

REVIEW

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Programmable metal-based immuno-photocatalytic nanoparticles for precision activation of anti-tumor immunity

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Abstract

In spite of the introduction of cancer immunotherapy for improving tumor suppression, the modality of this revolutionary treatment has faced a number of challenges because of immune evasion, poor tumor immunogenicity, and resistance in solid tumors. To address these challenges, immuno-photocatalytic nanoparticles have been engineered to enable spatiotemporal activation of antitumor immunity by integrating phototherapy with immune modulation. These multifunctional nanoplatforms utilize photo- or ultrasound-responsive cores to generate reactive oxygen species (ROS), stimulate immunogenic cell death (ICD) and enhance the release of tumor-associated antigens. Simultaneously, these platforms allow for the co-delivery of immune checkpoint inhibitors and adjuvants to remodel the tumor microenvironment (TME), enhance dendritic cell maturation, and stimulate cytotoxic T lymphocyte activation. Advanced materials, such as titanium dioxide, copper sulfide, and manganese-based nanostructures, are functionalized with targeting ligands, biodegradable coatings, and diagnostic agents to improve selectivity, circulation time, and imaging capabilities. These nanoparticles also utilize tumor-specific features, such as acidic pH and hypoxia, to trigger controlled drug release and activate various synergistic pathways such as pyroptosis, ferroptosis, and cuproptosis. Preclinical models have shown their substantial effects on tumor suppression, immune activation, and prevention of metastasis with minimal systemic toxicity. Clinically, these nanoplatforms possess a significant potential in overcoming current therapeutic barriers to enable the minimally invasive and highly specific treatment of immunologically resistant tumors. Clinical translation depends on a number of factors including biosafety, large-scale production and regulatory compliance. Immuno-photocatalytic nanomedicine represents a versatile, programmable approach that can be adopted to advance personalized long-term cancer immunotherapy.

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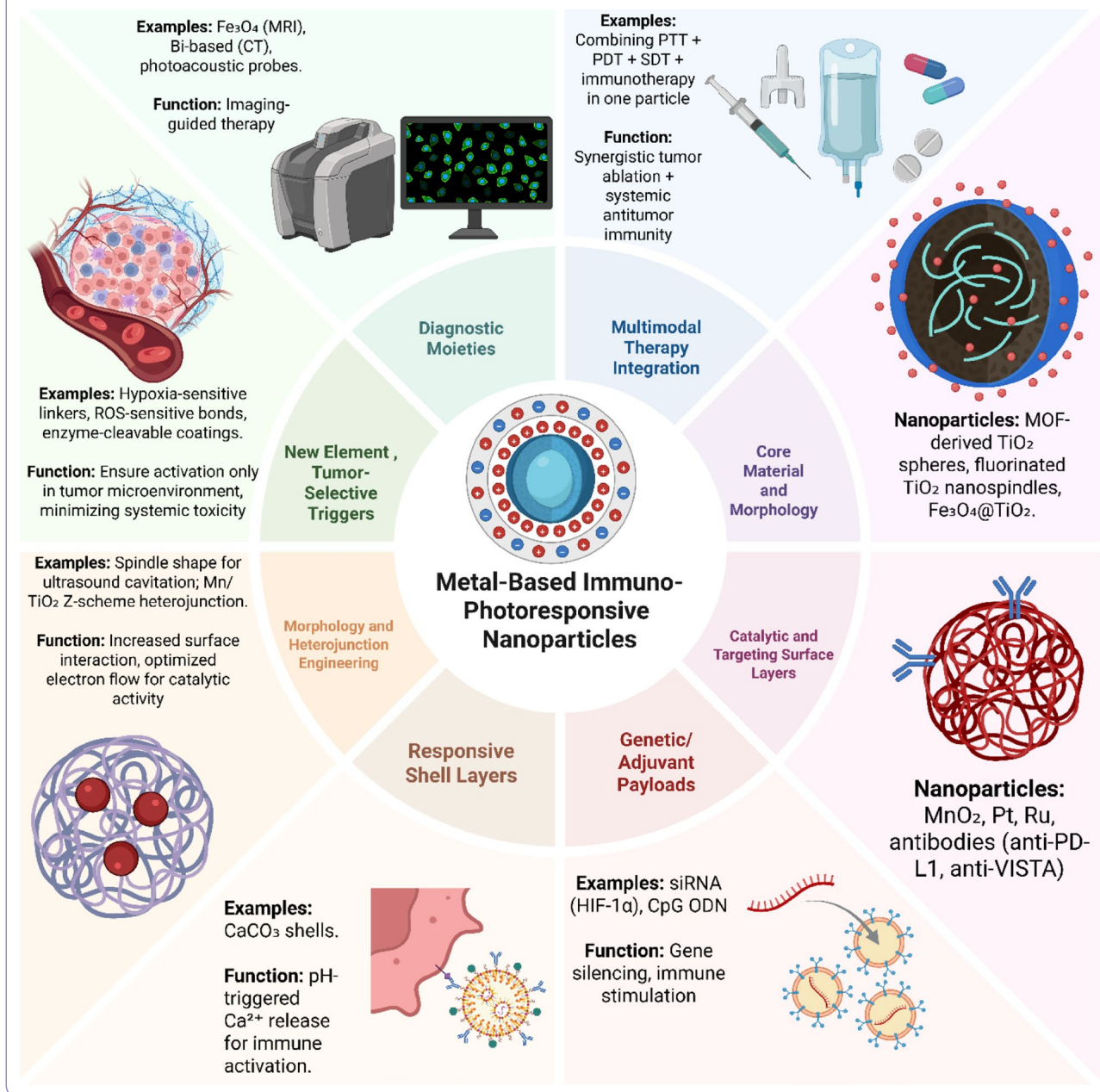


Highlights

- Nanoparticles enable spatiotemporal activation of immune responses via NIR or ultrasound.
- Synergistic induction of pyroptosis, ferroptosis, and cuproptosis enhances ICD.
- Dual-function platforms support both therapeutic and diagnostic (theranostic) applications.
- Tumor-selective release mechanisms minimize off-target toxicity.
- Promising preclinical results suggest a potential for clinical translation.

Keywords Immunogenic cell death, Photocatalytic nanoparticles, Tumor microenvironment, Cancer immunotherapy, Spatiotemporal drug delivery

Graphical Abstract



Questions:

- How can nanoparticle accumulation and activation be optimized in deep-seated or hypoxic tumors?
- What are the long-term immunological consequences of repeated nanoparticle-mediated activation?
- How can biosafety, biodegradability, and systemic clearance be standardized for clinical use?
- What is the optimal combination of adjuvants, checkpoint inhibitors, and photothermal agents for specific cancer types?
- How can real-time imaging be better integrated into therapeutic decision-making on these nanoplatforms?

Introduction

Cancer is still one of the leading causes of death worldwide and there are still challenges for its management in spite of the advances in diagnostic and therapeutic options. Traditional treatments including chemotherapy and radiotherapy demonstrate serious adverse impacts and encounter the problems in reducing cancer spread and recurrence. In recent years, immunotherapy has emerged as a promising alternative to cancer therapy, utilizing natural defences of body to identify and suppress tumor cells. Such approach is based on the comprehensive stimulation of immune responses that can attack primary and metastatic tumors, while potentially reducing tumor recurrence. Among current immunotherapies, various techniques such as CAR T-cell therapy, cancer vaccines, and immune checkpoint inhibitors have shown a massive potential. However, important limitations restrict their broader applications. Immune checkpoint inhibitors often fail in patients with non-immunogenic tumors, while CAR T-cell therapy faces difficulties in effectively treating solid tumors. These challenges highlight the pressing need for innovative strategies that can enhance the effectiveness of immunotherapy against cancer [1]. Although immunotherapy makes the treatment of cancer patients promising, the immune evasion and poor specificity of immunomodulators along with other limitations reduce its potential in cancer therapy. Therefore, nanomedicine has been introduced as a complementary approach to improving cancer immunotherapy.

One of the features of tumor cells is their capacity to suppress immunosurveillance and in this way, tumor microenvironment (TME) plays a significant function. The TME comprises tumor cells, stromal cells, immune cells, extracellular matrix, and interstitial fluid, all of which interact to facilitate tumor proliferation and immune evasion. Stromal cells reduce natural killer (NK) cells and cytotoxic T lymphocytes (CTLs) by enhancing immunological checkpoint markers such as PD-L1

and releasing immunosuppressive cytokines including TGF- β and IL-10. Moreover, tumor growth is exacerbated the immunosuppressive cell populations within the TME including myeloid-derived suppressor cells (MDSCs), regulatory T cells (Tregs), tumor-associated macrophages (TAMs), cancer-associated fibroblasts (CAFs), and dysfunctional dendritic cells (DCs). MDSCs restrict T-cell function by depleting arginine and generating nitric oxide, whereas Tregs modulate immunological responses via cytokine production, cytotoxic actions, and immune checkpoint expression. TAMs, frequently directed towards an M2 phenotype, facilitate angiogenesis and immune evasion, while DCs may become dysfunctional within the TME, thus impairing their capacity to activate antitumor immunity. CAFs facilitate tumor formation by releasing pro-tumorigenic molecules such as CXCL12 and TGF- β . Contemporary treatments, such as surgery, chemotherapy, and radiation, frequently do not completely eradicate malignancies and may also cause immunosuppression. Phototherapies, such as PDT and PTT, have enhanced selectivity and can activate anti-cancer immunity. Nonetheless, there are still challenges. Considering these limitations, nanoparticle-based methodologies are emerging as a viable strategy to augment cancer immunotherapy by enhancing drug delivery, altering the TME, and amplifying immune responses against neoplasms [2]. However, the development of novel and responsive nanoparticles can further improve the potential in immune system induction.

The limitations on cancer immunotherapy can be addressed by facilitating the targeted administration of immunomodulatory drugs, nucleic acids, and vaccines via nanoparticles. Their adjustable physical characteristics such as dimensions, morphology, charge, and surface ligands enable improved biodistribution, superior tumor targeting, and regulated immunogenicity. Nanoparticles can transport antigens directly to antigen-presenting cells, enhancing vaccination effectiveness and reducing tumor development in comparison to soluble antigens. They also enable transcutaneous vaccine administration by crossing the hydrophobic barrier in skin, allowing for DC recruitment and lymphatic transport. In nucleic acid-based therapeutics, nanoparticles protect DNA and RNA against degradation, addressing the constraints of free nucleic acids, including enzymatic destruction and inadequate cellular absorption due to charge repulsion. The siRNA-loaded nanoparticles have demonstrated their effectiveness in suppressing pro-tumor cytokines, whereas combination therapies, such as the co-delivery of tumor antigens, adjuvants, and gene-silencing RNAs, augment anticancer immune responses. Moreover, tumor lysate-loaded nanoparticles induce more robust DC activation and diminish tumor development compared to soluble lysates. In addition to vaccinations, nanoparticles

enable the concurrent silencing of numerous genes, as evidenced by the polyamine/lipid nanoparticles that target endothelial cell receptors. Their compatibility with imaging modalities, such as MRI utilizing iron oxide nanoparticles, facilitates real-time monitoring of therapy administration. Nonetheless, the usefulness of nanoparticles encounters challenges such as opsonization resulting in phagocytic clearance, inadequate penetration through biological barriers (the blood-brain barrier), and interstitial pressure within tumors impeding deep tissue diffusion. Upon reaching the target cells, nanoparticles frequently become ensnared in endolysosomal compartments, requiring sophisticated engineering to facilitate cytosolic or nuclear distribution of their payload. Notwithstanding these obstacles, nanoparticles possess a significant potential to transform cancer immunotherapy by improving precision, effectiveness, and combinatorial treatment approaches [3]. Therefore, it would be advantageous to introduce nanoparticles for improving cancer immunotherapy and suppressing immune evasion.

To address these emerging advances and challenges, this review aims to provide a comprehensive overview of immuno-photocatalytic nanoparticles as innovative agents for spatiotemporal activation of antitumor immunity. The focus is placed on the principles of design, functional mechanisms, and therapeutic potential of these nanoplatforms in modulating the TME, inducing immunogenic cell death (ICD), and in enhancing systemic immune responses. By systematically discussing various stimuli-responsive systems, synergistic death pathways, and immune-modulatory strategies, this review highlights the translational potential of multifunctional nanomedicine in cancer therapy. Particular attention is paid to the clinical implications, biosafety considerations, and future directions of further development and application of these technologies in personalized immunotherapy.

Design and synthesis of metal-based immuno-photoresponsive nanoparticles

Since the emergence of immunotherapy for the effective suppression of tumors, the design of materials as immuno-photoresponsive nanostructures has been accelerated, driving novelties in the field. In this regard, it has been shown that cancer immunotherapy can be enhanced by developing a multifunctional nanoplatform composed of metal-organic framework (MOF)-derived, oxygen-deficient titania nanoparticles (MCT_x NPs), designed to combine photodynamic and photothermal effects. These nanoparticles are derived from MIL-125 MOFs, whose conversion produces a porous titania structure abundant in oxygen vacancies, thus improving NIR absorption and photothermal efficiency. The surface is also adorned with manganese dioxide (MnO₂), with catalytic properties leveraged to diminish

intracellular glutathione, degrade endogenous hydrogen peroxide, and produce oxygen, thus mitigating hypoxia and enhancing ROS generation during treatment. This structural design facilitates high photothermal conversion, effective ROS production, and microenvironment modification, integrating tumor ablation with immune activation inside the singular, meticulously developed nanomaterial [4]. The design of nanomaterials can be further related to the induction of some specific biological mechanisms. A variety of cutting-edge nanomaterial was engineered in the form of fluorinated titanium oxide nanospindles (TiO_{2-x}F_x NSs), and was precisely tailored to function as ultrasound-responsive mediators of pyroptosis. This structural and compositional synergy enables the nanospindles to transduce ultrasound into localized mechanical and biochemical cues, activating the caspase-3/GSDME pathway and initiating proinflammatory pyroptotic cell death. Through this design, the material not only serves as a potent cell-killing agent but also as an immune activator, bridging physical stimulus responsiveness with precise immunomodulation in cancer therapy [5].

Along with such designs, it would be beneficial to develop nanomaterials suitable for the delivery of genes. The TiO₂@Ru@siRNA nanocomposite was precisely designed as a hypoxia-adaptive therapeutic platform, combining structural, photonic, and genetic functions into one platform. TiO₂ nanoparticles serve as a durable, biocompatible scaffold with elevated surface reactivity, facilitating effective ROS production upon light stimulation. These cores are adorned with a ruthenium-based photosensitizer, due to its dual Type I/Type II photodynamic efficacy, causing substantial ROS generation even under hypoxic conditions. The whole assembly is enveloped with siRNA aimed at hypoxia-inducible factor-1 α (HIF-1 α), with the nanoparticle design optimized for lysosomal evasion and cytoplasmic siRNA release in response to light-induced oxidative stress. This multi-layered material design enables effective photodynamic action and reprograms the TME at the genetic level simultaneously, integrating photochemistry with gene silencing for enhanced immunotherapeutic results [6].

The CaCO₃@Pt-TiO₂ (CaPT) nanocomposite was designed as a TME-responsive platform that integrates oxygen regulation, oxidative stress enhancement, and calcium-mediated immune activation into a single material system. As the principal sonosensitizing agent, TiO₂ is capable of producing ROS upon ultrasonic stimulation. Closely integrated into the TiO₂ surface, platinum nanoparticles function as catalytic enhancers to increase ROS production and degrade endogenous hydrogen peroxide, thereby mitigating hypoxia that usually constrains the effectiveness of sonodynamic therapy (SDT). A calcium carbonate shell encircles this core, serving as both a

structural element and a TME-responsive calcium store, which could dissolve in acidic TME to release substantial Ca^{2+} . A combination of this release with ROS stress induces ICD, whereas the hierarchical structure enables the spatially coordinated activation of each element. This design illustrates a multifunctional, stimulus-responsive nanoplatform on which each component fulfills a unique but synergistic purpose to achieve effective, hypoxia-resistant sonodynamic immunotherapy [7].

Along with the combination of therapies, these strategies can also be combined with imaging. The $\text{Fe}_3\text{O}_4@ \text{TiO}_2@ \text{VISTA mAb}$ (FTV) nanoplatform was also designed as a multifunctional core-shell system to combine imaging, SDT, and targeted immune checkpoint inhibition. The Fe_3O_4 core exhibits superparamagnetic characteristics, facilitating high-sensitivity MRI for accurate tumor identification and therapy assessment. This is enclosed within a TiO_2 shell, thereby triggering ICD and stromal disruption. The shell surface is also coupled with VISTA monoclonal antibodies, facilitating the selective binding to VISTA-overexpressing pancreatic cancer cells and ensuring that checkpoint suppression is confined to the TME. The hierarchical structure enables Fe_3O_4 to serve as an imaging agent, TiO_2 as a therapeutic ROS generator, and VISTA mAb as an immune modulator, which are combined to overcome stromal barriers and enhance the effectiveness of sonodynamic immunotherapy [8].

Multifunctional metal-based immuno-photoresponsive nanoplatforms have been engineered through precise structural, compositional, and surface modifications to integrate photothermal, photodynamic, and immuno-modulatory effects for cancer therapy. Various frameworks, such as MOF-derived oxygen-deficient titania, fluorinated TiO_2 nanospindles, and core-shell TiO_2 composites decorated with catalytic metals (MnO_2 , Pt, Ru), are applied to enhance light or ultrasound responsiveness, improve ROS generation, and modulate the TME by depleting glutathione, decomposing H_2O_2 , and alleviating hypoxia. Additional functionalities are incorporated via pH-sensitive shells (CaCO_3) for the release of immunostimulatory ions, or through the conjugation with nucleic acid payloads (siRNA) to silence key genes such as HIF-1 α , thereby promoting immune activation under hypoxic conditions. Targeting elements, including immune checkpoint antibodies (anti-PD-L1, anti-VISTA) and adjuvants (CpG ODN), are attached to direct nanoparticles toward tumor or immune cells, while diagnostic moieties (Fe_3O_4 , Bi-based agents) are included to enable MRI, CT, or photoacoustic imaging for treatment monitoring. Morphological tuning, such as the formation of spindle shapes for enhanced ultrasound cavitation efficiency, and heterojunction engineering, such as Mn/ TiO_2 Z-scheme systems, are performed

to optimize electron-hole separation for the maximum catalytic activity. By integrating tumor-selective triggers, multimodal therapeutic mechanisms (ICD, pyroptosis, ferroptosis, cuproptosis), and immune potentiation strategies, these nanomaterials are designed to ablate primary tumors and stimulate systemic antitumor immunity with the minimum systemic toxicity, reflecting a meticulous and programmable approach to materials development for advanced cancer photoimmunotherapy. These considerations given to material selection and design would be discussed specifically with details in Sect. 4. Figure 1 demonstrates the different designs of nanoparticles.

Mechanism of action

In biological assessments, the MCT_x nanoparticles subjected to near-infrared radiation (NIR) irradiation elicit significant tumor cell cytotoxicity, causing TME remodelling through GSH depletion, H_2O_2 degradation and hypoxia alleviation to stimulate ICD. Such event can accelerate DC maturation (upregulation of $\text{CD}^{80}/\text{CD}^{86}$), increase infiltration of cytotoxic T lymphocytes ($\text{CD}^{3+}\text{CD}^{8+}$), reduce Tregs, and enhance the levels of TNF- α and IFN- γ . In a murine melanoma model, the combination of anti-PD-L1 therapy inhibits both primary and distant rechallenged tumors with no systemic damage, indicating robust and safe immune activation for cancer treatment [4]. In addition to the direct regulation of immune cells, there has been a focus on the regulation of cell death pathways for enhancing cancer immunotherapy. $\text{TiO}_{2-x}\text{F}_x$ nanospindles trigger ultrasound-induced pyroptosis via the caspase-3/GSDME pathway, leading to elevated pyroptosis markers (cleaved GSDME, IL-1 β), DC maturation, and enhanced cytotoxic T cell infiltration. When combined with anti-PD-1 therapy, they suppress both primary and distant tumors, induce long-term immune memory, and show minimal toxicity, demonstrating a strong potential in overcoming immunotherapy resistance [5]. Since biological science is essential for understanding the genes and other factors involved in tumorigenesis, the genetic tools can be loaded on nanoplatforms to further suppress cancer progression. $\text{TiO}_2@ \text{Ru}@ \text{siRNA}$ nanocomposites integrate ROS generation with HIF-1 α silencing to alleviate hypoxia, downregulate PD-L1/NF- κB , enhance IL-24 secretion, stimulate CD^{4+} and CD^{8+} T cells, and trigger pyroptosis through GSDMD and caspase-1 activation, therefore transforming the tumor immunological microenvironment. This method significantly suppresses tumor development and malignant transformation in PDX and 4NQO-induced OSCC models without causing systemic toxicity, demonstrating a substantial potential for hypoxia-adaptive photodynamic immunotherapy [6].

BB-A-P nanorods, a variety of Z-scheme heterostructured semiconductor, produce O_2 , singlet oxygen, and

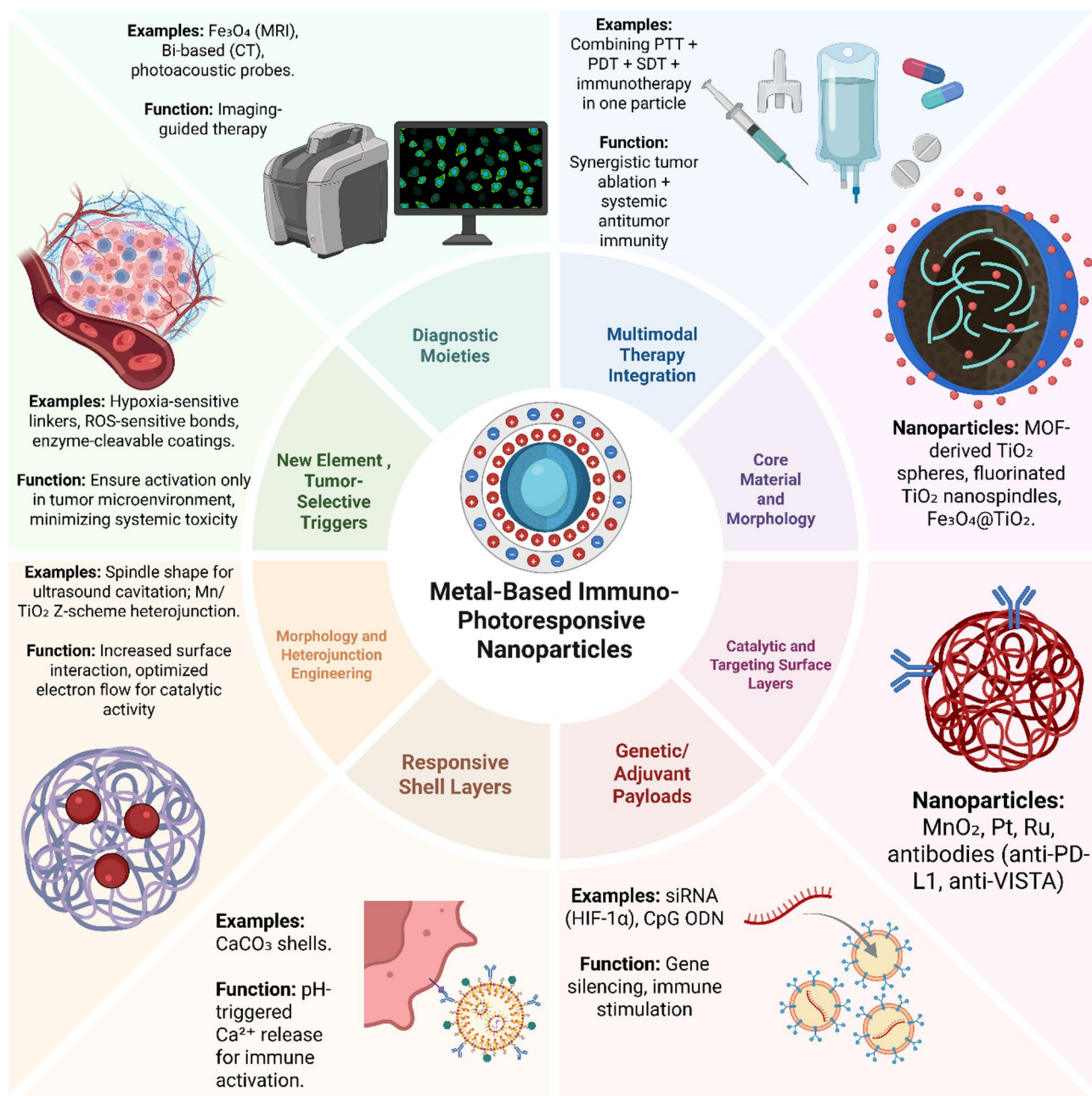


Fig. 1 The different designs of materials. The schematic diagram illustrates the programmable engineering of multifunctional immuno-photoresponsive nanoplatforms for cancer therapy. The core material and morphology are tailored for optimized light or ultrasound responsiveness, while catalytic and targeting surface layers enhance reactive oxygen species generation, relieve hypoxia, and achieve immune checkpoint inhibition. Genetic and adjuvant payloads are indicated for tumor microenvironment reprogramming, while responsive shell layers are depicted for pH-triggered ion release. Diagnostic moieties are incorporated to enable imaging-guided therapy, with morphology/heterojunction engineering demonstrated for improved catalytic performance. Tumor-selective triggers confine therapeutic activation within the tumor site, while multimodal therapy integration combines photothermal, photodynamic, sonodynamic, and immunotherapeutic effects. All features are shown to converge toward synergistic tumor ablation and systemic immune activation, emphasizing the coordinated material design. Abbreviations: SDT represents sonodynamic therapy; PTT represents photothermal therapy; PDT represents photodynamic therapy; MOF represents metal-organic framework; TiO₂ represents titanium dioxide; PD-L1 represents programmed cell death Ligand 1; HIF-1α represents hypoxia inducible factor-1α; MRI represents magnetic resonance imaging; and CT represents computed tomography. (Created with Biorender.com)

hydroxyl radicals when exposed to NIR light, triggering apoptosis and Caspase-1/GSDMD-mediated pyroptosis, which results in the release of DAMPs, facilitates ICD, and amplifies antitumor immunity. In addition to modifying the hypoxic TME, they enable CT imaging for therapeutic monitoring, which is a synergistic and biocompatible solution to hypoxia malignancies [9]. Bi₂S₃ nanorods function as contrast agents for CT/PA imaging and radiosensitizers, where the photothermal heating during radiotherapy enhances tumor oxygenation, diminishes HIF-1 α expression, and suppresses DNA repair by downregulating the proteins associated with repair mechanisms. This synergistic hyperthermia-radiotherapy method decreases angiogenesis, suppresses tumor development, and improves the effectiveness of treatment while demonstrating significant biocompatibility [10].

The multifunctional immuno-photocatalytic nanoparticles function through a coordinated interaction of physical, chemical, and immunological mechanisms that collectively reprogram the TME and stimulate systemic antitumor immunity. Upon targeted accumulation in tumors, photo- or ultrasound-responsive cores, such as oxygen-deficient TiO₂, fluorinated TiO₂ nanospindles, or bismuth- and copper-based heterostructures, absorb external stimuli (NIR light, ultrasound, X-rays) to generate ROS via photodynamic, sonodynamic, or chemodynamic processes. Catalytic components including MnO₂ and Pt deplete intracellular glutathione and decompose H₂O₂ to relieve hypoxia, while pH-responsive shells (CaCO₃) or redox-responsive matrices release immunomodulatory ions (Ca²⁺, Zn²⁺, Mn²⁺, Cu²⁺) in situ, further amplifying oxidative stress. These events initiate various forms of programmed cell death, including ICD, pyroptosis, ferroptosis, and cuproptosis, which are characterized by calreticulin exposure, HMGB1 release, ATP secretion, inflammasome activation, and pro-inflammatory cytokine production (TNF- α , IFN- γ , IL-1 β , IL-24). Concurrently, genetic and metabolic modulators (siRNA against HIF-1 α , PD-L1 downregulation, TAM repolarization, glycolytic inhibition) reshape the TME from immunosuppressive “cold” to inflamed “hot”, which enhances DC maturation (CD⁸⁰/CD⁸⁶ upregulation) and promotes infiltration and activation of cytotoxic CD⁸⁺ T lymphocytes while reducing Tregs and MDSCs. Certain designs incorporate immune checkpoint inhibitors (anti-PD-1/PD-L1, anti-VISTA) or adjuvants (CpG ODN) to further boost T cell responses, while imaging moieties (Fe₃O₄ for MRI, Bi-based for CT/PA) enable real-time treatment guidance. Therefore, these nanoparticles integrate tumor-selective activation, multi-modal cell-killing, microenvironment modulation, and immune potentiation into a single programmable platform, which suppresses primary and metastatic tumors sustainably with the minimum systemic toxicity. Detailed information

can be found in Sect. 4 where in-depth discussion will be conducted from the perspectives of material design and biological results. Figure 2 demonstrates the mechanism of action for these nanoparticles in cancer therapy.

