EURASIAN EXPERIMENT JOURNAL OF BIOLOGICAL SCIENCES (EEJBS)
ISSN: 2992-4138 ©EEJBS Publications
Volume 6 Issue 3 2025

Nano-Based Photothermal and Photodynamic Therapy in Cancer Treatment: From Bench to Bedside

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ABSTRACT

Cancer remains one of the most formidable challenges in modern medicine, necessitating the development of innovative, selective, and minimally invasive therapeutic strategies. Nano-based photothermal therapy (PTT) and photodynamic therapy (PDT) have emerged as promising modalities for cancer treatment owing to their spatiotemporal selectivity, reduced systemic toxicity, and synergistic potential. By leveraging nanotechnology, these therapies enhance tumor accumulation, improve photostability, and enable controlled drug release and multimodal imaging. In PTT, nanoparticles convert light energy into heat to ablate cancer cells, while PDT employs photosensitizers activated by specific wavelengths of light to generate cytotoxic reactive oxygen species (ROS). This review provides a comprehensive analysis of the mechanisms, design strategies, and types of nanomaterials utilized in nano-enabled PTT and PDT, including gold nanoparticles, carbon-based nanomaterials, upconversion nanoparticles, and metal–organic frameworks. We also explore recent preclinical and clinical advancements, highlighting the translational challenges such as tumor penetration, immunogenicity, and phototoxicity. Finally, we discuss future directions, including combinatorial approaches, tumor microenvironment targeting, and regulatory considerations for clinical translation. Nano-based phototherapies hold significant promise in advancing personalized cancer treatment from the laboratory to clinical application.

Keywords: Photothermal therapy, Photodynamic therapy, Nanomedicine, Cancer treatment, Reactive oxygen species

INTRODUCTION

Cancer remains one of the leading causes of morbidity and mortality worldwide, posing a significant challenge to global health systems[1–3]. Despite major advances in diagnostic techniques and therapeutic strategies, cancer continues to exact a heavy toll in terms of both human lives and healthcare expenditures[4–7]. Traditional treatment modalities such as chemotherapy, radiotherapy, and surgical resection have long formed the backbone of cancer management. While these approaches have achieved varying degrees of success, they are often associated with serious limitations, including non-specific toxicity, development of drug resistance, systemic side effects, and insufficient efficacy in eradicating cancer stem cells or metastatic lesions[8, 9].

The complexity and heterogeneity of tumors necessitate the development of more targeted, personalized, and minimally invasive therapies [10]. In this context, photothermal therapy (PTT) and photodynamic therapy (PDT) have emerged as promising non-invasive alternatives. Both modalities rely on external light sources to activate therapeutic agents, photothermal agents (PTAs) in the case of PTT, and photosensitizers (PSs) in PDT, within the tumor microenvironment[11, 12]. PTT functions by converting absorbed light into heat to induce localized hyperthermia and subsequent cancer cell death. PDT, on the other hand, involves the generation of reactive oxygen species (ROS), particularly singlet oxygen, upon light activation of a photosensitizer in the presence of molecular oxygen. The resulting oxidative stress leads to apoptosis or necrosis of malignant cells[13, 14]. Although PTT and PDT have shown considerable potential in preclinical and clinical settings, their therapeutic efficiency has often been constrained by challenges such as poor solubility of phototherapeutic agents, limited tumor penetration, premature degradation, off-target accumulation, and inefficient light delivery to deep-seated tumors. To overcome these limitations, nanotechnology has been increasingly explored as a platform to enhance the performance and precision of light-based therapies[15, 16].

