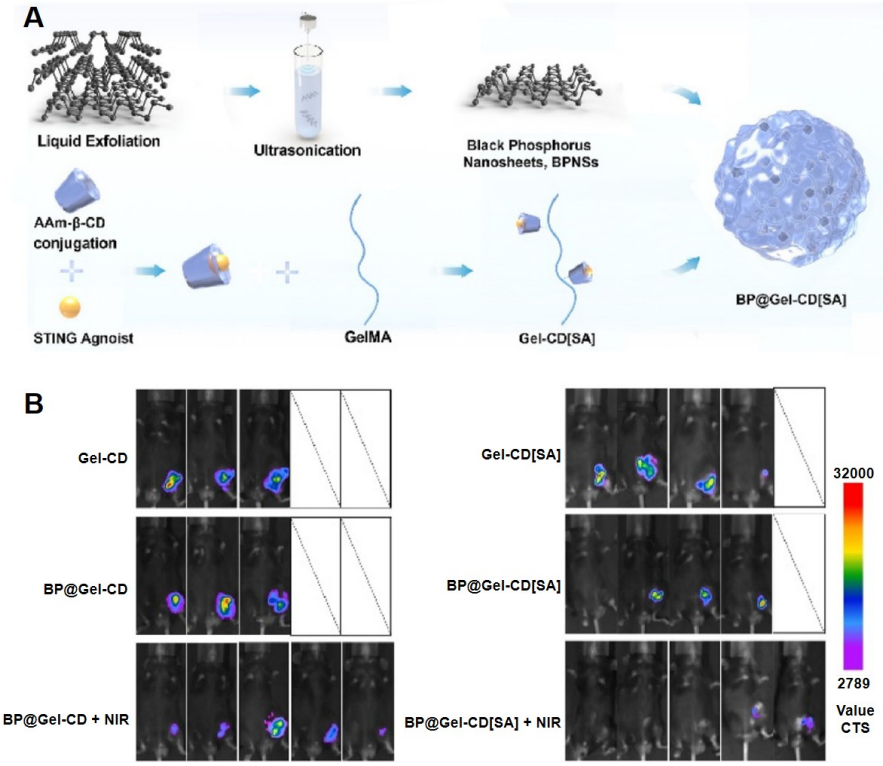

Fig. 5. The synthetic routes of BP@Gel-CD[SA] and its antitumor effects in combination with PTT. (**A**) Synthesis of BP@Gel-CD[SA] and (**B**) spectral images of representative imaging systems (IVIS) *in vivo* in different treatment groups of mice on day 28 [99]. Copyright 2025, Bioactive Materials.

the tumor-targeting peptide TMTP1. The resulting TP1-IM micelles demonstrated improved tumor accumulation, effective photothermal destruction of primary tumors, and triggered the formation of in situ tumor vaccines. Additionally, they significantly inhibited the spread of ovarian cancer and mitigated the immunosuppressive tumor microenvironment (TME) after PD-L1 inhibition, preventing tumor recurrence [123].

In another study, Sun *et al.* [124] developed an innovative nanogold adjuvant polymer (nGAP) by combining gold nanoclusters with poly (I: C), a TLR3 agonist known to stimulate immune responses. Upon exposure to NIR light, this composite material generates intense photothermal energy, effectively inducing ICD in tumors while simultaneously activating DCs. In preclinical trials using LLC mouse models, a single localized treatment with nGAP followed by NIR irradiation yielded remarkable results—completely eradicating tumors in 83% of cases.

PTT Induced ICD Combined With RT

The hypoxic microenvironment inherent to solid tumors often leads to radiation resistance and dose limitations. To overcome this, PTT has been introduced as a synergistic approach. Its NIR-induced localized hyperthermia can transiently dilate blood vessels and accelerate blood flow, thereby improving oxygenation and alleviating hypoxia-mediated radiation resistance [106]. Concurrently, thermal stress from PTT suppresses DNA damage repair and arrests cells at the radiation-sensitive G2/M phase, further enhancing radiosensitivity and overcoming resistance [125]. Therefore, combining PTT with RT achieves both sensitization and potency enhancement while reducing radiation doses. This strategy offers a rational and feasible approach to improving local tumor control rates and reducing distant recurrence [126].

RT directly damages DNA through high-energy ionizing radiation or kills cells by generating hydroxyl radicals (-OH) through water molecules [127–129]. However, the absorption efficiency of radiation by human tissues is relatively low, and the difference in radiation sensitivity between tumors and normal tissues is minimal. As a result, radiation therapy inevitably affects surrounding normal tissues while targeting tumors [130]. To address the problem of cancer cell resistance to X-ray radiation and the limited effectiveness of RT in treating TNBC, Liu and his team developed a novel class of ZrC NPs (Fig. 6**A**). These NPs exhibit exceptional light absorption in the NIR spectrum, allowing them to generate both heat and ROS upon NIR radiation exposure. Additionally, these NPs stimulate immunotherapy, potentiating the effects of RT. Preclinical studies have shown that these NPs enhance the efficacy of both PTT and RT, ultimately improving tumor control outcomes (Fig. 6**B**) [108].