Nanoparticle classification

Photo-structures

Metal oxides

Cancer immunotherapy has revolutionized the treatment of malignant tumors by harnessing the immune system of human body to target cancer cells, but its clinical efficacy remains limited due to poor immune responses and the presence of an immunosuppressive TME. To address these challenges, the strategies that induce ICD and remodel the TME are required to enhance immune activation and therapeutic outcomes. A new multifunctional nanopatform utilizing MOF-derived oxygen-deficient titania nanoparticles (MCT_x NPs) was designed to improve the effectiveness of cancer immunotherapy via a strategy integrating PDT and PTT. The nanoparticles were synthesized from MIL-125 MOFs and modified with oxygen vacancies and surface-deposited manganese dioxide (MnO₂), facilitating the effective absorption of NIR light and the production of ROS, including singlet oxygen (¹O₂) and hydroxyl radicals ($\cdot$ OH), upon 808 nm laser irradiation. A photothermal conversion efficiency of 37.9% was achieved, with temperature elevated by 46.2 °C, which depends on laser intensity and nanoparticle concentration. The MCT_x NPs demonstrated significant cytotoxicity against tumor cells in vitro, reducing viability under NIR irradiation and preserving biocompatibility with healthy cells simultaneously. The TME was altered by depleting GSH and catalytically decomposing hydrogen peroxide (H₂O₂), resulting in oxygen production and the mitigation of hypoxia. These modifications facilitated ICD, stimulated DC maturation (with CD⁸⁰/CD⁸⁶ expression), augmented cytotoxic T lymphocyte (CTL, CD³⁺CD⁸⁺) infiltration, diminished Tregs, and upregulated immune cytokines including TNF- α and IFN- γ . In conjunction with anti-PD-L1 checkpoint blockade treatment, MCT_x NPs achieved tumor suppression in primary tumors and in distant rechallenged tumors within mouse melanoma models, demonstrating partial systemic toxicity. A robust and secure approach was proposed to enhance anti-tumor immunity and overcome immunosuppressive obstacles, showing a significant potential for cancer photoimmunotherapy (Fig. 3) [4].

As a kind of programmed necrosis characterized by gasdermin-induced membrane rupture, pyroptosis is predominantly initiated by the activation of inflammatory caspases, including caspase-1, -4, -5, and murine caspase-11, in reaction to microbial infections or danger signals. Caspases cleave gasdermin D (GSDMD) to release its N-terminal fragment (GSDMD-NT), which

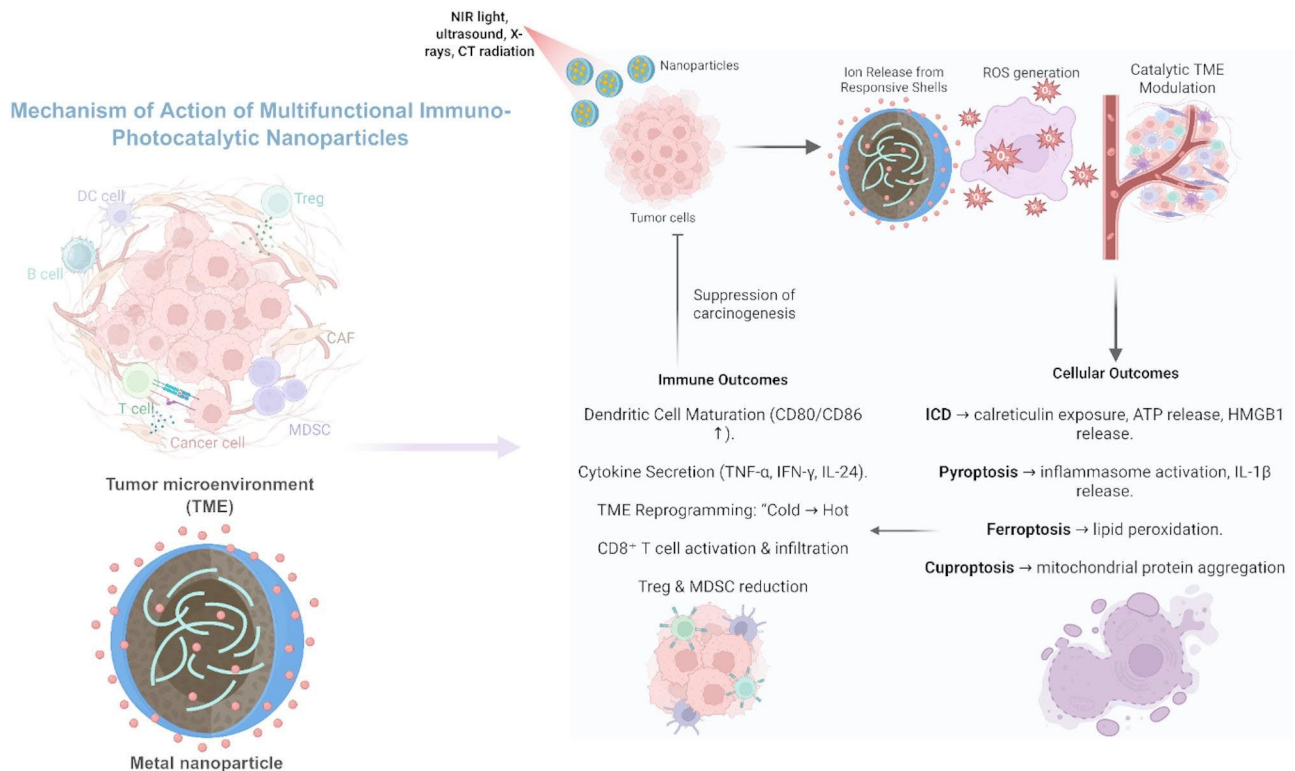


Fig. 2 The mechanism of action of nanoparticles. The figure illustrates the coordinated mechanism of action of multifunctional immuno-photocatalytic nanoparticles in cancer therapy. After selective accumulation within the tumor, the nanoparticles are activated by external stimuli such as near-infrared light, ultrasound, or X-ray, triggering the generation of reactive oxygen species via photodynamic, sonodynamic, or chemodynamic pathways. Catalytic components deplete intracellular glutathione, decompose hydrogen peroxide, and alleviate hypoxia, while pH- or redox-responsive shells release immunomodulatory ions such as Ca^{2+} , Mn^{2+} , or Cu^{2+} . These processes induce multiple forms of programmed cell death, including immunogenic cell death, pyroptosis, ferroptosis, and cuproptosis, accompanied by calreticulin exposure, ATP release, and pro-inflammatory cytokine secretion. The release of danger signals and cytokines promotes dendritic cell maturation, cytotoxic $\text{CD}8^+$ T lymphocyte infiltration, and the suppression of regulatory T cells and myeloid-derived suppressor cells, effectively reprogramming the tumor microenvironment from an immunosuppressive "cold" state to an inflamed "hot" state. The combined effects of direct tumor cell killing and systemic immune activation result in a sustainable regression of primary tumors, inhibition of metastases, and establishment of long-term antitumor immunity. Abbreviations: TME, tumor microenvironment; NIR, near-infrared radiation; CT, computed tomography; ROS, reactive oxygen species; ICD, immunogenic cell death; ATP, adenosine triphosphate; IL, interleukin; HMGB1, high mobility group box 1 protein; TNF, tumor necrosis factor; IFN, interferon; Treg, regulatory T cell; MDSC, myeloid-derived suppressor cell. (Created with Biorender.com)

binds specific phospholipids, such as phosphatidylinositol phosphates, phosphatidylserine, cardiolipin and oligomerizes, to form membrane pores, resulting in cell swelling, lysis, and the release of pro-inflammatory cytokines, including IL-1 β . This technique is applicable to eliminate infected cells internally without damaging adjacent human cells and eradicate bacteria directly in vitro. In addition to infection control, pyroptosis is also investigated in cancer treatment, with approaches such as acid-activatable nanophotosensitizers used to selectively trigger pyroptotic death in gasdermin-E-positive cancer cells, which allows for adjustable cytotoxicity while reducing systemic harm. More information on pyroptosis can be found in these studies [11–13]. The activation of ICD by novel therapeutic approaches has attracted considerable interest as a strategy to enhance antitumor immunity and optimize the outcome of cancer immunotherapy. Among such techniques, pyroptosis

as a proinflammatory variant of programmed cell death has demonstrated a significant potential in transforming immunologically "cold" malignancies into "hot" tumors by augmenting immune cell infiltration and cytokine secretion. In this regard, a unique nanoplatform consisting of fluorinated titanium oxide nanospindles ($\text{TiO}_{2-x}\text{F}_x$ NSs) was established to serve as the ultrasound-responsive inducers of pyroptosis for cancer immunotherapy. The nanospindles effectively produced cavitation effects under low-intensity ultrasound, resulting in the activation of the caspase-3/GSDME pathway and ensuing pyroptotic cell death. The increased expression of pyroptosis markers (such as cleaved GSDME and IL-1 β) was observed, and it was accompanied by substantial dendritic cell maturation ($\text{CD}86^+\text{CD}11c^+$) and heightened infiltration of cytotoxic T lymphocytes ($\text{CD}8^+$ T cells) inside the TME. In conjunction with anti-PD-1 treatment, $\text{TiO}_{2-x}\text{F}_x$ NSs demonstrated a significant inhibitory

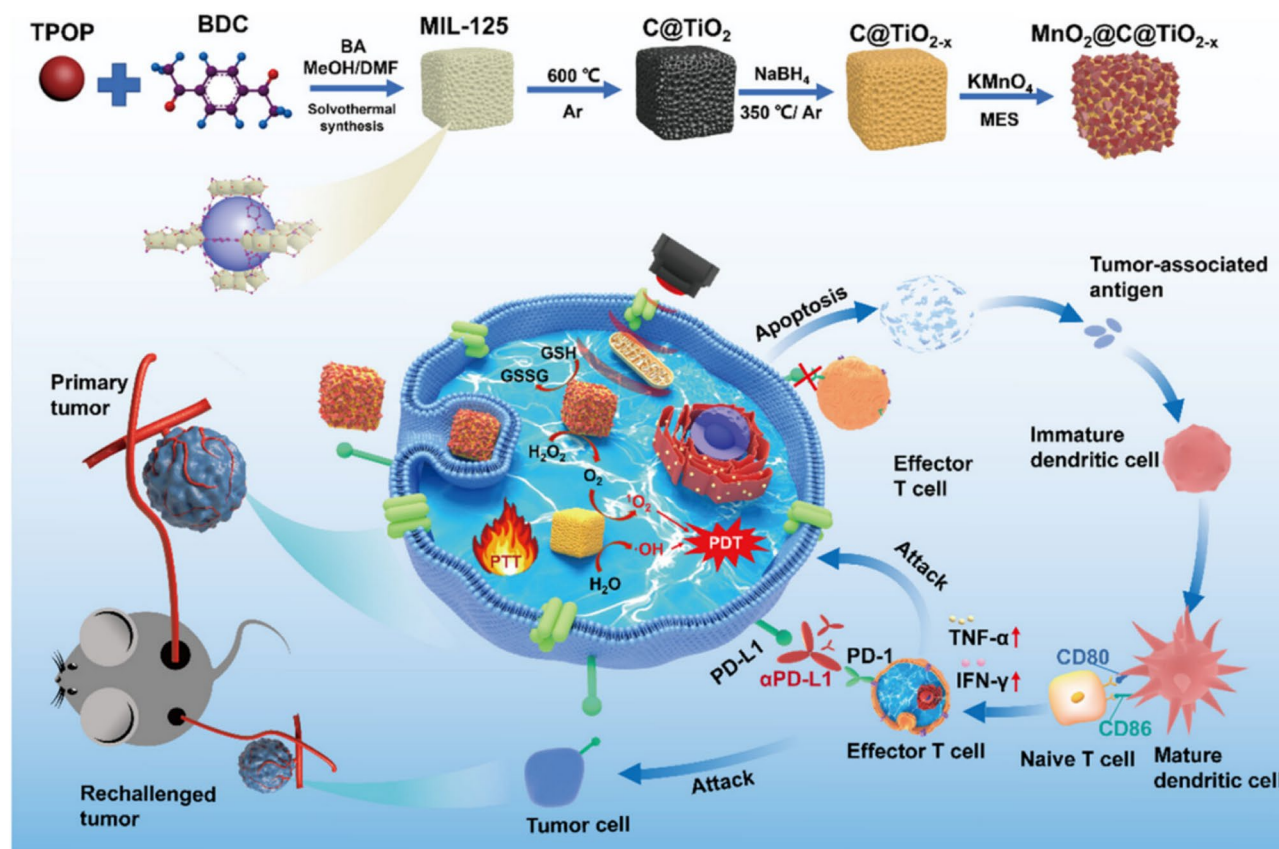


Fig. 3 The preparation of MCTx nanoparticles and their application in photodynamic/photothermal-enhanced immunotherapy for tumors. Abbreviations: BDC represents terephthalic acid; BA represents benzoic acid; DMF represents N, N-dimethylformamide; TiO_2 represents titanium dioxide; GSH represents glutathione; GSSG represents glutathione disulphide or oxidized glutathione; PD-L1 represents programmed death Ligand 1; $\text{TNF-}\alpha$ represents tumor necrosis factor- α ; $\text{IFN-}\gamma$ represents interferon- γ ; And MES represents 2-(N-Morpholino) ethanesulfonic acid. Reprinted with permission from ACS [4]

effect on primary tumors and in distant tumors, while providing enduring immunological memory and exhibiting low damage. These findings highlight the potential of ultrasound-induced pyroptosis as an effective approach to immune response enhancement and cancer immunotherapy [5].

A hypoxia-adaptive nanocomposite, known as $\text{TiO}_2@ \text{Ru@siRNA}$, was developed for the efficient photo-immunotherapy of oral squamous cell carcinoma (OSCC), addressing the difficulties presented by the hypoxic and immunosuppressive milieu in tumors. This multifunctional system is comprised of TiO_2 nanoparticles modified with a ruthenium-based photosensitizer and encapsulated with siRNA targeting HIF-1 α . Upon the exposure to visible light, the nanoparticles produce ROS via both Type I and Type II photodynamic mechanisms, which results in lysosomal degradation and facilitating the cytoplasmic release of siRNA, thus silencing HIF-1 α and mitigating hypoxia. This mechanism reduced the expression of PD-L1 and NF- κB , increased the production of immunostimulatory cytokines including IL-24, and led to the significant activation of CD^4^+ and CD^8^+ T cells, thereby transforming the immunological milieu.

The therapy further caused pyroptosis through the over-expression of GSDMD and cleaved caspase-1, further enhancing antitumor immunity. The in vivo investigations conducted using patient-derived xenograft (PDX) And 4NQO-induced rat models have revealed a substantial inhibitory effect on tumor proliferation and malignant transformation without systemic damage. This nanoplatform presents a therapeutically applicable method to improve the effectiveness of photodynamic immunotherapy in OSCC (Fig. 4) [6].

Ultrasound (US)-activated SDT has emerged as a potential oncological therapeutic modality, due to its high accuracy, sufficient tissue penetration, and few adverse effects. Nonetheless, its efficacy is frequently constrained by the hypoxic characteristics of the TME and the intrinsically poor quantum yield of traditional sonosensitizers. Recent attention has been directed to the ICD induced by calcium ion excess, since it might elicit robust anticancer immune responses and facilitate the remodeling of the tumor immunological microenvironment (TIM). To tackle these issues, a TME-responsive nanocomposite, known as $\text{CaCO}_3@ \text{Pt-TiO}_2$ (designated as CaPT), was synthesized by amalgamating calcium

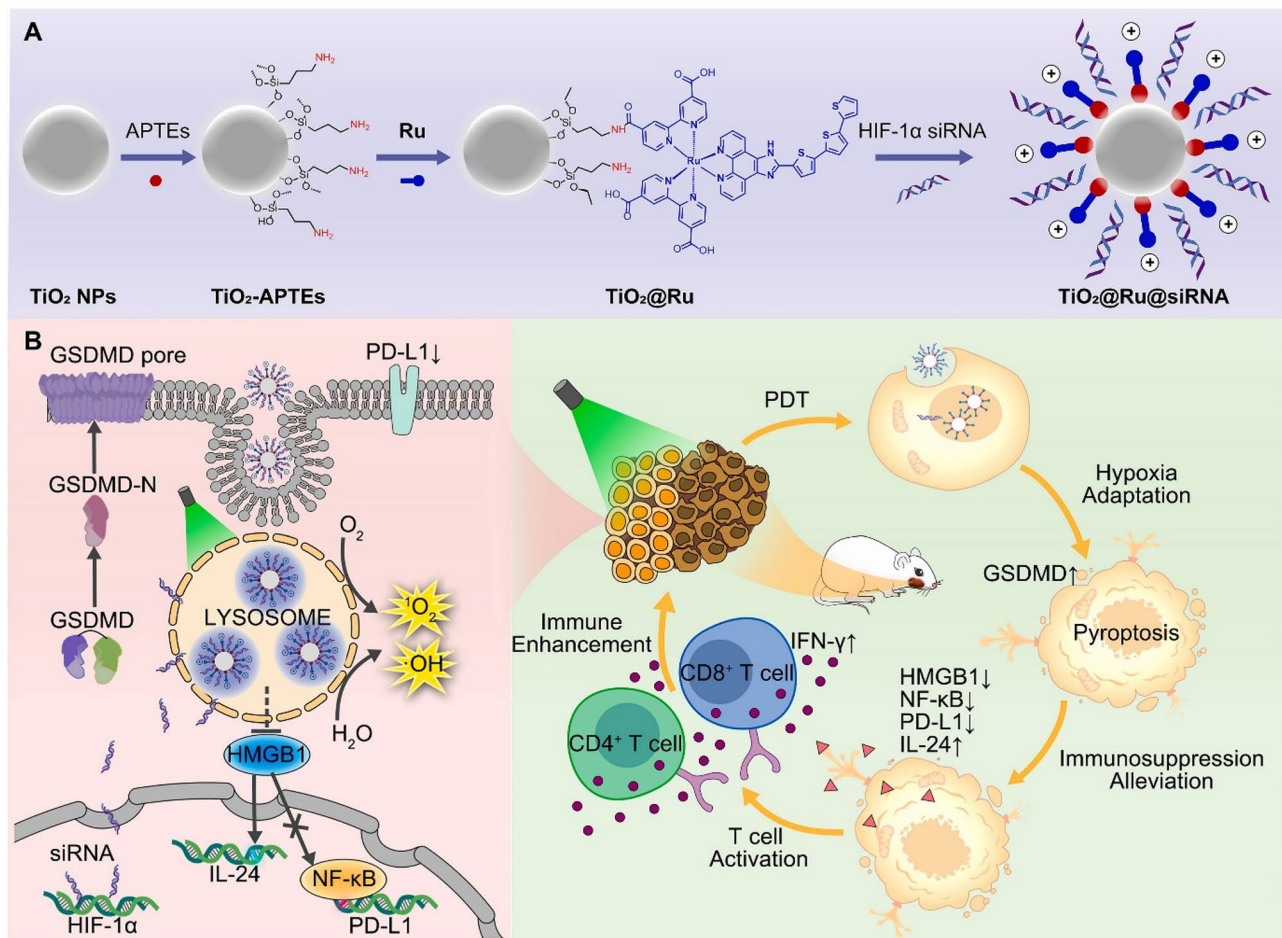


Fig. 4 (A) Fabrication of the nanocomposite $\text{TiO}_2\text{@Ru@siRNA}$. (B) The mechanism of action for $\text{TiO}_2\text{@Ru@siRNA}$. Abbreviations: ROS represents reactive oxygen species; HIF-1 α represents hypoxia-inducible factor-1 α ; HMGB1 represents high mobility group box-1 protein; NF- κ B represents nuclear factor-kappa B; PD-L1 represents programmed death ligand-1; IL-24 represents interleukin-24; GSDMD represents gasdermin D; PDT represents photodynamic treatment; and IFN- γ represents interferon gamma. Reprinted with permission from Elsevier [6]

carbonate (CaCO_3) and platinum (Pt) nanoparticles with TiO_2 . This combination amplifies oxidative stress in tumor cells to optimize sonodynamic immunotherapy. The Pt nanoparticles enhance the ROS production by TiO_2 during SDT and facilitate the breakdown of H_2O_2 to mitigate tumor hypoxia. In reaction to the TME, CaPT releases calcium ions in large quantities, thus exacerbating oxidative stress and facilitating pronounced ICD. This results in increased immune cell infiltration and converts the tumor TME from immunologically “cold” to “hot.” Both in vitro and in vivo studies have validated the enhanced therapeutic benefits of this combination sonodynamic-immunotherapy, while RNA sequencing has clarified its fundamental anticancer processes [7]. It is a significant challenge in pancreatic cancer immunotherapy to address the restricted permeability of immune checkpoint inhibitors (ICIs) caused by the thick stromal barrier and counteract the immunosuppressive TME. A core-shell nanoplatform consisting of $\text{Fe}_3\text{O}_4\text{@TiO}_2$ nanoparticles was engineered to encapsulate VISTA

monoclonal antibodies, with $\text{Fe}_3\text{O}_4\text{@TiO}_2\text{@VISTA mAb}$ (FTV) yielded. These nanoparticles were engineered to selectively target the overexpressed immunological checkpoint protein VISTA in pancreatic cancer, with the aim to improve magnetic resonance imaging (MRI)-guided SDT-enhanced immunotherapy. Experimental results were obtained through laser confocal microscopy and flow cytometry to validate that FTV nanoparticles are proficiently identified and ingested by Panc-2 tumor cells. In vivo investigations revealed that ultrasound-activated TiO_2 -based SDT causes ICD, facilitates the release of DAMPs, and augments T-cell infiltration into the TME. Furthermore, ultrasonic exposure disturbed the thick fibrotic stroma and enhanced tumor vascularization, thus augmenting the efficacy of immune treatments (Fig. 5) [8].

SDT provides targeted and non-invasive benefits for the treatment of solid tumors, whilst immune checkpoint blockade therapy, including anti-PD-L1 antibodies (aPD-L1), shows a significant potential for cancer treatment.

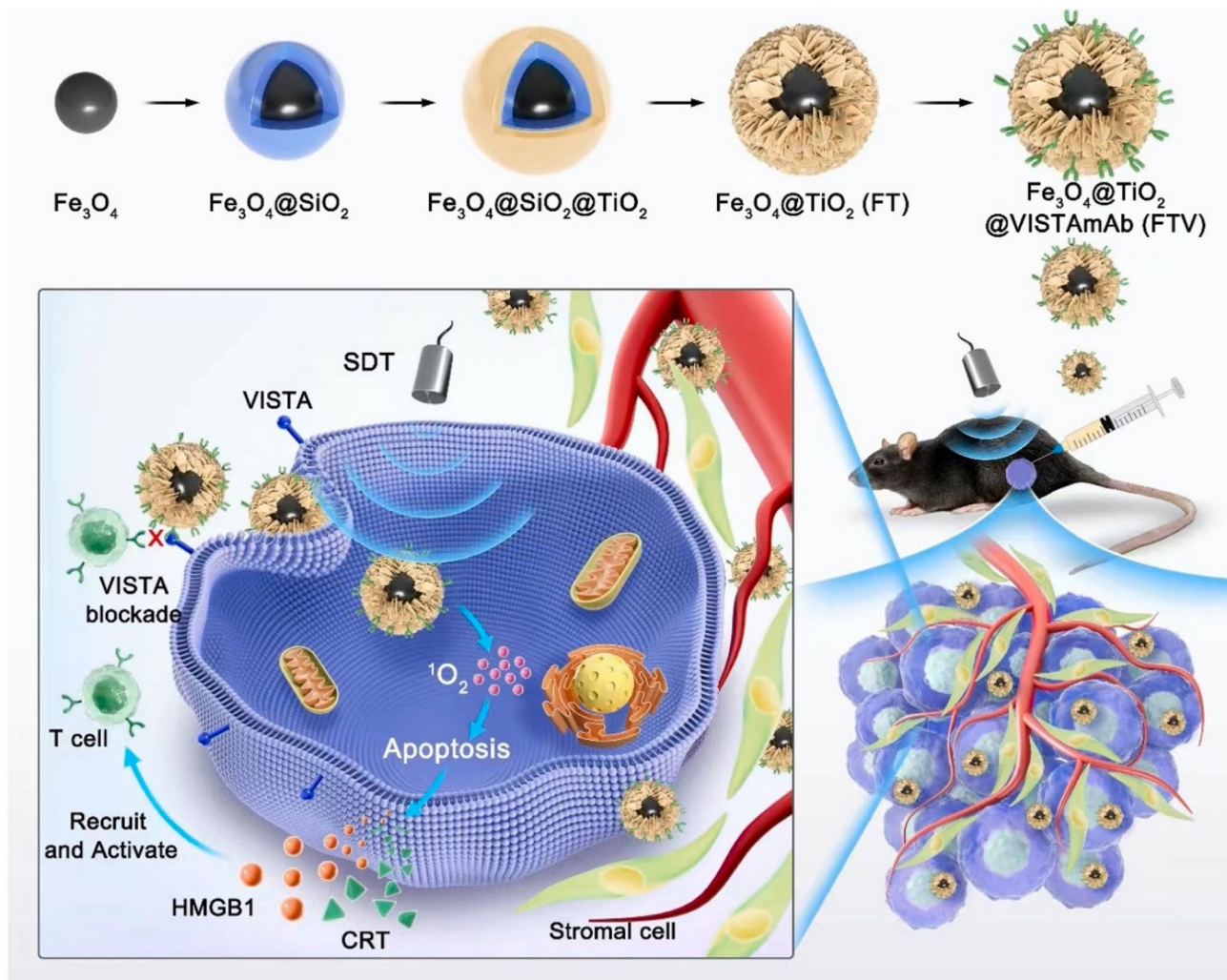


Fig. 5 The synthesis of $\text{Fe}_3\text{O}_4@TiO_2@VISTAmAb$ nanoparticles and the integration of TiO_2 -based sonodynamic therapy with VISTA antibody treatment for pancreatic cancer. Abbreviations: TiO_2 , titanium dioxide; SDT, sonodynamic therapy; CRT, calreticulin; and HMGB1, high mobility group box 1 protein. Reprinted with permission from Elsevier [8]

Nonetheless, both methodologies encounter constraints in antitumor effectiveness owing to certain inherent obstacles. It has been recently discovered that the integration of SDT with immunotherapy and nanoparticles might improve the outcome of treatment. A cascade immuno-sonodynamic therapy (immuno-SDT) strategy was developed to augment the efficacy of aPD-L1 through a multifunctional nanosonosensitizer, which consists of TiO_2 , the sonosensitizer Chlorin e6 (Ce6), and the immune adjuvant CpG oligonucleotide (CpG ODN), thus resulting in the formation of the TiO_2 -Ce6-CpG complex. The nanosonosensitizers possess a homogeneous polycrystalline structure with drug-loading capabilities. The ultrasonic exposure of TiO_2 -Ce6-CpG significantly suppresses tumor proliferation while eliciting adaptive immunological responses, with TiO_2 -Ce6 augmenting SDT effects and CpG promoting immune activation. This method, when used in combination with

aPD-L1 treatment, not only inhibits the original tumor but also stimulates systemic antitumor immunity, thus suppressing distant, non-irradiated cancers. Under this integrated approach, malignant malignancies are treated by combining nanosonosensitizer-enhanced sonodynamic therapy with immune checkpoint inhibition [14].

Non-small cell lung cancer (NSCLC) continues to be a predominant cause of cancer-related death globally, with therapeutic efficacy restricted by tumor immune evasion and the resistance to standard therapies. A potential solution is to augment the cytotoxic immune response and regulate gene expression with miRNA-based techniques. A study focuses on examining a combinatorial immunotherapeutic approach that integrates CTLs with microRNA-34a (miR-34a) to enhance the targeting of NSCLC cells. As a tumor-suppressive microRNA, miR-34a has been demonstrated to downregulate PD-L1 expression and critical oncogenic pathways, thereby

augmenting the antitumor immune response. The co-administration of activated CTLs with miR-34a markedly enhanced tumor cell death and inhibited cell proliferation, migration, and invasion in NSCLC models. The combined treatment significantly enhanced CTL-mediated cytotoxicity and reduced PD-L1 expression levels, thereby augmenting T cell activation and infiltration. These findings highlight the potential of miR-34a in enhancing tumor sensitivity to immune cell-based treatments and support the progression of miRNA-guided immunotherapy in lung cancer treatment [15].