The integration of nanotechnology with phototherapy has revolutionized the delivery, stability, and tumor specificity of phototherapeutic agents. Engineered nanocarriers such as liposomes, dendrimers, polymeric nanoparticles, mesoporous silica nanoparticles, gold nanoparticles, and carbon-based nanomaterials can encapsulate or conjugate PTAs or PSs, thereby protecting them from rapid metabolism or clearance and enhancing their pharmacokinetic profiles[17–21]. These nanostructures also exploit the enhanced permeability and retention (EPR) effect commonly observed in tumor vasculature, allowing preferential accumulation in tumor tissues while minimizing systemic toxicity[22–25]. Moreover, nanocarriers can be surface-modified with targeting ligands such as antibodies, aptamers, peptides, or small molecules that recognize specific biomarkers overexpressed on cancer cells. This active targeting strategy further improves the specificity of therapeutic delivery and reduces damage to surrounding healthy tissues. Importantly, the modularity of nanoplatforms allows for the co-delivery of multiple therapeutic agents, including chemotherapeutic drugs, immunomodulators, or gene-editing tools along with phototherapeutic compounds, enabling synergistic or combinatorial therapies for enhanced efficacy[26, 27].

An exciting frontier in nano-based phototherapy is the development of multifunctional theranostic systems that integrate diagnostic imaging capabilities with therapeutic interventions[28]. Such systems enable real-time monitoring of drug distribution, treatment response, and disease progression. For example, nanoparticles loaded with magnetic resonance imaging (MRI), computed tomography (CT), photoacoustic, or fluorescence imaging agents can guide the application of light and monitor the therapeutic outcome in a non-invasive manner[29]. This convergence of therapy and diagnostics not only personalizes treatment regimens but also reduces the trial-and-error associated with conventional approaches.

Furthermore, stimuli-responsive nanocarriers capable of responding to environmental cues such as pH, temperature, redox conditions, or enzymatic activity can enhance drug release at the tumor site, thereby increasing therapeutic payload availability while limiting off-target effects[30, 31]. Light itself can serve as a remote and controllable stimulus to trigger the release of therapeutic agents precisely at the tumor site, achieving spatiotemporal control over treatment. Despite the impressive progress, several hurdles must be addressed before the full clinical potential of nano-enabled PTT and PDT can be realized[32]. These include issues related to large-scale synthesis, reproducibility, long-term toxicity, immune clearance, regulatory approval, and cost-effectiveness. Rigorous in vivo validation and translational studies are essential to bridge the gap between bench-top research and bedside applications[32].

This review aims to provide a comprehensive overview of the current state of nano-based photothermal and photodynamic therapy in cancer treatment. We begin by discussing the fundamental principles and mechanisms underlying PTT and PDT, followed by a detailed examination of nanomaterials and design strategies employed to optimize their performance. We also highlight recent advances in preclinical and clinical research, explore emerging trends such as immunophototherapy and combination regimens, and outline the challenges and prospects associated with the clinical translation of these novel therapeutic platforms. Together, these insights underscore the promise of nanotechnology-assisted PTT and PDT in the next generation of precision oncology.

2. Principles of Photothermal and Photodynamic Therapy

2.1 Photothermal Therapy (PTT): Photothermal therapy (PTT) is an emerging cancer treatment modality that leverages the ability of certain nanoparticles to absorb light, particularly in the near-infrared (NIR) region and convert it into heat[33–35]. This localized heating effect raises the temperature of the tumor microenvironment to approximately 42–45°C, a range sufficient to induce irreversible damage to cancer cells through protein denaturation, membrane disruption, and mitochondrial dysfunction. The induced hyperthermia can lead to cell death primarily via apoptosis or necrosis, depending on the extent and duration of thermal exposure.

A critical factor in the efficacy of PTT is the photothermal conversion efficiency of the nanoparticles used[36, 37]. This efficiency is influenced by the particles' optical properties, such as surface plasmon resonance (as observed in gold-based nanostructures), size, shape, and structural stability. Materials commonly used in PTT include gold nanorods, graphene oxide, carbon nanotubes, and transition metal dichalcogenides due to their excellent light absorption and biocompatibility. The use of NIR light (700–1100 nm) is advantageous because it allows deeper tissue penetration (up to several centimeters), bypassing the strong absorption of light by water and biological chromophores such as hemoglobin and melanin[38]. This property makes PTT particularly suitable for treating tumors located deeper within tissues.