In another approach to improving tumor sensitivity

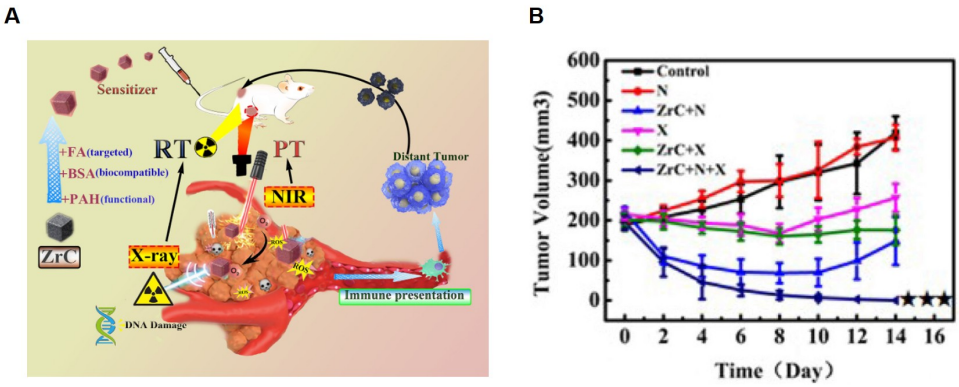

Fig. 6. Synthetic routes of nanomaterials combined with PTT and RT and their antitumor effects. (**A**) Process diagram of ZrC NPs PTT combined with RT and (**B**) tumor volume after treatment [108]. Copyright 2021, Front Oncol.

to RT, researchers designed pure organic NPs with the aggregation-induced emission (AIE) emitter 2TT-oC6B as the core. These NPs demonstrate superior stability, photothermal conversion efficiency, biocompatibility, and NIR absorption and emission properties. Under PTT, 2TT-oC6B NPs generate heat, leading to an increase in the G2/M phase of the cell cycle and heightened sensitivity to RT. Simultaneously, PTT activates ICD through DAMPs, characterized by increased CRT and ATP levels and decreased HMGB1. This ultimately leads to cell apoptosis and achieves synergistic therapy between PTT and RT. The results showed that while the NPs + NIR, RT, and NPs + RT groups exhibited varying degrees of tumor suppression, the NPs + PTT + RT group demonstrated complete tumor regression, proving that PTT significantly enhances the efficacy of RT and that their combined application has substantial antitumor effects [131].

PTT Induced ICD Combined With Chemotherapies

Chemotherapy remains a cornerstone of cancer treatment in modern medicine, yet it faces persistent limitations such as poor drug localization, severe adverse reactions, and the development of tumor resistance [132]. Nanomaterial-based drug delivery systems offer a promising solution to these challenges, utilizing either passive accumulation through the enhanced permeability and retention (EPR) effect or active targeting via surface-conjugated ligands. Additionally, when combined with PTT, localized hyperthermia can amplify drug efficacy by improving cellular uptake and synergistically enhancing cytotoxicity, thereby creating a combined therapeutic impact that surpasses the effects of individual treatments [133].

Huang *et al.* [109] engineered a novel PEI-GCP(Z)/mPEG@PTX@IR783 (PPI) NPs system, which boasts exceptional water solubility and impressive drug-loading capabilities (Fig. 7**A**). These PPI NPs demonstrate remarkable encapsulation efficiency for both the chemotherapeutic agent paclitaxel (PTX) and the NIR dye IR783. The platform synergistically combines the cytotoxic properties of PTX with PTT upon exposure to 808 nm laser light. This dual-action mechanism effectively triggers ICD, stimulates DCs maturation, and enhances the proliferation of CTLs and effector memory T cells. As a result, the treatment shows robust antitumor efficacy and establishes durable immune protection in TNBC models (Fig. 7**B–C**).

Long *et al.* [134] developed an innovative tumor-targeted nanomedicine called CS-1@PB [HM]NPs. Subsequent *in vivo* studies demonstrated that this approach not only inhibited the progression of primary tumors in the 4T1 cell model but also markedly suppressed metastatic tumor growth in the 4T1 xenograft model.

PTT Induced ICD Combined With CDT

CDT utilizes the Fenton or Fenton-like reaction (a catalytic reaction based on metal ions) to convert hydrogen peroxide (H_2O_2) in the TME into more toxic -OH, inducing oxidative stress and selectively killing tumor cells [135]. However, the low efficiency of *in vivo* Fenton reactions remains a major bottleneck, limiting the effectiveness of CDT [136]. PTT elevates the TME temperature through localized heating, significantly accelerating Fenton reaction kinetics and thus amplifying the yield of -OH radicals. When CDT and PTT are combined, this synergistic approach not only addresses PTT's reduced efficacy due to inadequate light penetration depth but also enhances CDT's oxidative stress capabilities by leveraging temperature-dependent reaction rate acceleration [137].

