

Nanomaterial-Based Tumor Photothermal Immunotherapy

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Abstract: In recent years, photothermal therapy (PTT) particularly nanomaterial-based PTT is a promising therapeutic modality and technique for cancer tumor ablation. In addition to killing tumor cells directly through heat, PTT also can induce immunogenic cell death (ICD) to activate the whole-body anti-tumor immune response, including the redistribution and activation of immune effector cells, the expression and secretion of cytokines and the transformation of memory T lymphocytes. When used in combination with immunotherapy, the efficacy of nanomaterial-based PTT can be improved. This article summarized the mechanism of nanomaterial-based PTT against cancer and how nanomaterial-based PTT impacts the tumor microenvironment and induces an immune response. Moreover, we reviewed recent advances of nanomaterial-based photothermal immunotherapy and discussed challenges and future outlook.

Keywords: nanomaterials, cell death mechanism of PTT, tumor microenvironment, immunogenic cell death, photothermal immunotherapy

Introduction

Cancer has become one of the most serious threats to human health in the last few decades. According to estimates from the International Cancer Research Agency (ICRA) in 2018, there were over 18.1 million new cancer cases and 9.6 million cancer deaths in the globe.¹ Tumor metastases are the main reason for nearly 90% of all cancer-related deaths. For many patients, when they were diagnosed with cancer, metastasis has already occurred. It was noticed that over 80% of patients diagnosed with lung cancer present with metastatic disease.^{2–6} Chemotherapy, hormonal therapy and radiation therapy serve palliative purposes in the metastatic cancers and offer a modest extension of survival. However, the therapeutic effect is still unsatisfactory.³

The human immune system has a powerful mechanism to eliminate abnormal cells by constantly examining “self-labeling” or “non-self-antigens” on the cell surface.^{7–9} The broad definition of immunotherapy is the use of the body’s natural defenses against disease. Cancer immunotherapy aims to activate host immune system to fight cancer cells.^{10–13} In the past decade, cancer immunotherapy has made great progress and has been applied to clinical studies, including monoclonal antibodies,¹⁴ dendritic cell (DC)-based vaccine,^{15,16} chimeric antigen receptor (CAR) T cells,^{17,18} whole-cell vaccine^{19,20} and immune checkpoint inhibitors.^{21–26} However, several recent studies have revealed that these therapeutic methods exhibited inconsistent therapeutic responses to different patients. In addition, the cascading

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effects of inflammatory media, organ toxicity, hematopoietic system dysfunction and other side effects also limit the clinical optimization of these methods.^{27–31}

A satisfactory tumor therapy strategy cannot only eliminate the primary tumors but also activate the host immune system and eliminate the metastatic and residual tumor cells. Combining local therapy with immunotherapy is a good choice to improve the therapeutic effect while making full use of the benefits of immunotherapy.^{32–36}

Recent years, photothermal therapy (PTT), employing tumor site targeted photothermal conversion nanomaterials to convert light energy into heat under near-infrared (NIR) light irradiation to kill tumor cells, has been recognized to be an effective and minimally invasive therapeutic strategy for treating primary tumors.^{37,38} By local administration of photosensitizers and minimally invasive NIR radiation, hyperthermia prompted by PTT can be controlled to minimize the damage to non-targeted tissues. Interestingly, recent revisions have shown that hyperthermia can induce dying tumor cells to release antigens, pro-inflammatory cytokines, and immunogenic intracellular substrates, thus promoting immune activation. Nanomaterials with a photothermal effects are widely used to enhance PTT, including gold nanoparticles such as gold nanoshells (GNSs),^{39–41} gold nanorods (GNRs),^{42–44} gold nanocages (GNCs),^{45–47} gold nanostars (GNSs),^{48–50} carbon nanomaterials, such as single-walled carbon nanotubes (SWCNTs),^{51–53} graphene,^{54–56} semiconductor nanoparticles, such as copper sulfide (CuS),^{57–59} molybdenum disulfide (MoS₂)^{60–62} organic NIR dyes such as indocyanine green (ICG),^{63–68} IR780,^{69–71} IR820^{72–74} as well as other PTT nanomaterials. In addition to direct killing effect, it is recognized that a key role caused by PTT is immunogenic cell death (ICD).^{75–79} During ICD, dendritic cells (DCs) capture the released damaged-associated molecular patterns (DAMPs) and tumor-associated antigens (TAAs), then processed and presented to adaptive immune cells to activate specific immune response.^{76,79–81}

Researchers have recognized the potential benefits of PTT when it was introduced to compensate for some inherent drawbacks of immunotherapy. Nanomaterials for PTT can be further modified with immunostimulants or other immune drugs to enhance the whole body's anti-tumor immune responses. This nanomaterial-based PTT cannot only directly ablation of tumors but also induce continuous antitumor immune effects, known as photothermal immunotherapy. This article summarized the mechanism of nanomaterial-based PTT against cancer, recent

advances of nanomaterial-based photothermal immunotherapy, and also discussed challenges and future outlook.

Nanomaterial-Based PTT for Tumor Treatment

It is well known that temperature is one of the most important parameters determining the dynamics and viability of organisms,^{82–84} temperature-induced changes at the cellular level are determined by the intensity and duration of the temperature increment.^{85,86} Depending on the magnitude of the temperature increment, the effects on tumor cells can be classified as follows:⁸⁷ (1) when the temperature rises slightly to 41°C, the transmembrane diffusion rate and blood flow speed of the cells will be accelerated; (2) at the temperature of 41–48°C, proteins will aggregate, and increases sensitivity to radiation and chemotherapy. At this temperature of more than 60 minutes, will cause irreversible damage to cells; (3) at the temperature of 48–60°C, even 4–6 minutes will cause irreversible damage to the cells, resulting in a severe denaturation of proteins and serious damage to DNA. This thermal response behavior of cells is the basis for cancer treatment using PTT.

Nanomaterial-based PTT is a new type of nanotechnology, using the photothermal conversion ability of nanomaterials to convert light energy into heat energy to kill tumor cells (Figure 1A).⁸⁸ Compared with the existing mainstream treatment methods, PTT is a spatiotemporal controlled, minimally invasive, high selectivity to localized cancer, good anti-cancer effect treatment. Besides, PTT is suitable for the treatment of solid tumors, particularly for treating superficial tumors, as the poor blood supply in cancerous tissue leading poorer heat resistance than normal tissues.^{89–91} Usually, PTT chooses 650–900 nm NIR light as the light source because tissue absorption in this area is weak, resulting in deep tissue penetration and low tissue damage.^{92,93} In addition, the satisfactory photothermal reagents used in PPT should be characterized by low or non-toxic, high NIR absorption, and high photothermal conversion efficiency.^{94–96} Nanomaterials with a photothermal effects are widely used to enhance PTT and have achieved encouraging therapeutic results.⁹⁷ Photothermal agents mainly include gold nanomaterials, like GNSs, GNRs, GNCs, GNSs;^{39–50} carbon nanomaterials such as SWCNTs, graphene, fullerene,^{51–56,98–100} semiconductor nanomaterials such as MoS₂, WS₂, Bi₂Se₃,^{60–62,101–104} organic NIR dyes such as ICG, IR780, IR820 (Figure 1B).^{63–74}