As a unique, non-apoptotic kind of controlled cell death induced by iron-dependent Lipid peroxidation, originally identified in 2012, ferroptosis is characterized by diminished mitochondria with thick membranes, decreased or missing cristae, and disrupted outer membranes. This condition results from impaired redox homeostasis, excessive production of ROS, and abnormal iron metabolism, frequently initiated by small compounds such as erastin, RSL3, or therapeutic pharmaceuticals such as sorafenib and sulfasalazine. Ferroptosis mechanistically involves the suppression of the cystine/glutamate antiporter (SLC7A11), depletion of glutathione, and inactivation of glutathione peroxidase 4 (GPX4), resulting in the unregulated lipid peroxidation. The regulation is a complex process, involving the metabolic and signaling pathways spanning several organelles, such as mitochondria, endoplasmic reticulum, lipid droplets, and the peroxisomes with modulators including NRF2, HSPB1, and p53 adjusting susceptibility. Ferroptosis is associated with the resistance to cancer therapy, neurodegenerative diseases, ischemia-reperfusion injury, organ failure, and immune regulation. Therefore, it is a promising but complex target for the therapeutic modulation via inducers and inhibitors such as ferrostatin-1 or iron chelators. More information on ferroptosis can be found in these studies [16–20].

Despite the potential of SDT for malignant tumor treatment, its practical implementation has been obstructed by the scarcity of efficient sonosensitizers. A research was performed to examine the effect of heteroatom doping concentration in MOFs on interface formation after pyrolysis by varying the manganese source percentage. This method resulted in the in situ formation of Z-scheme heterojunctions, $\text{Mn}_x\text{O}_y/(\text{A/R})\text{TiO}_2$ (MTO), from MIL-125- NH_2 (Ti/Mn). The interfacial electron transfer mechanism improved charge carrier separation and maintained redox-active components, therefore greatly enhancing the efficiency of ROS formation. MTO efficiently reduced glutathione upon accumulation at the tumor site, hence alleviating the immunosuppressive TME. The combined heterojunctions and Mn_xO_y components facilitated both SDT and synergistic CDT, enhancing ICD. Moreover, the absorption of Mn^{2+} by

DCs and the secretion of tumor-associated antigens during ICD triggered the stimulator of interferon genes (STING) pathway, facilitating DC maturation and T cell activation. The activated T cells subsequently released elevated quantities of interferon- γ , therefore enhancing $\text{Mn}^{3+}/\text{Mn}^{2+}$ -induced ferroptosis in metastatic tumor cells. The integration of MTO-mediated synergistic SDT/CDT with PD-L1 checkpoint inhibition produced vaccine-like effects, eliciting robust systemic immunity and enduring immunological memory that can inhibit tumor growth, metastasis, and recurrence. This study presented a self-amplifying nanoplatform utilizing multifunctional MOF-derived Z-scheme heterojunctions for integrated sonodynamic treatment, chemodynamic therapy, and immunotherapy (Fig. 6) [21].

Multifunctional nanoparticles are essential for attaining synergistic multimodal anticancer effects. This method employed zinc oxide (ZnO) nanoparticles as pH-sensitive carriers to encapsulate the chemotherapeutic agent doxorubicin (DOX) and the photosensitizer indocyanine green (ICG), while biocompatible low-molecular-weight heparin (LMHP) served as a gatekeeping material to facilitate combined PTT, PDT, chemotherapy, and immunotherapy. In the acidic TME, ZnO degraded to release lethal Zn^{2+} ions, initiating tumor-specific release of DOX and ICG. Simultaneously, ZnO promoted the formation of oxygen and ROS to augment PDT. Laser irradiation of the released ICG produced supplementary ROS for PDT and increased local temperatures for successful PTT. The administration of DOX resulted in direct cytotoxicity via chemotherapy, but both DOX and ICG facilitated ICD, hence enhancing anticancer immune responses. In vitro and in vivo assessments revealed substantial inhibition of tumor growth, metastasis, and recurrence, underscoring the formidable therapeutic promise of this multifunctional nanoplatform [22]. Creating a highly efficient and tumor-specific treatment strategy that targets primary tumors while simultaneously activating the host immune system to eradicate distant metastases is a considerable clinical hurdle. A multifunctional nanocomposite, $\text{AuNP@mSiO}_2@\text{DOX-ZnO}$, was developed to integrate the photothermal properties of gold nanoparticles (AuNPs), the pH-responsive and tumor-selective attributes of zinc oxide quantum dots (ZnO QDs), and the chemotherapeutic efficacy of DOX. The device was assessed for its photothermal efficacy, pH-responsive drug release, and selective absorption by tumor cells. The immune response was evaluated by analyzing immune cell populations in vivo and investigating the expression of ICD markers in vitro. Mouse models of unilateral and bilateral subcutaneous melanoma, together with lung metastases, were employed to investigate antitumor effectiveness. ZnO-capped nanoparticles demonstrated a substantial DOX loading capacity and facilitated effective

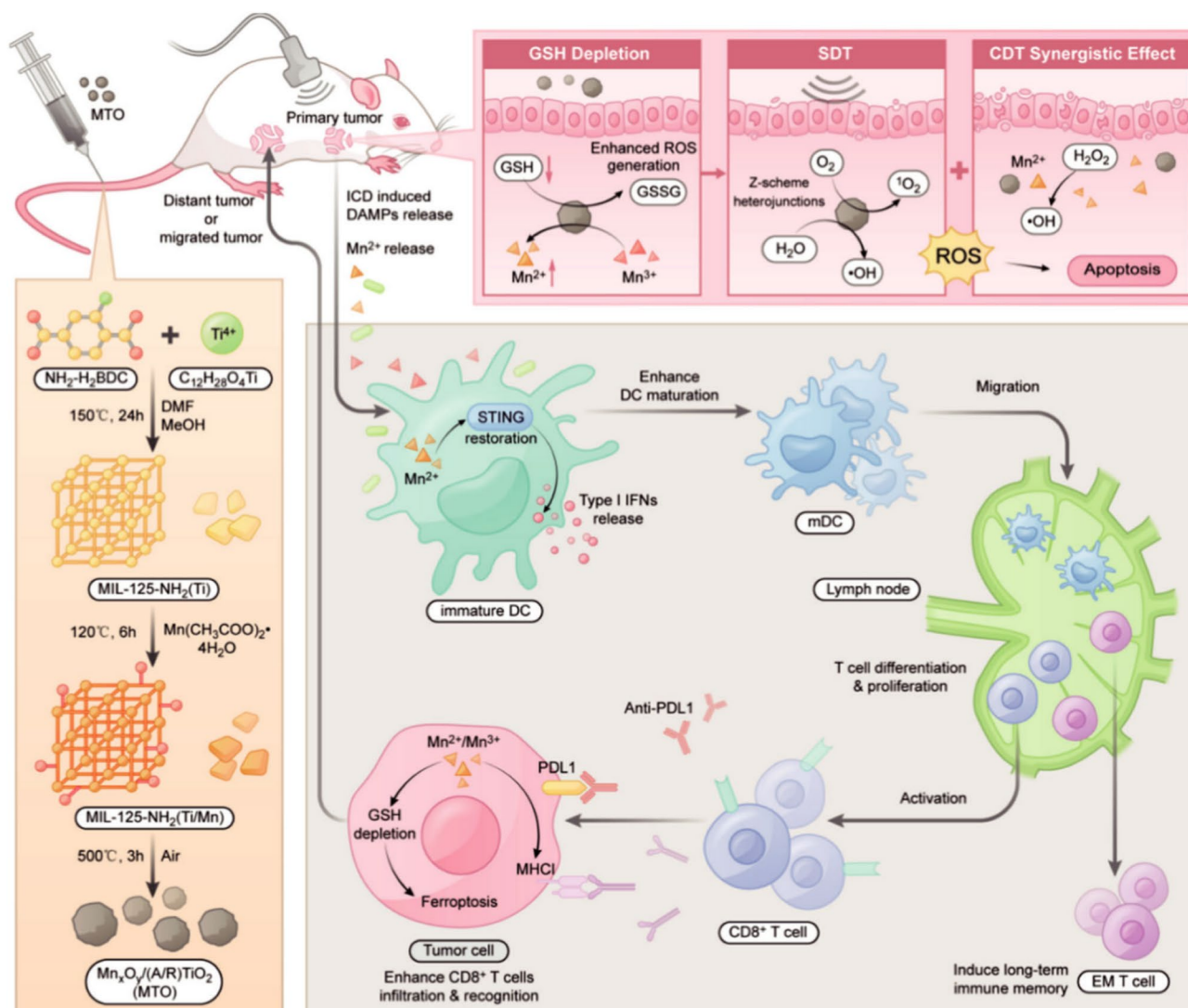


Fig. 6 Schematic Representation of the Synthesis of MTO and Its Antitumor Properties as a Multifunctional Sonosensitizer for Self-Enhancing Synergistic Therapy. Abbreviations: GSH, glutathione; GSSG, glutathione disulphide or oxidized glutathione; ROS, reactive oxygen species; CDT, chemodynamic therapy; SDT, sonodynamic therapy; DC, dendritic cell; PD-L1, programmed cell death Ligand 1; MHC-I, major histocompatibility complex. Reprinted with permission from ACS [21]

drug release under acidic circumstances (pH 5.0). The nanocomposite remarkably suppressed tumor development in melanoma-bearing mice when subjected to low-power laser irradiation. ZnO exhibited selective targeting of melanoma cells and was able to induce ICD. Furthermore, both AuNP@mSiO₂-mediated photothermal treatment and DOX facilitated direct tumor cell destruction and augmented ICD. This approach enhanced DC maturation and enabled effector T cell infiltration into tumor tissues, resulting in the inhibition of local tumor development and distant lung metastases. The results emphasize ZnO's capacity to elicit strong antitumor immunity through ICD induction and reinforce the nanocomposite's multifunctionality in addressing localized and

metastatic malignancies, presenting significant promise for therapeutic use [23].

Despite significant advancements in cancer immunotherapy, mastocarcinoma presents a significant challenge because of its spatiotemporally diverse metabolism-driven immune evasion and highly immunosuppressive TME, leading to reduced immune responses. A TME-activated nanoimmunomodulator was engineered, consisting of ultrasmall gold (Au) and Cu₄O₃ active components affixed to reconstructed layered double hydroxide nanosheets (Au–Cu₄O₃/re-LDHs), intended to impair tumor metabolism and enhance immune response against mastocarcinoma. These nanosheets exhibit effectively distributed Au and Cu₄O₃ particles, offering synergistic redox-active sites with multifunctional enzyme-like

properties. Consequently, Au–Cu₄O₃/re-LDHs promote a series of enzyme-mimicking reactions that focus on essential metabolic components, resulting in substantial reductions of glucose and nicotinamide adenine dinucleotide (NAD⁺), as well as the production of many hydroxyl radicals in 4T1 breast cancer cells. This metabolic disruption hinders glucose absorption, diminishes the proton-motive force, obstructs mitochondrial electron transport chains, And triggers death in 4T1 cells, so disassembling mastocarcinoma metabolic functions. The resultant metabolic disruption increases the adaptive immune response and inhibits lactate formation from extracellular glycolysis, therefore mitigating the immunosuppressive TME and providing a more advantageous immunological setting (Fig. 7) [24].

Radiotherapy and immunotherapy are now routine therapies for NSCLC; nevertheless, their efficacy is frequently compromised by the requirement for elevated radiation doses and a typically poor immune response rate. A multi-faceted strategy employing a radio-immuno-enhancer, ZnO–Au@mSiO₂, has been devised to induce apoptosis in tumor cells and restructure the immunosuppressive TME to address these constraints. This nanoplatform incorporates gold nanoparticles as radiosensitizers and zinc ions as immune activators, markedly augmenting the antiproliferative effects of radiation while concurrently eliciting immunological responses via several mechanisms. The technology induces ICD under low-dose X-ray irradiation, enhances immunological checkpoint blockade (ICB) targeting PD-1/PD-L1, and activates the cGAS-STING pathway,

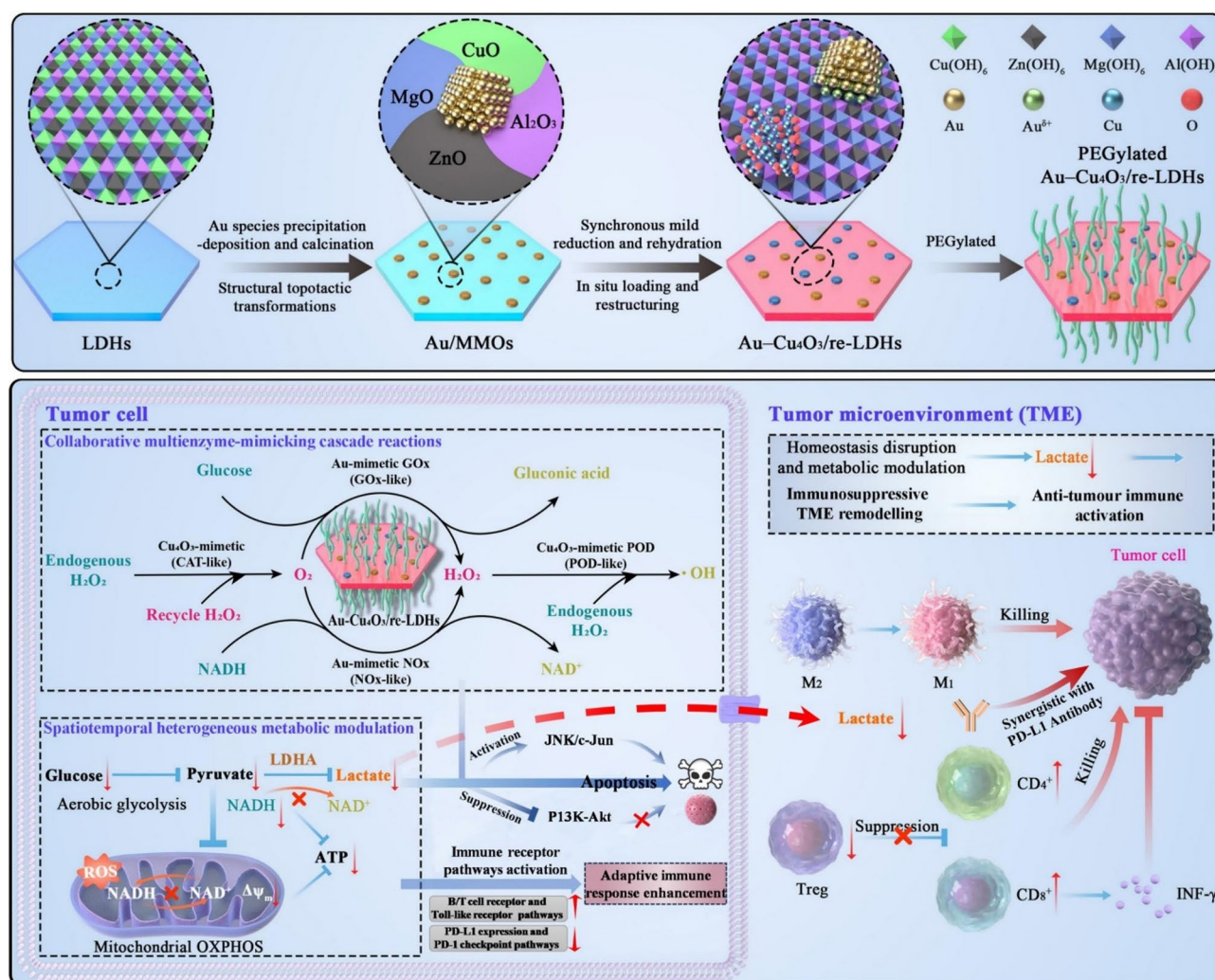


Fig. 7 Schematic depiction of the synthesis of Au–Cu₄O₃/re-LDHs, with the spatiotemporal heterogeneous metabolic disruption-activating immunotherapy initiated by cooperative multienzyme-mimicking cascade events involving highly scattered ultrasmall Au and Cu₄O₃ active species. Abbreviations: LDH, lactate dehydrogenase; TME, tumor microenvironment; NADH, nicotinamide adenine dinucleotide (NAD) + hydrogen (H); P13K, phosphoinositide 3-kinases; Akt, protein kinase B; JNK, Jun N-terminal kinase; PD-L1, programmed cell death Ligand 1; ATP, adenosine triphosphate; OXPHOS, oxidative phosphorylation; Treg, regulatory T cell; IFN-γ, Interferon Gamma. Reprinted with permission from Elsevier [24]

therefore rejuvenating tired T cells. This radio-immuno-enhancer significantly enhances anticancer immunity, evidenced by an elevated ratio of cytotoxic and helper T cells, reflecting robust immunogenic and therapeutic potential [25].

Regulating intracellular ionic balance to trigger antigen-specific immune responses has attracted considerable interest in cancer treatment. A dual-pathway nanoreactor, $\text{Au-Cu}_{2-x}\text{Se@ZIF-8@P18}$ nanoparticles (ACS-Z-P NPs), was designed to target danger-associated molecular patterns (DAMPs) and deliver zinc ions (Zn^{2+}) and ROS into the TME. The Zn^{2+} liberated from the MOFs accumulated in the cytoplasm, impairing the transcription of zinc-regulated proteins and causing DNA damage, which eventually initiated pyroptosis and ICD via the caspase-1/gasdermin D (GSDMD) signaling pathway. Under laser irradiation, the nanoreactor

surmounted immunosuppressive barriers within the TME by augmenting ROS generation through a Fenton-like reaction cascade. The increased production of ROS activated inflammasomes and facilitated the release of DAMPs, hence enhancing pyroptosis and ICD. The ensuing cascade reconfigured the immunosuppressive TME, enhanced antigen presentation by DCs, and fortified tumor-specific T-cell responses. This sequence of events efficiently triggered antigen-specific immune responses and further strengthened the induction of pyroptosis and ICD (Fig. 8) [26].

Triple-negative breast cancer (TNBC) is characterized by its aggressive behavior, elevated rates of metastasis and recurrence, and inadequate response to immunotherapy, resulting in restricted treatment alternatives. To tackle these issues, polydopamine-coated zinc-copper bimetallic nanoplateforms ($\text{Cu-ZnO}_2\text{@PDA}$, designated

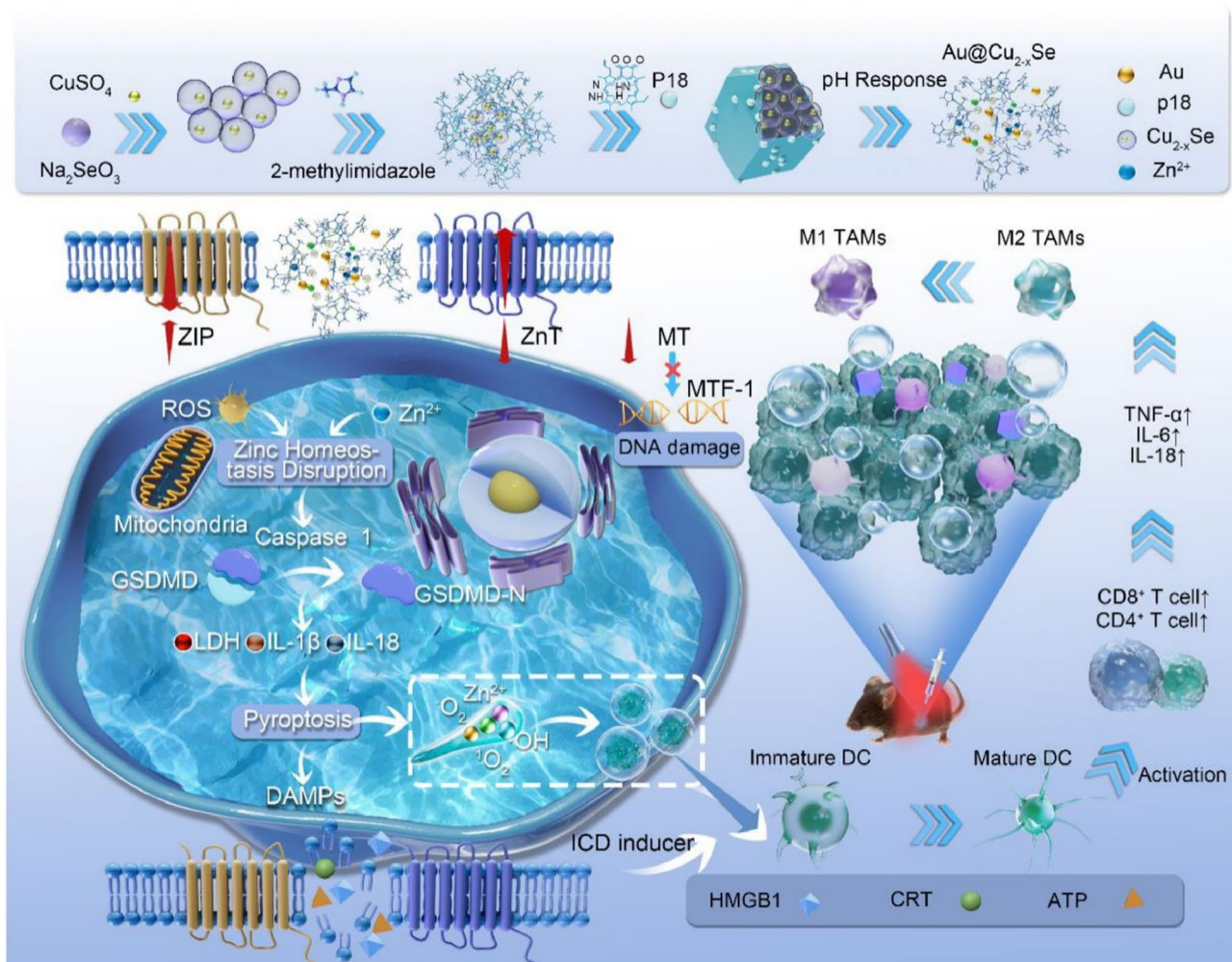


Fig. 8 Schematic representation of the synthesis process and therapeutic mechanism of ACS-Z-P nanoparticles. Abbreviations: ZIP, solute Linkage carrier 39; ZnT, solute Linkage carrier 30; ROS, reactive oxygen species; GSDMD, gasdermin D; LDH, lactate dehydrogenase; IL, interleukin; DAMP, danger-associated molecular patterns; ICD, immunogenic cell death; DC, dendritic cell; TNF, tumor necrosis factor; TAM, tumor-associated macrophages. Reprinted with permission from Elsevier [26]

as CZP NPs) have been engineered to facilitate photo-thermal-enhanced cuproptosis and stimulate the cGAS-STING pathway. This strategy seeks to counteract the immunosuppressive TME in TNBC, elevate PD-L1 expression, and improve the therapeutic efficacy of Anti-programmed death-ligand 1 antibody (α PD-L1) immunotherapy. In the acidic TME, CZP nanoparticles release copper and zinc ions with hydrogen peroxide, which collectively produce highly oxidative hydroxyl radicals and inhibit iron-sulfur cluster proteins. These effects undermine mitochondrial integrity, facilitate the release of mitochondrial DNA (mtDNA), and trigger irreversible cuproptosis. The interplay between mtDNA and zinc ions enhances the cGAS-STING pathway, eliciting a robust antitumor immune response and increasing tumor sensitivity to α PD-L1 therapy. The therapeutic benefits are markedly enhanced when paired with 808 nm near-infrared laser irradiation for photothermal treatment. The integration of CZP NPs with α PD-L1 immunotherapy significantly amplifies antitumor immunity and efficiently inhibits the evolution of TNBC [27].

Chemotherapy can elicit tumor immunotherapy via ICD, although the exact modulation of the resultant immune response is a difficulty. A controlled ultrasonic-triggered chemo-immunotherapy nanoagonist has been created, utilizing a pH- and ROS-responsive PEG-polyphenol matrix to combine the sonosensitizer zinc oxide (ZnO) with the chemotherapeutic drug DOX. The resultant nanoparticles, PZnO@DOX, are engineered to breakdown selectively in acidic environments, therefore releasing both DOX and zinc ions. US irradiation induces the generation of ROS by sonodynamic treatment, hence enhancing medication release. Subsequent to PZnO@DOX therapy paired with ultrasound, compromised tumor cells expel double-stranded DNA (dsDNA) from both the nucleus and mitochondria into the cytoplasm. The dsDNA fragments, in conjunction with zinc ions, activate the STING pathway by binding to cyclic GMP-AMP synthase (cGAS), resulting in the development of dendritic cells. This cascade amplifies DOX-induced ICD and activates antigen-specific T cell immunological responses, providing a meticulously regulated method for chemo-immunotherapy (Fig. 9) [28].

To address the enduring constraints of radiation, especially in hypoxic TMEs that are resistant to ROS creation, Au-ZnO heterostructured nanomaterials were engineered and produced as potent radiosensitizers with improved ROS production. Nanomaterials were developed by integrating the high atomic number of gold with the semiconductive photocatalytic characteristics of ZnO, resulting in a spatially ordered Au head and ZnO rod that enhance interfacial charge separation and facilitate electron transport. Under X-ray irradiation, significantly elevated amounts of ROS, including hydroxyl

radicals ($\cdot$ OH) and superoxide anions ($\cdot$ O₂⁻), were seen in the Au-ZnO group relative to ZnO or Au alone, as verified by electron spin resonance (ESR) spectroscopy and fluorescent probes. In vitro, the nanomaterials resulted in a decrease in tumor cell viability under irradiation, far surpassing control groups. Hypoxia was mitigated by higher ROS transport and better oxygen consumption, accompanied by the reduction of HIF-1 α signaling. In vivo investigations utilizing 4T1 tumor-bearing mice shown significant tumor growth reduction in the Au-ZnO combined with radiation group, with tumor sizes diminished after 15 days, while histological examination indicated enhanced apoptosis and reduced angiogenesis. Biodistribution studies verified tumor-specific accumulation, with minimal systemic toxicity seen. Statistically substantial variations ($p < 0.01$) in ROS levels, cell survival, and tumor regression validated the enhanced radiosensitizing efficacy of the heterostructure. The findings suggest that Au-ZnO nanomaterials are a viable and biocompatible approach to surmount radioresistance in solid tumors by enhancing ROS production and alleviating hypoxic constraints [29].

Metal sulfides

The PCD pathway is essential for maintaining physiological equilibrium by removing functionally redundant, infection-susceptible, or possibly tumorigenic cells, therefore aiding in cancer prevention and illness management. PCD includes several types such as apoptosis, cuproptosis, ferroptosis, and pyroptosis. The utilization of solid-state electron-mediated Z-scheme heterostructured semiconductor nanomaterials, which improve electron-hole (e^- - h^+) separation for promoting PCD, is yet inadequately investigated. In this regard, Bi₂S₃-Bi₂O₃-Au-PEG nanorods (BB-A-P NRs), a Z-scheme heterostructured semiconductor, were synthesized to demonstrate robust redox properties and advantageous biocompatibility. Upon activation by NIR light, these nanorods emulate catalase function by producing oxygen (O₂) and transforming it into singlet oxygen (¹O₂) via electron-hole transfer. Within the TME, they engage with hydrogen peroxide (H₂O₂) and water (H₂O) to generate hydroxyl radicals ($\cdot$ OH), which trigger apoptosis. The resultant oxidative stress triggers the Caspase-1/GSDMD-dependent pyroptosis pathway, leading to cellular pyroptosis and the generation of DAMPs. This inflammatory type of cell death facilitates ICD and amplifies anticancer immune responses. Moreover, BB-A-P nanorods facilitate computed tomography (CT) imaging for therapeutic assessment. By concurrently activating dual forms of programmed cell death and altering the tumor micro-environment, BB-A-P provides a cohesive and synergistic method for cancer treatment, representing a viable option for addressing hypoxic tumors [9].