To overcome challenges such as low internalization efficiency of CDT materials, GSH-mediated ROS scavenging, and sluggish reaction kinetics, Wang *et al.* [138] developed a manganese-doped nanomaterial (Mn LMOP) for combined photothermal and chemodynamic tumor therapy. The incorporation of manganese enables Mn LMOP to function as both a Fenton-like reaction catalyst and an effective photothermal agent, triggering ICD in tumors while boosting therapeutic outcomes. Remarkably, tumor growth was nearly completely suppressed in both the Mn-LMVP+NIR and Mn-LMOP+NIR treatment cohorts,

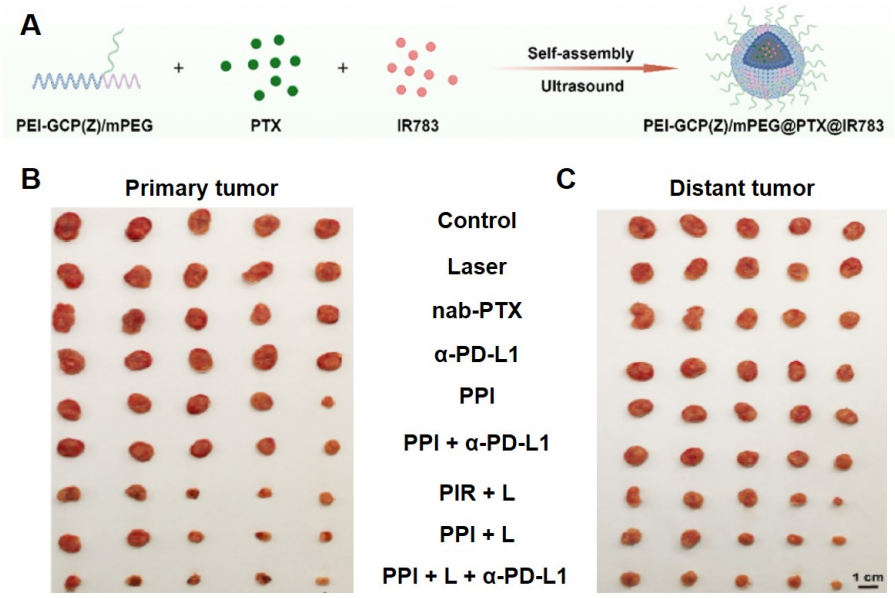

Fig. 7. Synthetic routes of PEI-GCP(Z)/mPEG@PTX@IR783 and their antitumor effects in combination with PTT and chemotherapy. (**A**) The schematic showed the preparation process of NPs (PEI-GCP(Z)/mPEG@PTX@IR783), the picture of the (**B**) primary tumor and (**C**) distant tumor after treatment [109]. Copyright 2025, Materials Today Bio.

demonstrating the potent antitumor efficacy of this combinatorial approach.

Liu *et al.* [112] designed "stepwise charge reversal" engineered gold nanoparticles (Au-MBP NPs): these particles transition from negative to positive charges sequentially along the pH gradient, which decreases with tumor depth. This charge reversal allows the NPs to anchor layer by layer to tumor cells, achieving complete tumor penetration. Once inside the tumor cells, these NPs generate PTAs in situ, facilitating tumor-specific PTT. Simultaneously, chelated Cu^{2+} ions are reduced to Cu^{+}, which act as a catalyst to convert H_2O_2 into hydroxyl free radicals, thereby exerting CDT effects. This dual-action approach combines tumor-specific PTT and CDT to create a synergistic effect. In the 4T1 bilateral tumor model, this strategy demonstrated near-complete regression of primary tumors and substantially suppressed lung metastasis. Bai *et al.* [139] reported an Ag-induced redshift absorption Ag@CuS-TPP@HA core-shell nanomedicine. In this system, TPP and hyaluronic acid (HA) jointly mediate dual targeting of tumor mitochondria. Under excitation by 1064 nm NIR-II, the Ag sites catalyze Fenton-like reactions to produce ROS. Simultaneously, CuS generates a potent photothermal effect. Together, these effects trigger ICD, unleashing a flood of TAAs and DAMPs. This dynamic combination of CDT/PTT-triggered ICD and ICBs effectively counteracts the tumor's immunosuppressive environment, jumpstarting a robust immune response.

PTT Induced ICD Combined With PDT

PDT can significantly increase tumor cells' vulnerability to PTT by reshaping the TME. Conversely, the localized hyperthermia triggered by PTT dilates blood vessels, accelerates circulation, and enhances oxygenation in tissues, which in turn amplifies PDT's effectiveness, creating a synergistic relationship between the two therapies [140]. Specifically, PTT directly destroys cancer cells through thermal energy, while PDT relies on photosensitizers to produce ROS upon light exposure, inducing oxidative stress and ultimately leading to tumor cell death [141]. These two approaches are mechanistically complementary and synergistically effective.