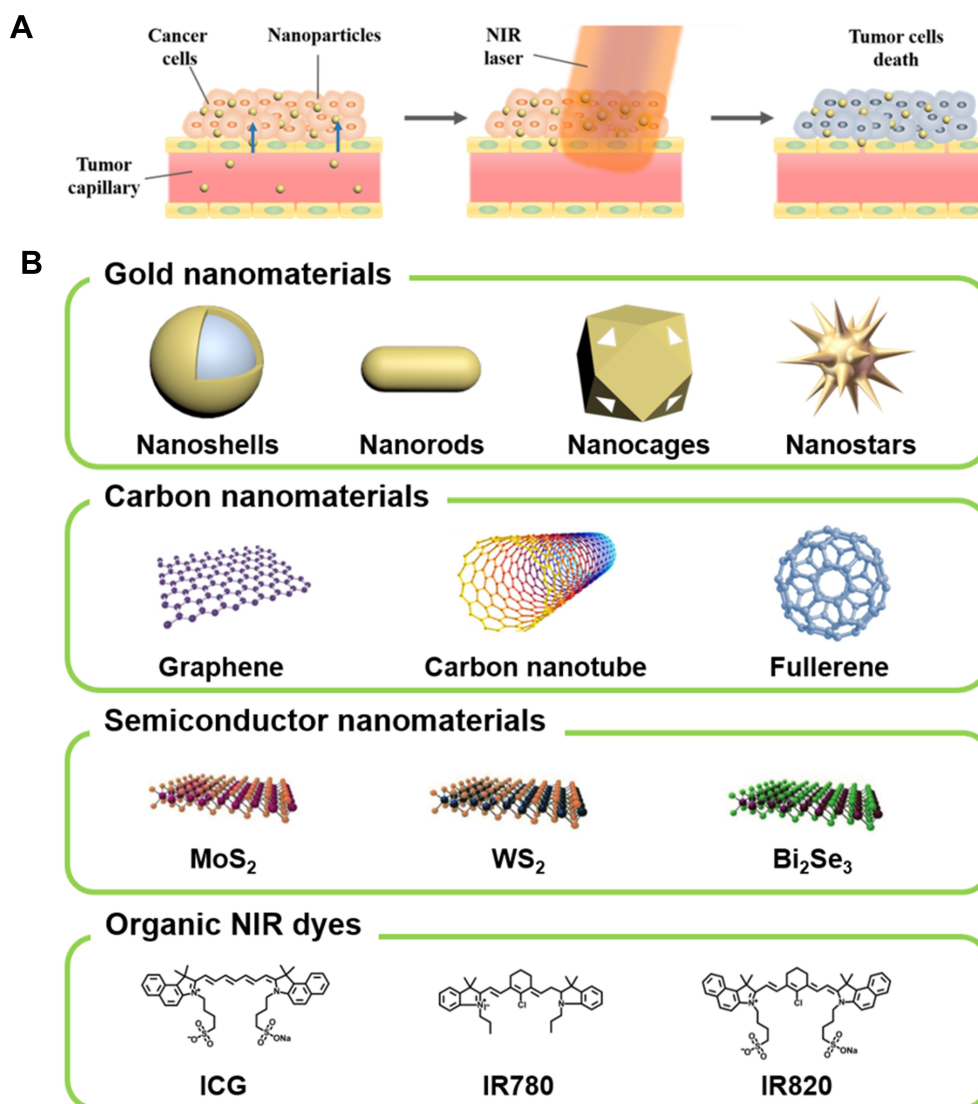


Figure 1 (A) Schematic illustration of nanoparticle-based PTT. Reproduced from Riley RS, Day ES. Gold nanoparticle-mediated photothermal therapy: applications and opportunities for multimodal cancer treatment. *Wiley Interdiscip Rev Nanomed Nanobiotechnol.* 2017;9(4):1449. Copyright 2017, John Wiley and Sons.⁸⁸ (B) Four major photothermal agents for PTT, including gold nanoparticles, carbon nanomaterials, semiconductor nanomaterials and organic NIR dyes. Reproduced from Kim H, Beack S, Han S, et al. Multifunctional photonic nanomaterials for diagnostic, therapeutic, and theranostic applications. *Adv Mater.* 2018;30(10):1701460. Copyright 2018, John Wiley and Sons.⁹⁷

However, there are still some ambiguity in PTT. Many studies on PTT have found that PTT can effectively kill tumor cells and eliminate tumors, but the specific mechanism of cell death is understudied. It is necessary to understand the path of PTT-induced cell death, so that the response of tumors to different PTT can be understood. Then, by regulating the parameters of treatment to achieve the desired effect, moreover, more appropriate and effective treatments can be designed for each case.

How PTT Induces Cell Death

Even though PTT is already in clinical trials,^{105,106} we know little that how PTT induces cell death. According to the

published articles on PTT for cancer treatment, it is difficult to find a universal cell death mechanism. The cell death mechanism caused by PTT is associated with a variety of factors, such as the properties of tumors, the time of irradiation, the heat absorbed by the cell, the level of internalization of the nanomaterials.¹⁰⁷ Therefore, the cellular response to PTT is complex. Following, the mechanism of PTT-induced cell death is analyzed, showing the complexity of this process.

PTT and Apoptosis/Necrosis

Cancer hyperthermal therapy refers to the treatment that raises the cell temperature to 41–48°C, which leads to a range of cell damage, including cell membrane damage,

intracellular protein degeneration, damage of RNA/DNA synthesis, and eventually leads to cell apoptosis.^{82,108–111} PTT also has a similar effect to hyperthermia. However, whether PTT induces apoptosis or necrosis remains unclear, and maybe a single mechanism is insufficient to describe the effects of PTT.

Recent studies demonstrate that the cell death mechanism of PTT can be influenced by the laser type, nanomaterials location, photothermal dose. Huang et al¹¹² investigated the mechanism of PTT to human oral squamous cell carcinoma (HSC-3) cells, using cytoplasm-targeted peptide (RGD) or nuclear-targeted peptide (NLS) functionalized gold nanosphere. PTT studies showed that nanosecond pulsed lasers irradiation can only cause necrosis, regardless of where the nanomaterials were located in the cell. When treating cells with the continuous wave (CW) laser, cell death was attributed to apoptosis with gold nanosphere located in the nucleus; however, when the gold nanospheres were in the cytoplasm, higher energy led to necrosis, while lower energy caused apoptosis. This indicated that the effects of localization and laser type are quite complex and may affect the mechanism of cell death in PTT. The effect of nanomaterials location using folate-functionalized gold nanorods (F-GNRs) was described by Tong et al in 2007.¹¹³ Malignant human oral epidermoid cancer (KB) cells were incubated with the F-GNRs for 6 h and 17 h to ensure that the nanoparticles were delivered to the cell surface or the perinuclear region, respectively. PTT carried out by CW laser irradiation, the results showed that when F-GNRs were inside the cell, it need 60mW laser intensity to kill the cell, but only need 6mW when F-GNR were on the cell surface. This indicated that the location of nanomaterials was important for the effectiveness of PTT, and F-GNRs on the cell surface had a better heat transfer effect. Further analysis of the cell death mechanism found that F-GNRs-mediated cavitation caused the rupture of the cell membrane. Membrane rupture led to the influx of extracellular Ca^{2+} followed by degradation of the actin network, resulting in a large number of blebbing response. Finally, the mode of cell death was thought to be apoptosis. Ali et al¹¹⁴ developed a mild PTT strategy to induce cancer cell apoptosis, by fixing the GNRs concentration (7.5 nM), laser power (5.8 w/cm²) and adjusting the laser exposure time. They irradiated the human breast cancer (MCF-7) cells and found that after 2 min laser exposure, the cells mainly apoptosis (42.7% apoptosis and 2.89% necrosis), while 5 min laser

exposure led to a significant increase in necrosis cells (20.17% apoptosis and 15.5% necrosis). This demonstrated that high-dose of PTT can lead to necrosis, while low-dose of PTT can promote apoptosis. Li and Gu¹¹⁵ reported the effects of changes in laser energy during PTT on cervical cancer (HeLa) cells. After incubation with GNRs for 6 h, HeLa cells received a femtosecond pulsed scanning laser irradiated. When the laser power was 27.8 w/cm², 10 scans induced apoptosis, while increasing it to 30 times led to necrosis. When the laser power was reduced to 13.9 w/cm², multiple scans only induced apoptosis. However, the laser power was increased to 55.6 w/cm², only one scan can lead to necrosis. This suggested that laser power could affect the pathway of cell death.

To better understand the specific mechanisms involved, the apoptotic cell death was further investigated by examining biomarkers of the apoptotic pathways. Pérez-Hernández et al¹¹⁶ have found that PTT-specific-induced apoptosis was mediated by the intrinsic mitochondrial pathway via the activation of Bid (Figure 2A). Mocan et al¹¹⁷ established that hyperthermia after PPT can induce the depolarization of mitochondrial membrane, thus activating the free radical flux and oxidation state within the cell, and regulating cell damage through the apoptotic pathway. Ali et al¹¹⁸ found that the metabolism of phenylalanine after PTT was disrupted and activated key proteins in several apoptosis pathways, such as HADHA and ACAT1. Additionally, this group¹¹⁹ also found that cytochrome c and p53-related apoptosis mechanisms were associated with PTT-induced apoptosis. Proteomics analysis identified a variety of apoptosis pathways, such as caspase cascade, granzyme B signal, BAD protein phosphorylation.

PTT and Heat Shock Proteins

In the PTT process, many functional biological macromolecules were expressed to assist a variety of biological processes, such as the folding of new polypeptides, the formation of protein complexes, and the promotion of intracellular protein transport, to protect cells from adverse conditions. Heat shock proteins (HSPs) refer to a group of proteins produced by cells under the induction of stressors, especially at high temperatures. They are also chaperonins that bind to denatured proteins during heat stress and preventing them from aggregating, and then promote refolding of the protein after temperature recovery. Therefore, HSPs are associated with PTT-induced cell death mechanism.^{120–124}

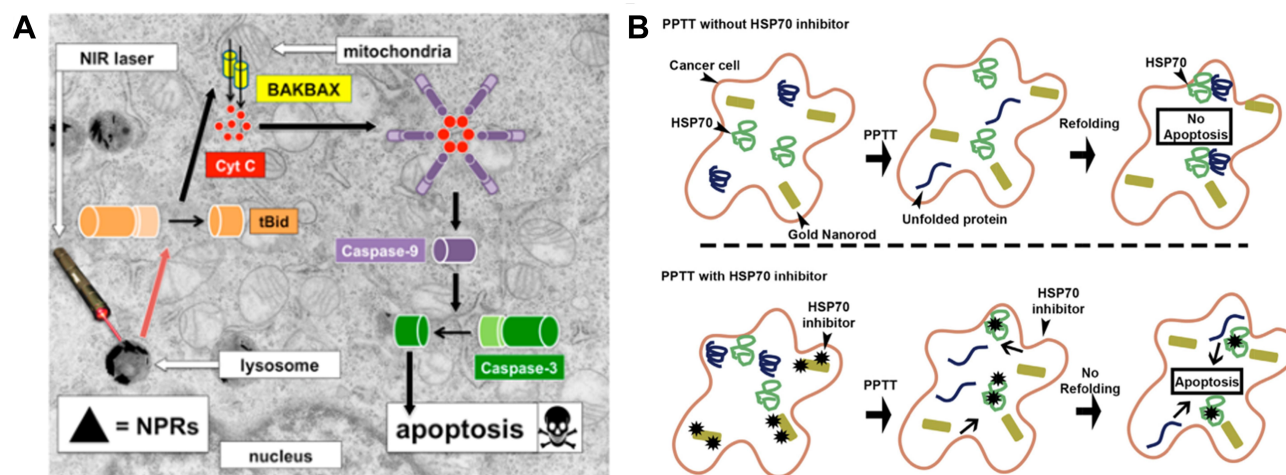


Figure 2 (A) Mechanism of apoptosis after NIR laser-irradiation. Reproduced with permission from Pérez-Hernández M, Del Pino P, Mitchell SG, et al. Dissecting the molecular mechanism of apoptosis during photothermal therapy using gold nanoprisms. *ACS Nano*. 2015;9(1):52–61. ¹¹⁶ Copyright 2015, American Chemical Society. **(B)** Schematic illustration of HSP70 inhibitor optimized PTT. Reproduced with permission from Ali MRK, Ali HR, Rankin CR, et al. Targeting heat shock protein70 using gold nanorods enhances cancer cell apoptosis in low-dose plasmonic photothermal therapy. *Biomaterials*. 2016;102:1–8. ¹²⁸ Copyright 2016, Elsevier.