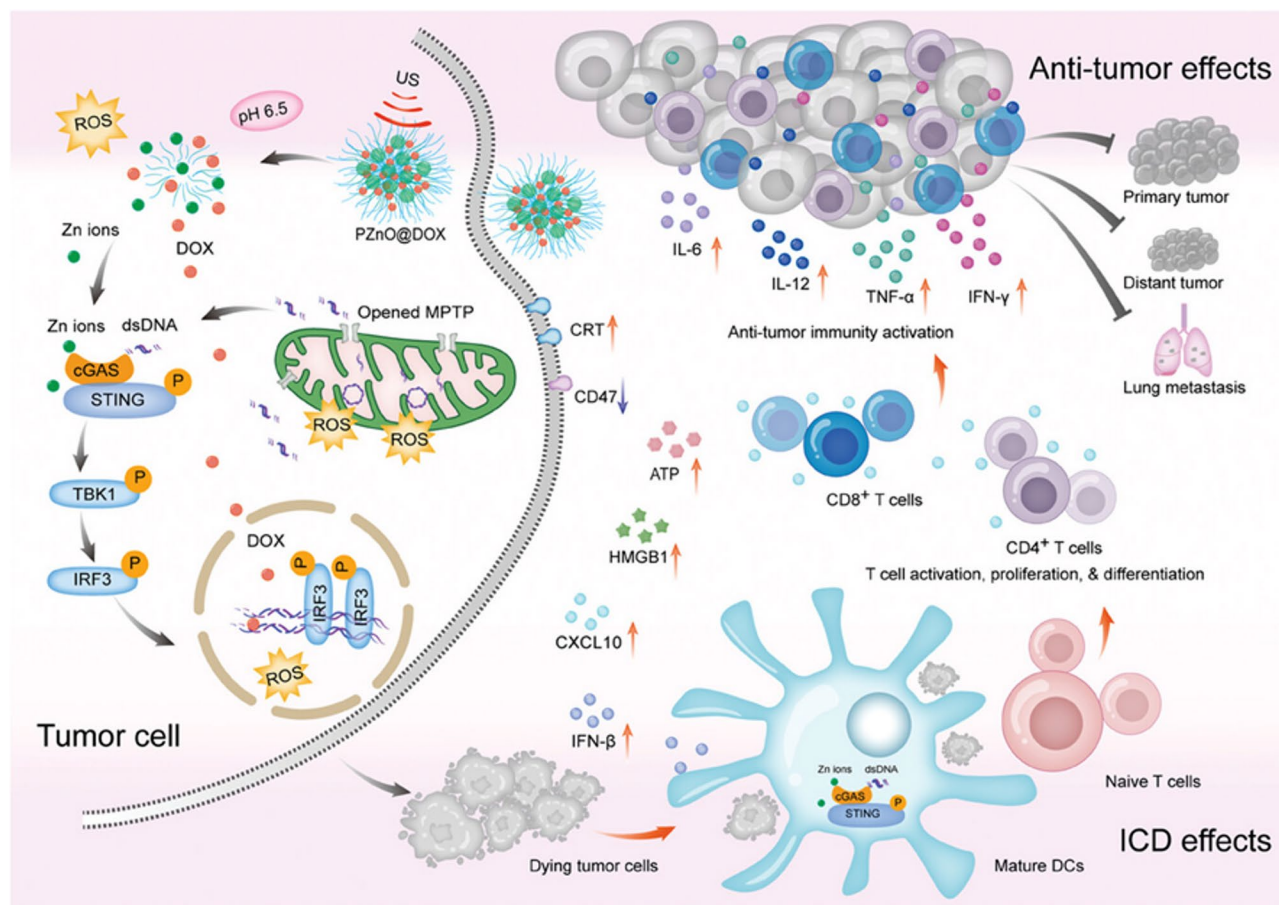


Fig. 9 The ultrasound-activated STING pathway nanoagonist enhances chemotherapy-induced immunogenic cell death by using pH and ROS dual-responsive PEG-polyphenol nanoparticles. Abbreviations: ROS, reactive oxygen species; DOX, doxorubicin; US, ultrasound; STING, cGAMP–stimulator of interferon genes; cGAS, Cyclic GMP–AMP synthase; TBK1, Tank-binding kinase 1; IRF3, interferon regulatory factor 3; CRT, calreticulin; ATP, adenosine triphosphate; HMGB1, high mobility group box 1 protein; CXCL10, C-X-C motif chemokine Ligand 10; IFN, interferon; ICD, immunogenic cell death; DC, dendritic cell; IL, interleukin. Reprinted with permission from Wiley [28]

Nanotechnology-driven strategies that improve radiotherapy (RT) while incorporating multimodal imaging are of considerable importance for the progression of cancer treatment. An experiment developed Bi₂S₃ nanorods with multifunctional capabilities, acting as contrast agents for X-ray CT and photoacoustic (PA) imaging, while also demonstrating exceptional biocompatibility. Experimental findings from both in vitro and in vivo investigations revealed that these Bi₂S₃ nanoagents significantly intensified the lethal effects of radiation by increasing the localized radiation dosage and enhancing anti-tumor efficacy via photothermal augmentation. The generated heat increased oxygen levels in hypoxic tumor areas, thereby diminishing the production of HIF-1 α , which is crucial in facilitating radio-resistance. This suppression further disrupted DNA repair pathways by downregulating proteins linked to DNA repair. The integration of radiotherapy and nanoagent-induced hyperthermia significantly curtailed tumor spread by diminishing the expression of angiogenic factors. This single-component nanoagent

facilitates CT/PA imaging-guided radiotherapy and synergistically improves radiotherapeutic results through photothermal effects and modification of the TME [10].

Stimulating a robust immune response is crucial for addressing solid tumors and averting recurrence. Cuproptosis, along with the concomitant elevation of ROS, has been demonstrated to elicit ICD and modify the tumor immunological milieu, therefore activating systemic immunity. To utilize this approach, Bi₂O_{3-x}S_x-CuS p–n heterojunction nanoparticles (BCuS NPs) were engineered to elicit systemic immune responses and efficiently inhibit both latent and recurring cancers. BCuS initiated a Fenton-like reaction under acidic conditions, producing extremely hazardous ROS under ultrasound, which led to cuproptosis and ferroptosis. The integration of these mechanisms with ICD induction mitigated immunosuppression in the TME and improved the efficacy of immunotherapy. In vivo investigations validated the in vitro results, demonstrating substantial tumor suppression via the interplay of many cell death mechanisms.

The BCuS sonosensitizer presents a potential approach for multimodal cancer therapy by combining SDT with cuproptosis, ferroptosis, and immune activation [30].

US and X-ray treatments provide considerable promise in oncological treatment owing to their ability to penetrate deep tissues; yet, their effectiveness may be constrained in the absence of powerful radiosensitizers. A degradable bismuth-based heterojunction radiosensitizer, $\text{BiF}_3\text{-Bi}_2\text{O}_3\text{-x:S}_x\text{-PEG}$ (BFOSP), was developed via anion-exchange-regulated charge separation engineering to overcome this issue. This heterojunction configuration adjusted the bandgap, increased charge carrier mobility, and augmented ROS production efficiency by the incorporation of oxygen and sulfur anions. These adjustments enhanced the synergistic effects of SDT and RT, enabling SDT to decrease the necessary radiation dosage and augment therapeutic efficacy while reducing adverse effects. Moreover, the degradable characteristics of BFOSP and its capacity to cause oxidative stress disturbed the redox equilibrium of the TME. This resulted in the activation of several cell death pathways, including apoptosis, ferroptosis, and ICD, eventually eliciting a systemic immunological response. The BFOSP radiosensitizer constitutes a potential approach for improving the safety and efficacy of combined SDT and radiotherapy in cancer treatment [31].

Photoimmunotherapy integrates the localized effects of PDT and PTT with systemic immune activation, presenting a viable approach for addressing metastatic malignancies. The practical use of porphyrin-based photosensitizers is frequently obstructed by inadequate water solubility and aggregation, which reduce their therapeutic efficacy. To address these restrictions, a bismuth-based MOF, designated Bi-TCPP, was synthesized utilizing tetrakis(4-carboxyphenyl)porphyrin (TCPP) as the organic ligand. This MOF produces nanosheets exhibiting better π - π stacking and Superior semiconductor characteristics, leading to improved ROS production And more water dispersibility. Under 635 nm Light irradiation, Bi-TCPP has a photothermal conversion efficiency of 41.5% and efficiently depletes GSH in the TME, hence elevating oxidative stress. Bi-TCPP produces pyroptosis during phototherapy, facilitating the release of immune-related molecules, hence boosting ICD and eliciting vigorous immunological responses. This results in substantial suppression of tumor proliferation and metastasis. Bi-TCPP, produced by a straightforward technique, selectively promotes apoptosis, necrosis, and pyroptosis in vitro and in vivo, establishing it as a powerful agent for efficient tumor-targeted photoimmunotherapy [32].

Photoactivated immunotherapy provides significant potential for the treatment of malignant and metastatic cancers, since it effectively integrates localized therapy with systemic immune activation. A semiconductor

nanomaterial consisting of copper indium selenium (RCIS) and encapsulated in an erythrocyte membrane was developed to target primary and metastatic cancers. The copper ions in RCIS facilitate chemodynamic treatment, and its small bandgap for efficient NIR light-activated photothermal and photodynamic immunotherapy. Furthermore, RCIS serves as a nanocarrier for NLG919, An indoleamine 2,3-dioxygenase-1 (IDO-1) inhibitor, resulting in the formation of RNCIS nanoparticles. Upon NIR irradiation, RNCIS nanoparticles release NLG919 at tumor locations due to photothermal activation, resulting in increased recruitment of cytotoxic T cells and facilitation of M1 macrophage polarization, hence enhancing immune responses. RNCIS nanoparticles display significant cytotoxicity towards cancer cells and efficiently eradicate primary and metastatic tumors. This method highlights the considerable promise of narrow bandgap semiconductor nanomaterials as multifunctional platforms for near-infrared-responsive, controlled release, and synergistic photoimmunotherapy [33].

RT is a prevalent cancer treatment; nevertheless, its therapeutic efficacy is frequently undermined by non-specific radiation damage to both malignant and benign tissues. A multipurpose nanosphere system was designed to concurrently address many components of radiotherapy, enhancing radiosensitization while avoiding adverse effects. These nanospheres include the high atomic number element bismuth (Bi), which effectively absorbs ionizing radiation and significantly improves RT efficacy evidenced by decrease in cell viability when Bi_2S_3 was used in conjunction with X-ray irradiation compared to X-rays alone. Moreover, the incorporation of 3-bromopyruvate (3BP), a metabolic inhibitor, diminishes the heightened oxygen consumption typical of tumor cells, mitigating hypoxia and thus enhancing radiation-induced DNA damage. The combination index (CI) of 0.46 at a fraction affected (fa) of 0.5, determined by the Chou-Talalay technique, validated a synergistic interaction between Bi_2S_3 And 3BP. This combined method also triggered excessive autophagy via processes related to starvation and redox imbalance, hence enhancing tumor cell death. Furthermore, the nanospheres demonstrate significant X-ray attenuation and elevated NIR absorption, facilitating their use as dual-modality contrast agents for CT and photoacoustic (PA) imaging. This meticulously engineered platform provides a potential strategy for improving radiotherapy results via coordinated radiosensitization, metabolic regulation, activation of pro-death autophagy, and real-time imaging functionalities (Fig. 10) [34].

Monotherapy frequently proves inadequate in efficiently addressing cancers due to intrinsic limits in tumor response pathways, adversely impacting therapeutic results. A collaborative therapeutic nanosystem (BBSP)

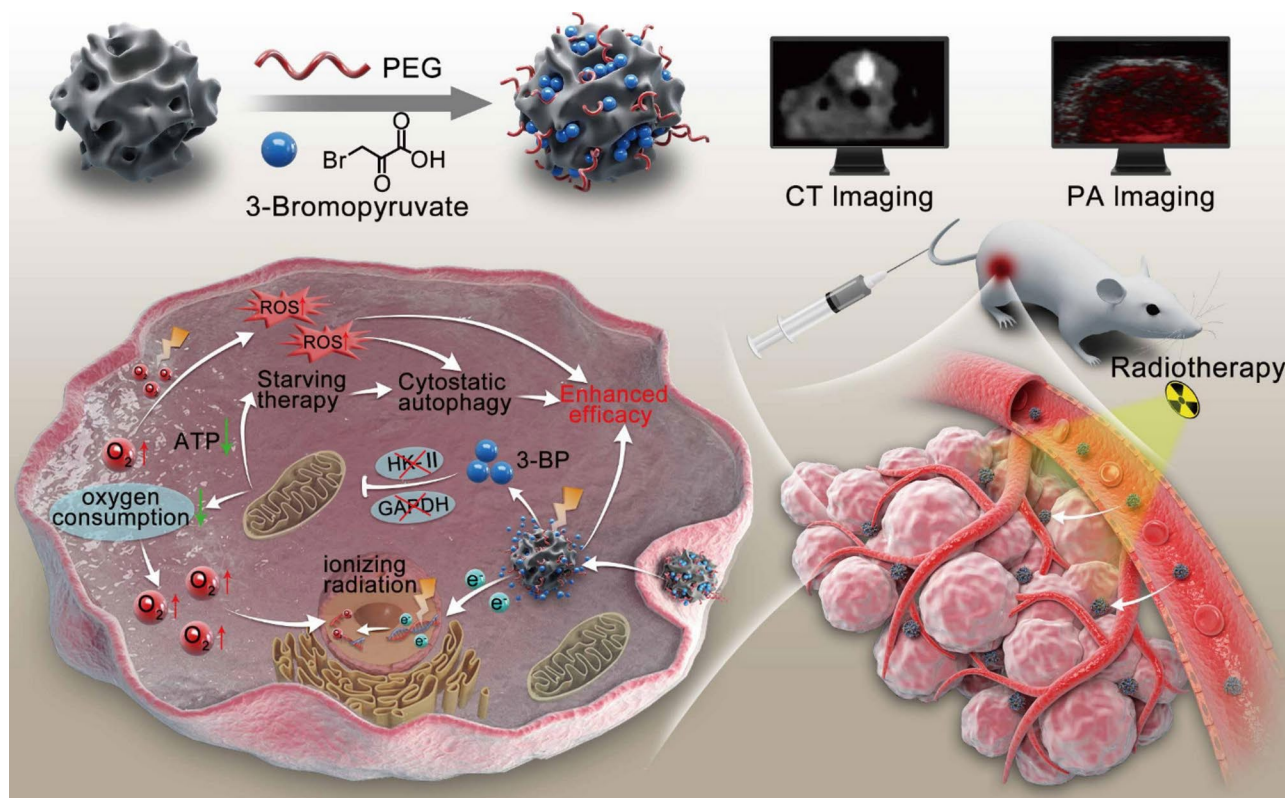


Fig. 10 Schematic representation of the synthesized Bi₂S₃-3BP nanospheres for enhanced radiosensitization via ionizing radiation amplification, oxygen consumption mitigation, pro-apoptotic autophagy induction, and dual imaging monitoring/guidance using CT/PA techniques. Abbreviations: PEG, polyethylene glycol; CT, computed tomography; PA, photoacoustic; 3-BP, 3-Bromopyruvate; ATP, adenosine triphosphate; ROS, reactive oxygen species. Reprinted with permission from Springer BMC Nature [34]

was developed to tackle this difficulty by combining PDT and PTT. This device utilizes sulfur ion-doped bismuth fluoride (BiF₃) semiconductor nanospheres, whereby Sulfur doping reduces the band gap and improves Light absorption by generating oxygen vacancies. And exploiting the local Surface plasmon resonance effect of bismuth. These alterations enhance carrier separation efficiency. And overall photoreactivity. During 520 nm laser irradiation, the nanospheres facilitate electron transfer to oxygen molecules, resulting in the production of ROS, whereas holes in the valence band oxidize GSH. Furthermore, bismuth ions interact with GSH, resulting in a further reduction in its levels. RNA sequencing indicated a downregulation of GPX4, a crucial regulator of ferroptosis, indicating that the therapy promotes ferroptotic cell death in conjunction with apoptosis. The augmented light absorption resulting from sulfur doping also leads to increased photothermal and oxidative damage, therefore successfully suppressing tumor development. BBSP is a robust multimodal platform that synergistically integrates PDT and PTT to induce ferroptosis and apoptosis, presenting a viable approach for enhanced tumor treatment [35].

ICD is crucial in cancer immunotherapy since it stimulates the immune system via the release of tumor-associated antigens from deceased cells. While small-molecule medicines have been therapeutically utilized to induce ICD, attaining accurate regulation of ICD induction during tumor therapy is crucial for improving therapeutic results. A dual-response technique utilizing ultrasound and light is proposed for concurrent tumor treatment and regulated ICD activation. This method employs a topological synthesis technique to generate sulfur-doped bismuth oxide (Bi₂O_{3-x}S_x or BS) using BiF₃ (BF) as a template, yielding a morphology-controlled bismuth-based nano-semiconductor with a small bandgap. BS produces ROS by a sonocatalytic process when subjected to ultrasonic stimulation. These ROS, together with BS-mediated glutathione depletion, provoke oxidative stress that efficiently initiates ICD. Moreover, sulfur doping allows BS to operate as a photothermal agent when exposed to light, hence permitting synergistic tumor ablation via the integration of photothermal and oxidative actions. The integration of ivermectin (IVM) into the BS matrix creates a composite (BSM), hence improving the therapeutic efficacy. The BSM system, influenced by both light and ultrasound, enhances DC maturation and intensifies ICD.

This ICD-mediated hyperthermia and SDT combination is a viable option for synergistic cancer treatment and gives a regulated means for augmenting ICD induction [36].

SDT encounters substantial constraints owing to the inadequate efficacy of traditional sonosensitizers and the intricacies of the TME. A metal-sensitized sonocatalyst idea has been presented to tackle these issues, wherein noble metals augment the sonocatalytic efficacy of semiconductors. This method involves the incorporation of gold nanorods onto wide-bandgap bismuth oxide, resulting in a catalytic nanosystem that illustrates this principle. The use of Au nanorods enhances the separation of ultrasound-induced electron-hole pairs in bismuth oxide, resulting in augmented production of various ROS and better photothermal effects. Furthermore, bismuth oxide diminishes intratumoral glutathione, therefore disturbing the redox equilibrium within the TME. The synergistic actions of ROS and heat elicit ICD, therefore counteracting tumor-induced immunosuppression. This therefore

facilitates dendritic cell maturation and augments CD8⁺ T cell infiltration, providing a potent approach to boost the effectiveness of SDT-driven immunotherapy (Fig. 11) [37].

A novel radiosensitizing nanoplatform was developed by conjugating Bi₂S₃ nanoparticles with *Ganoderma lucidum* polysaccharides (GLPs), resulting in GLP-Bi₂S₃ nanoparticles that possess both therapeutic and immunomodulatory properties, aimed at enhancing the efficacy and safety of RT while reducing its side effects. Bismuth's elevated atomic number facilitates enhanced X-ray absorption, thereby intensifying localized radiation effects, while GLPs provide immunostimulatory and Antioxidative advantages. The produced nanoparticles had significant NIR absorbance and remarkable stability, with a size of around 50 nm that enabled passive tumor targeting through the enhanced permeability and retention (EPR) effect. The nanoparticles exhibited photothermal characteristics under 808 nm laser irradiation, facilitating dual-mode treatment. In vitro investigations

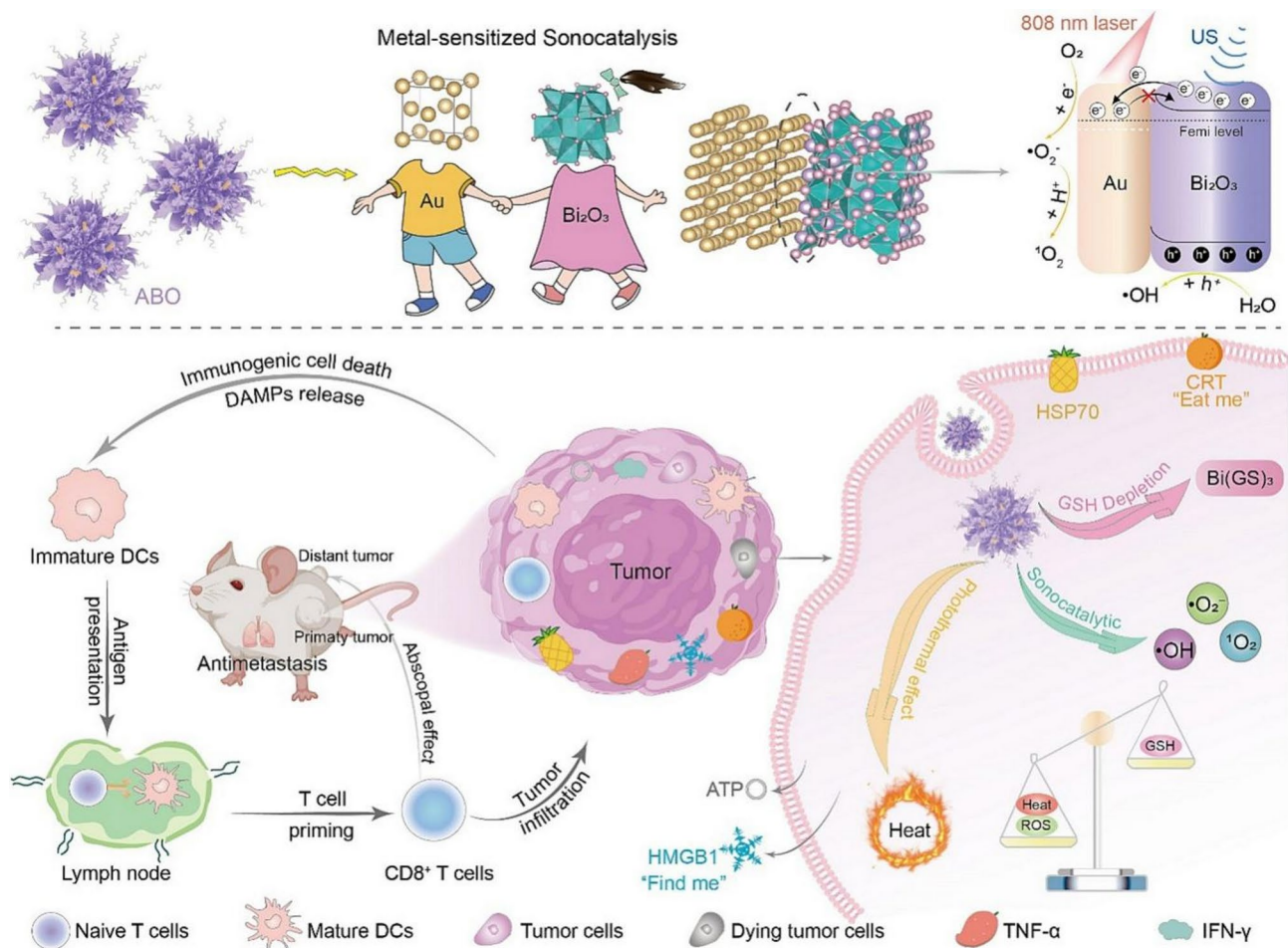


Fig. 11 Schematic representation of the mechanism of sonocatalytic reactive oxygen species formation by ABO nanocatalysts and the process of eliciting immunogenic cell death in tumor cells. Abbreviations: DAMP, damage-associated molecular patterns; DC, dendritic cell; TNF, tumor necrosis factor; IFN, interferon, HSP70, Heat shock 70. Reprinted with permission from Elsevier [37]

of 4T1 breast cancer cells revealed a considerable increase in radiation-induced apoptosis in the GLP-Bi₂S₃ + RT cohort, accompanied by elevated ROS production and DNA damage, as shown by γ -H2AX foci formation. In vivo, 4T1 tumor-bearing mice administered GLP-Bi₂S₃ NPs in conjunction with radiotherapy exhibited decrease in tumor volume over 15 days, significantly surpassing the efficacy of radiotherapy alone. Augmented immunological responses were noted, characterized by heightened infiltration of CD⁴⁺ and CD⁸⁺ T cells, alongside the elevation of pro-inflammatory cytokines (IL-2, IFN- γ), hence substantiating the immunoadjuvant function of GLPs. No notable toxicity or weight reduction was seen, and histological examination verified no off-target injury. Statistically substantial enhancements ($p < 0.001$) were observed in tumor suppression, apoptosis, and immune activation parameters. This work presents a secure and highly efficient radiosensitizing nanoplatform that synergistically integrates physical dose augmentation with biological immune regulation, providing a viable strategy for enhanced cancer treatment [38].

Microwave (MW) hyperthermia is acknowledged as a safe and effective minimally invasive therapy for malignancies; yet, its clinical efficacy is frequently constrained by the heat sink effect and inadequate immune activation. A multifunctional nanoplatform was designed to address these constraints, incorporating a bimetallic metal-organic framework (BM) that serves as a nano immunological modulator, a tumor vessel-disrupting agent, and a gas-producing prodrug to augment the therapeutic efficacy of microwave hyperthermia. In this system, combretastatin A4 phosphate (CA4P) functions as a vascular disruptive agent, efficiently reducing heat dissipation by targeting and impairing tumor vasculature. Furthermore, the BM component mitigates endogenous ROS, therefore promoting the release of hydrogen sulfide (H₂S) gas from Bi₂S₃, which aids in the activation of immune cells. In vivo investigations validate that the synergistic effects of vascular disruption and immune activation significantly augment the antitumor response, illustrating the promise of this integrated approach to enhance the efficacy of MW hyperthermia-based cancer treatment [39].

Ovarian cancer (OC), recognized for possessing the highest fatality rate among gynecological cancers, necessitates the advancement of novel, efficacious, and low-toxicity treatment strategies. Ferroptosis, a kind of programmed cell death induced by iron-dependent lipid peroxidation, presents opportunities for tumor suppression and immune activation. A two-dimensional (2D) piezoelectric nanoagonist, Bi₂MoO₆-MXene (BMO-MXene), was developed to trigger ferroptosis in a controlled ultrasonic way. The establishment of a Schottky heterojunction between Bi₂MoO₆ and MXene led to a bandgap reduction of 0.44 eV, improved carrier

separation, and decreased electron-hole recombination, therefore augmenting the formation of ROS during ultrasonic stimulation. Through precise spatiotemporal ultrasonic activation, BMO-MXene reduced ovarian cancer cell growth, enhanced lipid peroxidation, altered mitochondrial membrane potential, and downregulated critical ferroptosis-regulating proteins, including glutathione peroxidase and cystathionine transporter. This cascade resulted in significant ferroptotic cell death, which in turn initiated ICD, enhancing DC maturation and fostering systemic antitumor immunity. BMO-MXene serves as an effective nanoplatform for producing ferroptosis, enhancing ovarian cancer therapy via a synergistic sonodynamic-ferroptosis-immunogenic cell death pathway (Fig. 12) [40].

Immunotherapy is essential in addressing metastatic malignancies, and its effectiveness can be augmented by integrating it with photothermal treatment, which eliminates tumor cells via hyperthermia and facilitates antigen release to increase immune responses. To realize this synergistic effect, a core-shell nanocomplex was constructed by encapsulating ovalbumin (OVA) and copper sulfide nanoparticles (CuS-NPs) within poly(lactide-co-glycolic acid) nanoparticles (PLGA-NPs), resulting in CuS@OVA-PLGA-NPs. The CuS-NPs exhibited robust photothermal characteristics, efficiently eliminating 4T1 tumor cells in vitro. NIR light irradiation produced heat that facilitated the release of OVA, resulting in increased concentrations of immune-related cytokines such as IL-6, IL-12, and TNF- α , along with the activation of CD⁸⁺ T cells. Treatment with either OVA-PLGA-NPs or CuS-NPs in conjunction with NIR irradiation inhibited primary tumor development, but did not significantly impact distant tumors. Conversely, CuS@OVA-PLGA-NPs subjected to NIR irradiation demonstrated significant inhibition of primary tumors owing to the synergistic effects of photothermal ablation and immune activation. This therapy notably elicited a strong immunological response, demonstrated by extensive infiltration of CD⁸⁺ T cells in both primary and distant tumors, thus inhibiting the advancement of metastatic lesions [41].