Xiang *et al.* [110] engineered an AIE photosensitizer called PTQ-TPA3 that targets lysosomes, with an impressive photothermal conversion efficiency of 39.45%. This photosensitizer generates 1.3 times more type I ROS than ICG under low oxygen conditions. Guided by multimodal imaging, PTQ-TPA3 NPs initiate apoptosis in Panc02 cells through a one-two punch of photothermal and photodynamic effects. This process sparks the release of DAMPs, fostering robust ICD and mediating effective phototherapy. This dual-pronged approach efficiently eradicates cancer cells and activates the body's systemic antitumor defenses.

Similarly, Yu *et al.* [142] introduced a temperature-responsive mechanism to develop adaptive switchable Cy5 TPA NPs. During the low-temperature stage, PDT dominates to generate ROS, while as the tumor temperature increases, the system automatically transitions to PTT dominance. Critically, during ICD, this transition from PDT to PTT dominance facilitates the stepwise generation and release of DAMPs. These NPs demonstrate remarkable efficacy in light-based immunotherapy, excelling in ICD induction, DCs maturation, and T-cell activation. As a result, they enhance programmed ICD, promote DCs maturation,

and bolster systemic immune memory, effectively curbing tumor metastasis.

Finally, Zhang *et al*. [100] integrated chemotherapy into the aforementioned bimodal approach and designed a BP@Decitabine nanomaterial system (BDM) encapsulated within the myeloid-derived suppressor cell (MDSC) membrane. This multimodal treatment model integrates PTT, PDT, chemotherapy, and immunotherapy. The system operates on multiple fronts: PTT induces localized tumor hyperthermia, while PDT generates ROS that disrupt mitochondrial function and trigger cancer cell death. Furthermore, decitabine-driven chemotherapy disrupts the tumor cell cycle at the G2/M phase, amplifying apoptotic effects. Most notably, BDM's ability to provoke ICD stimulates the body's natural immune defenses against tumors, creating a synergistic boost in therapeutic efficacy.

PTT Induced ICD Combined With Other Therapies

PTT Induced ICD Combined With GT

As standalone therapies, both GT and PTT have notable limitations: GT typically has a slow onset and limited response rate, while PTT can only achieve local tumor ablation and struggles to control potential metastasis. In recent years, the emergence of photothermal-gene integrated nanocarriers has successfully combined these two strategies into a GT-PTT collaborative model, which has garnered significant attention across multiple scientific fields. In this integrated system, GT enhances the sensitivity of tumor cells to PTT by upregulating the expression of heat-sensation-related genes. Simultaneously, the thermal effects generated by PTT increase the permeability of the cell membrane, promoting NPs internalization, the dissociation of intracellular NPs, and gene release. This enhances and accelerates the expression of exogenous genes, amplifying the therapeutic effect [143].

In their groundbreaking study, Tang *et al*. [65] developed an innovative photothermal genome editing approach, creating guanidine-functionalized AuNRs to deliver HSP-Cas9 plasmids into tumor cells (Fig. 8**A**). The system takes advantage of AuNRs' ability to absorb near-infrared II (NIR-II) light and convert it into localized heat, triggering both Cas9-mediated PD-L1 gene editing and ICD. This dual mechanism reprograms the TME, significantly enhancing the efficacy of anti-PD-1/PD-L1 checkpoint blockade therapy. Animal studies demonstrated remarkable outcomes: mice receiving the ANP/HSP-Cas9 treatment followed by NIR-II laser irradiation (ANP/P (+)) exhibited substantially delayed tumor progression compared to controls (Fig. 8**B**). This precision-targeted strategy holds great promise for improving cancer treatment by synergizing genome editing with immune checkpoint blockade, offering a more effective approach to combat resistant tumors.

PTT Induced ICD Combined With Gas Therapy

Gas therapy enables the precise delivery of endogenous gaseous messengers, including nitric oxide (NO), oxygen (O_2), hydrogen sulfide (H_2S), sulfur dioxide (SO_2), hydrogen (H_2), and carbon monoxide (CO) [144]. Owing to its "green" safety profile, low residual risk, excellent biocompatibility, diverse target sites, and reversible regulation, gas therapy has shown broad therapeutic potential in the treatment of infections, neurodegenerative diseases, cardiovascular diseases, and tumors [145,146].

Gas therapy and PTT exhibit notable synergistic effects in inducing ICD. Specifically, NO can elevate intracellular ROS levels in tumor cells, while the photothermal effect of PTT further intensifies oxidative stress, leading to enhanced lipid peroxidation and ER stress, thereby amplifying ICD signaling [147]. Beyond ROS generation, gaseous messengers also exert direct immunomodulatory effects by regulating immune checkpoints and cellular metabolic pathways. For example, NO has been reported to downregulate PD-L1 expression and modulate NF-κB–associated signaling and metabolic pathways in tumor and immune cells, consequently enhancing T-cell–mediated antitumor immunity[148]. In parallel, NO can influence immune cell metabolism and cytokine signaling, promoting DCs activation and T-cell responses [148].