Some studies supported the idea that inhibiting various HSPs, including HSP60, HSP70, and HSP90, could reduce the heat resistance of tumor cells, enhance tumor sensitivity to PTT and improve PTT efficiency.^{125–136} Wang et al¹³⁴ developed a novel vanadium oxide composite loaded with ICG (VO₂-ICG). In acidic tumor microenvironment, VO₂ NPs were decomposed and VO²⁺ released simultaneously, which could not only inhibit the function of HSP60 but also generate hydroxyl radical (•OH) by catalyzing H₂O₂ in tumor. In addition, the VO₂ NPs also released ICG during decomposition, allowing for the NIR luminescence imaging and PTT. The inhibition of HSP60 reduced the heat resistance of cells and the production of •OH increased oxidative stress in cells, which further improved the efficiency of PTT. Small interfering RNA (siRNA) and small molecular inhibitors have been used to inhibit the HSPs expression and enhanced the PTT efficiency. An effective and versatile PTT platform based on hollow GNShs functionalized with siRNA against HSP70 was designed by Wang et al.¹²⁹ Efficient downregulation of HSP70 after laser irradiation was achieved in vitro and in vivo. Finally, sensitized cancer cells to heat, and improved PTT efficiency. Ali et al¹²⁸ investigated and applied GNRs to test how different cell lines responded to PTT and correlated their response to PTT to their HSP70 levels. Three different epithelial origin cancer cell lines: HSC (oral), Huh7.5 (liver) and MCF-7 (breast) were heated to the same temperature. Compared with HSC and MCF-7 cells, the apoptosis of Huh7.5 cells increased significantly after PTT. HSP70 is known to

enhance the cells' resistance to heat, so they measured relative HSP70 levels in these cells after PTT. The results showed that the HSP70 level of Huh7.5 cell was 10 times lower than that of HSC and MCF-7 cells. Then, the expression of HSP70 was down-regulated by siRNA, and all three cell lines showed a significant increase in apoptosis after PTT. To enhance PTT, they further conjugated GNRs with HSP70 inhibitor quercetin, and obtained results similar to siRNA, the conjugation of HSP70 inhibitor enhanced the effect of PTT (Figure 2B). Jiang et al¹³³ synthesized a flowerlike Lu:Nd@NiS₂ core-shell nanoparticles loaded with a natural HSP90 inhibitor-phenolic epigallocatechin 3-gallate (EGCG). Under laser irradiation, EGCG was released from Lu:Nd@NiS₂ and bound to HSP90 to reduced cell's resistance to heat, resulting in better therapeutic effect at the same temperature rise. However, the role of HSPs should not be overlooked in the immune system, such as HSPs being able to present antigens to DCs and induce anti-tumor immune response.¹³⁷ Therefore, HSP inhibitors are not suitable for all treatments.

PTT Impacts the Tumor Microenvironment and Immune Response

PTT in Tumor Microenvironment

Tumor microenvironment (TME) plays a vital role in cancer development and metastasis. It consists of extracellular matrix (ECM), various cell types, blood vessels, interstitial fluid and other tumor-related components (Figure 3).^{138–140} In many types of solid tumors, dense ECM and tumor matrix supply

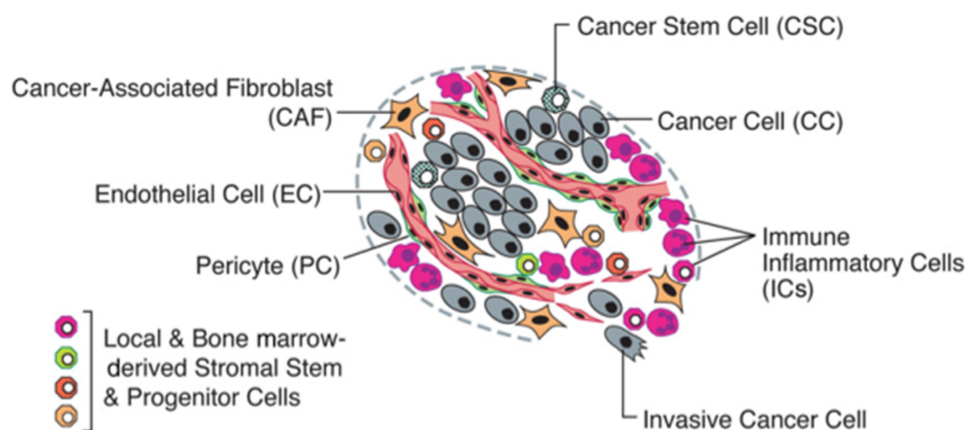


Figure 3 The Cells in the Tumor Microenvironment. Reproduced with permission from Hanahan D, Weinberg RA. Hallmarks of cancer: the next generation. *Cell*. 2011;144(5):646–674.¹⁴⁰ Copyright 2011, Elsevier.

the development of the tumor, also as a natural barrier to the effective spread of therapeutic drugs. Additionally, the rampant proliferation of tumor cells and the extension of dysfunctional blood vessels can cause tumors to form a hypoxia and acidification microenvironment, significantly affecting the therapeutic effect of various therapies.¹⁴¹ Moreover, cancer cells can recruit a large number of immunosuppressive cells, including regulatory T cells, tumor-associated macrophages (TAMs) and myeloid-derived suppressor cells (MDSCs), to form immunosuppressive TME. Which can suppress anti-tumor immune effects, protect tumor cells from attack, and promote tumor growth.^{142,143}

Research results show that nanomaterials can have a great impact on TME. It has been well known that PTT can increase the temperature of local tumors, resulting in increased blood flow inside the tumor and improved hypoxia in the TME. Thus, many recent studies have shown that the combination of PTT with photodynamic therapy or radiation therapy can significantly improve the synergetic effects by effectively alleviating the hypoxia in the tumor.^{144–147} Additionally, increased tumor blood flow due to PTT can also lead to increased microvascular permeability, which may widen the therapeutic window for poorly permeable cancers and enhance targeted drug delivery.^{148,149} Moreover, gold nanoparticles are inherently capable of regulating TME. Saha et al¹⁵⁰ demonstrated that bare gold nanoparticles can regulate the secretome of cells to reduce the growth of desmoplastic tissue and inhibit tumor growth, thus interfering with crosstalk between pancreatic cancer cells and pancreatic stellate cells.

PTT Induction of Immune Response

Immunotherapy is a promising treatment of cancer that supports body immune system fight cancer. The generation of an anti-tumor immune response involves some key steps: Initially, TAAs released from tumor cells are captured by DCs, which can efficiently phagocytose, process and deliver tumor antigens. Then, mature DCs migrate to the lymph nodes to present the tumor antigens to T cells, activating the effector T cell responses to tumor-specific antigens. Finally, activated effector T cells migrate and infiltrate to the tumor region, where they specifically identify and kill cancer cells. Furthermore, the killed cancer cells release more TAAs, increasing the breadth and depth of the immune response during the cycle's subsequent.^{151,152}

To induce a specific anti-tumoral immune response, TAAs are required in cancer vaccines. However, it is difficult to screen out a generic TAAs for multiple types of cancers. Surprisingly it has been noticed that ablative cancer treatments, like PTT, can cause immunogenic death of tumor cells.^{75,76} This immunogenic cell death (ICD) is characterized by the release of TAAs, DAMPs, and pro-inflammatory cytokines from the dead cells that help present TAAs to immune cells, resulting in an antigen-specific immune response.^{77,78} The advantage of PTT as part of immune therapy is that localized tumor ablation can release TAAs to form a broad spectrum in situ cancer vaccine.