Moreover, PTT can be integrated with targeted delivery systems to improve tumor specificity and minimize damage to surrounding healthy tissue. Surface modification with ligands, antibodies, or peptides allows nanoparticles to selectively accumulate in cancerous tissues through active targeting, enhancing therapeutic outcomes[39]. When combined with other modalities like chemotherapy or immunotherapy, PTT can overcome multidrug resistance and stimulate anti-tumor immune responses, making it a versatile and powerful component of modern oncological strategies.

2.2 Photodynamic Therapy (PDT): Photodynamic therapy (PDT) is a minimally invasive cancer treatment that utilizes light-activated chemical compounds known as photosensitizers (PS) to generate cytotoxic reactive oxygen species (ROS)[40]. The therapy relies on a triad: a photosensitizing agent, a specific wavelength of light (usually in the visible to near-infrared spectrum), and molecular oxygen. Upon exposure to light, the photosensitizer transitions from its ground state to an excited singlet state, followed by intersystem crossing to a longer-lived triplet state. In this state, it can transfer energy to surrounding oxygen molecules, leading to the generation of ROS, predominantly singlet oxygen ($^1O_2$), as well as free radicals and superoxide anions[40]. These ROS initiate oxidative stress within tumor cells, damaging cellular organelles, lipids, proteins, and DNA [41, 42]. Depending on the intensity and localization of oxidative stress, PDT can induce various forms of cell death, including apoptosis, autophagy, or necrosis. Furthermore, the vascular damage induced by ROS may disrupt tumor blood supply, and the treatment can enhance the presentation of tumor-associated antigens, potentially initiating anti-tumor immune responses[43, 44].

An ideal photosensitizer should have strong light absorption in the therapeutic window (600–800 nm), high quantum yield for ROS generation, and selective accumulation in tumor tissues. Commonly used photosensitizers include porphyrins, phthalocyanines, chlorins, and newer nanoformulations that improve solubility, pharmacokinetics, and tumor targeting[45]. PDT's non-invasive nature, spatial selectivity (only illuminated areas are affected), and reduced systemic toxicity make it an attractive alternative or adjunct to traditional therapies like chemotherapy and radiotherapy. However, its clinical efficacy can be limited by tumor hypoxia, light penetration depth, and non-specific photosensitizer distribution[45]. Recent advancements focus on developing nanoparticle-based delivery systems and oxygen-generating or hypoxia-activated PDT agents to overcome these limitations and expand the clinical utility of this promising therapeutic strategy.

3. Nanoplatforms in PTT and PDT

3.1 Gold-Based Nanomaterials

Gold-based nanomaterials, particularly gold nanoparticles (AuNPs), nanorods, nanoshells, and nanostars, have garnered significant attention for their applications in photothermal therapy (PTT) and photodynamic therapy (PDT) due to their exceptional optical properties[46]. These nanoparticles exhibit strong surface plasmon resonance (SPR), which enables them to absorb near-infrared (NIR) light efficiently and convert it into localized heat, a key mechanism in PTT. Moreover, their surfaces are highly versatile and can be easily functionalized with a variety of molecules, including targeting ligands, therapeutic drugs, and polymers, to enable selective delivery to tumor tissues. In PDT applications, gold nanoparticles serve as excellent carriers for photosensitizers such as chlorin e6, helping to increase the local concentration of the drug and improve its light absorption efficiency[47, 48]. The plasmonic properties of AuNPs also enhance the production of reactive oxygen species (ROS) upon light activation, further boosting PDT efficacy. Additionally, the biocompatibility, ease of synthesis, and tunable size and shape of AuNPs make them favorable for clinical translation. Their capability to enable simultaneous imaging, targeting, and therapy commonly known as theranostics adds further value to their role in precision cancer nanomedicine[48].