In addition to NO, other gas molecules such as H_2S and CO can modulate macrophage polarization and activate innate immune pathways, including STAT3, AMPK [149,150], and cGAS–STING [151], further reinforcing the immunogenic effects of PTT-induced ICD [152]. Moreover, NO improves tumor vascular perfusion and alleviates PTT-induced local hypoxia, thereby suppressing HIF-1α–mediated immunosuppression and enhancing ICD efficacy [153]. While PTT primarily induces the release of classical DAMPs such as CRT, ATP, and HMGB1, gas therapy (e.g., H_2S) can additionally trigger nuclear DNA leakage, enhance cGAS–STING pathway activation, increase type I interferon (IFN-β) expression, and further strengthen antitumor immunity [154].

Collectively, the integration of gas therapy with PTT synergistically enhances ICD through ROS amplification, complementary DAMP release, and remodeling of the tumor immune microenvironment, providing a promising strategy for tumor immunotherapy [155]. Beyond immune suppression, HIF-1α has emerged as a central stress-response hub that mediates tumor metabolic adaptation, chemoresistance, and malignant progression under hypoxic conditions [156,157]. In addition to these cellular stress programs, recent studies indicate that hypoxia-induced HIF-1α activation is also closely associated with tumor cell autophagy, which facilitates antigen processing, ER stress maintenance, and DAMPs exposure, thereby functioning as an auxiliary mechanism that enhances ICD-associated immune priming [158,159]. In certain contexts, autophagy has been shown to promote ATP secretion, CRT translo-

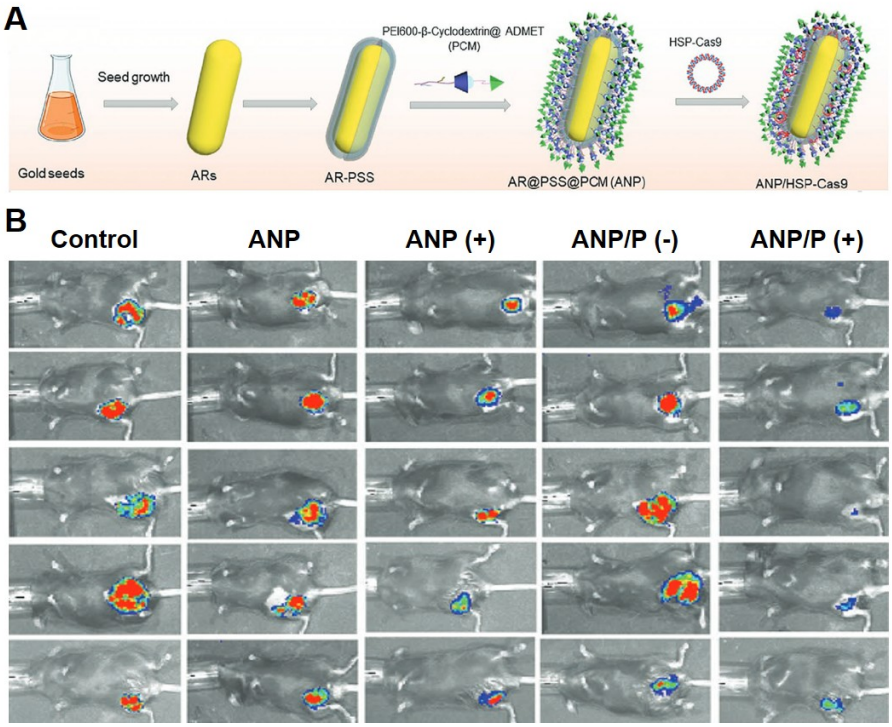

Fig. 8. Synthetic routes of ANP/HSPCas9 plasmid and its antitumor effects in combination with PTT and GT. (**A**) Process of preparation of ANP/HSPCas9 plasmid complex. (**B**) Representative bioluminescence images of mice *in vivo* after different treatments on day 21 [65]. Copyright 2021, Advanced Materials.

cation, and antigen cross-presentation by DCs, ultimately strengthening T-cell–mediated antitumor immunity [160]. These findings suggest that NO-mediated modulation of the hypoxia/HIF-1α axis may not only alleviate hypoxia-induced immunosuppression but also influence autophagy-dependent pathways that enhance tumor immunogenicity and ICD induction. Taken together, such multifaceted immunometabolic effects provide an expanded mechanistic rationale for integrating gas therapy into PTT-induced ICD strategies.

Li *et al.* [113] constructed an ultrasound-laser dual-response calcium carbonate-PDA-manganese oxide nanoparticles (CPM NPs) and utilized its "gas-driven" strategy to synergize photothermal-immunotherapy. In an acidic TME, CPM NPs decompose to release dual gases of CO_2 and O_2, while simultaneously precipitating Ca^{2+}/Mn^{2+}. The CO_2 bubbles are instantaneously ruptured by ultrasonic cavitation, mechanically perforating the cancer cell membrane, while O_2 rapidly reverses hypoxia, down-regulates HSPs, and relieves immunosuppression. Under NIR laser excitation, PDA generates mild photothermal effects, which, in synergy with gas and ions, induce highly effective ICD. This significantly amplifies the antitumor immune response and enhances the efficacy of PTT combined with immunotherapy.