During ICD, TAAs and DAMPs are released by dying tumor cells. TAAs can enhance the antigen-specific T cell response, while the release of DAMPs can serve as the “dangerous” signal of immune stimulation to enhance the engulfment of tumor antigens by DCs, induce DCs maturation and activate T-cells, thereby initiating anti-tumor immune

response. Many of the immunogenic factors involved in the death of apoptotic cells have been identified as DAMPs, such as calreticulin (CRT),^{153,154} ATP,^{155,156} high mobility group box 1 (HMGB-1)^{157,158} and HSPs.^{159,160} ATP acts as a chemical attractor to recruit antigen present cells (APCs); CRT acts as an “eat-me” signal, facilitating APCs to engulf dying tumor cells and their fragments.¹⁶¹ HMGB-1 and HSPs stimulate antigen presentation to T cells (Figure 4).^{162,163}

It is important to note that PTT-induced ICD requires an appropriate thermal dose, “more is better” do not

apply to every situation. Sweeney et al¹⁶⁴ explored the thermal “window” of ICD by Prussian blue nanoparticle-based PTT (PBNP-PTT) in neuroblastoma animal model. To determine whether a cell is in the process of ICD, the criteria is that the intracellular ATP and HMGB1 should be decreased while the surface CRT should be increased. They found that ICD markers were highly expressed within an optimal temperature window (63.3–66.4°C), however, higher (83.0–83.5°C) or lower (50.7–52.7°C) temperatures both produced lower expression (Figure 5).

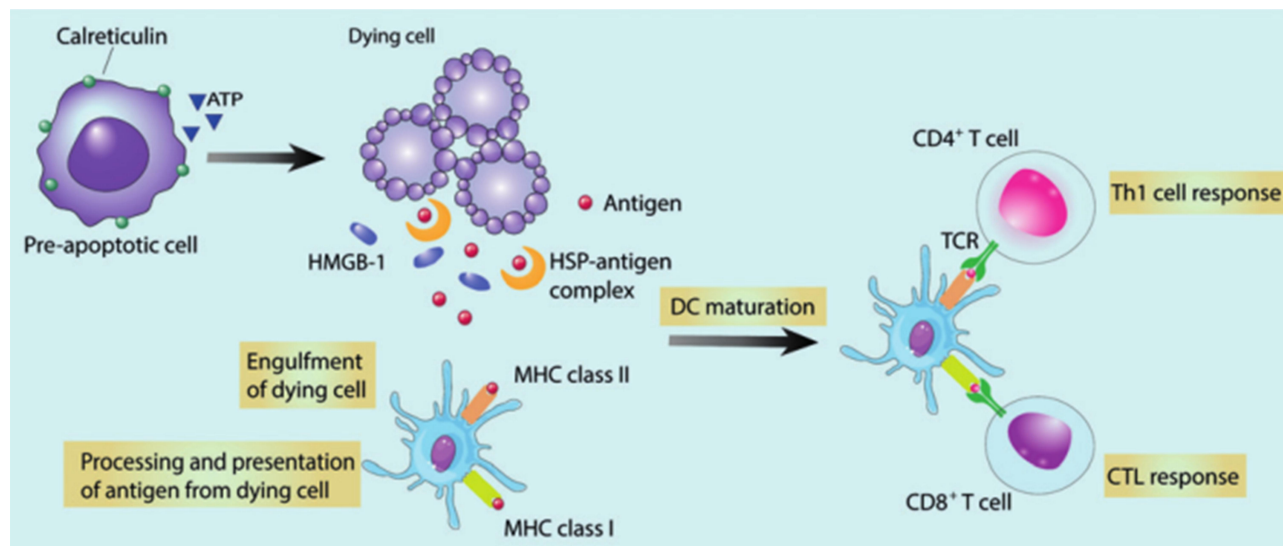


Figure 4 Characteristics of immunogenic cell death (ICD). Reproduced with permission from Duan X, Chan C, Lin W. Nanoparticle-mediated immunogenic cell death enables and potentiates cancer immunotherapy. *Angew Chem Int Ed Engl.* 2019;58(3):670–680.¹⁶³ Copyright 2019, John Wiley and Sons.

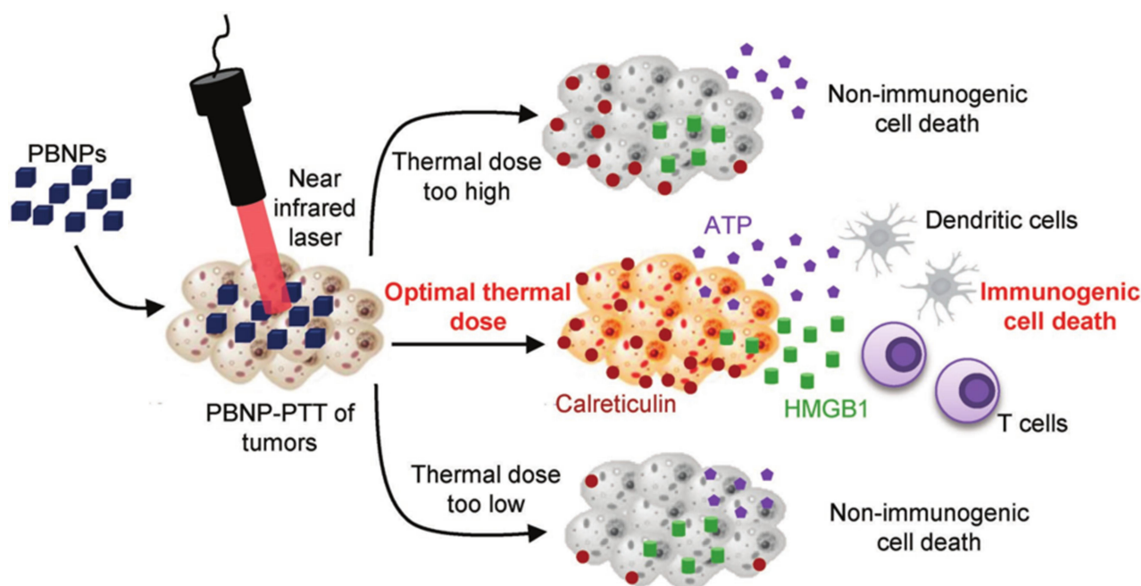


Figure 5 PTT generates ICD when an optimal thermal dose is administered to tumors. Reproduced with permission from Sweeney EE, Cano-Mejia J, Fernandes R. Photothermal therapy generates a thermal window of immunogenic cell death in neuroblastoma. *Small.* 2018;14(20):1800678.¹⁶⁴ Copyright 2018, John Wiley and Sons.

This finding was subsequently confirmed by vaccination studies in neuroblastoma models. The tunability of the ICD presented in this work may also apply to other nanomaterial-based PTT, and perhaps the “more is better” approach is not suitable for these therapies, and there may be the optimal window for treatment.

Nanomaterial-Based Photothermal Immunotherapy

Cancer immunotherapy has achieved remarkable clinical responses owing to its unique advantages, with specific anti-tumor induction and long-term immuno-memory response. However, the response rate is low, and the potential side effects are still the major barriers to the widespread use of immunotherapy in the clinic.^{28,29,31}

Recent researches mainly have focused on the immune response after nanomaterial-based PTT. On one hand, nanodrugs can be actively or passively targeted to the tumor site, and then tumor cells are killed by PTT. On the other hand, TAAs and cell fragments are released, activating the systemic immunity and further killing residual or metastatic tumors. Furthermore, the generation of immune-memory could prevent cancer recurrence. This nanomaterial-based PTT can directly eliminate tumors and induce sustained antitumor immune effects called photothermal immunotherapy.¹⁶⁵

However, the tumor fragments produced by PTT may not be sufficient to effectively activate the anti-tumor response. Therefore, nanomaterials for PTT can be further combined with immunostimulants or other immune drugs to enhance the whole body's anti-tumor immune responses.

Photothermal Immunotherapy Combined with Immunoadjuvant

Numerous researches have established that immunostimulation induced by PTT alone was insufficient. One effective way is to add immunoadjuvants, which are a class of substances that act as an auxiliary or enhanced substance in the immune response. Nanotechnologies are very effective in immune responses, mainly when nanoparticle-based PTT combined with immunoadjuvants, it can trigger the immune responses, increasing the infiltration of immune cell in the tumor site. This effect cannot only inhibit the recurrence of primary tumor but also inhibit or eradicate metastatic tumors.

In the past few years, PTT in conjunction with an immunoadjuvant has become an epidemic strategy to enhance the immune response to cancer. As attractive photothermal agents, gold nanoparticles with different morphologies like GNRs, GNShs have been investigated combine with immunoadjuvants. Zhou et al¹⁶⁶ designed and synthesized GNRs based hybrid nanomaterial's mPEG-GNRs@BSA/R837 through functionalization of BSA-bioinspired GNRs with the imiquimod (R837, an FDA approved immunoadjuvant recognized by the toll-like receptor 7), to treat melanoma by PTT and immunotherapy. The mPEG-GNRs@BSA/R837 significantly increased the secretion levels of TNF- α , IL-6, and IL-12 and the percentages of mature DCs also increased a lot (65.1%). At the same time, after 7 days of treatment, mPEG-GNRs@BSA/R837 combined with laser irradiation effectively enhanced the infiltration of CD8⁺ T cells. More importantly, the nanocomposite combined with laser irradiation was found in animal tumor models to prevent lung metastasis of cancer cells, and to form long-term immune memories in response to tumor re-challenges. A drug delivery system based on the GNShs and an immunoadjuvant CpG oligodeoxynucleotides (CpG, an immunoadjuvant recognized by endosomal toll-like receptor 9) has been made by Zhang et al.¹⁶⁷ PTT could destroy tumor cells at a macro level, and finally immunotherapy could track and kill cancer cells throughout the body. Yata et al¹⁶⁸ synthesized a composite immunostimulatory hydrogel consisting of a hexapod-like structured DNA, CpG and gold nanoparticles. The hydrogels plus laser irradiation increased the tumor temperature and the expression of HSP70 in tumor tissue, as well as the amount of antitumor inflammatory mediators, such as TNF- α , IL-6 and IFN- γ . In addition, the therapy significantly slowed tumor growth and increased the survival rate of tumor-bearing mice.