3.2 Carbon-Based Nanomaterials

Carbon-based nanomaterials such as graphene oxide (GO), carbon nanotubes (CNTs), and carbon quantum dots (CQDs) have emerged as promising platforms for cancer phototherapy owing to their excellent photothermal conversion efficiency, large surface area, and good biocompatibility[49]. These materials exhibit strong NIR absorption and can generate significant heat under irradiation, making them suitable for photothermal therapy (PTT). Their unique sp2-hybridized carbon structures allow π–π stacking interactions with aromatic photosensitizers (PSs), facilitating high loading efficiency and stable drug encapsulation. Furthermore, carbon nanomaterials can support dual-mode therapy by combining PTT with photodynamic therapy (PDT), wherein the PSs produce reactive oxygen species (ROS) upon light exposure[50]. Surface functionalization of carbon nanomaterials with hydrophilic polymers, peptides, or antibodies enhances their dispersibility in physiological conditions and improves tumor-specific targeting. For example, polyethylene glycol (PEG) modification increases biostability and circulation time, while antibody conjugation ensures selective tumor accumulation. Their photostability and low cytotoxicity further contribute to their attractiveness for therapeutic applications. Moreover, carbon nanomaterials also possess intrinsic fluorescence, especially CQDs, allowing for image-guided therapy[51]. Overall, their multifunctionality, ease of modification, and compatibility with various light-responsive agents make carbon-based nanomaterials valuable in the design of advanced nanoplatforms for PTT/PDT-mediated cancer treatment.

3.3 Upconversion Nanoparticles (UCNPs)

Upconversion nanoparticles (UCNPs) are a class of nanomaterials that can absorb low-energy near-infrared (NIR) light and emit higher-energy visible or ultraviolet (UV) light through a nonlinear optical process known as upconversion[52]. This unique property makes UCNPs highly advantageous for deep-tissue photodynamic therapy (PDT), where conventional photosensitizers (PSs) requiring UV or visible light can be activated within

tissues that would otherwise be inaccessible due to limited light penetration. Typically composed of rare-earth-doped host lattices such as $NaYF_4$ doped with Yb^{3+} and Er^{3+} or Tm^{3+}, UCNPs exhibit high stability, low photobleaching, and minimal background autofluorescence, which is beneficial for imaging and therapeutic applications[53]. In cancer phototherapy, UCNPs can be conjugated or co-loaded with PSs so that NIR excitation triggers emission in the visible range to activate PSs, resulting in ROS generation. This enables spatially controlled therapy with minimal damage to surrounding healthy tissues. UCNPs also offer excellent photostability and can be modified with biocompatible coatings or ligands to enhance targeting, cellular uptake, and circulation time[54]. Moreover, their multifunctional capabilities support simultaneous diagnosis and therapy (theranostics), making them valuable tools for image-guided cancer treatments involving deep-tissue PTT/PDT.

3.4 Metal–Organic Frameworks (MOFs)

Metal–organic frameworks (MOFs) are an emerging class of hybrid materials composed of metal ions or clusters coordinated to organic ligands, resulting in highly porous, crystalline architectures[51]. Their large surface area, tunable pore sizes, and high loading capacity make MOFs attractive for drug delivery and phototherapy applications. In the context of photodynamic therapy (PDT) and photothermal therapy (PTT), MOFs can encapsulate or incorporate photosensitizers (PSs), chemotherapeutic agents, or other therapeutic payloads within their framework[55]. Their intrinsic porosity allows for sustained and controlled release, while their light-responsiveness enables spatiotemporal control of therapy. Some MOFs are designed to generate reactive oxygen species (ROS) upon light activation, serving as self-activating PS carriers. Others can convert light energy into heat, offering a dual-mode PDT/PTT function. MOFs can also be engineered for tumor targeting by surface functionalization with ligands, polymers, or antibodies[55]. Additionally, MOFs show promise in overcoming hypoxia-associated resistance in tumors by delivering oxygen or catalyzing in situ oxygen generation[55]. Their biodegradability and biocompatibility can be fine-tuned by selecting appropriate metal centers (e.g., iron, zirconium) and organic linkers. Overall, MOFs represent a versatile and potent platform for integrated cancer therapy through light-responsive mechanisms and targeted delivery systems.