Transition metal chalcogenides, such as copper molybdenum sulfide (Cu₂MoS₄), have attracted considerable attention due to their superior catalytic characteristics. The existence of multivalent metal ions, including Cu⁺/Cu²⁺ and Mo⁴⁺/Mo⁶⁺, along with their significant absorption in the NIR spectrum, suggests that Cu₂MoS₄ (CMS) might be a viable choice for anticancer treatment. This amalgamation of electrical adaptability and NIR responsiveness highlights its promise in biological applications, especially in oncological therapy [42]. The combination of cuproptosis and ICD offers a viable approach to augmenting immunotherapy in cancer treatment. Nonetheless, its efficacy is frequently undermined by resistance

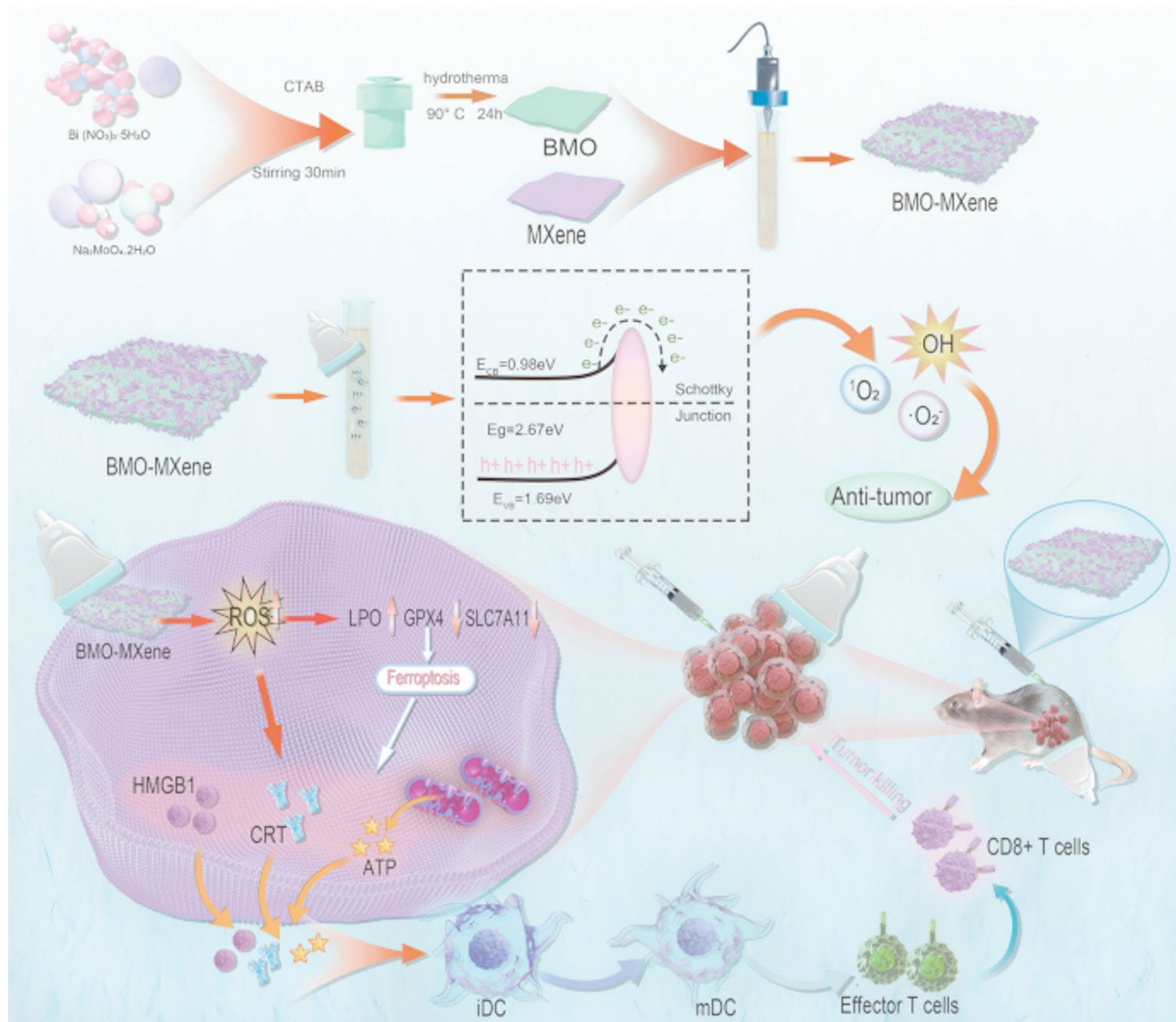


Fig. 12 Schematic representation of the anticancer mechanism of two-dimensional piezoelectric BMO-MXene. Under ultrasonic excitation, the sono-sensitizer BMO-MXene functioned as a ferroptosis inducer, promoting immunogenic cell death and augmenting anti-tumor immunity in ovarian cancer. Abbreviations: CTAB, hexadecyl trimethyl ammonium bromide; DC, dendritic cell; LPO, lipid peroxidation; GPX4, glutathione peroxidase; SLC7A11, cystine/glutamate transporter; HMGB1, high mobility group box 1 protein; CRT, calreticulin; ATP, adenosine triphosphate. Reprinted with permission from Springer Nature [40]

mechanisms present in the TME. To address these issues, a TME-responsive nanoinducer, DSF/CuS-C, was engineered by incorporating disulfiram (DSF) and copper sulfide onto a CpG oligonucleotide template, which furthermore functions as a Toll-like receptor agonist. This multifunctional construct is engineered to enhance tumor cell sensitivity to cuproptosis while concurrently augmenting ICD-mediated antitumor immunity. The nanoinducer facilitates the repolarization of M2 macrophages to a pro-inflammatory phenotype and, through a photothermal action, increases the accumulation of lipoylated mitochondrial proteins and produces proteotoxic stress characteristics of sensitive cuproptosis. These

strategies jointly elicit a robust immune response, successfully inhibiting breast tumor development in a mouse model. As a TME-activated therapeutic platform, DSF/CuS-C exhibits a synergistic strategy to enhance cuproptosis and immune activation, presenting a promising pathway for the progression of breast cancer immunotherapy [43].

T-cell depletion and poor tumor immunogenicity substantially restrict the efficacy of immune-mediated tumor eradication in melanoma. This work used an amphiphilic polyethylene glycol-poly(2-hexoxy-2-oxo-1,3,2-dioxaphospholane) copolymer with a thermally sensitive flowable core (mPEG-b-PHEP) to encapsulate IR780 dye and

manganese zinc sulfide nanoparticles (ZMS), resulting in the formation of polymer micelles (PPIR780-ZMS). These micelles facilitated accurate regulation of ZMS release in response to NIR stimulation. The Mn^{2+} -induced CDT, activated by photothermal effects, augmented the formation of ROS, operating as in vivo “smart bomblets.” PPIR780-ZMS enhanced ICD in cancer, marked by significant exposure of DAMPs. This approach facilitated the recruitment and proliferation of cytotoxic ($\text{CD}8^+$) and helper ($\text{CD}4^+$) T cells within tumor sites, altering the immunosuppressive TME to target both primary tumors and pulmonary metastases while preserving safe systemic cytokine levels. The stimulation of the Mn^{2+} -mediated cGAS–STING signaling pathway enhanced the antitumor immune response, providing a viable method to expand the use of Mn-based nanostructures (Fig. 13) [44].

The amalgamation of PTT with immune activation using biomimetic nanoplatforms is an advanced approach to addressing critical obstacles in cancer treatment. A hollow copper sulfide-based nanoplatform ($\text{HCuS}@$

OVA@CM , referred to as COC) was developed for accurate homotypic targeting and efficient melanoma treatment. This approach encapsulates the OVA antigen into hollow CuS nanoparticles, which are coated with B16F10 melanoma cell membranes to facilitate tumor-specific accumulation. Under 1064 nm NIR-II irradiation, the COC nanoplatform demonstrated a photothermal conversion efficiency of 16.0%, enhancing its therapeutic efficacy. In vitro evaluations demonstrated that the platform successfully elicited ICD, enhanced antigen presentation, and DC maturation. In vivo investigations demonstrated that COC-mediated photothermal therapy substantially suppressed tumor development while without inducing considerable weight loss, suggesting low systemic toxicity. This biomimetic design improves tumor targeting accuracy and increases immune responses, making it a viable contender for advanced melanoma therapy and wider anticancer applications [45].

Immunotherapy presents a potential strategy for tumor treatment; yet, its clinical efficacy is constrained by poor immunogenicity, hypoxia, and an immunosuppressive

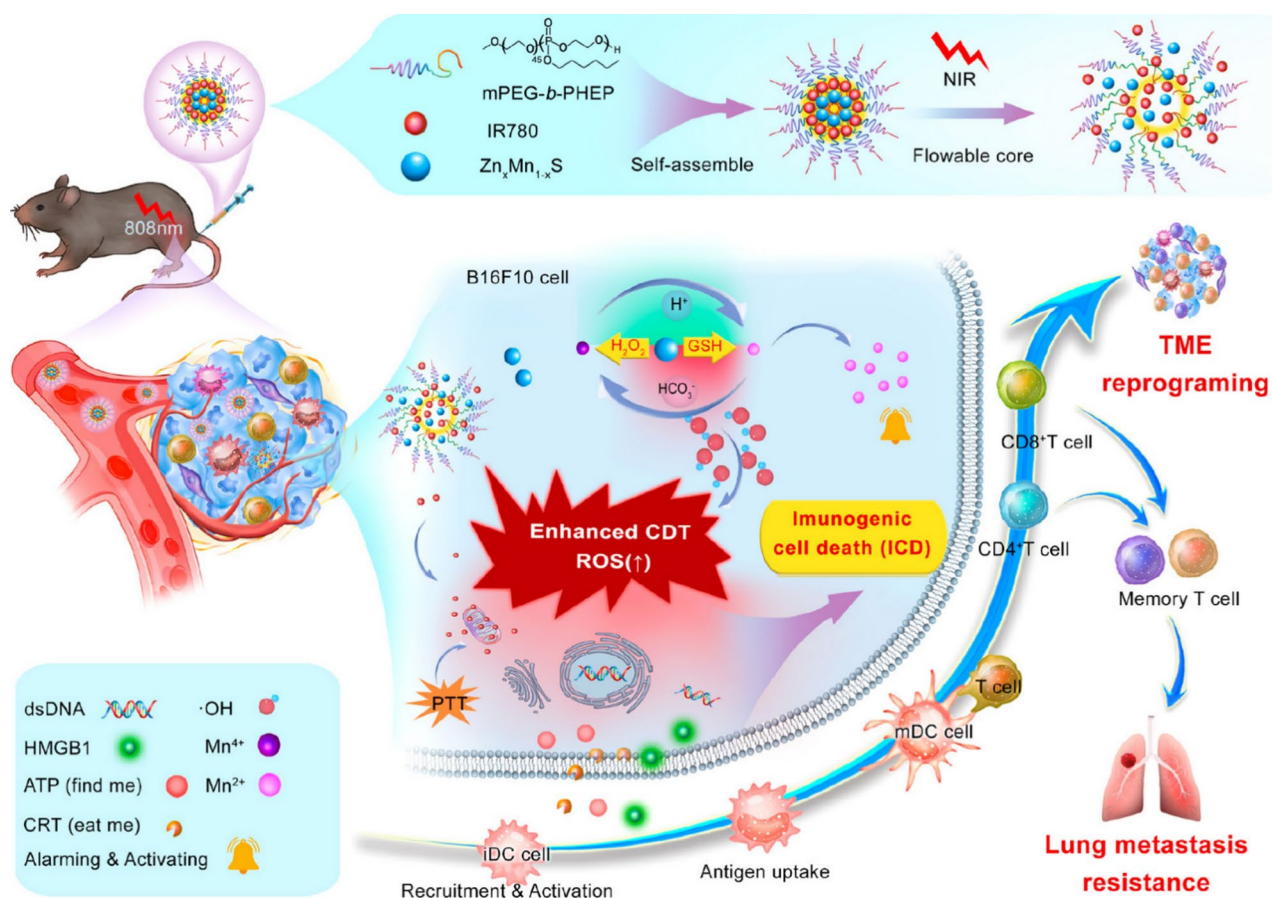


Fig. 13 Schematic Representation of Self-Assembly PPiR780-ZMS Releasing IR780 and ZMS under NIR Irradiation for Tumor Microenvironment Conditioning via Augmented CDT-Related Immunogenic Cell Death. Abbreviations: mPEG, Methoxypoly(ethylene glycol); NIR, near-infrared radiation; CDT, chemodynamic therapy; ROS, reactive oxygen species; ICD, immunogenic cell death; PTT, photothermal therapy; DC, dendritic cell; TME, tumor microenvironment. Reprinted with permission from ACS [44]

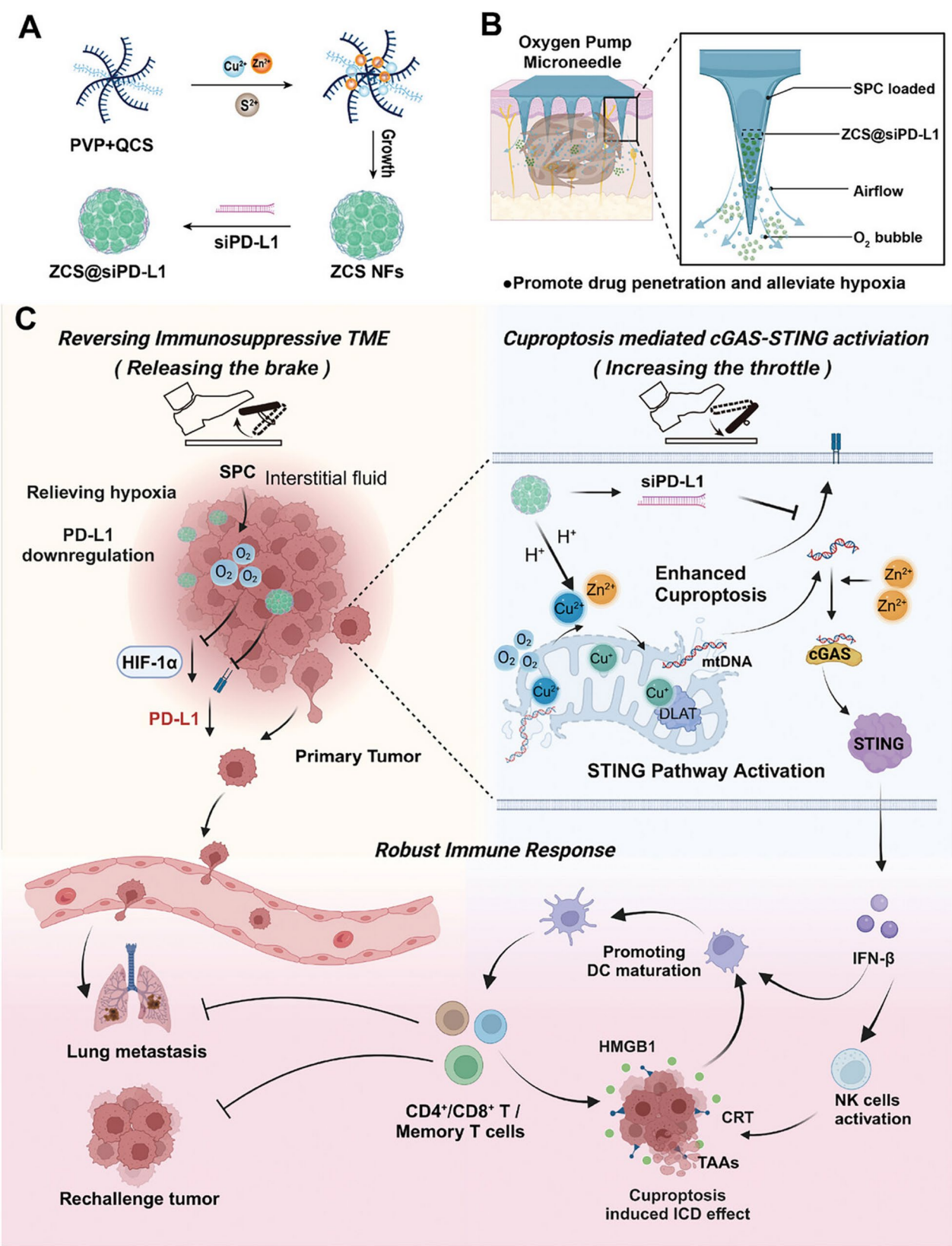


Fig. 14 (See legend on next page.)

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Fig. 14 Schematic representation of ZCS@siPD-L1 synthesis and anti-tumor approach. **(A)** ZCS nanofibers are manufactured utilizing quaternary chitosan (QCS, 10%, w/w) and polyvinylpyrrolidone (PVP, 90%, w/w) as stabilizers, whereas ZCS@siPD-L1 is formulated by incorporating siPD-L1 into ZCS nanofibers via electrostatic contact. **(B)** Oxygen pump microneedles enhance medication permeation and mitigate hypoxia by SPC dissolution, resulting in the generation of oxygen bubbles. **(C)** OPMNs-ZCS@siPD-L1 augment immunogenicity through cuproptosis-induced STING pathway activation and immunogenic cell death effects (“increasing the throttle” method), while counteracting the immunosuppressive tumor microenvironment via siPD-L1 and mitigating hypoxia through OPMNs (“releasing the brake” strategy). Abbreviations: PVP, polyvinylpyrrolidone; QCS, quaternary chitosan; ZCS, zinc-doped copper sulfide; PD-L1, programmed cell death Ligand 1; SPC, Sodium Percarbonate; cGAS, Cyclic GMP-AMP synthase; STING, stimulator of interferon genes; IFN, interferon; NK, natural killer; CRT, calreticulin; HMGB1, high mobility group box 1 protein; ICD, immunogenic cell death; HIF, hypoxia inducible factor. Reprinted with permission from Wiley [46]

TME. Oxygen pump microneedles (OPMNs) infused with zinc-doped copper sulfide nanoflowers (ZCS NFs) and PD-L1 small interfering RNA (siPD-L1) (OPMNs-ZCS@siPD-L1) have been engineered to augment tumor immunotherapy. ZCS NFs enhance tumor immunogenicity by activating cuproptosis, whereas siPD-L1 mitigates TME suppression, enhances drug penetration, and alleviates hypoxia via the production of oxygen bubbles. Additionally, cuproptosis-induced mitochondrial DNA (mtDNA) and Zn^{2+} together stimulate the STING pathway, provoking a robust immunological response. OPMNs-ZCS@siPD-L1 enhances sensitivity to cuproptosis and induces ICD both in vitro and in vivo, effectively suppressing tumor development and metastasis. The integrated strategy of “enhancing the throttle” (cuproptosis-mediated STING activation and ICD induction) and “removing the brake” (PD-L1 suppression and hypoxia alleviation) constitutes an innovative method for advancing percutaneous tumor immunotherapy (Fig. 14) [46].

To effectively tackle the challenges of heterogeneity and immune suppression in cancer, numerous multifunctional copper sulfide (CuS)-based nanoplateforms have been developed, amalgamating PTT, CDT, PDT, chemotherapy, ferroptosis induction, and immunotherapy into cohesive “all-in-one” systems. These nanosystems, frequently altered with targeted ligands, polymers, or immune modulators, exhibit improved tumor selectivity, biocompatibility, and therapeutic efficacy. One method utilizes a CuS nanoplateform encapsulated with docetaxel and enveloped in a polymer-peptide conjugate, facilitating targeted chemo-phototherapy characterized by high drug release efficacy, substantial cytotoxicity, and robust ROS production, leading to significant tumor suppression and apoptosis while minimizing systemic toxicity. Another technique employs CpG-templated CuS nanoflowers alongside disulfiram to induce cuproptosis and ICD, repolarize macrophages, and mature DCs, therefore augmenting immune responses in breast cancer treatment. Moreover, sophisticated CuS-based constructions such as CuS-PEG@Apt specifically target TNBC by integrating PTT, ferroptosis, and adenosine pathway inhibition, therefore enhancing anti-tumor immunity and directly destroying tumor cells. NIR-II-responsive systems such as AuNBP@CuS provide dual PTT and PDT, as well as CDT, by harnessing plasmonic effects and

tumor-acidic Fenton-type reactions to cause ICD and stimulate adaptive immunological responses, resulting in tumor ablation and immune activation. Moreover, CuS nanoparticles modified with PEG-maleimide sequester tumor antigens released during hyperthermia, transforming them into immune stimulators that, when combined with immune checkpoint blockade (anti-PD-L1), lead to significant CD^{8+} T cell infiltration and inhibition of both primary and metastatic tumors. These new nanotherapies collectively illustrate the significant potential of CuS-based systems to synergistically combine photothermal, chemotherapy, phototherapy, and immunotherapy for improved cancer treatment results [47–51].

Recent advancements in multifunctional CuS-based nanotherapeutics have facilitated the development of highly synergistic platforms that amalgamate PTT, PDT, CDT, chemotherapy, ferroptosis, and immunotherapy to improve cancer treatment efficacy while reducing side effects. A strategy entails encapsulating CuS nanoparticles within mesoporous silica modified with zinc phthalocyanine and hyaluronic acid, facilitating targeted DOX delivery and efficient ROS generation and hyperthermia upon NIR irradiation, thereby achieving significant cytotoxicity against TNBC cells. An advanced design features an intelligent dendrimer-based nanodevice containing CuS and the vascular disrupting agent DMXAA, surface-modified with the LyP-1 peptide for targeted breast cancer therapy; this nanoplateform disrupts tumor blood and lymphatic vessels, induces ICD, and promotes M1 macrophage polarization, thereby effectively inhibiting metastasis. A microbial nanohybrid of *E. coli* and Cu_2O nanoparticles for colon cancer utilizes tumor-specific H_2S to generate CuxS, facilitating NIR-II photothermal therapy and activating ferroptosis and cuproptosis, therefore reversing immunosuppression and augmenting systemic immunity in conjunction with immune checkpoint inhibition. A thermosensitive hydrogel (DSUC-Gel) containing “sea urchin-like” CuS nanoparticles, dihydroartemisinin, and sulfasalazine facilitates localized release triggered by the acidic TME, effectively addressing CDT resistance via ROS generation, ferroptosis induction, and ICD, thereby significantly reducing tumor growth. Moreover, CuS nanoparticle-mediated photothermolysis, in conjunction with TLR9 agonists and anti-PD-1 treatment, augments antigen presentation and T cell

activation, hence improving abscopal tumor suppression and survival in mice models. Collectively, these varied and sophisticated CuS-based nanoplatforms provide adaptable and promising approaches for precise, multimodal cancer treatment with promise for clinical use [48, 52–55].

Quantum Dots

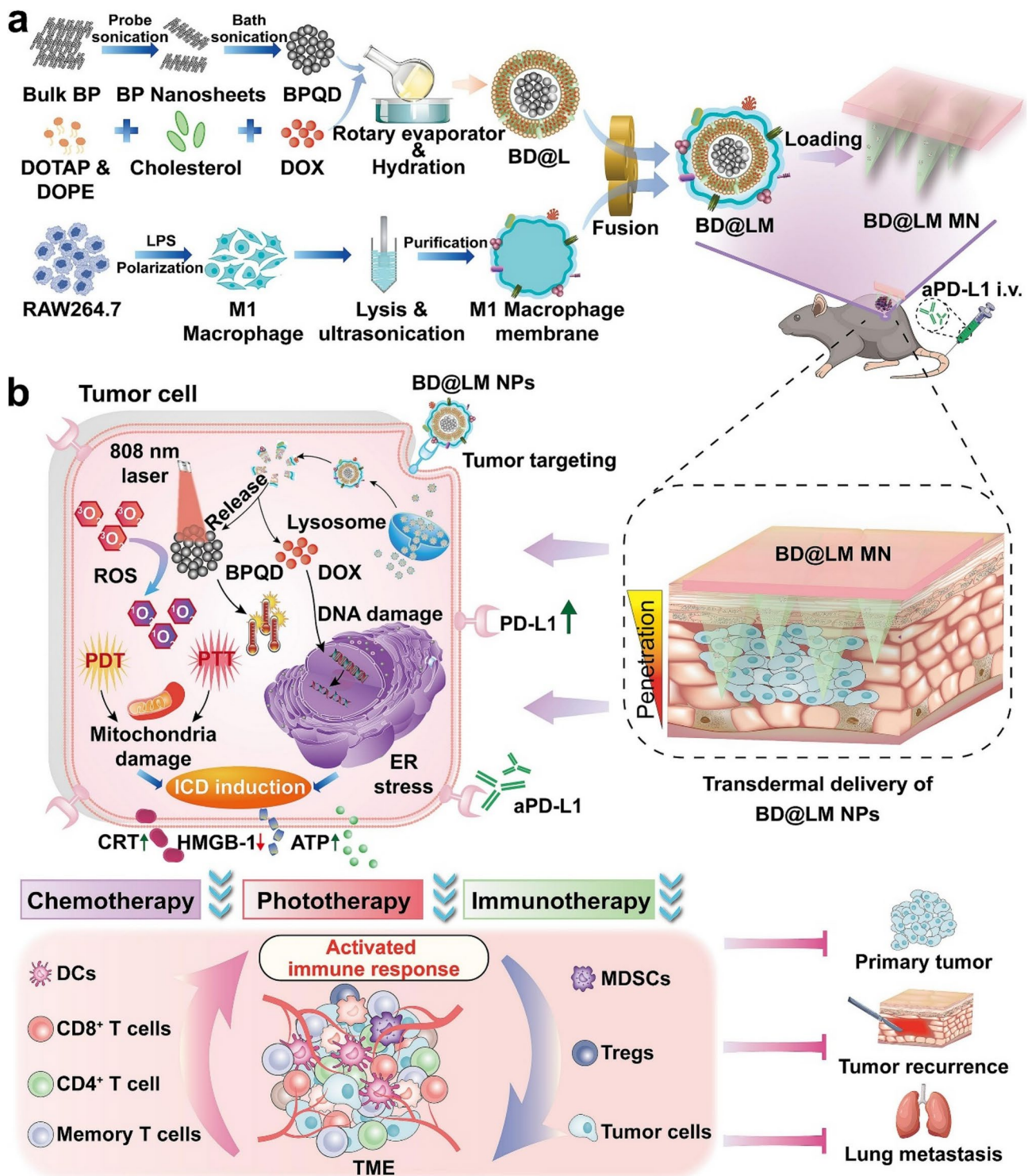
Immunotherapy possesses considerable promise in oncological treatment; nevertheless, the systemic delivery frequently results in side effects that prevent its practical use. A bioadhesive injectable hydrogel was developed to construct localized immune niches for the immunomodulation of the TME and catalytic immunotherapy. The design features a phenolic single-atom nanozyme (SAN), which is generated in situ by attaching palladium (Pd) single atoms onto catechol-grafted carbon quantum dots (DA-CQD@Pd). This SAN, incorporated into the hydrogel, demonstrates peroxidase-like catalytic activity, facilitating the targeted production of ROS to trigger apoptosis in tumor cells. The hydrogel is further integrated with the immune adjuvant CpG oligodeoxynucleotide (CpGODN), which is delivered in a regulated way to reduce systemic exposure and protect the adjuvant against degradation. Upon administration, the hydrogel clings to the tumor location, establishing a localized platform for immune activation. The hydrogel, when combined with systemic treatment of an immune checkpoint inhibitor (anti-PD-L1), promotes localized immunomodulation, increases therapeutic effectiveness, and significantly suppresses tumor metastasis via a synergistic catalytic immunotherapy mechanism [56].

The spread and recurrence of cancer after surgical resection continue to pose significant challenges to achieving favorable treatment results. To tackle this difficulty, a photo-immune nanoparticle enveloped in M1 macrophage membranes (BD@LM) has been developed, especially intended to capitalize on the inflammatory milieu following surgery. These nanoparticles co-encapsulate BPQDs, which act as photosensitizers, alongside the chemotherapeutic drug DOX, facilitating chemophototherapy to elicit ICD in tumor cells. This ICD promotes DC development and triggers a vigorous immunological response. To facilitate effective intratumoral administration, BD@LM is integrated into a biodegradable microneedle patch that circumvents the dermal barrier and improves localized therapeutic concentration. This method substantially enhances the effectiveness of immune checkpoint blockade therapy with anti-PD-L1 (aPD-L1). In preclinical models of orthotopic and post-surgical breast cancers and melanoma, the therapy significantly inhibited tumor development. This also led to robust T cell activation, decreased populations of immunosuppressive cells, and a significant enhancement in

memory T cell production, signifying the establishment of long-term immunological memory that can avert tumor recurrence. This technique provides a robust platform that combines bioinspired nanoparticle gorka.orive@ehu.es with microneedle delivery to enhance checkpoint blockade treatment (Fig. 15) [57].

In the recent years, there have been significant advances regarding the application of nanoparticles in cancer therapy to improve blood circulation time, reduce immune clearance and accelerate tumor suppression. A versatile multifunctional nanoplatform known as BPP@RTL has been developed that integrates BPQD for phototherapy, paclitaxel (PTX) for chemotherapy, and Poly-Metformin (PM) for immunomodulation within hybrid liposomes cloaked by fused cancer cell and red blood cell membranes, facilitating precise tumor targeting and prolonged circulation [58]. This method, when used in conjunction with aPD-L1 immune checkpoint inhibition, markedly enhances DC maturation and T cell activation, primarily eliminating primary tumors and inhibiting Lung metastasis in a 4T1 breast cancer model. In a broader context, synergistic photo-immunotherapy integrating PDT and PTT with immune activation has obtained attention for addressing limitations such as metastasis and recurrence by inducing ICD, releasing tumor-specific antigens (TSAs) and DAMPs, and enhancing CTL infiltration [59]. Strategies in this domain focus on reversing the tumor immunosuppressive milieu, modulating immune-tumor cell interactions, And augmenting ICD efficiency, while tackling existing technical obstacles. In addition, innovative Z-scheme CD-based photothermal agents known as 2D ultrathin nonmetallic BxC/C Janus quantum sheets demonstrate reduced fluorescence and improved NIR-II photothermal conversion efficiency, facilitating effective, biocompatible, synergistic photothermal-immunotherapy with significant tumor eradication and minimal harm to healthy tissues [60].

A novel strategy was developed that combines BBPQDs-based PTT with anti-PD-L1 immunotherapy, recognized as a significant advancement in the treatment of TNBC, an aggressive and therapy-resistant Subtype. BBPQDs demonstrated enhanced tumor-targeting capability via homologous targeting, resulting in substantial accumulation And retention at the tumor site. BBPQDs, under 808 nm NIR irradiation, elicited a temperature increase of up to 58.1 °C in vivo and facilitated DC maturation, hence augmenting anticancer immune activation. In mouse models, this combination treatment more successfully controlled primary tumor development compared to monotherapies and dramatically prevented distant tumor growth and lung metastasis, resulting in nearly absent visible metastases in rechallenged animals. Furthermore, immunological memory was evidenced by an increased percentage of splenic effector memory



T cells, signifying substantial long-term protection. No notable systemic toxicity was seen. These findings highlight the therapeutic potential of BBPQDs-mediated photothermal immunotherapy in addressing TNBC recurrence and metastasis (Fig. 16) [61].