Besides gold nanoparticles, carbon nanoparticles are another attractive photothermal agents. Taking advantage of the carrier nature of SWCNTs, Zhou et al¹⁶⁹ modified SWCNTs with an immunoadjuvant glycated chitosan (GC, an immunoadjuvant that improves antigen transport between the epithelium and promotes antigen phagocytosis). After 980 nm laser irradiation, tumor cells were killed by the photothermal effect of SWCNT and the damaged cells produced antigens that were recognized by the immune system. Meanwhile, GC could induce a stronger anti-tumor immune response. Animal studies showed that the combination of PTT and SWCNT-GC not only effectively killed the local and metastatic tumors but also

produced an effective long-term anti-tumor immune response. Tao et al¹⁷⁰ synthesized a graphite oxide (GO) based complex GO-PEG-PEI-CpG through combination of GO, polyethyleneimine (PEI), polyethylene glycol (PEG) and immunoadjuvant CpG. Under laser irradiation, the nanocomposite generated local hyperthermia and accelerated intracellular migration of the nanoparticles. In vivo experiments also showed that the GO-PEG-PEI-CpG had a synergistic photothermal and immune effect on cancer treatment. Moreover, nanographene and graphene quantum dots also have been studied as photothermal agent for photothermal immunotherapy.

Sulfide metallic nanoparticles are also the popular choice as photothermal agents. Guo et al¹⁷¹ have developed chitosan-coated hollow CuS nanoparticles that assemble the immunoadjuvants CpG (HCuSNPs-CpG) to treat the primary and distant tumor. After 900 nm laser irradiation, the structure broke down into the chitosan-CpG nanocomplexes (Chi-CpG-NPs), and small CuS nanoparticles (SCuSNPs). The released Chi-CpG-NPs were uptake into plasmacytoid dendritic cells (pDCs). Under CpG stimulation, pDCs secreted IFN- α , promoting NK cell to activate innate immunity. Meanwhile, HCuSNPs-mediated photothermal ablation destroyed tumor cells and released TAAs to myeloid dendritic cells (mDCs). These mDCs subsequently migrated to lymph nodes, where they cross-prime tumor antigen-specific T cells. Then, the antigen-specific CD8⁺ T cells were recruited to primary tumor and distant site tumor, triggering adaptive immune response (Figure 6). Jang et al¹⁷² also functionalized CuS nanoparticles with lipopolysaccharide (LPS-CuS) for photothermal immunotherapy application. LPS is an immunoadjuvant that mediates immune activation by interacting with toll-like receptor 4. After laser irradiation, LPS-CuS induced ablation of CT26 tumor and released TAAs. Then, the LPS and TAAs promoted DCs activation and enhanced the tumor antigen-specific immune responses. Finally, LPS-CuS mediated PTT not only cured the primary tumors of the mice but also completely resisted secondary tumor injection in the spleen. Besides, CpG loaded MoS₂ nanosheets also showed photothermal enhanced immunological activity, which dramatically reduced the viability of tumor cells.

Aside from sulfide metallic nanoparticles, organic dyes like indocyanine green (ICG) and its derivatives are another widely used photothermal agents. Chen et al¹⁷³ first reported the use of ICG-loaded glyated chitosan gel for photothermal

immunotherapy in 1997. After 805 nm laser irradiation, tumor cells were immediately destruction and concomitantly stimulated the immunological defense system against residual and metastatic tumor cells. Finally, eliminated both primary and metastatic tumor burden, and improved the survival rate of the rats. Li et al¹⁷⁴ designed and synthesized a PTT agent IR-7-lipo/HA-CpG through surface functionalization of IR-7-lipo (fluorophore loaded liposomes) with a multivalent immunoadjuvant (HA-CpG), where IR-7 is a NIR active heptamethine cyanine dye. After 808 nm laser irradiation, IR-7-lipo induced tumor cell necrosis and released TAAs, while the multivalent immunoadjuvant improved the co-stimulatory molecules expression and promoted antigen presentation. Moreover, IR-7-lipo/HA-CpG could significantly reduce the amount of MDSCs to decrease immunosuppression and increase the number of CD8⁺ effector T cells to potentiate the anti-tumor immunity of the host. Most importantly, due to the enhanced anti-tumor immune response, combined photothermal immunotherapy could effectively eliminate tumors and inhibit tumor metastasis of the mice. Dong et al¹⁷⁵ designed a composite hydrogel that contained CpG self-crosslinked nanoparticles and IR820 to achieve photothermal immunotherapy. IR820-hydrogel can effectively generate heat to eliminate the tumor and produced photothermal-induced tumor antigens. CpG self-crosslinked nanoparticles can boost immune response to melanoma. The combination of the two part got a synergistic effect. Further analysis found an increase in the number of CD8⁺ T cells and a decrease in the number of MDSCs in TME. In addition, the self-fluorescent IR820-hydrogel can be imaging to guide treatment and this visible photothermal immunotherapy offers the potential for precise cancer treatment. Moreover, Prussian blue nanoparticles (PBNPs) also have been used as a photothermal agent in photothermal immunotherapy. Other existing photothermal nanomaterials combined with immunoadjuvants for photothermal immunotherapy are listed in Table 1.

Photothermal Immunotherapy Combined with Immune Checkpoint Inhibitor

Immune response has checkpoints to maintain immune homeostasis and prevent its improper activation, immune checkpoint blockade refers to the use of antibodies that block negative regulatory receptors on T cells to enhance the endogenous natural immune responses. In a number of preclinical trials, immune checkpoint inhibitors have been shown to release T-cell-mediated immunosuppressive

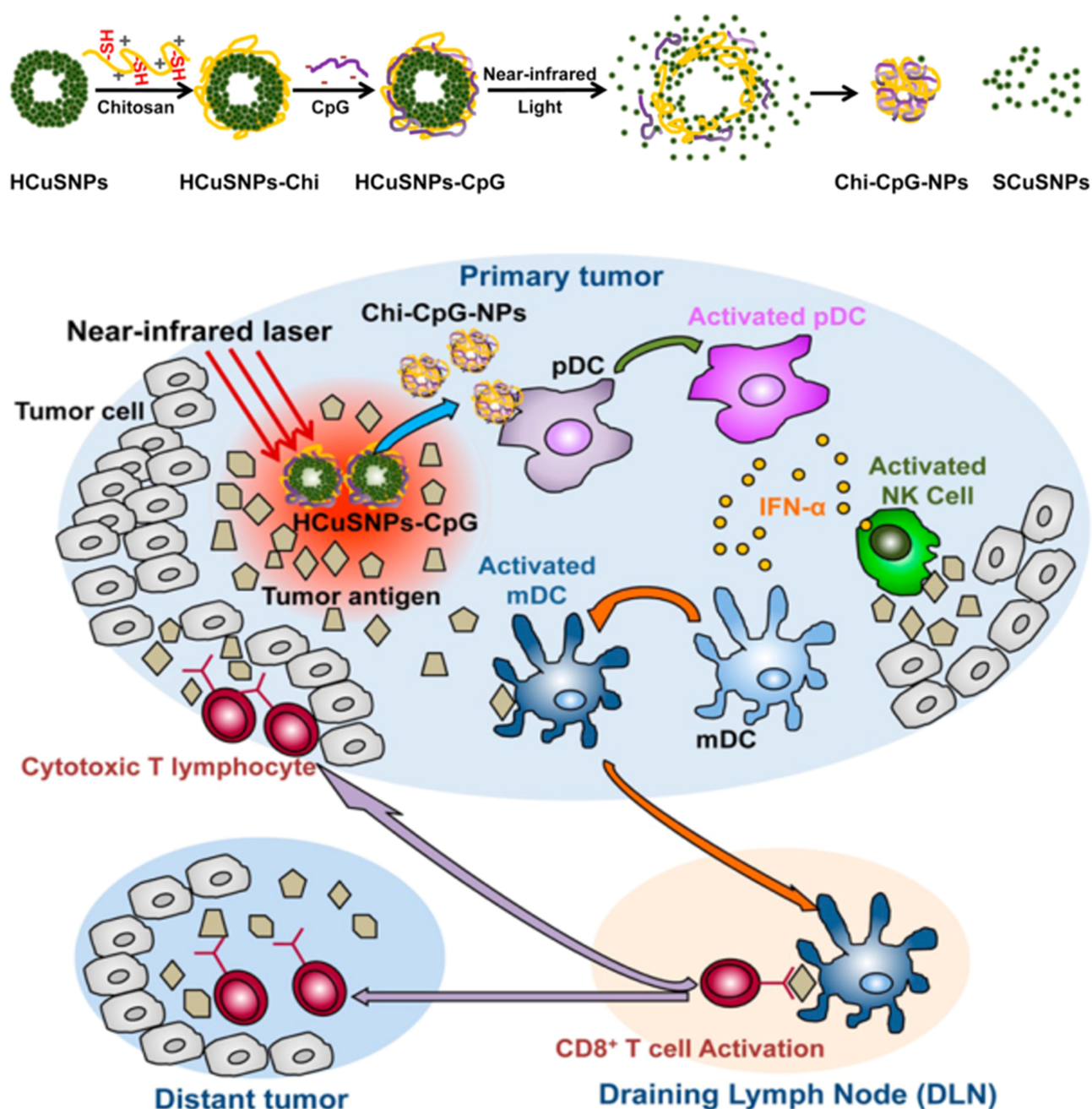


Figure 6 Schematics diagram of combined photothermal and immunotherapy using chitosan-coated hollow copper sulfide nanoparticles. Reproduced with permission from Guo L, Yan DD, Yang D, et al. Combinatorial photothermal and immuno cancer therapy using chitosan-coated hollow copper sulfide nanoparticles. *ACS Nano*. 2014;8(6):5670–5681.¹⁷¹ Copyright 2014, American Chemical Society.