PTT Induced ICD Combined With Starvation Therapy

Starvation therapy refers to a novel therapeutic strategy that induces metabolic disorders in tumor cells by depriving them of their energy substrates, primarily glucose [161]. The core mechanism involves the rapid depletion of glucose within the tumor using catalysts such as GOx, which blocks ATP generation, thereby inhibiting tumor proliferation and sensitizing tumor cells to downstream treatments. This therapy offers high targeting precision and is less likely to induce systemic toxicity. However, when used alone, it faces limitations such as incomplete glucose depletion, tumor tolerance, and potential malnutrition [162]. Recent studies have shown that combining starvation therapy with PTT can leverage complementary advantages. On one hand, starvation-induced ATP deficiency significantly inhibits the expression of HSPs, reduces tumor thermotolerance, and facilitates the occurrence of ICD in tumor cells [111]. On the other hand, photothermal heating accelerates blood stasis and metabolite accumulation in the tumor, amplifying the oxidative stress and energy crisis caused by starvation [163].

For example, the AuPtAg-GOx nanoenzyme designed by Wang *et al.* [111] induces a synergistic immune response by starving the tumor and then inducing mild PTT. AuPtAg-GOx effectively promotes the occurrence of ICD, increases the proportion of tumor-infiltrating lymphocytes (TILs), and transforms immunologically "cold" tumors into "hot" tumors. In parallel research, Li *et al.* [164] engineered a

biomimetic nanoplatform called AuDRM, which incorporates both gold nanoparticles (Au NPs) and the immunostimulant R837, cloaked in pH-responsive cellular membranes. These smart membranes not only enhance R837 loading efficiency but also enable precise tumor targeting through homologous binding mechanisms. Upon reaching cancerous tissue, the system selectively releases its payload of gold NPs and R837. Real-time bioluminescence imaging shows that when AuDRM is combined with laser irradiation, the excellent therapeutic effect of PTT is evident. Au NPs induce a mild temperature increase in tumor cells, further inducing ICD, releasing tumor antigens, and generating vaccine-like functions against both primary tumors and metastases. This combination treatment induces long-term immune memory effects, suppressing tumors and achieving synergistic therapeutic benefits from both PTT and starvation therapy.

Triple-mode Therapies Based on PTT Induced ICD

In addition to the dual-mode synergistic strategies discussed above, PTT combined with triple-mode therapy has emerged as a frontier hotspot. By incorporating RT, chemotherapy, chemokinetics, or immunoregulation, the photothermal effect can be significantly amplified, and the ICD effect enhanced. This results in a substantial increase in overall antitumor efficacy.

PTT induced ICD combined with immunotherapy and PDT

The combination of PTT, immunotherapy, and PDT forms a multimodal collaborative treatment strategy that integrates the unique advantages of each approach. This combination achieves multiple goals, including local efficient tumor killing, efficient induction of ICD, and activation of systemic immunity, significantly improving anti-cancer effects, especially in inhibiting primary tumors and distant metastasis [140].

Zhang *et al.* [114] engineered a specialized BP nanoparticle functionalized with PEGylated hyaluronic acid (HA) to serve as a versatile platform for combined photothermal, photodynamic, and photoimmunotherapy applications (Fig. 9**A**). The experimental results shown in Fig. 9**B–C** clearly demonstrate the therapeutic efficacy of these HA-BP NPs, revealing their ability to stimulate DCs maturation and activate effector cells. This immunological cascade ultimately triggers a robust antitumor immune response, effectively combating the disease.

PTT Induced ICD Combined With Immunotherapy and Chemotherapy

The combination of PTT with chemotherapy and immunotherapy not only achieves the triple synergy of "local efficient killing + systemic immune activation + drug resistance reversal", but also effectively overcomes the limitations of single therapies. This combination demonstrates strong potential in antitumor, anti-metastasis, and recurrence reduction, making it an important development direction for the comprehensive treatment of advanced tumors [165].

Wang *et al.* [115] constructed a hyaluronic acid-modified liposome nano-platform (HA/Lipo@MTO@IMQ), co-loaded with the chemotherapy drug mitoxantrone hydrochloride (MTO) and TLR7/8 agonist imiquimod (IMQ). This platform maximizes the activation of ICD and significantly eradicates tumors by combining PTT, immunotherapy, and chemotherapy. MTO induces potent ICD effects, promoting DCs maturation and CTLs infiltration. Additionally, TLR7/8 agonists exhibit strong pro-maturation properties for DCs while enhancing ICD, reshaping the tumor immune microenvironment, and boosting tumor-killing efficacy. Similarly, Tang *et al.* [166] co-encapsulated curcumin nanoparticles (PCUR NPs) and indole oxime (IND), an IDO inhibitor, in the thermosensitive Pluronic F127 hydrogel (PCUR NPs/IND@Gel) to form an injectable chemical-photothermal immune nanocarrier system. Under NIR laser irradiation, PCUR NPs generate high fever and induce strong ICD, while IND blocks immune checkpoints. Following intratumoral administration, this approach led to a significant increase in apoptosis of 4T1 tumor cells, heightened activation of DCs in lymph nodes, and induction of vigorous $CD8^+$ and $CD4^+$ antitumor immune responses. The treatment resulted in a substantial reduction of Tregs within the tumor, remarkable suppression of tumor growth, and extended survival periods in mice bearing 4T1 tumors. This multifaceted therapeutic strategy demonstrated exceptional synergistic antitumor effects.