Recent advancements in photoimmunotherapy for cancer treatment emphasize several techniques to surmount tumor hypoxia, immunosuppression, and resistance to immune checkpoint inhibition. One method highlights the development of QTANHOH, a photosensitizer targeting histone deacetylase (HDAC) that demonstrates robust type-I/II ROS generation and significant phototoxicity ($IC_{50} < 10$ nM) in both normoxic and hypoxic environments [62]. This compound not only inhibits HDAC activity but also stimulates the immune microenvironment, resulting in total tumor eradication and suppression of metastasis in breast cancer models. Another strategy employs multifunctional nanoassemblies, PC@GCpD(Gd), which incorporate polydopamine-stabilized graphene quantum dot photosensitizers, CpG oligodeoxynucleotide-based immune adjuvants, and $Gd^{3+}/Cy3$ imaging probes for dual photothermal and photodynamic tumor eradication and immune activation through TLR9-mediated cytokine release and DC maturation, resulting in nearly complete suppression of EMT6 tumors with real-time MR and fluorescence imaging guidance [63]. Nuclear-targeting size-engineered nanoparticles (aPD-L1/ZnPc/GQD-PEG, PZGE) reveal that ultrasmall 5 nm particles demonstrate enhanced nuclear penetration, induce DNA damage, amplify IFN-I-mediated innate immune responses, transform “cold” tumors into “hot” tumors, increase cytotoxic T-cell infiltration, and counteract PD-L1 suppression, thereby effectively managing distant oral squamous cell carcinoma [64].

To overcome the constraints of immune checkpoint blockade (ICB) treatment, such as low immunogenicity and inadequate T-cell infiltration in immunologically “cold” tumors, two synergistic nanoplateform techniques are proposed that combine phototherapy with ICB to augment anti-tumor immunity. One method involves the engineering of red carbon dot-doped Cu–metal–organic framework nanoparticles (Cu-MOF@RCD) as nano-reactors responsive to the tumor microenvironment and NIR stimuli. These nanoparticles can decompose endogenous H_2O_2 through Fenton-like reactions, diminish glutathione to alleviate ROS scavenging, and generate PTT effects, thereby collectively ROS levels to enhance PDT and CDT [65]. This platform, in conjunction with anti-PD-L1 antibody, produces synergistic benefits in PDT, PTT, CDT, drug-gene therapy (DG), and ICB, effectively eliminating primary tumors and inhibiting distant tumor development and metastasis. The second strategy involves the creation of a comprehensive nanoplateform (aPD-L1@GdCDs) by conjugating an anti-PD-L1

antibody with gadolinium-doped NIR emitting carbon dots. These carbon dots are non-toxic in darkness but, upon mild NIR laser irradiation, generate synergistic photothermal and photodynamic effects, resulting in ICD that enhances antigen exposure and promotes significant CD^{8+} T-cell infiltration [66]. This significantly enhances tumor ablation and anti-metastatic effectiveness compared to phototherapy or immune checkpoint blockade alone, with real-time multimodal imaging (FLI/PAI/MRI) facilitating treatment guiding. Collectively, these platforms illustrate how the integration of ROS-enhancing phototherapies with immune checkpoint blockade might transform “cold” malignancies into “hot” tumors, hence improving systemic anti-tumor immune responses and long-term therapeutic results.

Emerging materials

A multifunctional Au-modified Ti_3C_2 MXene ($Au-Ti_3C_2$) nanosheet system is recognized as a significant development in nanoplateform-based cancer therapy, designed to combine PTT, enzyme dynamic therapy (EDT), and immune activation for efficient tumor destruction. $Au-Ti_3C_2$ demonstrated exceptional photothermal conversion efficiency under 808 nm laser irradiation, enhancing tumor surface temperatures, hence facilitating targeted ablation. The implanted glucose oxidase (GOx) stimulated the conversion of glucose to generate H_2O_2 , which was then degraded by Au nanoparticles into harmful $\cdot OH$ radicals, resulting in significant EDT effects. The combinatory therapy in vivo significantly inhibited tumor development and elicited robust immunological responses, as shown by an increase in mature dendritic cells ($CD^{80+}CD^{86+}$ up to 36.2%) and cytotoxic T lymphocytes. Moreover, immunological memory was created, diminishing tumor recurrence and lung metastasis in rechallenged animals. No notable toxicity was observed, highlighting the platform's biosafety and therapeutic promise in synergistic cancer therapy [67].

The therapeutic efficacy of RT is frequently impeded by insufficient DNA damage in tumor cells, collateral damage to Healthy tissues, And inherent radioresistance stemming from active DNA repair processes. A multifunctional two-dimensional nanomaterial, known as APMP, has been developed to address these restrictions. This structure comprises a core of MXene nanosheets enveloped in gold nanorods And a cisplatin shell, further stabilized by polyvinyl alcohol. APMP utilizes its distinctive electrical configuration And robust photothermal characteristics to augment RT effectiveness by improving radiosensitization and obstructing DNA repair. In vitro studies demonstrate that APMP enhances ROS production by roughly 2.6-fold relative to RT alone, markedly augmenting tumor radiosensitivity. When integrated with PTT, APMP facilitates localized hyperthermia, thereby

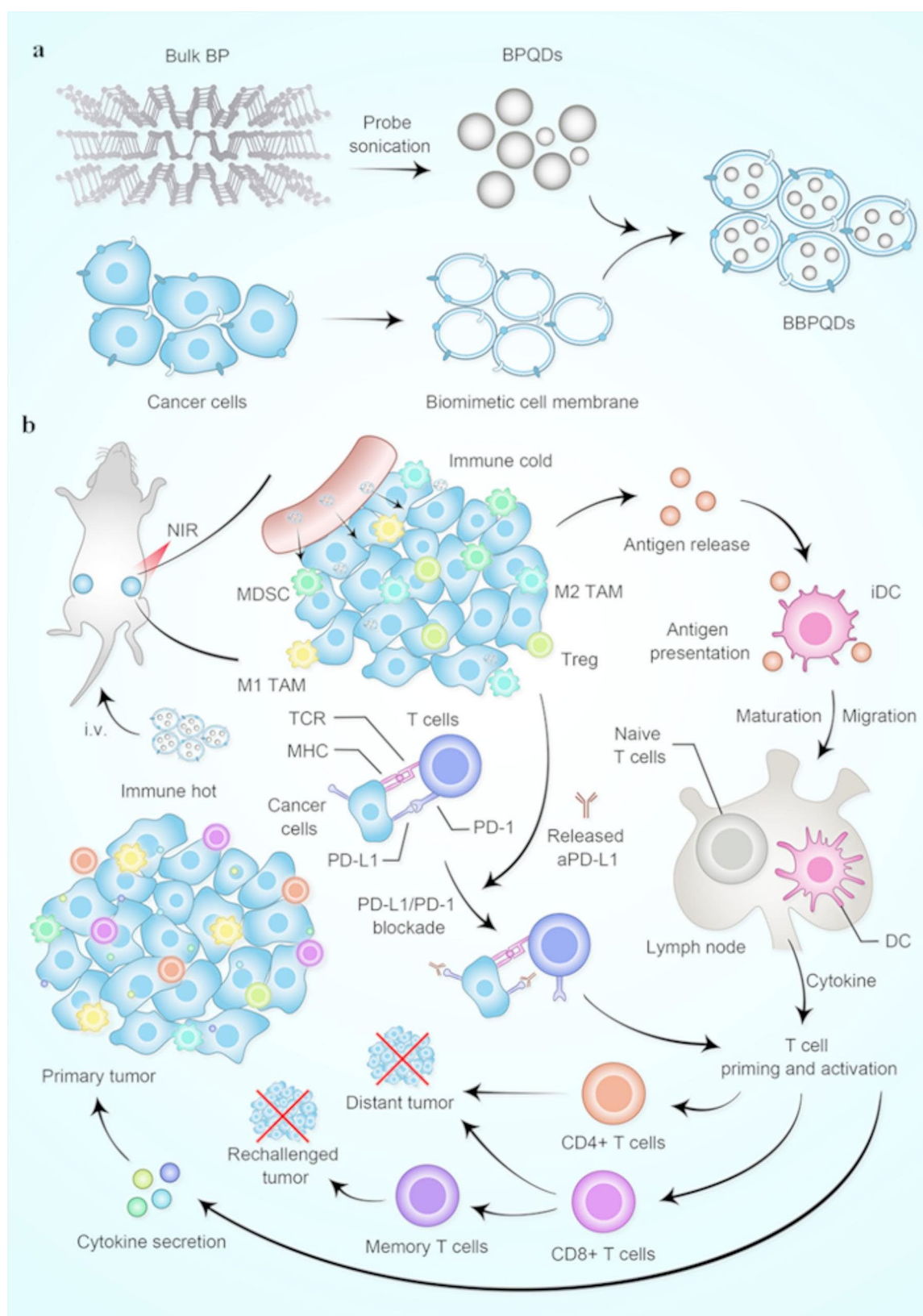


Fig. 16 (a) illustration of the synthesis process of BBPQDs. (b) Potential mechanism of BBPQDs-mediated photothermal therapy in conjunction with immune checkpoint blockade therapy for antitumor treatment. Abbreviations: BP, black phosphorus; BPQD, black phosphorus quantum dots; NIR, near-infrared radiation; MDSC, myeloid-derived suppressor cells; TAM, tumor-associated macrophage; Treg, regulatory T cell; DC, dendritic cell; TCR, T-cell receptor; MHC, major histocompatibility complex; PD-L1, programmed cell death Ligand 1. Reprinted with permission from BMC Springer Nature [61]

compromising glioblastoma cell integrity and mitigating resistance to radiation. The platform also promotes ICD, which enhances immune activation and provides a synergistic approach for combination immunotherapy. This core-shell nanoplatform facilitates targeted tumor elimination while reducing systemic toxicity, offering a viable approach for enhancing glioblastoma treatment and illustrating the combination of radiotherapy sensitizers with immunotherapy for better clinical results [68].

Cryoablation (CRA) is a minimally invasive technique for localized tumor eradication that has sometimes exhibited systemic immune activation referred to as the “abscopal effect.” The incidence of this immune-mediated condition is infrequent and variable. A sequential treatment method was devised to improve repeatability and efficacy by integrating cGAS-STING pathway activation with moderate photothermal therapy (mPTT) before CRA. This method employs customized Ti_3C_2 -based nanosheets ($\text{Ti}_3\text{C}_2@\text{Au-PEG-DMXAA}$) that include gold nanoparticles for improved imaging-guided administration, are PEGylated for stability, and are loaded with the STING agonist DMXAA. The gold nanoparticle component facilitates CT-guided delivery, whereas the mPTT generated by these nanosheets enhances immunogenic tumor cell apoptosis. This mechanism, in conjunction with STING pathway activation, promotes DC maturation, TAM repolarization, and cytotoxic T cell infiltration. The subsequent CRA eliminates the initial “hot” tumor and progressively releases tumor-associated antigens in situ, so serving as a tailored cancer vaccine. This dual-phase therapy not only induces strong systemic anticancer immunity but also creates enduring immunological memory, thereby diminishing the likelihood of tumor recurrence and metastasis (Fig. 17) [69].

BP nanosheets (NSs), due to their distinctive physicochemical properties including hydrophilicity, biodegradability, corrugated crystal structure, and photothermal responsiveness, have emerged as highly promising nanomaterials in cancer therapy, particularly in integrated chemo-photo-immunotherapeutic approaches. Despite difficulties in producing uniform BP nanosheets owing to the top-down synthesis approach, a plug-and-play ultrasonic bubble bursting technique has been devised to generate nanosheets with enhanced uniformity, facilitating their application as multifunctional platforms for targeted drug delivery, immune modulation, and phototherapy [70]. For instance, BP nanosystems have been infused with DOX, polyethylene glycol–chitosan targeting agents, and PD-L1/small interfering RNA to attain synergistic effects in colorectal cancer treatment. Subsequent investigations validated that DOX-loaded BP nanosystems (BP-DOX) demonstrate pH- and photo-responsive drug release, resulting in significantly improved tumor inhibition rates [71]. Investigations demonstrated that

BP exposure may increase oxidative stress and inflammation in non-tumor tissues, highlighting the necessity for biomimetic and targeted therapies. This resulted in the creation of red blood cell membrane- and RGD peptide-coated BPs (RGD-RBC@BP), which exhibited better tumor targeting, extended circulation, improved cellular uptake, and effective photothermal tumor ablation. In the context of immunotherapeutic integration, Cordyceps sinensis polysaccharides (CSP), recognized for their immunomodulatory properties, were co-encapsulated with BP to form BP/CSP@PDA–PEG–FA nanoparticles [72]. This formulation not only facilitated photothermal ablation of tumor cells but also induced a phenotypic shift in TAMs from M2 (tumor-promoting) to M1 (tumor-suppressing), thereby augmenting T cell-mediated responses in breast cancer models. A multifunctional system was developed to directly address tumor immune evasion, encapsulating decitabine-loaded BP nanosheets within MDSC membranes (BDM) to exploit TME targeting, induce ICD, and initiate cell cycle arrest [73]. This method exhibited significant in vivo tumor suppression by reducing immune-suppressive cells and enhancing cytotoxic T cell infiltration and dendritic cell activation. These integrated findings together demonstrate a logical progression of BP-based nanoplatforms from traditional chemo-phototherapies to sophisticated immunomodulatory and biomimetic systems, highlighting their increasing promise for precise, multi-modal, and therapeutically applicable cancer treatments.

The management of “immune cold” cancers is considerably impeded by their low immunogenicity and extremely immunosuppressive milieu, which collectively obstruct effective antitumor immunity. To address these obstacles, a drug-free NIR-activated nitric oxide (NO)-releasing nanogasholder ($\text{NO}_{\text{PS}}@\text{BP}$) was engineered, including a nitrate-containing polymeric NO donor as the outer shell and BP as the inner core energy converter. Upon NIR irradiation, the BP core produces photothermal heat and functions as a reductant, initiating fast and localized nitric oxide release from the outer layer. This spatiotemporally regulated nitric oxide burst, alongside mild photothermal effects, concurrently induces ICD, facilitating DC maturation and CTL infiltration, while also reversing immunosuppression by inhibiting Tregs, suppressing M2 macrophages, and downregulating PD-L1 expression. $\text{NO}_{\text{PS}}@\text{BP}$ demonstrates significant therapeutic effectiveness against both primary and metastatic tumors in B16F10 melanoma models by a synergistic strategy that incorporates NO gas treatment, immunotherapy, and photothermal therapy. This multifunctional platform provides a potential approach to transform immunological-cold tumors into immune-responsive tumors by enhancing ICD and modifying the immune TME (Fig. 18) [74].

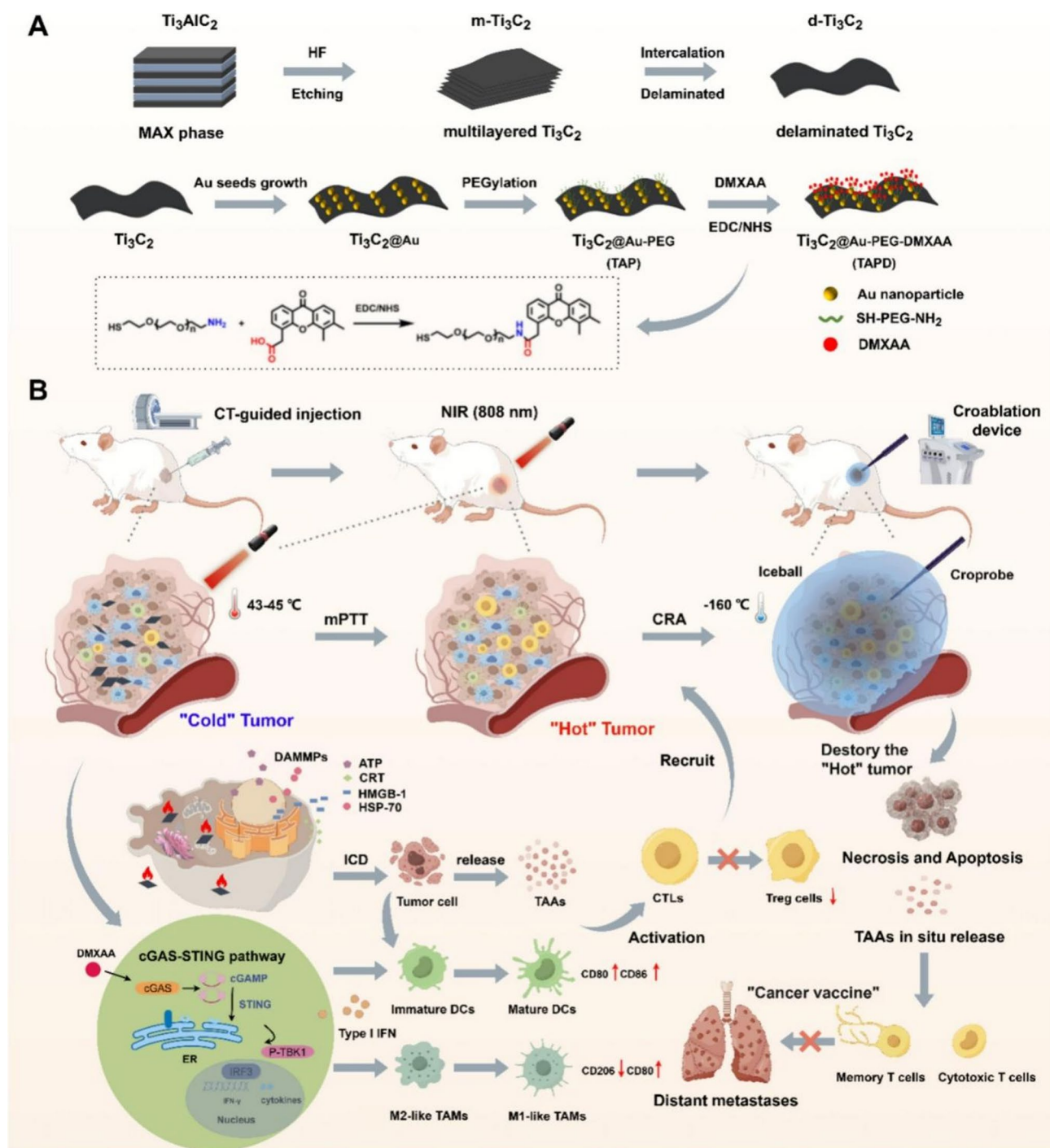


Fig. 17 (A) schematic representation of the synthesis of $\text{Ti}_3\text{C}_2@Au\text{-PEG-DMXAA}$ (TAPD) functional nanosheets and (B) the synergistic tumor treatment approach. Abbreviations: PEG, polyethylene glycol; NIR, near-infrared radiation; CT, computed tomography; mPTT, mild photothermal therapy; CRA, Cryoablation; TAAs, tumor-associated antigens; Treg, regulatory T cell; CTL, cytotoxic T lymphocyte; DC, dendritic cell; IFN, interferon; ATP, adenosine triphosphate; CRT, calreticulin; HMGB1, high mobility group box 1 protein; ICD, immunogenic cell death; cGAS, cyclic GMP-AMP synthase; STING, stimulator of interferon genes; ER, endoplasmic reticulum; TBK1, Tank-binding kinase 1; IRF3, interferon regulatory factor 3. Reprinted with permission from Elsevier [69]

Targeting and stealth components

Three novel nanomedicine approaches are highlighted to enhance cancer immunotherapy by regulating the PD-1/PD-L1 immune checkpoint, using phototherapy and

targeted delivery. Elpro, a photodynamic degrader aimed against breast cancer, integrates an EGFR-targeting peptide (QRHKPRE) with the photosensitizer protoporphyrin IX (PpIX) to encapsulate the EGFR inhibitor afatinib,

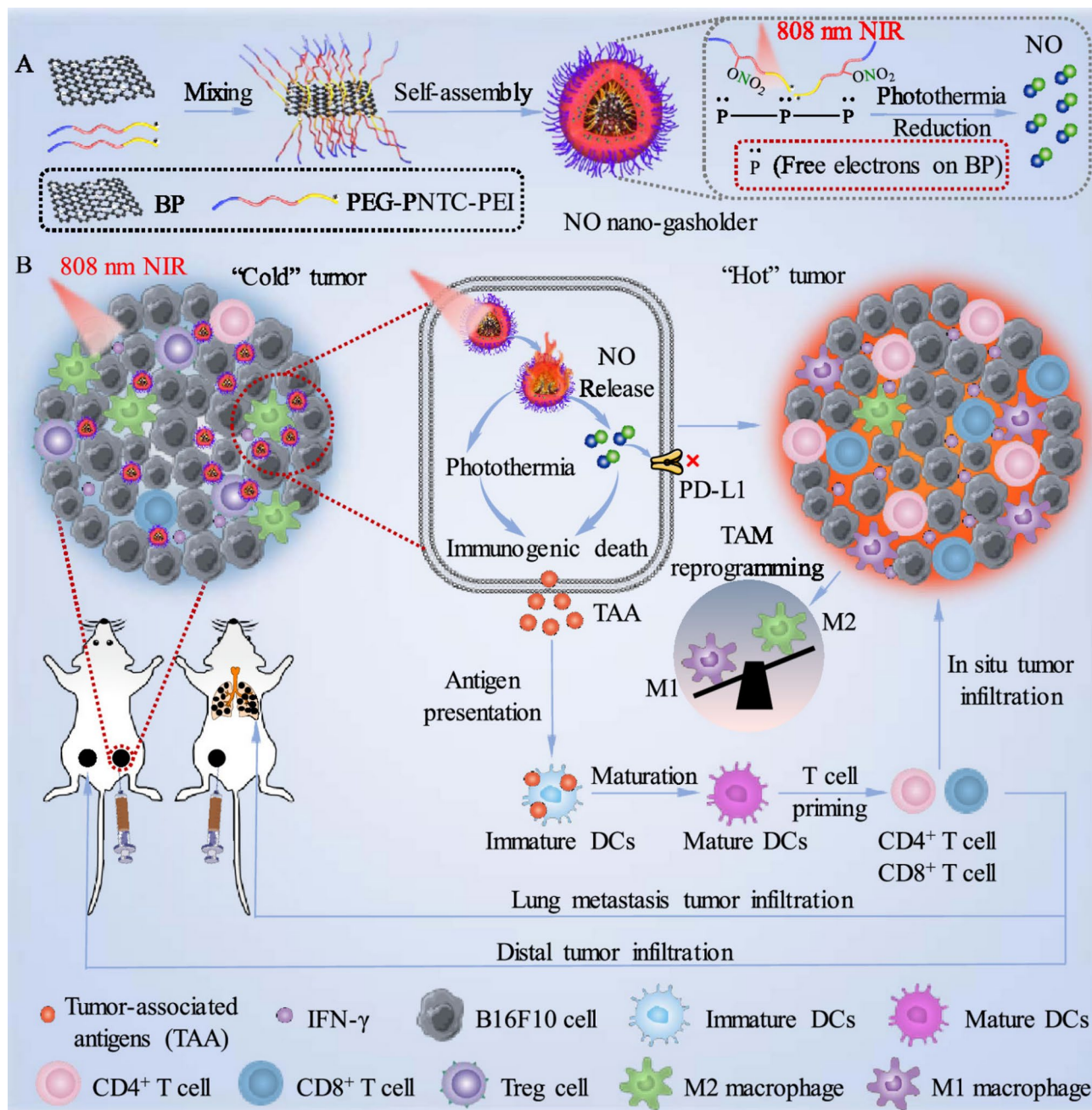


Fig. 18 (A) Fabrication of NIR-enabled nitric oxide burst of drug-free NOPS@BP nanogasholder, consisting of an exterior layer of polymeric nitric oxide donor and an inner core of black phosphorus serving as an energy converter. (B) Advancement of drug-free NOPS@BP for augmenting tumor immunogenicity, restructuring the tumor immunosuppressive microenvironment, hence facilitating effective tumor suppression and metastasis prevention. Abbreviations: BP, black phosphorus; PNTC, poly(nitrate carbonate); PEG, poly(ethylene glycol); PEI, pentaethylenehexamine; NIR, near-infrared radiation; NO, nitric oxide; PD-L1, programmed cell death Ligand 1; TAM, tumor-associated macrophages; DC, dendritic cell; IFN, interferon; TAA, tumor-associated antigen; Treg, regulatory T cell. Reprinted with permission from ACS [74]

resulting in nanomicelles that preferentially accumulate in EGFR-overexpressing breast cancer cells [75]. Following PDT-induced ROS formation, Elpro not only triggers ICD to release tumor-associated antigens but also degrades EGFR, resulting in PD-L1 downregulation and enhanced anti-tumor immunity against both

primary and metastatic illness. Secondly, a molecularly engineered nanoplateform substitutes cumbersome, unstable anti-PD-L1 antibodies with an anti-PD-L1 peptide (APP) chemically conjugated to the photosensitizer IR780, resulting in nanoparticles with accurate APP loading (48.4 wt%), PDT functionality, and ICD induction,

facilitating concurrent tumor cell destruction and PD-1/PD-L1 inhibition to mitigate both primary and metastatic tumors [76]. Third, a therapeutics-based multifunctional nanosystem incorporates tumor-targeting and penetration enhancement through an MMP-2-responsive peptide containing Lyp-1, photothermal therapy utilizing IR820 as both carrier and photosensitizer, and PD-1/PD-L1 blockade via a d-peptide Antagonist, achieving over 97.5% primary tumor inhibition within 24 h and complete eradication when combined with photothermal therapy, while also decelerating distal tumor progression [77]. These techniques collectively exhibit precise, synergistic, and tumor-responsive designs aimed at maximizing immunotherapy efficacy while reducing systemic toxicity.

Immunotherapy has received heightened focus in the management of TNBC, but its efficacy is hindered by the tumor's poor immunogenicity and the existence of an ITM. A dual-modified liposomal system, CS/LyP-1-PC Lip, has been developed to address these problems. This formulation includes paclitaxel (PTX) and cryptotanshinone (CTS), and is surface-modified with LyP-1

peptide and chondroitin sulfate (CS) to elicit chemoimmunotherapeutic effects through the induction of ICD and the inhibition of STAT3 signaling. The architecture facilitates improved tumor targeting through p32 and CD44 receptor-mediated endocytosis. Upon entering the TME, hyaluronidase destroys the chondroitin Sulfate layer, Hence promoting medication release. CTS boosts the cytotoxic efficacy of PTX against 4T1 tumor cells, whereas PTX induces ICD and increases cytotoxic T lymphocyte infiltration, therefore eliciting an anticancer immune response. Simultaneously, CTS inhibits STAT3 activity, resulting in a decrease of Tregs, M2-type TAMs, and MDSCs, therefore collectively remodeling the ITM. This dual-targeting liposomal technology demonstrates considerable tumor suppression and significantly reduces lung metastasis in preclinical TNBC models, presenting a viable approach for improved chemoimmunotherapy in TNBC (Fig. 19) [78].

A-Cy-Ni-RGD, a self-assembling nanoparticle system targeting three specific sites, was designed to improve the effectiveness of radiation and provide real-time monitoring of hypoxia in $\alpha v \beta 3$ -positive, hypoxic malignancies.