mechanisms and promote cytotoxic T lymphocytes (CTLs) responses.¹⁷⁶ Two major immune checkpoints, cytotoxic T lymphocyte antigen-4 (CTLA-4) and programmed cell death protein 1 (PD-1)/programmed cell death-ligand 1 (PD-L1), are the hot topic of current research. Their inhibitors like Ipilimumab, Pembrolizumab and Atezolizumab have been approved by the FDA on the basis of striking clinical trial results in melanoma, renal cell carcinoma, and lung cancer,

providing great potential in cancer immunotherapy.^{177–179} Therefore, blocking these negative signals is another strategy to elicit an immune response with PTT.

CTLA-4, as an immune checkpoint, is a critical negative regulator of T cell activation, which is constitutively expressed by regulatory T cells and up-regulated after T cell activation. Researchers have found that blocking CTLA-4 could inhibit the development of tumor by increasing activities of effector

Table I Photothermal Nanomaterials Combined with Immunoadjuvants for Photothermal Immunotherapy

Photothermal Nanoparticles	Immunoadjuvants	Effector Cells	Cytokines	Tumors	References
GNR	CpG	–	TNF- α , IL-6	Murine hepatocellular carcinoma cell H22	[188]
GNR-DNA hydrogels	CpG	–	TNF- α , IL-6, IL-12p40, IFN- γ	Murine T lymphoma cell EG7-OVA	[168]
Ovalbumin assembled gold nanorods (OVA-GNR)	CpG	DCs, CD8 ⁺ T cells	IL-6, IL-12, IL-1 β	Murine breast cancer cell 4T1	[189]
Bovine serum albumin coated gold nanorods (BSA-GNRs)	R837	DCs, CD8 ⁺ T cells	TNF- α , IL-6, IL-12	Murine melanoma cell B16-F10	[166]
GNR-PEI	CpG	DCs, CD8 ⁺ T cells, CD4 ⁺ T cells	–	Murine breast cancer cell 4T1	[190]
Gold nanoshell	CpG	DCs, CD8 ⁺ T cells, CD4 ⁺ T cells	IL-2, IL-6, IFN- γ	Murine gastric cancer cell MFC	[167]
NIR heptamethine cyanine dye IR-7 loaded liposomes (IR-7-lipo)	CpG	DCs, CD8 ⁺ T cells, CD4 ⁺ T cells	TNF- α , IL-6, IL-12	Murine colon cancer cell CT26	[174]
IR820-hydrogel	CpG	DCs, CD8 ⁺ T cells	TNF- α , IL-2, IFN- γ	Murine melanoma cell B16	[175]
IR820 thermosensitive liposomes (IR820-TSL)	R837	DCs	TNF- α , IL-12p70, IFN- γ	Murine gastric cancer cell MFC	[191]
Single-walled carbon nanotube (SWNTs)	Glycated Chitosan (GC)	–	DAMPs	Murine breast cancer cell EMT6	[169]
Graphene oxide sheets conjugated with PEI and PEG (GO-PEG-PEI)	CpG	–	TNF- α , IL-6	Murine colon cancer cell CT26	[170]
Mitochondria-Targeted Nanographene	CpG	–	TNF- α , IL-6, IL-12, INF- γ	Murine breast cancer cell EMT6	[192]
Polydopamine coated graphene quantum dots (GQD-PDA)	CpG	DCs, CD8 ⁺ T cells, CD4 ⁺ T cells	TNF- α , IL-6	Murine breast cancer cell EMT6	[193]
Chitosan-coated hollow CuS nanoparticles (HCuSNPs-Chitosan)	CpG	DCs, CD8 ⁺ T cells, NK cells	IL-2, IFN- γ	Murine breast cancer cell EMT6	[171]
MoS ₂ nanosheets	CpG	DCs	TNF- α , IL-6	Murine breast cancer cell 4T1	[194]
Lipopolysaccharide coated copper sulfide nanoparticles (LPS-CuS)	Lipopolysaccharide (LPS)	DCs	TNF- α , IL-6, IL-12p40, IFN- γ	Murine colon cancer cell CT26	[172]
Polydopamine coated Al ₂ O ₃ nanoparticles (PDA-Al ₂ O ₃)	CpG	DCs	TNF- α , IFN- γ	Murine melanoma cell B16-F10	[195]
Folic acid coated polydopamine nanoparticles (FA-PDA)	R837	DCs	TNF- α , IL-12p40	Murine hepatocellular carcinoma cell H22	[196]
Prussian blue nanoparticles (PBNPs)	CpG	DCs, CD8 ⁺ T cells	–	Murine neuroblastoma cell Neuro2a	[197]

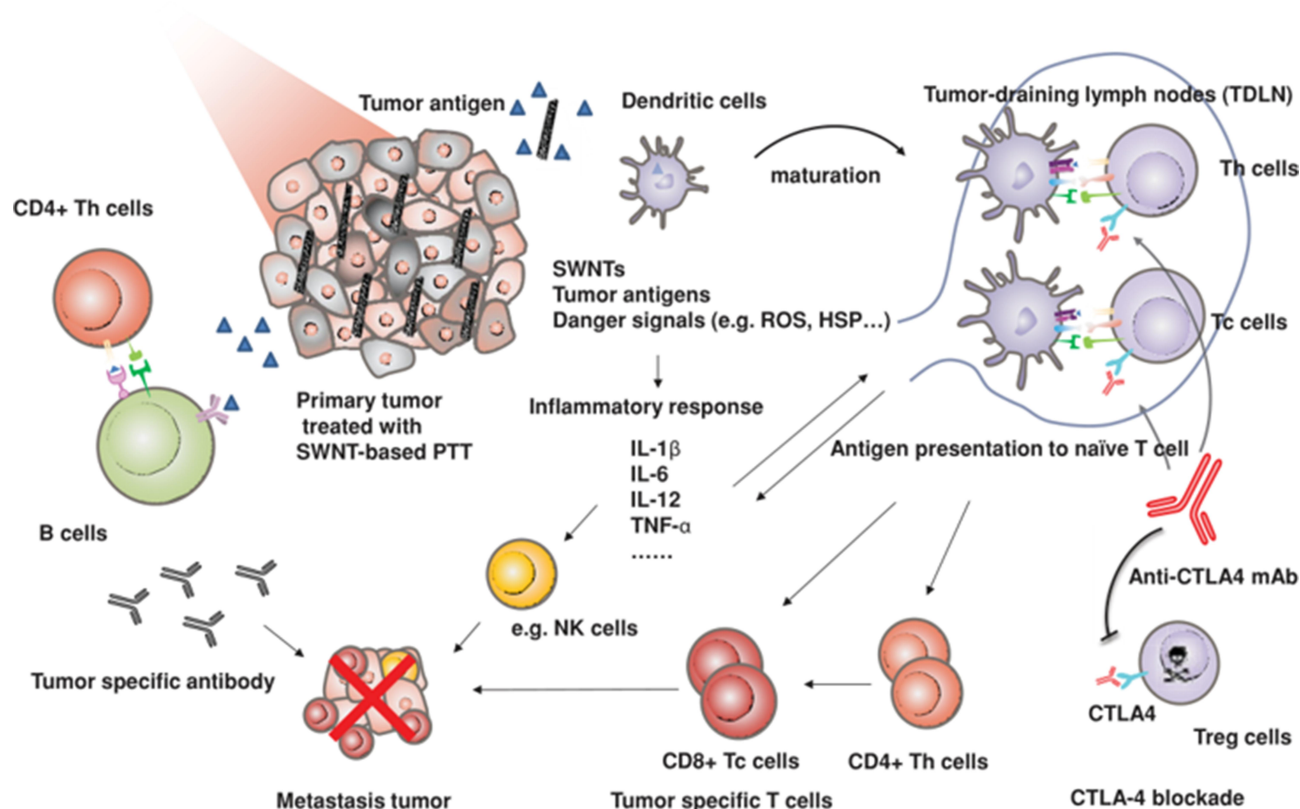


Figure 7 Schematic diagram of nanoparticle-based PTT together with anti-CTLA-4. Reproduced with permission from Wang C, Xu L, Liang C, et al. Immunological responses triggered by photothermal therapy with carbon nanotubes in combination with anti-CTLA-4 therapy to inhibit cancer metastasis. *Adv Mater.* 2014;26(48):8154–8162.¹⁸⁰ Copyright 2014, John Wiley and Sons.

T cells and reducing the immunosuppressive activity of regulatory T cells in the TME. Combining anti-CTLA-4 antibody with PTT has been exploited in photothermal immunotherapy.