PTT Induced ICD Combined With PDT and Chemotherapy

PTT destroys cell membranes and protein structures through thermal effects, PDT induces cell apoptosis by generating ROS, and chemotherapy interferes with DNA replication or cell division through the use of drugs [20]. These three mechanisms complement each other and synergistically enhance antitumor effects, effectively overcoming the limitations of insufficient efficacy, strong drug resistance, or significant toxic side effects associated with single therapies [20]. Cheng *et al.* [116] developed an innovative Fe_3O_4/g-C_3N_4@PPy-DOX nanocomposite that integrates chemotherapy, PTT, and PDT under magnetic targeting. This multimodal approach substantially boosts tumor eradication while minimizing harm to healthy tissues. In the experiment, the nanocomposite material was irradiated with a 638 nm laser, enhancing the PDT effect through Fe_3O_4 and g-C_3N_4, while PPy efficiently achieved photothermal heating. Simultaneously, DOX was released to enhance chemotherapy-induced cell death. The treatment reduced the survival rate of HepG2 cells to 28.1%, demonstrating excellent synergistic therapeutic ability.

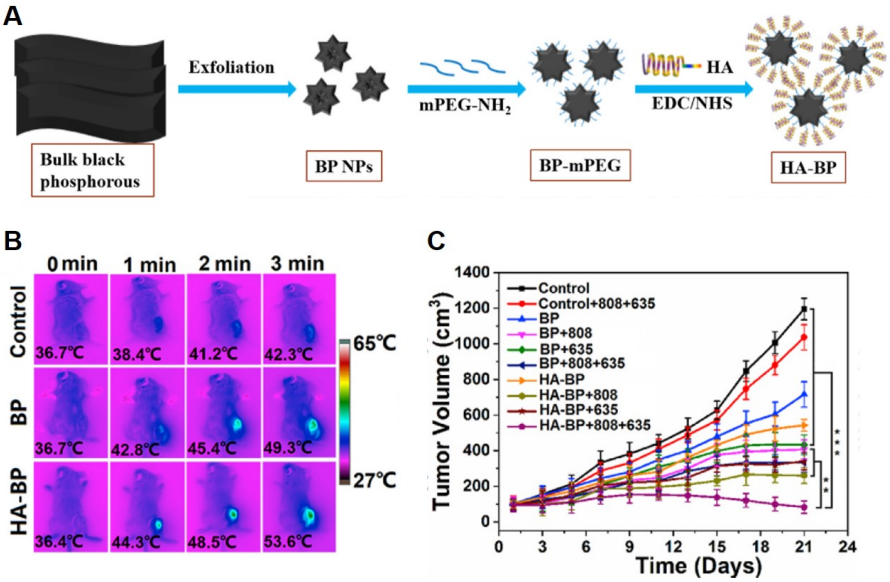

Fig. 9. Synthesis and anticancer efficacy of HA-BP NPs combined with PTT, immunotherapy, and PDT. (**A**) The synthetic scheme of HA-BP NPs. (**B**) Thermal imaging depicting the effects on 4T1 tumor-bearing mice following exposure to an 808 nm laser within a three-minute window. (**C**) The fluctuation in tumor size across various treatment modalities [114]. Copyright 2021, Bioactive Materials.

Conclusions and Prospects

PTT stands out as a minimally invasive, reusable, and low-impact therapeutic modality. In recent years, NIR-II–responsive PTAs have attracted growing interest owing to their deeper tissue penetration, higher maximum permissible exposure, and reduced light scattering compared with conventional NIR-I systems. These advantages highlight the potential of NIR-II–based platforms for improving therapeutic precision, particularly in deep-seated tumors. Nevertheless, whether NIR-II PTAs will become the dominant direction for clinical translation depends on practical considerations, including material safety, biodegradability, scalable manufacturing, and the clinical availability of NIR-II laser devices. At present, NIR-II PTT is more likely to complement rather than replace established NIR-I platforms.