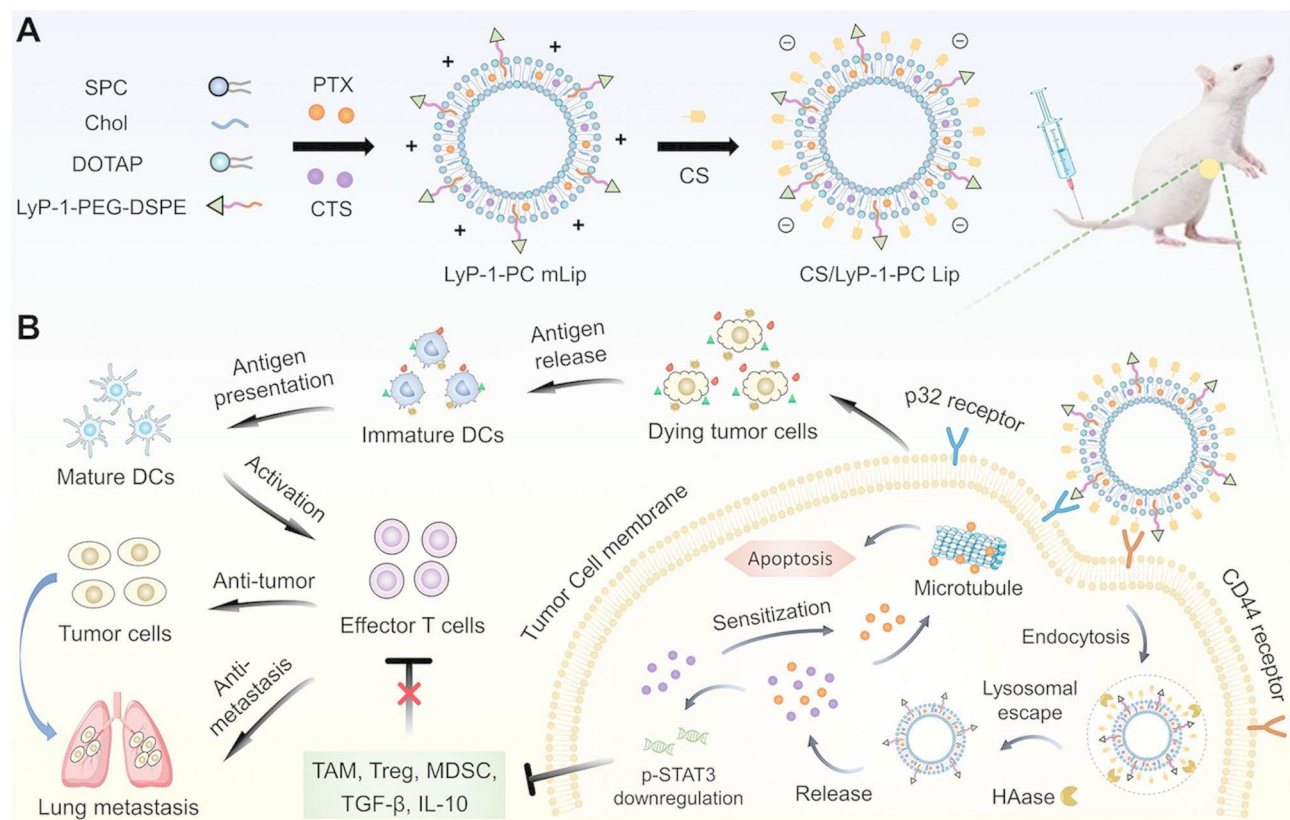


Fig. 19 Schematic representation of the synthesis of LyP-1/CS dual-modified liposome (CS/LyP-1-PC Lip), along with its intracellular trafficking pathway and therapeutic mechanism. (A) Synthesis of CS/LyP-1-PC Lip. (B) CS/LyP-1-PC Lip augments TNBC chemoimmunotherapy by inducing immunogenicity and suppressing STAT3 activation. Abbreviations: PTX, paclitaxel; CTS, cryptotanshinone; CS, chondroitin sulfate; DC, dendritic cell; TAM, tumor-associated macrophage; Treg, regulatory T cell; MDSC, myeloid-derived suppressor cell; TGF, transforming growth factor; IL, interleukin; STAT3, signal transducer and activator of transcript-3. Reprinted with permission from Wiley [78]

These nanoparticles, consisting of a nitroimidazole-linked radiosensitizer, selectively aggregate in tumors and are enzymatically transformed into Cy-Ni-RGD NPs, resulting in augmented NIR fluorescence (FL₇₁₀) and dual photoacoustic (PA) signals. Under hypoxic conditions, further reduction by nitroreductase (NTR) enhances nanoparticle size and fluorescence while modifying PA signals, facilitating accurate monitoring of tumor targeting and hypoxia. Low-dose X-ray irradiation enhances NTR activity, resulting in increased protein labeling and DNA damage, as well as the induction of robust ICD. This enhances antitumor immunity, inhibits tumor growth and metastasis, and significantly prolongs Life in a 4T1 breast cancer model. The research highlights the potential of A-Cy-Ni-RGD nanoparticles as radiotheranostic agents for enhanced imaging-guided radio-immunotherapy in resistant hypoxic malignancies (Fig. 20) [79].

Three sophisticated nanotherapeutic systems are introduced to improve cancer treatment by combining tumor-targeted radiosensitization or PDT with immune modulation. The biodegradable silk sericin-based nanoassembly Pt@Bi₂Se₃-RGD (PBR) provides high-Z elements for radiosensitization and reacts to tumor-specific acidic pH and MMP-9 overexpression, deconstructing into Bi, Se, and Pt nanoparticles for safe elimination. Photoacoustic imaging-guided PBR, in conjunction with radiation, amplifies anti-PD-L1 effectiveness, elicits strong immune responses, and inhibits both primary and metastatic cancers, perhaps through the Areg/EGFR/Bcl-2 apoptotic pathway [80]. Secondly, C/J-LipoRGD liposomal nanodrugs co-deliver catalase to breakdown tumor H₂O₂ and mitigate hypoxia, in conjunction with the BRD4 inhibitor JQ1 to downregulate PD-L1 expression and disrupt DNA damage repair, hence reversing T-cell fatigue and enhancing radiosensitivity [81]. This method, when used in conjunction with α PD-1, results in total tumor eradication and metastasis elimination in 80% of mice, with a long-term Survival exceeding 80 days. Third, pH-responsive porphyrin-peptide nanosheets (PRGD) encapsulating the IDO inhibitor NLG919 (PRGD/NLG919) specifically target tumor cells overexpressing α v β 3 integrin, producing significant singlet oxygen under acidic TME conditions and eliciting strong photocytotoxicity following laser irradiation [82]. This PDT-immune combination treatment markedly increases CD³⁺CD⁸⁺ and CD³⁺CD⁴⁺ T-cell populations, provoking robust adaptive immune responses and augmenting systemic antitumor immunity. These multifunctional nanoplateforms together tackle hypoxia, immunosuppression, and treatment resistance, providing powerful synergistic approaches for successful radio- and photo-immunotherapy.

Chemotherapy is fundamental to cancer treatment, since certain medications can trigger ICD and bolster immune responses; nevertheless, their restricted tumor

specificity frequently diminishes therapeutic effectiveness. A TME-responsive drug delivery system (Ag₂S-PAsp-cRGD) was designed to include DOX for targeted chemo-photothermal-immunotherapy. Ag₂S nanoparticles were modified with polyaspartic acid (PAsp) for drug loading and functionalized with the cRGD peptide to improve tumor targeting. In vivo imaging validated efficient tumor accumulation, facilitating accurate DOX administration. The inherent photothermal characteristics of Ag₂S nanoparticles not only eradicated tumor cells but also enabled the regulated release of DOX, enhancing its chemotherapeutic efficacy. This combo medication elicited significant ICD, enhancing antigen presentation and T cell activation, hence provoking a vigorous systemic immune response. The treatment successfully eradicated primary tumors, inhibited recurrence, and curtailed metastasis, showcasing significant anticancer effectiveness using combined photo-chemo-immunotherapy [83]. Table 1 further evaluates the application of such nanoparticles in cancer photo-immunotherapy.

Discussion and future perspectives

The development of immuno-photocatalytic nanoparticles introduces a paradigm shift in the precision and controllability of cancer immunotherapy. By leveraging external stimuli such as NIR light or ultrasound, these nanoparticles enable spatiotemporal activation of anti-tumor immune responses while minimizing damage to surrounding healthy tissues. This localized activation not only enhances therapeutic specificity but also provides real-time tunability of treatment intensity. The capability to synchronize ROS generation, immune checkpoint blockade, and antigen release within the TME addresses several long-standing challenges, including poor immunogenicity and resistance to immune interventions. Importantly, the multifunctional integration within these nanoplateforms allows for targeted delivery, real-time imaging, and controlled therapeutic release all essential for advancing toward personalized medicine. However, despite these innovations, achieving uniform light penetration and precise activation in deep-seated tumors remains a significant hurdle, necessitating further engineering of photoresponsive systems or alternate energy modalities such as X-rays and magnetic fields for deeper activation. A major barrier to effective immunotherapy is the immunosuppressive nature of the TME, which inhibits immune cell infiltration and antigen presentation. The multifunctional nanoparticles demonstrate robust capabilities to remodel the TME through multiple pathways: depleting glutathione, elevating oxygen levels, and modulating immune cell populations such as Tregs and M2 macrophages. For instance, systems including MnO₂-coated titania and Cu-Mn nanoflowers catalyze the decomposition of H₂O₂ to release oxygen, thereby

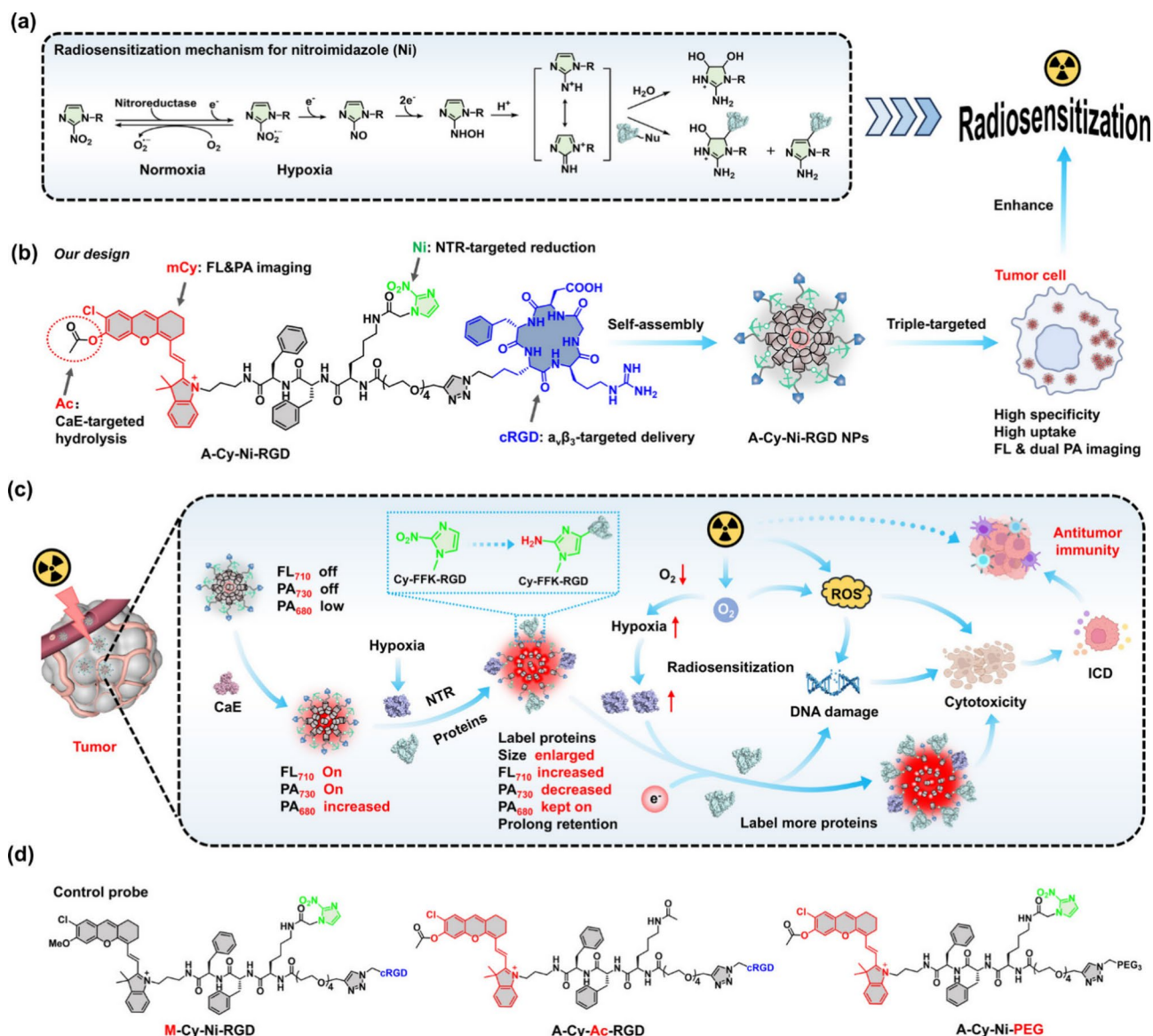


Fig. 20 (a) The overall design and operational mechanism of A-Cy-Ni-RGD nanoparticles (NPs) are depicted as follows: The radiosensitization pathway is facilitated by the nitroimidazole (Ni) molecule, which, under hypoxic circumstances, undergoes reduction by nitroreductase (NTR), hence amplifying DNA damage during radiation. (b–c) A-Cy-Ni-RGD comprises a chemical structure that integrates a nickel-based radiosensitizer, a near-infrared fluorescent dye (Cy), and an RGD peptide for targeting, which self-assembles into triple-targeted nanoparticles (A-Cy-Ni-RGD NPs). These nanoparticles are engineered to enhance tumor-specific radiosensitization. The suggested method entails $\alpha\beta_3$ -integrin-mediated endocytosis into 4T1 breast tumor cells, wherein intracellular carboxylesterase (CaE) cleaves the protecting groups off A-Cy-Ni-RGD, therefore transforming it into Cy-Ni-RGD nanoparticles exhibiting increased fluorescence at 710 nm and dual photoacoustic emissions at 680 and 730 nm. In hypoxic settings, NTR further diminishes Ni, instigating covalent interactions with endogenous proteins, augmenting nanoparticle size, diminishing the PA730 signal, and amplifying FL710, so facilitating real-time monitoring of hypoxia levels. These protein-bound nanoparticles exhibit prolonged retention in hypoxic tumor cells, allowing efficient low-dose X-ray (2 Gy) irradiation directed by fluorescence/photoacoustic imaging. Radiation-induced reactive oxygen species (ROS) inflict DNA damage and subsequently diminish oxygen levels, exacerbating hypoxia, elevating NTR activity, and intensifying DNA damage and protein malfunction. This approach elicits robust immunogenic cell death (ICD), which amplifies immune activation, inhibits tumor proliferation, averts metastasis, and extends longevity. (d) The system is validated using control probes: M-Cy-Ni-RGD, A-Cy-Ac-RGD, and A-Cy-Ni-PEG, each missing one or more functional components to illustrate the significance of the complete A-Cy-Ni-RGD NP design. Abbreviations: ROS, reactive oxygen species; ICD, immunogenic cell death. Reprinted with permission from Wiley [79]

alleviating hypoxia and improving ROS-based therapies. Concurrently, immune adjuvants such as CpG and R848, along with checkpoint inhibitors, synergistically activate the cGAS-STING pathway and enhance DC maturation

and T cell priming. These effects collectively convert “cold” tumors characterized by minimal immune activity into “hot” tumors with robust cytotoxic lymphocyte infiltration. Future research should investigate the long-term

Table 1 The nanoparticles in photo-immunotherapy of cancer

Nanoparticle composition	Size (nm)	Stimulus type	Photocatalytic function	Immuno-modulatory strategy	Targeted cell death pathway(s)	Tumor model used	Therapeutic outcome	Refs
CaCO ₃ @Pt-TiO ₂ nano-composite (CaPT), consisting of CaCO ₃ shell and Pt-decorated TiO ₂ core	185 nm	US-triggered SDT	ROS generation by TiO ₂ enhanced by Pt; Pt prevents e ⁻ /h ⁺ recombination and catalyzes H ₂ O ₂ to produce O ₂	Induction of ICD, DAMPs release (CRT, HMGB-1, ATP), DC maturation, CD ⁸ ⁺ T cell activation	Apoptosis, ferroptosis, necrosis; triggered by ROS and Ca ²⁺ overload	4T1 breast cancer cells (in vitro and in vivo)	Enhanced tumor suppression, immune activation, reversal of cold tumor microenvironment to hot, increased survival	[7]
Au-Cu ₄ O ₃ /re-LDHs – Ultrasmall gold (Au) and copper oxide (Cu ₄ O ₃) moieties anchored on reconstructed layered double hydroxide (re-LDH) nanosheets	155 nm	TME-activated – triggered by metabolic conditions in mastocarcinoma; no external physical stimulus like light or ultrasound is used	Collaborative multienzyme-mimicking cascade reactions – Depletes glucose and NAD ⁺ , generates hydroxyl radicals (•OH), disrupts mitochondrial function and proton-motive force	Metabolism disruption-induced immune sensitization enhances adaptive immune response, reduces extracellular lactate, alleviates immunosuppressive TME	Apoptosis through mitochondrial dysfunction, energy depletion, and ROS (•OH) generation	4T1 breast cancer (mastocarcinoma), Both in vitro (4T1 cells) and in vivo (murine models)	Suppressed tumor growth and metastasis, Improved immune response and immunotherapy sensitivity, disruption of cancer metabolism	[24]
Bi ₂ S ₃ -Bi ₂ O ₃ -Au-PEG nanorods (BB-A-P NRs) – A Z-scheme heterostructured semiconductor functionalized with polyethylene glycol for biocompatibility	113.07 nm	Near-Infrared (NIR) light (808 nm, 1.2 W/cm ²) – Activates the nanorods under tumor-specific conditions (hypoxia, H ₂ O ₂)	Z-scheme electron transfer enables: (1) Catalase-like O ₂ generation; (2) ¹ O ₂ and •OH generation via H ₂ O ₂ and H ₂ O reaction; (3) enhanced ROS via e ⁻ /h ⁺ separation	Induction of immunogenic cell death (ICD) through: ROS-induced apoptosis and Caspase-1/GSDMD-mediated pyroptosis → DAMPs release → immune activation	Apoptosis and Pyroptosis – Triggered by ROS, mitochondrial dysfunction, and Caspase-1/GSDMD pathway	B16F10 melanoma model – Both in vitro (B16F10 cells) and in vivo (C57BL/6 mice with subcutaneous tumors)	Effective tumor suppression – Reduced tumor volume, enhanced immune activation (CRT, Caspase-1, Ki-67 markers), improved survival, minimal systemic toxicity	[9]
Erythrocyte membrane-encapsulated copper indium selenide (RCIS) nanoparticles loaded with NLG919 (RNCIS NPs)	43.48 ± 11.48 nm	Near-infrared (NIR) light (808 nm)	Photothermal therapy (PTT), photodynamic therapy (PDT), chemodynamic therapy (CDT)	IDO-1 inhibition, dendritic cell (DC) maturation, cytotoxic T lymphocyte (CTL) recruitment and proliferation, M1 macrophage polarization	Immunogenic cell death (ICD) characterized by ATP release and calreticulin (CRT) exposure; direct ROS- and heat-induced cytotoxicity	4T1 murine breast cancer model (with both primary and metastatic tumors)	Significant elimination of both primary and metastatic tumors; enhanced anti-tumor immune response including increased T cell infiltration and macrophage repolarization	[33]

Table 1 (continued)

Nanoplatfrom composition	Size (nm)	Stimulus type	Photocatalytic function	Immuno-modulatory strategy	Targeted cell death pathway(s)	Tumor model used	Therapeutic outcome	Refs
Sulfur-doped bismuth oxide ($\text{Bi}_2\text{O}_{3-x}\text{S}_x$, BS) nano-semiconductors synthesized by topological reduction of BiF_3 , loaded with ivermectin (BSM nanoagonist)	30 nm	Ultrasound (sonodynamic), 730 nm near-infrared (NIR) light (photothermal)	ROS generation via sonocatalysis and strong photothermal heating ($\eta = 33.6\%$) due to narrow bandgap and sulfur doping	Ivermectin-induced immuno-genic cell death (ICD), enhanced by ROS and hyperthermia; DC maturation, T-cell activation (especially CD^8^+), reduced Tregs (Foxp3 ⁺)	ICD via ATP secretion, HMGB1 release, CRT exposure; oxidative stress and heat-mediated tumor ablation	4T1 murine breast cancer model (BALB/c mice)	Near-complete tumor eradication under combined ultrasound + NIR treatment; enhanced immune infiltration, suppressed immunosuppressive microenvironment, minimal side effects	[36]
Bimetallic Ce-Mn metal-organic framework (MOF) loaded with bismuth sulfide (Bi_2S_3 , an H_2S prodrug) and combretastatin A4 phosphate (CA4P), coated with hyaluronic acid (BMBCH)	250 nm	Microwave (MW) irradiation at 433 MHz, 0.9 W for 5 min	Includes ROS scavenging and O_2 generation for tumor microenvironment (TME) modulation; MW-induced H_2S release and hyperthermia	H_2S gas from Bi_2S_3 activates cytotoxic T lymphocytes (CTLs) BM reshapes TME via ROS scavenging and O_2 production Increased CD^8^+ T-cell infiltration CA4P enhances vascular permeability for immune infiltration	Hyperthermia-induced tumor ablation H_2S -mediated immune killing Indirect immune-mediated apoptosis (CTL activation)	BALB/c mouse model bearing 4T1 breast cancer tumors	Dramatic tumor volume reduction (to 25 mm ³ in BMBCH + MW group) One tumor completely eradicated Strong CD^8^+ T cell infiltration and CTL activation Minimal systemic toxicity; high biosafety profile	[39]
$\text{CuS@mSiO}_2\text{-Pc(DOX)@HA}$ (Copper sulfide core, mesoporous silica shell, loaded with ZnPc and DOX, coated with hyaluronic acid)	80 ± 10 nm	NIR Laser (808 nm for PTT, 670 nm for PDT)	Generation of ROS via ZnPc under 670 nm; photothermal Heating via CuS under 808 nm	HA targeting CD^{44+} TNBC cells; HAase-triggered drug release	Apoptosis through synergistic chemotherapy (DOX), PDT (ROS), and PTT (hyperthermia)	4T1 murine TNBC cells (in vitro)	Synergistic CT/PTT/PDT; enhanced cytotoxicity to 4T1 cells; high specificity and reduced off-target effects	[52]
$\text{AuNNP@Cu}_2\text{O@F127-Lip/DATS}$ ($\text{AuNNP@Cu}_2\text{O@D}$)	160 nm (DLS size)	Glutathione (GSH)-triggered, 808 nm laser irradiation	In situ generation of CuS enabling photothermal therapy (PTT) and photodynamic therapy (PDT) via SPR effect	Depletion of intracellular GSH and production of H_2S (gas therapy) to enhance oxidative stress	Apoptosis via ROS accumulation, mitochondrial dysfunction, GSH depletion	4T1 breast cancer (in vitro and in vivo)	Significant tumor inhibition, enhanced selectivity for cancer cells over normal cells, prolonged survival in mice, low systemic toxicity	[84]

Table 1 (continued)

Nanoplatfrom composition	Size (nm)	Stimulus type	Photocatalytic function	Immuno-modulatory strategy	Targeted cell death pathway(s)	Tumor model used	Therapeutic outcome	Refs
BD@LM (BPQDs and DOX co-loaded liposomes coated with M1 macrophage membrane, delivered via microneedle patch)	101.7 ± 0.8 nm	NIR light (808 nm), inflammatory tumor microenvironment (post-surgical)	Photothermal and photodynamic therapy via black phosphorus quantum dots (BPQDs)	M1 macrophage membrane coating promotes targeting and immune activation; ICD induces dendritic cell maturation; enhanced PD-L1 checkpoint blockade	Immunogenic cell death (ICD), apoptosis via ROS, mitochondrial dysfunction, ATP release, CRT and HMGB-1 exposure	4T1 breast tumor (orthotopic and post-surgery) and B16F10 melanoma (orthotopic and post-surgery)	Effective inhibition of primary and recurrent tumor growth, metastasis suppression, strong T-cell activation, reduced immunosuppressive cells, long-term immune memory established, enhanced aPD-L1 immunotherapy	[57]
Ag ₂ S-cRGD nanoparticles	~ 15 nm	Near-infrared (NIR) 808 nm laser irradiation	Photothermal conversion efficiency ~ 41.02%, strong NIR fluorescence and photoacoustic imaging ability	Multiple photothermal therapy (PTT) cycles to induce necrotic cell death, dendritic cell maturation, and T-cell activation	Necrosis	4T1 breast tumor-bearing mice	High-dose multiple PTT cycles (3 LICs) completely eliminated tumors without recurrence; induced systemic immune response delaying distal tumor growth; no significant toxicity to major organs; high biosafety in vitro and in vivo	[85]
Ti ₃ C ₂ @TiO _{2-x} -PEG (TTP) nanohybrid with oxygen vacancies	Hydrodynamic diameter ~ 170 nm; in situ grown TiO ₂ NPs ~ 10 nm on Ti ₃ C ₂ sheets (~ 150 nm lateral size)	Dual: NIR-II 1064 nm laser (PTT) and ultrasound (SDT)	Photothermal conversion efficiency ~ 35.8%; strong ¹ O ₂ and ·OH generation under ultrasound due to oxygen vacancies and narrowed band gap	Therapeutic effect via synergistic PTT/SDT enhancing tumor cell killing	Apoptosis and necrosis (synergistic effect confirmed by TUNEL and H&E staining)	4T1 breast tumor-bearing mice	Complete tumor eradication with combined PTT + SDT; significant apoptosis; no tumor recurrence in treated period; stable body weight; negligible systemic toxicity; effective dual-modal PA/PT imaging-guided therapy	[86]

Table 1 (continued)

Nanoplatfrom composition	Size (nm)	Stimulus type	Photocatalytic function	Immuno-modulatory strategy	Targeted cell death pathway(s)	Tumor model used	Therapeutic outcome	Refs
IL@H-PP: Hollow mesoporous CuS nanoparticles loaded with ISRIB (SG inhibitor) and LA (phase-change material), surface-modified with pHLP-PEG for pH-driven targeting	HCuS: 190.0 ± 2.4 nm; IL@H-P: 219.9 ± 2.8 nm; IL@H-PP: 222.1 ± 1.3 nm	NIR 808 nm laser irradiation	Photothermal conversion via CuS with good stability; temperature up to 55.2 °C; laser-triggered ISRIB release via LA melting; Cu ²⁺ release enhances ROS generation	pH-driven tumor targeting via pHLP; ISRIB inhibits PTT-induced stress granule (SG) formation, sensitizing PTT; Cu ²⁺ -induced ROS polarizes TAMs from M2 to M1; induces ICD (CRT exposure, HMGB1, ATP release); promotes DC maturation and T cell activation	Apoptosis and necrosis (enhanced under acidic pH with PTT); ICD-mediated immune cell activation	4T1 breast tumor-bearing mice (primary, lung metastasis, brain metastasis models)	Significant primary tumor suppression; complete prevention of lung metastasis in some cases; inhibition of brain metastases; increased CD ⁸⁺ and CD ⁴⁺ T cell infiltration; strong DC maturation; high M1/M2 TAM ratio; pH-driven targeting enhanced efficacy; no major systemic toxicity	[87]
Hybrid bacteria (<i>Bifidobacterium bifidum</i> , B.b) loaded with glutathione-capped Ag ₂ S QDs via GC-mediated electrostatic assembly	Ag ₂ S QDs: 5.3 nm; B.b@QDs bacterial carrier ~ 1–2 μm (natural size)	NIR 808 nm laser irradiation	Photothermal conversion efficiency ~ 29.9%; stable NIR fluorescence for biodistribution tracking; maintains 45 °C for PTT without harming bacterial viability	M2→M1 TAM polarization (↑CD ⁸⁰⁺ , ↓CD ²⁰⁶⁺); ↑TNF-α and IL-6 secretion; induces ICD (↑CRT exposure); promotes CD ⁸⁺ and CD ⁴⁺ T cell infiltration; deep hypoxia-targeted tumor penetration via bacterial motility	Apoptosis and necrosis (H&E and TUNEL); ICD-mediated immune activation	4T1 breast tumor-bearing mice	Tumor inhibition rate up to 77.3% (B.b@QDs + NIR); significant TAM repolarization; enhanced CTL infiltration; complete tumor penetration (~ 1 cm); no major weight loss or blood abnormalities; good in vivo biocompatibility	[88]
PBP@CpG (Black Phosphorus (BP) embedded in polydopamine (PDA) with CpG oligonucleotides)	BP lateral size: ~2.6 nm; BP thickness: ~1 nm; PBP diameter: ~150 nm; size increases after DA and CpG modification	750 nm pulsed laser (photoacoustic cavitation)	Strong NIR absorption; high photoacoustic conversion efficiency; enhanced photostability; protection from oxidation	CpG as immune adjuvant to promote DC maturation, enhance CD ⁸⁺ T-cell infiltration, and upregulate IFN-γ and granzyme B	Apoptosis (Annexin V-FITC positive); immunogenic cell death (CRT exposure, HMGB1 release)	EMT-6 tumor-bearing mice	Significant tumor growth inhibition; enhanced immune activation; no significant systemic toxicity; improved tumor visualization by PAI; high biocompatibility	[89]

Table 1 (continued)

Nanopatform composition	Size (nm)	Stimulus type	Photocatalytic function	Immuno-modulatory strategy	Targeted cell death pathway(s)	Tumor model used	Therapeutic outcome	Refs
BPCP (Black Phosphorus nanosheets (BP NSs) ~ 250 nm lateral size, ~ 5.2 nm thickness, PEG-bPEI modified, loaded with CpG oligonucleotides)	Lateral size: ~250 nm; Thickness: ~5.2 nm; Hydrodynamic size increases after CpG loading	808 nm NIR laser (2 W/cm ²) for photothermal therapy (BPTT)	Strong NIR absorption; Photothermal conversion efficiency ~ 28.41%; Stable photothermal effect over cycles	CpG as immune adjuvant to enhance DC maturation, T-cell activation, and cytokine secretion (IL-2, TNF- α , IFN- γ); macrophage-mediated phagocytosis activation	Necroptosis via RIP1/RIP3 pathway; Immunogenic cell death (CRT exposure, HMGB1 release, ATP secretion)	Bilateral 4T1 breast tumor model in Balb/c mice (primary and distant tumors)	Significant suppression of both primary and distant tumors; systemic immune activation; enhanced infiltration of CD4 ⁺ and CD8 ⁺ T cells; reduced Tregs; high cytokine levels; good biocompatibility; no systemic toxicity	[90]
CD47-engineered 4T1 cell membrane-coated Ti ₃ C ₂ nanosheets loaded with GOX, CPO, and TPZ (meTGCT)	~ 180 nm	808 nm (photothermal) + 635 nm (photodynamic) laser irradiation	1O ₂ generation via Ti ₃ C ₂ PDT; cascaded enzymatic catalysis (GOX $\rightarrow$ H ₂ O ₂ , CPO $\rightarrow$ HClO); enhanced catalytic activity via photothermal effect	CD47 overexpression for immune escape and competitive SIRP α binding to promote macrophage-mediated phagocytosis of tumor cells	Photothermal therapy (PTT), photodynamic therapy (PDT), enzyme dynamic therapy (EDT) via ROS and HClO generation, hypoxia-activated chemotherapy via TPZ, and starvation therapy	4T1 breast tumor-bearing mice	Complete tumor remission in some mice, significant tumor growth inhibition (V/V ₀ = 0.003 with laser), prolonged survival, low systemic toxicity, high tumor targeting and accumulation, synergistic multi-modal therapy	[91]
Cu ₉ S ₅ @mSiO ₂ -PpIX@MnO ₂ with CpG (CSPM@CpG)	Core Cu ₉ S ₅ ~20 nm; CSP ~47.6 nm; Mesopores 2.43 nm	NIR laser (650 nm for PDT, 808 nm for PTT), pH-responsive CpG release	ROS generation via PpIX (¹ O ₂), catalase-like MnO ₂ shell for O ₂ production, photothermal conversion	CpG oligonucleotide delivery to stimulate IL-12 secretion in dendritic cells; combined with aPD-L1 checkpoint blockade	Apoptosis (early and late) and necrosis via PDT/PTT synergy	4T1 murine breast tumor (in vitro and in vivo)	Significant tumor growth inhibition; synergistic effect of PDT + PTT + immunotherapy; high CTL infiltration; prevention of lung metastasis; no significant systemic toxicity	[92]

Table 1 (continued)

Nanoplatfom composition	Size (nm)	Stimulus type	Photocatalytic function	Immuno-modulatory strategy	Targeted cell death pathway(s)	Tumor model used	Therapeutic outcome	Refs
CuS@TAPB-DMTP-COFs coated with BSA-FA, loaded with DOX (CuS@COFs-BSA-FA/DOX)	CuS NPs: ~13 nm; COFs: ~300 nm diameter; pore size ~2.53 nm	NIR laser (808 nm, PTT), acidic TME (pH-responsive), dual stimuli (pH + NIR) drug release	Fenton-like CuS catalytic activity generating $\cdot\text{OH}$ from H_2O_2 (CDT); photo-thermal heating from CuS; pH-dependent fluorescence for imaging	FA ligand for tumor targeting; DOX chemotherapy to elevate H_2O_2 for enhanced CDT	Apoptosis and necrosis from combined PTT/CDT/chemotherapy; ROS-mediated oxidative stress	4T1 murine breast tumor (in vitro and in vivo)	Synergistic PTT/CDT/chemotherapy; 81.85% tumor growth inhibition with laser; high tumor necrosis; selective tumor accumulation; minimal systemic toxicity; biocompatible and hemo-compatible	[93]

consequences of continuous immune activation and identify strategies to avoid potential autoimmunity or immune escape via antigenic variation.