Wang et al¹⁸⁰ found that SWCNT-based PTT together with anti-CTLA-4 antibody could regulate the adaptive immune responses, especially cellular immunity to treat metastatic cancer. As shown in Figure 7, upon thermal ablation by PEG-coated SWCNTs, TAAs were released along with the danger signals to induce DCs maturation, and then the antigens were presented, eventually recruiting tumor-specific CD8⁺ T cells. Meanwhile, anti-CTLA-4 could effectively reduce the immunosuppressive activity of regulatory T cells and increase the ratios of CD4⁺ and CD8⁺ T cells to regulatory T cells. As a result, combined with anti-CTLA-4 therapy, SWCNT-based PTT could inhibit the growth of cancer cells in subcutaneous tumor model and lung metastasis model. Mejia et al¹⁸¹ reported PBNPs-based PTT combined with anti-CTLA-4 to treat neuroblastoma. PBNPs-based PTT could reduce tumor burden and produce an immune response, and anti-CTLA-4 could promote the

penetration of T cells in the tumor area. They observed that 55.5% of mice treated with photothermal immunotherapy had a survival rate of more than 100 days. Additionally, these long-term survived mice exhibited protection against neuroblastoma rechallenger.

Aside from CTLA-4 immune checkpoint, antibody against PD-1/PD-L1 have also been exploited in photothermal immunotherapy. PD-1, as an immune checkpoint, is highly expressed in activated T and B cells. As a ligand of PD-1, PD-L1 is a protein overexpressed on the surface of tumor cells, which contributes to the suppression of the immune system and cancer immune evasion. The PD-1/PD-L1 pathway mediates tumor immunosuppression by inhibiting T cell proliferation and inducing the activation of T cell apoptosis. To reverse tumor-mediated immunosuppression, anti-PD-1/PD-L1 antibodies have been designed to block the PD-L1/PD-1 interaction. Liu et al¹⁸² used GNS-mediated PTT combined with anti-PD-L1 to treat MB49 bladder cancer and achieved complete eradication of primary tumors and distant-untreated tumors (Figure 8). The cured mice received re-challenge of MB49

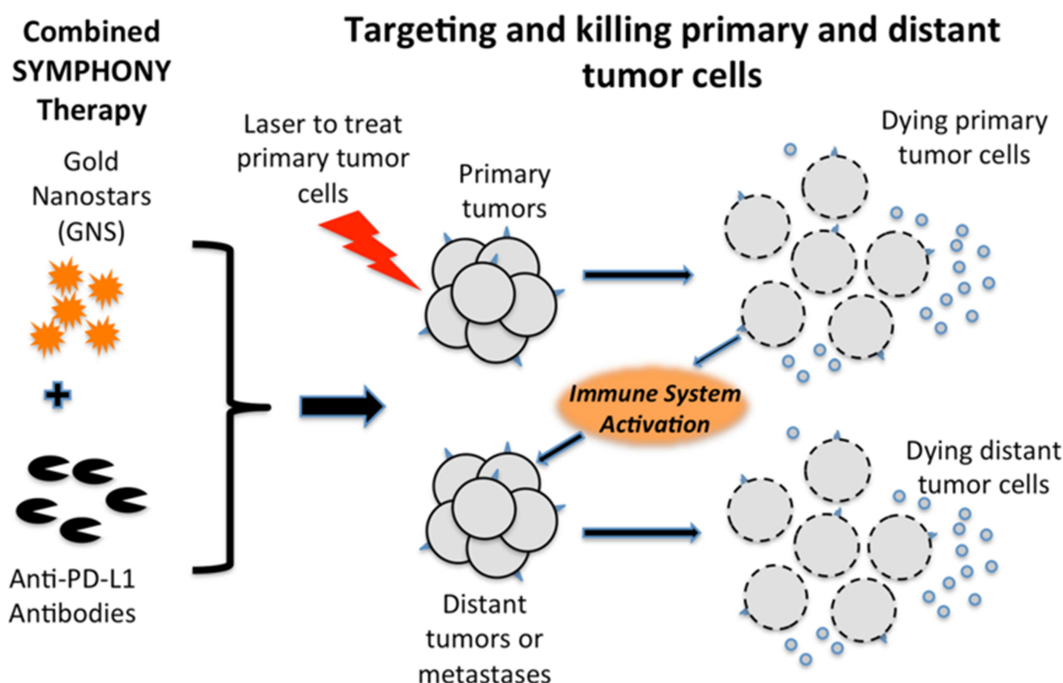


Figure 8 Schematic diagram of nanoparticle-based PTT together with anti-PD-L1. Reproduced from Liu Y, Maccarini P, Palmer GM, et al. Synergistic immuno photothermal nanotherapy (SYMPHONY) for the treatment of unresectable and metastatic cancers. *Sci Rep.* 2017;7(1):8606. Creative Commons license and disclaimer available from: (<http://creativecommons.org/licenses/by/4.0/legalcode>, <http://creativecommons.org/licenses/by/4.0/legalcode>).¹⁸²

cells and had no new tumor formation after 60 days, suggesting that the photothermal immunotherapy effectively induced long-term immunity to MB49 cells. Peng et al¹⁸³ used NIR dyes (IR820) chemotherapy drugs (docetaxel, DTX) to prepare nanoparticles with high drug-loading rates. In addition, a 27 amino acid polypeptide (named CF27) containing 12 units of amino acid PD-L1 agonist was introduced that could block the immune checkpoint PD-1/PD-L1 and self-crosslinking of drug-loading nanoparticles. Chemotherapy and PTT combined with PD-1/PD-L1 blockage led a much better therapeutic outcome, including more mice were cured and did not relapse for 90 days, indicating that the immune system could be stimulated during the treatment.

Moreover, combining the immunoadjuvant and immune checkpoint inhibitors for photothermal immunotherapy exhibited strong antitumor immune responses. Chen et al¹⁸⁴ developed a poly (lactic-co-glycolic acid) (PLGA)-based nanoparticle loaded with ICG and the immunoadjuvant R837. It is worth noting that the PLGA-ICG-R837 nanoparticles are composed of three clinically approved components and therefore have high clinical application potential. After laser irradiation, photothermal effects caused by ICG could generate TAAs that acted as vaccine. With the assistance of R837, the released antigen would be treated by DCs and presented to T cells, resulting in strong anti-tumor immunity.

Combined with anti-CTLA-4 antibody, the immunosuppressive activity of regulatory T cells could be inhibited. Animal experimental results showed that the combination therapy could not only effectively inhibit tumor metastasis in breast cancer (4T1) and colorectal cancer (CT26) murine models but also produced long-term immune memories (Figure 9). Li et al¹⁸⁵ designed a SWCNT modified by immunoadjuvant glycated chitosan (GC) and anti-CTLA-4 antibody to treat metastatic mammary tumors in mice. After 1064 nm laser irradiation, the primary tumor was ablation by PTT. The treatment activated the body's anti-tumor immunity, which inhibited lung metastasis and prolonged the animal's survival time. Anti-CTLA-4 antibody could suppress the activity of immunosuppressive regulatory T cells and further enhance the immune response. These results showed that the combination of PTT, immunoadjuvant and immune checkpoint inhibitors could effectively suppress primary tumors, inhibit metastases, and provide a new treatment strategy for metastatic cancers. Other existing photothermal nanomaterials combined with immune checkpoint inhibitors for photothermal immunotherapy are listed in Table 2.

PTT-Based Combinatorial Treatments

Combining PTT with other therapies has great potential to improve cancer treatment. A combination of two or more

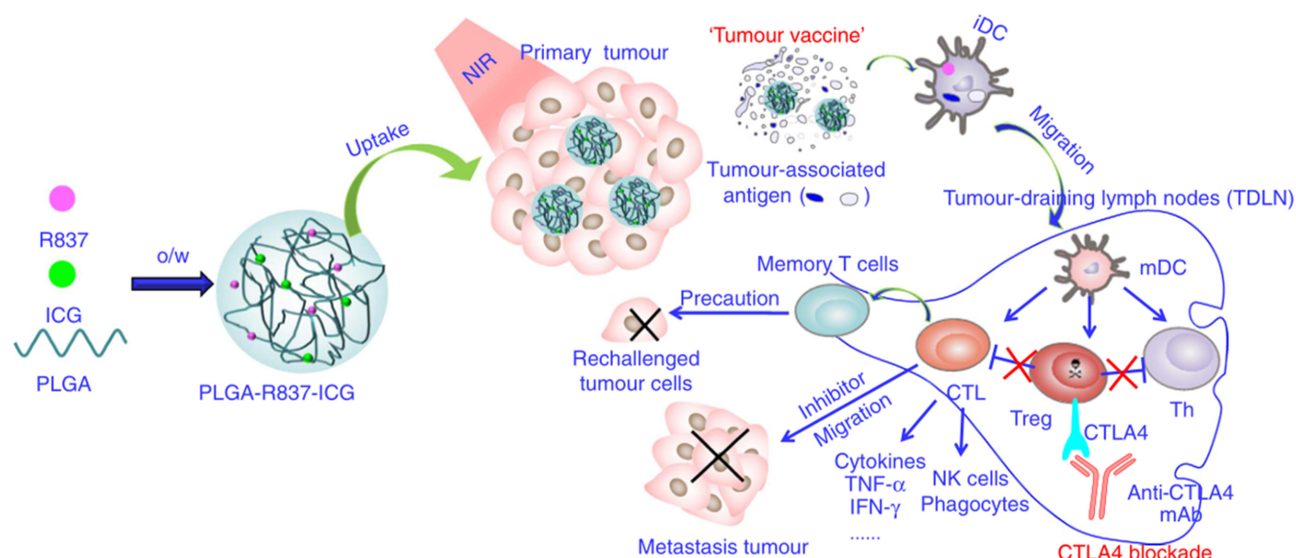


Figure 9 Schematic diagram of PTT with immunoadjuvant nanoparticles together with anti-CTLA-4. Reproduced with permission from Chen Q, Xu L, Liang C, et al. Photothermal therapy with immune-adjuvant nanoparticles together with checkpoint blockade for effective cancer immunotherapy. *Nat Commun.* 2016;7(1):13193. Creative Commons license and disclaimer available from: (<http://creativecommons.org/licenses/by/4.0/legalcode>, <http://creativecommons.org/licenses/by/4.0/legalcode>).¹⁸⁴