Despite encouraging preclinical outcomes, the clinical translation of PTT still faces several critical challenges. At the material level, although precious metal– and carbon-based nanomaterials exhibit high photothermal conversion efficiency, their long-term *in vivo* biocompatibility, circulatory stability, and clearance pathways remain insufficiently understood. In contrast, organic and small-molecule PTAs generally display better biodegradability and can be eliminated via renal or hepatobiliary routes [167], whereas many inorganic nanomaterials tend to accumulate in reticuloendothelial organs such as the liver and spleen [6]. Strategies, including ultrasmall size engineering, surface modification, and biodegradable coatings, have been explored to improve metabolic clearance. Notably, PBNPs represent a rare class of inorganic PTAs with intrinsic biodegradability and FDA-approved clinical use, underscoring the importance of clearance behavior in translational development [97].

At the physical level, light attenuation by biological tissues limits treatment depth, while inappropriate thermal dosing may either damage surrounding healthy tissues or induce HSPs–mediated thermotolerance. At the therapeutic strategy level, current combination regimens often lack standardization, particularly with respect to nanocarrier modification density, drug release kinetics, and real-time treatment monitoring.

Looking forward, overcoming these barriers will require the coordinated advancement of material innovation and therapeutic strategy design. From a translational perspective, future photothermal nanomedicines should consider not only photothermal conversion efficiency but also cellular responsiveness to thermal stress. Approaches such as mild hyperthermia, optimized irradiation protocols, and rational combinations with strategies that modulate heat shock responses may enhance ICD induction while minimizing thermotolerance. Achieving a precise balance between photothermal efficacy and cellular stress adaptation will be essential for improving clinical performance.

In parallel, material development should prioritize PTAs with NIR dual-region responsiveness, intrinsic biodegradability, and diverse elemental compositions to reduce long-term toxicity and improve tissue penetration. From a technological standpoint, scalable fabrication strategies—such as one-step microfluidic synthesis of multimodal nanoplatforms—may facilitate improved tumor targeting, real-time pharmacokinetic monitoring, and reliable translation into early-phase clinical trials. More importantly, the development of photothermal strategies with multidimensional control over temperature, time, and spa-

tial distribution may enable an optimal balance between therapeutic efficacy and safety.

In summary, although significant challenges remain, PTT-based nanomedicine continues to evolve beyond localized thermal ablation toward a systemic immunomodulatory strategy. By inducing ICD, PTT has the potential to transform localized heat treatment into a form of in situ cancer vaccination, offering new opportunities for precision oncology. With continued progress in material design, treatment standardization, and clinical evaluation, photothermal immunotherapy is expected to play an increasingly important role in future cancer treatment paradigms.

List of Abbreviations

PTT, photothermal therapy; NPs, nanoparticles; ICD, immunogenic cell death; DAMPs, damage-associated molecular patterns; DCs, dendritic cells; IARC, international agency for research on cancer; RT, radiotherapy; PTAs, photothermal agents; NIR, near-infrared; HSPs, heat shock proteins; PDT, photodynamic therapy; GT, gene therapy; CRT, calreticulin; HMGB1, high-mobility group box 1; ATP, adenosine triphosphate; TAAs, tumor-associated antigens; ER, endoplasmic reticulum; ROS, reactive oxygen species; TLRs, toll-like receptors; TLR4, toll-like receptor 4; CTLs, cytotoxic T lymphocytes; LSPR, localized surface plasmon resonance; AuNRs, gold nanorods; GNCs, gold nanocages; Cu_2O, cuprous oxide; TDSP Exos, tumor-derived signal peptide exosomes; LP, liposomes; GSH, glutathione; CNTs, carbon nanotubes; GE, graphene; GO, graphene oxide; CQDs, carbon quantum dots; MCNs, mesoporous carbon nanomaterials; CuS, copper sulfide; TNBC, triple-negative breast cancer; CDT, chemodynamic therapy; Tregs, regulatory T Cells; PB-NPs, prussian blue nanoparticles; BP, black phosphorus; BPNSs, black phosphorus nanosheets; MDSC, myeloid-derived suppressor cell; BDM, BP@Decitabine@MDSCs; PDA, polydopamine; ICG, indocyanine green; TME, tumor microenvironment; ICBs, immune checkpoint blockers; SA, STING agonist; MPLA, monophosphoryl lipid A;EPR, enhanced permeability and retention; AIE, aggregation-induced emission; GOx, glucose oxidase; HA, hyaluronic acid; MTO, mitoxantrone hydrochloride; IMQ, imiquimod.

Availability of Data and Materials

Not applicable.

Author Contributions

LW, QSZ, and ZFG conceived and outlined the structure of the review. RW, ZHL, QH, and XSW conducted literature collection and analysis. YJL, YH, and QL contributed to data interpretation, figure preparation, and critical discussion of the reviewed studies. DXL and SC assisted in manuscript organization and visualization. YJX provided important academic guidance on the overall research framework and contributed constructive intellectual input during manuscript drafting and revision. LW and QSZ drafted the manuscript, and ZFG supervised the work and provided critical revisions. All authors read and approved the final manuscript for this submission. All authors agree to be accountable for all aspects of the work and to ensure that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Ethics Approval and Consent to Participate

Not applicable.

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Conflict of Interest

The authors declare no conflict of interest.

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