Another highlight is the exploitation of various programmed cell death (PCD) mechanisms, including pyroptosis, ferroptosis, and cuproptosis, to amplify ICD and systemic antitumor immunity. These mechanisms induce potent inflammatory responses that promote DC recruitment and antigen presentation. For example, Bi_2S_3 -based nanorods activate caspase-mediated pyroptosis, releasing IL-1 β and GSDMD, while $\text{TiO}_2\text{@Ru@siRNA}$ not only silences HIF-1 α but also triggers pyroptosis and checkpoint inhibition under hypoxic conditions. The combinatorial nature of these death pathways ensures redundancy in tumor-killing mechanisms, reducing the chance of resistance development. However, the differential susceptibility of tumor subtypes to specific cell death pathways is not fully understood. It will be crucial for future studies to develop decision-making frameworks or predictive biomarkers to guide which type of PCD-inducing nanoparticle to use for a given tumor phenotype, especially in heterogeneous or metastatic disease. Although preclinical studies in murine models show remarkable tumor regression and immune activation, translating these nanoplatfoms into human clinical use involves overcoming several regulatory and biological challenges. Biodegradability, off-target toxicity, systemic clearance, and immunogenicity of the nanoparticle components must be rigorously assessed. Many platforms utilize metals such as titanium, copper, or manganese, which may accumulate or interact unpredictably with physiological processes over long-term use. Moreover, batch-to-batch consistency in nanoparticle synthesis and surface functionalization is critical for reproducibility and regulatory approval. The incorporation of diagnostic imaging agents such as DOTA-Gd or Bi_2S_3 adds

an additional layer of complexity, requiring compliance with both therapeutic and diagnostic regulatory pathways. To bridge these gaps, more studies should focus on pharmacokinetics, biosafety evaluations, and scalable manufacturing processes, while also exploring biodegradable or organic alternatives that maintain efficacy but reduce long-term systemic burden. The most promising direction for immuno-photocatalytic nanoparticle therapy is in its customization and integration with other therapeutic modalities. Patient-specific tumor profiling could inform the design of nanoparticles with tailored immune modulators, responsive cores, and targeting ligands. Combining these platforms with gene editing tools including CRISPR or mRNA-based payloads may further enhance tumor selectivity and immune system training. Furthermore, combining nanoparticle immunotherapy with standard treatments such as radiotherapy or immune checkpoint blockade could overcome resistance mechanisms and yield synergistic outcomes. Artificial intelligence and machine learning could also be leveraged to optimize nanoparticle design, predict biodistribution, and personalize treatment regimens.

Pre-clinical models and clinical challenges

Pre-clinical cancer models possess unique strengths, limitations, and translational significance, and should be regarded as complementary instruments in oncology and drug development. Ectopic xenografts from established tumor cell lines are economical, reproducible, and beneficial for preliminary screening, yet they possess limited physiological relevance; orthotopic models more accurately replicate TME interactions and metastasis but are technically challenging; genetically engineered mouse models (GEMMs) simulate tumor development in an immune-competent context with pertinent genetics, although they are time-intensive and expensive;

primary patient-derived tumorgrafts maintain tumor heterogeneity and effectively predict clinical responses, albeit requiring fresh tissue and extended establishment periods; carcinogen-induced models replicate incremental tumorigenesis and immune interactions but develop slowly. No individual model consistently predicts human outcomes independently; therefore, a comprehensive, stage-appropriate portfolio approach encompassing many model types provides the most reliable evaluation of innovative cancer therapies [94].

Organoid culture systems, developed from the realization that healthy mouse intestinal stem cells can be cultivated long-term in Matrigel with essential growth factors, have facilitated the prolonged *ex vivo* propagation of both healthy and malignant human tissues, encompassing colorectal, pancreatic, gastric, prostate, and liver cells. The patient-derived cancer organoids have been developed that preserve architecture, cellular variety, and genomic stability, closely mimicking *in vivo* tissues, by supplementing the medium with factors such as Wnt, R-spondin1, EGF, Noggin, and inhibitors of TGF- β and p38 MAPK. This innovation provides a robust framework for investigating cancer biology, enhancing medication discovery, and progressing personalized medicine [95].

Xenograft models, established by implanting human tumor cells or fragments into immunodeficient mice, exhibit varying engraftment success based on the level of immune suppression, with very immunodeficient strains such as NOD-scid IL2RG^{-/-} demonstrating the greatest acceptance. Subcutaneous xenografts are manageable and easily monitored, although they inadequately mimic human TME interactions and clinical treatment responses. In contrast, orthotopic implantation more effectively maintains these characteristics and enhances metastasis rates, albeit it presents greater technical challenges and monitoring difficulties. Limitations arise from the lack of a functional immune system, which is essential in tumor progression and therapeutic response, resulting in possible inconsistencies between preclinical and clinical results. Initiatives to “humanize” the TME, such as the co-transplantation of human stromal cells or the utilization of humanized immune system mice, have enhanced physiological relevance but continue to face hurdles such as ligand-receptor mismatches. Conversely, autochthonous mouse models, encompassing chemically induced tumors and GEM, facilitate tumor initiation and progression within an authentic stromal and immune environment, resulting in cancers that closely resemble human counterparts in histology, genetics, and metastatic behavior. Technological advancements including Cre-loxP and inducible gene expression systems permit exact geographic and temporal regulation of tumor-related mutations, producing extremely relevant

models (p53/Rb-deficient ovarian malignancies, K-ras-driven lung adenocarcinomas). Nonetheless, GEM models encounter limitations such as prolonged and variable tumor latency, substantial maintenance expenses, genetic background influences, breeding intricacies, and restricted accessibility due to intellectual property constraints, while their predictive efficacy for human clinical outcomes has yet to be thoroughly validated. Recent non-germline GEM methodologies employing viral delivery of recombinases to adult tissues seek to surmount certain obstacles. Comprehensive preclinical evaluation across all models is enhanced by many endpoints tumor size, growth rate, histology, immunological infiltration, angiogenesis, apoptosis, and omics-based pathway analyses to augment mechanistic comprehension and clinical significance in cancer medication development [97].

Humanized mouse models, developed by implanting human immune cells or tissues into immunodeficient mice, are essential for investigating cancer immunotherapies; however, they encounter obstacles including graft-versus-host disease (GvHD), inadequate immune reconstitution, improper immune cell maturation, and engraftment failures. Proposed solutions encompass genetic alterations (such as MHC class I/II knockouts and cytokine transgenes), the utilization of supporting cells, and the enhancement of stem cell sources to augment immune cell variety, maturation, and functionality. These models have effectively replicated clinical responses to medicines such as anti-PD1/PD-L1 inhibitors, adoptive cell transfer, bispecific antibodies, therapeutic cancer vaccines, oncolytic viruses, and combination regimens, providing translational insights and forecasting patient variability. They have facilitated innovative approaches for resistant tumors, enhanced tumor-immune modeling, and guided the development of combination therapies, with anticipated future uses aimed at refining personalized medicine and expediting the translation of immuno-oncology advancements [96].

In addition to these established platforms, emerging pre-clinical cancer models are increasingly integrating advanced bioengineering and computational tools to bridge existing translational gaps. Microfluidic “tumor-on-a-chip” systems, for instance, recreate dynamic fluid flow, nutrient gradients, and multi-cellular interactions within precisely controlled microenvironments, enabling real-time Analysis of tumor behavior, drug penetration, and metastatic dissemination under physiologically relevant conditions. Similarly, 3D bioprinting technologies permit the fabrication of highly customizable tumor constructs containing patient-derived cells, extracellular matrix components, and vasculature-mimicking channels, which improve the study of spatial heterogeneity and therapeutic distribution. Coupling these experimental systems with high-throughput omics profiling,

single-cell sequencing, and machine learning algorithms allows for the identification of predictive biomarkers and optimization of treatment regimens with unprecedented precision. Furthermore, advances in CRISPR-based genome editing enable the rapid generation of tailored *in vitro* and *in vivo* cancer models that recapitulate specific mutational landscapes, resistance mechanisms, and tumor–immune dynamics. By combining traditional and next-generation approaches in an iterative, feedback-driven framework, it is possible to achieve a more comprehensive and predictive understanding of cancer biology, thereby enhancing the efficiency, ethical responsibility, and clinical relevance of oncology drug development.

One major clinical challenge lies in achieving targeted accumulation and deep-tissue activation of nanoparticles in complicated TME, particularly in deep-seated, hypoxic, or poorly vascularized malignancies. While EPR effects can assist passive targeting, variable tumor vasculature and high interstitial fluid pressure often hinder uniform distribution. Additionally, biological barriers such as the blood–brain barrier and dense stromal matrices as in pancreatic or breast cancers, further impede penetration. Although strategies including surface functionalization with targeting ligands, cell membrane coating, or the incorporation of pH/redox-responsive release systems can improve localization, they must demonstrate consistent efficacy across heterogeneous patient populations. Achieving spatiotemporal activation also requires overcoming limitations in light or ultrasound penetration, where NIR absorption, sonosensitizer efficiency, and oxygenation constraints directly affect therapeutic performance. The need for clinically compatible, minimally invasive activation modalities that work effectively in diverse anatomical contexts remains a critical barrier. Another pressing challenge concerns biosafety, biodegradability, and systemic clearance, which are essential for regulatory approval and patient safety. Many metal-based nanostructures, such as those containing titanium, bismuth, or copper, raise concerns about long-term retention, potential organ accumulation, and chronic toxicity. Even when acute toxicity is minimal in pre-clinical models, questions remain regarding the fate of residual nanoparticles, their metabolic byproducts, and any unforeseen immunological or inflammatory consequences over extended time frames. The immune system's complex interactions with nanoparticles ranging from unwanted immunosuppression to excessive inflammation demand careful immunotoxicology profiling. Standardizing manufacturing methods to ensure reproducibility, batch-to-batch consistency, and stability under clinical storage and administration conditions is equally important. Without robust safety and quality control frameworks, translational progress will be hampered

despite strong laboratory efficacy data. A further clinical challenge is optimizing therapeutic combinations and immune modulation without inducing adverse immune events. These nanoplateforms frequently integrate PTT or PDT with immune adjuvants, checkpoint inhibitors, or gene-silencing agents, aiming to synergistically induce ICD and reshape the tme. However, determining the optimal combination of adjuvants, dosing schedules, and activation parameters for specific tumor types is complex, as immune responses vary widely among patients. Overactivation of the immune system can lead to auto-immune-like toxicities, cytokine release syndromes, or systemic inflammation, while underactivation risks therapeutic failure. Moreover, the long-term immunological consequences of repeated nanoparticle-mediated stimulation remain poorly understood, including the potential for immune exhaustion or tolerance. Integrating real-time imaging, biomarker monitoring, and adaptive treatment algorithms into clinical workflows could help personalize regimens, but developing such systems requires significant interdisciplinary coordination between materials scientists, oncologists, and imaging specialists.

Numerous current clinical and preclinical investigations examine approaches to surmount resistance or broaden access to immune checkpoint inhibitor treatment in various malignancies. In relapsed/refractory Hodgkin lymphoma following checkpoint treatment, the combination of the JAK inhibitor ruxolitinib with nivolumab resulted in a 53% response rate, decreased immunosuppressive myeloid cells, and revitalized depleted T cell performance [98]. In locally advanced mismatch repair-deficient colon cancer, the phase 2 NICHE-2 study demonstrated that neoadjuvant nivolumab combined with ipilimumab was safe, facilitated timely Surgery in 98% of patients, And elicited pathological responses in 98% (68% complete), with no recurrences observed after a median follow-up of 26 months [99]. In resource-limited environments for advanced Head And neck squamous cell carcinoma, the incorporation of low-dose nivolumab into triple metronomic chemotherapy enhanced 1-year Survival rates from 16.3 to 43.4% without a rise in severe toxicity, presenting a cost-effective option [100]. In a phase 2 study for metastatic non-small cell lung cancer resistant to anti-PD-1 therapy, the addition of the JAK1 inhibitor itacitinib resulted in a 67% response rate by augmenting CD⁸ T cell plasticity [101]; nevertheless, sustained inflammation was indicative of resistance. Manganese (Mn²⁺) is crucial for cGAS-STING-mediated antitumor immunity, facilitating dendritic cell and NK cell activation, enhancing CD⁸⁺ T cell responses, and working in conjunction with PD-1 blockade in preclinical and early clinical investigations, enabling dose reduction and reinstating responses

in advanced solid tumors [102]. Additionally, a phase II trial combining radiation, ipilimumab, And nivolumab in microsatellite-stable colorectal And pancreatic cancers demonstrated disease control in 25% And 20% of patients, respectively, with increased rates among those who completed radiation, indicating potential advantages in immunotherapy-resistant cancers characterized by low tumor mutational burden and enriched NK cells and HERVK RNA expression [103].

Recent advancements in cancer immunotherapy encompass both early and late-stage diseases, innovative biomarkers, and vaccination methods. The NICHE trial demonstrated that neoadjuvant ipilimumab combined with nivolumab prior to Surgery is both safe And feasible for early-stage colon cancer, eliciting pathological responses in 100% of mismatch repair-deficient (dMMR) tumors (95% major or complete) And in 27% of mismatch repair-proficient (pMMR) tumors, with CD⁸⁺PD-1⁺ T cell infiltration serving as a predictor of benefit in pMMR cases [104]. In metastatic castration-resistant prostate cancer, the phase 3 sipuleucel-T study shown a 22% relative decrease in death And a 4.1-month median overall survival advantage compared to placebo, but without a delay in disease progression, and only modest immune-related adverse events [105]. In operable urothelial carcinoma, ctDNA positive post-surgery identified patients at elevated relapse risk who had survival advantages from adjuvant atezolizumab compared to observation, with ctDNA clearance and immune-related tumor markers associated with non-relapse outcomes [106]. DC vaccination in melanoma, aimed at tumor missense mutation-derived neoantigens, enlarged and varied the neoantigen-specific T cell receptor repertoire, uncovering novel HLA-presented epitopes [107]. In the context of recurrent or metastatic head and neck squamous cell carcinoma (HNSCC) [108], immune checkpoint inhibitors nivolumab And pembrolizumab have revolutionized treatment following FDA approval between 2016 And 2019 for platinum-refractory and first-line scenarios. The SITC consensus guidelines now standardize patient selection, sequencing, monitoring, biomarker testing, and toxicity management to enhance their application in U.S. clinical practice.

Metal-based immuno-photocatalytic nanoparticles provide a unique opportunity to transform the landscape of cancer immunotherapy by uniting spatially precise photodynamic or photothermal activation with immune system priming. Their design enables tumor-targeted accumulation through both passive (enhanced permeability and retention) and active (ligand-mediated) mechanisms, ensuring that light-triggered activation occurs predominantly within the TME. Upon activation, these nanoparticles can induce robust ICD, leading to the release of tumor antigens and damage-associated

molecular patterns (DAMPs) that recruit and mature DC. The inclusion of specific metals, such as manganese, copper, or iron, can add potent immunostimulatory effects for instance, manganese directly engages the cGAS–STING pathway to drive IFN production, amplifying antitumor immune responses and converting “cold” tumors into “hot” ones responsive to checkpoint blockade. Photocatalytic ROS generation can also be tailored in type and intensity, fostering localized inflammation that boosts CD⁸⁺ T cell infiltration and reverses T cell exhaustion without the systemic toxicity seen in high-dose immunotherapies. This local, controlled immune activation could synergize with established modalities such as PD-1/PD-L1 or CTLA-4 inhibitors, potentially overcoming resistance mechanisms observed in relapsed or refractory disease. In clinical translation, these nanoparticles could be deployed in biomarker-driven strategies, where activation is timed to coincide with optimal immune readiness such as pre-surgical neoadjuvant use to shrink tumors and seed systemic immunity, or post-surgical adjuvant use to eliminate micrometastatic disease in high-risk patients identified by ctDNA positivity. Multifunctional designs could integrate antigen payloads, immune adjuvants, or pathway-specific modulators like JAK–STAT inhibitors directly into the nanoparticle matrix, enabling the simultaneous reprogramming of immunosuppressive myeloid cells and restoration of effector T cell function. This mirrors clinical benefits seen in combinations such as JAK inhibition with checkpoint therapy, but with a localized, precision-controlled delivery to minimize adverse effects. In settings with limited resources, such photo-triggered immune interventions could be paired with low-dose checkpoint inhibitors to improve survival outcomes without a proportional increase in toxicity, providing a cost-effective yet potent option. Furthermore, combining these systems with imaging functionalities could allow real-time tracking of biodistribution, activation, and immune response, enabling adaptive therapy adjustments to counteract tumor evolution.

Conclusion and remarks

The development of immuno-photocatalytic nanoparticles has been recognized as a promising advancement in the integration of phototherapy, immunomodulation, and targeted drug delivery within a single, spatiotemporally controlled nanoplatform. By enabling precise activation of therapeutic pathways through external stimuli such as light or ultrasound, these systems overcome major challenges associated with conventional cancer treatments, including nonspecific cytotoxicity, ITM, and limited tissue penetration. The ability to induce localized immune activation while minimizing systemic side effects is expected to significantly enhance the therapeutic index

and broaden treatment applicability across various tumor types. Synergistic induction of multiple programmed cell death pathways including pyroptosis, ferroptosis, and cuproptosis has been shown to intensify antitumor immune responses and reprogram the TME. When combined with immune checkpoint blockade and immune-stimulatory agents, these nanoparticles facilitate robust activation of DCs, cytotoxic T lymphocytes, and long-term immunological memory. Diagnostic components such as MRI or CT contrast agents have also been integrated into these nanoplateforms, allowing for real-time tracking of therapeutic progression and improving the precision of treatment administration. As a result, these multifunctional systems are being positioned as versatile tools in the shift toward personalized cancer immunotherapy. Clinically, immuno-photocatalytic nanoparticles are expected to serve as powerful adjuncts to existing cancer therapies or potentially function as stand-alone treatments in immunologically “cold” tumors that are unresponsive to current immunotherapeutics. However, before clinical implementation, further investigation is required to evaluate long-term safety, biocompatibility, degradation profiles, and large-scale manufacturing consistency. Regulatory considerations must also be addressed, particularly for systems that function as both diagnostic and therapeutic agents. With continued interdisciplinary optimization, these platforms hold the potential to redefine oncological treatment paradigms, providing a highly targeted and systemically effective approach to combat both primary and metastatic cancers.

The innovative aspects of immuno-photocatalytic nanoplateforms stem from their ability to integrate precise, stimulus-responsive cancer ablation with potent immune modulation in a single multifunctional system. Unlike conventional cancer therapies such as chemotherapy, radiotherapy, or surgery which often target only the primary tumor and may fail to generate durable systemic immunity, these nanoplateforms are designed to induce ICD through PTT, PDT, SDT, or catalytic reactions triggered by localized light or ultrasound. By releasing tumor-associated antigens and DAMPs, they effectively transform “immune-cold” tumors into “immune-hot” environments, priming the body’s immune system to attack both local and distant cancer cells. Their programmable architecture enables spatiotemporal control, with activation occurring only under specific TME conditions such as acidity, hypoxia, or high glutathione levels thereby minimizing collateral damage to healthy tissues. Furthermore, these platforms can be co-loaded with immune adjuvants, checkpoint inhibitors, or gene-silencing agents, allowing for a customizable therapeutic payload that can be adapted for different cancer types and patient immune profiles. The unique advantages of

these nanoplateforms also lie in their multimodal, theranostic capabilities that combine therapy and diagnostics in a single construct, which is rarely achieved in standard cancer treatments. Advanced designs incorporate high-Z metals or contrast agents that allow real-time imaging via MRI, CT, or photoacoustic modalities, enabling clinicians to monitor nanoparticle biodistribution, treatment response, and tumor regression with high precision. Their ability to exploit synergistic cell death pathways such as pyroptosis, ferroptosis, and cuproptosis provides a level of therapeutic potency beyond what single-modality treatments can provide, especially against drug-resistant or hypoxic tumors. By reshaping the TME, repolarizing TAMs, and promoting long-term immune memory, they not only destroy existing cancer cells but also reduce recurrence and metastasis risk, addressing one of the most persistent limitations of conventional approaches. This convergence of targeted therapy, immune activation, and diagnostic feedback represents a paradigm shift toward highly personalized, minimally invasive, and durable cancer treatment strategies.

Metal-based immuno-photocatalytic nanoparticles represent a promising frontier in cancer therapy, providing a unique integration of photodynamic and immunomodulatory functions that could influence epigenetic regulation as a future research avenue. The ROS generated by these nanoparticles under light activation, in concert with immune-mediated signaling cascades, may modulate critical epigenetic mechanisms such as DNA methylation, histone modification, and non-coding RNA expression in tumor cells. Such modulation has the potential to reprogram aberrant gene expression patterns, restore tumor suppressor activity, and disrupt oncogenic signaling pathways, thereby enhancing therapeutic efficacy and reducing the possibility of cancer recurrence. By simultaneously initiating direct cytotoxic effects and triggering durable, heritable changes in gene expression, this approach could provide a synergistic means of sensitizing tumors to immune clearance and preventing adaptive resistance. Future perspectives envision the design of multifunctional nanoplateforms capable of precisely targeting the TME, coupling light-driven catalytic activity with immune activation to achieve both localized tumor eradication and systemic, epigenetically mediated long-term remission.

Future research on immuno-photocatalytic nanoplateforms should prioritize enhancing endosomal escape, as this step is critical for maximizing the bioavailability of nucleic acid drugs, immunoadjuvants, and other intracellularly active agents. Despite sophisticated targeting, multiple nanoparticles become trapped in endolysosomal compartments after cellular uptake, where acidic degradation can inactivate payloads. Strategies to improve escape include the incorporation of pH-responsive

polymers, proton sponge–effect materials, membrane-disruptive peptides, and photothermal or photomechanical triggers that destabilize vesicular membranes. The stimuli-responsive coatings that disassemble in the acidic or redox-rich tumor milieu can facilitate rapid cytosolic release upon endocytosis. Pairing these escape mechanisms with imaging capabilities would allow real-time confirmation of intracellular delivery efficiency, thereby enabling adaptive treatment regimens. Such research priority is particularly relevant for therapies relying on siRNA, mRNA, or CRISPR components, where cytosolic or nuclear access is essential for gene modulation and downstream immune activation. Another pressing priority lies in improving deep tumor penetration and mitigating immunotoxicity. Dense extracellular matrices, abnormal vasculature, and high interstitial fluid pressures significantly restrict nanoparticle distribution, especially in hypoxic tumor cores where immune activation is most needed. Multifunctional designs such as size-shrinkable nanoparticles that respond to enzymatic or pH triggers, or matrix-degrading carriers functionalized with collagenase or hyaluronidase can enhance penetration while maintaining systemic stability. Concurrently, tailoring surface chemistry and release kinetics to minimize off-target immune activation will be critical for controlling immunotoxicity, which remains a major translational barrier. Modular nanoplateforms capable of co-delivering TME-modulating agents with checkpoint inhibitors could normalize vasculature, reduce fibrosis, and promote immune infiltration without triggering systemic cytokine storms. Incorporating biodegradable, metabolically inert components and leveraging biomimetic coatings such as cell membranes can further reduce toxicity risks. Moreover, balancing these design elements deep penetration, precise immune modulation, and safety will be vital for advancing these therapies toward clinical viability.

Nanotoxicity remains a critical concern in the clinical translation of immuno-photocatalytic nanomaterials, particularly because materials such as CuS, TiO₂, BP, and GQDs can exert toxic effects on healthy tissues if they leach or degrade in vivo. Excessive release of copper ions from CuS can induce oxidative stress, disrupt mitochondrial function, and cause irreversible damage to normal cells. Similarly, TiO₂, while widely used for its photocatalytic properties, can generate ROS indiscriminately, leading to DNA damage and inflammation in healthy tissues. BP is prone to the rapid degradation in aqueous environments, producing phosphate species that may disturb cellular homeostasis, while GQDs due to their small size and high surface reactivity can penetrate cellular organelles and disrupt normal biochemical processes, causing cytotoxicity and potential genotoxicity. These risks highlight the importance of careful nanoparticle engineering, dose

optimization, and targeted delivery strategies to avoid off-target toxicity while maintaining therapeutic efficacy. To address these safety concerns, several strategies have been proposed to mitigate toxicity and control nanoparticle metabolism after administration. Surface functionalization with biocompatible polymers (PEGylation) or cell membrane coatings can reduce non-specific interactions, improve colloidal stability, and prolong circulation while minimizing uptake by healthy cells. Incorporating biodegradable matrices or stimuli-responsive linkers allows for controlled disassembly of nanoparticles into non-toxic metabolites that can be cleared via renal or hepatic pathways. For example, encapsulating CuS or TiO₂ cores in degradable silica shells, lipid layers, or polymer coatings can prevent uncontrolled ion release while ensuring tumor-specific activation. BP degradation can be slowed through antioxidant coatings, while GQD surface passivation can limit ROS overproduction in non-target tissues. Understanding the in vivo fate of these materials through pharmacokinetic studies, excretion profiling, and long-term biocompatibility assessments is essential to ensure that their breakdown products are efficiently metabolized and excreted without causing chronic accumulation or delayed toxicity. By integrating precise material engineering with rigorous biosafety evaluation, the therapeutic benefits of these advanced nanoplateforms can be realized while safeguarding healthy tissue function.

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Author contributions

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Competing interests

The authors declare no competing interests.

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