therapeutic modalities could help overcome the deficiencies of individual therapy. Some recent studies have found that PTT combined with other treatments can induce anti-tumor immunity to metastatic cancers. Nam et al¹⁸⁶ demonstrated that PTT combined with chemotherapy could trigger potent anti-tumor immunity against disseminated tumors. They developed a polydopamine-coated spiky gold nanoparticle (SGNP@PDA) combined with chemotherapy drug doxorubicin (DOX) for chemo-PTT. This stratagem could elicit robust anti-tumor responses and eliminate local as well as untreated distant tumors, leading to a remarkable survival rate of >85% in a bilateral murine tumor model of CT26 colon carcinoma. Moreover, treated animals exhibit long-term resistance against tumor re-challenge, indicating establishment of immunological memory against tumor recurrence. Jin et al¹⁸⁷ designed a multifunctional PC₁₀A/DOX/MoS₂ hydrogel for chemo-photothermal-photodynamic therapy of 4T1 tumor. The MoS₂ nanosheet in the hydrogel was simultaneously utilized as photothermal agent and photodynamic agent for the generation of hyperthermia and reactive oxygen species, respectively. After 808 nm laser irradiation, PC₁₀A/DOX/MoS₂ hydrogel could significantly increase the number of CD8⁺ and CD4⁺ T cells in lymph nodes to potentiate the anti-tumor immunity of the host. Most importantly, the activation of antitumor immune effects could suppress the growth of primary 4T1 breast tumors and distal lung metastatic nodules. These results demonstrated that the PC₁₀A/DOX/MoS₂ hydrogel

was promising to be utilized in antitumor immunity therapy triggered by photothermal therapy and photodynamic therapy for malignant tumor.

Summary and Future Outlook

In summary, nanomaterial-based photothermal immunotherapy has displayed encouraging treatment effects. It provides an alternative to traditional cancer treatment, due to its effectiveness in killing tumor cells, reversing drug resistance, minimizing the side effects on healthy cells as well as boosting the immune response. This article summarized the mechanism of nanomaterial-based PTT against cancer and how nanomaterial-based PTT impacts the tumor microenvironment and induces an immune response and the most recent progress regarding nanomaterial-based photothermal immunotherapy. Changes in the laser type, nanomaterials location and photothermal dose play key roles in the cell death mechanism of PTT. Another important role of PTT is causing the ICD of the tumor cell. ICD is characterized by the release of TAAs, DAMPs, and pro-inflammatory cytokines to facilitate the presentation of TAAs to adaptive immune cells, activating the antigen-specific immune response. However, PTT-induced ICD requires an appropriate thermal dose. The nanomaterial-based photothermal immunotherapy cures the cancers through the following mechanisms. First, tumor cells are killed by PTT; then TAAs are released to stimulate the system immune effect, thereby activating the immune effector cells. With the aid of immunoadjuvants or immune checkpoint inhibitors, an

Table 2 Photothermal Nanomaterials Combined with Immune Checkpoint Inhibitors for Photothermal Immunotherapy

Photothermal Nanoparticles	Checkpoint Blockade	Effector Cells	Cytokines	Tumors	References
Gold nanostar (GNS)	Anti-PD-L1	CD8 ⁺ T cells, CD4 ⁺ T cells, B cells	–	Murine bladder cancer cells MB49	[182]
Hollow gold nanoshell (HAuNS)	Anti-PD-I	CD8 ⁺ T cells, CD4 ⁺ T cells	TNF- α , IL-2, IFN- γ	Murine breast cancer cell 4T1, murine colon cancer cell CT26	[198]
Au@Pt nanoparticles	Anti-PD-L1	CD8 ⁺ T cells, CD4 ⁺ T cells	TNF- α , IL-6, IL-12p70, IFN- γ	Murine breast cancer cell 4T1	[199]
IR780 micelles	IDO	CD8 ⁺ T cells, CD4 ⁺ T cells	–	Murine breast cancer cell 4T1	[200]
ICG Hydrogel	Anti-PD-L1	DCs, CD8 ⁺ T cells	TNF- α , IL-6, IFN- γ	Murine breast cancer cell 4T1	[201]
NIR dyes IR820	Anti-PD-L1	CD8 ⁺ T cells, CD4 ⁺ T cells	TNF- α , IL-6, IL-12p70, IFN- γ	Murine breast cancer cell 4T1	[183]
IRDye800CW	Anti-PD-L1	CD8 ⁺ T cells	TNF- α , IL-2, IL-4, IL-6, IL-1 β , IFN- γ	Murine breast cancer cell 4T1	[202]
Single-walled nanotubes (SWNTs)	Anti-CTLA-4	DCs, CD8 ⁺ T cells, CD4 ⁺ T cells, CD20 ⁺ T cells	TNF- α , IL-6, IL-12, IL-1 β	Murine breast cancer cell 4T1, murine melanoma cell B16	[180]
Black phosphorus quantum dots (BPQDs)	Anti-PD-I	DCs, CD8 ⁺ T cells, CD4 ⁺ T cells	TNF- α , IFN- γ	Murine breast cancer cell 4T1, murine melanoma cell B16F10	[203]
Red blood cell membranes coated black phosphorus quantum dot nanovesicles (BPQD-RMNVs)	Anti-PD-I	DCs, CD8 ⁺ T cells, CD4 ⁺ T cells	TNF- α , IFN- γ	Murine breast cancer cell 4T1	[204]
Prussian blue nanoparticle (PBNP)	Anti-CTLA-4	CD8 ⁺ T cells, CD4 ⁺ T cells	–	Murine neuroblastoma cell Neuro2a	[181]
Hollow gold nanoshells (HAuNS)	Anti-PD-I	DCs, CD8 ⁺ T cells	TNF- α , IL-2, IL-12p70, IFN- γ	Murine breast cancer cell 4T1, murine colon cancer cell CT26	[205]
Reduced graphene oxide (rGO)-based nanosheets	Anti-PD-L1 and IDO	DCs, CD45 ⁺ leukocytes, CD8 ⁺ T cells, CD4 ⁺ T cells, NK cells	IFN- γ	Murine colon cancer cell CT26	[206]
Single-walled carbon nanotube (SWNT)	Anti-CTLA-4 and glycated chitosan (GC)	DCs, CD8 ⁺ T cells	IFN- γ	Murine breast cancer cell 4T1	[185]
Fe ₃ O ₄ -R837 spherical superparticles (SPs)SPs	Anti-PD-L1 and R837	DCs, CD8 ⁺ T cells, CD4 ⁺ T cells, NK cells, B cells	TNF- α , IL-6, IFN- γ	Murine breast cancer cell 4T1	[207]

(Continued)

Table 2 (Continued).

Photothermal Nanoparticles	Checkpoint Blockade	Effector Cells	Cytokines	Tumors	References
PLGA-ICG-R837	Anti-CTLA-4 and R837	DCs, CD8 ⁺ T cells	TNF- α , IL-6, IL-12p70, IFN- γ	Murine breast cancer cell 4T1, murine colon cancer cell CT26	[184]
PEG modified PDA loaded with carbon dots (PDA-PEG-CD)	Anti-PD-L1 and R848	CD8 ⁺ T cells	TNF- α , IFN- γ	Murine breast cancer cell 4T1	[208]

enhanced antitumor immunity can be achieved for the treatment of primary and metastatic tumors.

However, there remain some crucial challenges and opportunities for further and higher demand for the nanomaterial-based PPT agent in photothermal immunotherapy. Firstly, the safety and targeting of nanoparticle-based PTT must be considered, and the feasibility in deep tumors and metastatic tumors should be considered. The standardization of the treatment is also a big challenge, as researches are still at the laboratory stage, it is difficult to compare the effectiveness of different nanoparticle platforms from different laboratories. If the conditions of the treatments like the type of nanoparticles, the type of cancer, the laser intensity can be standardized, it will help accelerate the clinical transformation of this treatment. Moreover, the immune response caused by PTT in vivo is complex and its mechanisms are not fully clear. The intensity and controllability of the immune response must be emphasized. Furthermore, more research is needed to monitor the dynamic immune response and to understand the specific effects of each combination on TME, with the aim of providing guidance for individual patients to choose the best combination. Therefore, it is necessary to further study on further studies photothermal immunotherapy strategy based on nanoparticles. This new model has great potential to be an important complement to traditional cancer treatment strategies.

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Disclosure

The authors report no conflicts of interest in this work.

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