4. Advantages of Nano-Based PTT and PDT

Nano-enabled photothermal therapy (PTT) and photodynamic therapy (PDT) offer several distinct advantages over traditional cancer treatments such as chemotherapy, radiotherapy, and surgery[56]. One of the most significant benefits is targeted delivery. Nanoparticles can be functionalized with ligands, antibodies, peptides, or aptamers that specifically bind to overexpressed receptors on cancer cells, enhancing selective accumulation at tumor sites and minimizing off-target effects. This improves therapeutic efficacy while reducing systemic toxicity[56].

Another major advantage is controlled activation. Unlike systemic therapies, PTT and PDT are triggered only when the nanoparticle is irradiated with a specific wavelength of light, ensuring localized treatment that spares surrounding healthy tissues[57]. This minimally invasive approach reduces recovery time and complications associated with surgery or systemic drug exposure. Furthermore, the synergistic potential of combining nano-based PTT and PDT with other therapeutic modalities such as chemotherapy or immunotherapy can lead to enhanced treatment outcomes, overcoming drug resistance and increasing tumor eradication rates[58]. Additionally, theranostic capabilities, the integration of diagnostic imaging and therapy, are achievable with multifunctional nanoparticles, allowing real-time monitoring of drug distribution, tumor response, and treatment efficacy[58]. This enables more precise and personalized treatment strategies, which are crucial in modern oncology.

5. Preclinical and Clinical Advancements

Extensive preclinical research has validated the efficacy of nano-based PTT and PDT across a wide spectrum of malignancies. For instance, PEGylated gold nanorods have demonstrated robust tumor ablation in murine models of breast and prostate cancer via efficient photothermal conversion under near-infrared (NIR) light[59]. Similarly, upconversion nanoparticles (UCNPs) loaded with porphyrin-based photosensitizers have enabled deep-tissue photodynamic therapy in glioblastoma models, owing to their ability to convert NIR light into visible wavelengths that activate the photosensitizer[60]. Beyond proof-of-concept studies, nano-based phototherapies are progressing into the clinical domain. Gold nanoshells (AuroShell, developed by Nanospectra Biosciences) have undergone early-phase clinical trials in patients with localized prostate cancer, showing promising tumor reduction and minimal side effects. Although traditional photosensitizers like Photofrin, Verteporfin, and Temoporfin are already approved for PDT in certain cancers, their delivery limitations and off-target phototoxicity have driven interest in nanoformulations that enhance solubility, circulation time, tumor specificity, and therapeutic index[61].

The future of clinical translation appears promising, particularly as researchers refine nanoparticle designs for greater targeting accuracy, biocompatibility, and controlled activation. These developments are critical to

bridging the gap between bench and bedside, ultimately improving survival rates and quality of life for cancer patients.

6. Challenges in Clinical Translation

Despite the substantial promise of nano-based PTT and PDT, several critical challenges hinder their full clinical adoption. One major limitation is light penetration depth. Near-infrared (NIR) light, although better than visible light, still suffers from limited tissue penetration, making it difficult to treat deep-seated tumors effectively. Strategies such as using longer-wavelength NIR-II light or implantable light sources are under exploration but are not yet standard.

Tumor heterogeneity presents another major obstacle. Variations in tumor vasculature, interstitial pressure, and hypoxia affect the uniform distribution and accumulation of nanoparticles, as well as the efficiency of reactive oxygen species (ROS) generation required for PDT. Inconsistent delivery can lead to suboptimal therapeutic outcomes and resistance.

Additionally, phototoxicity is a concern. Accidental or off-target light activation can damage surrounding healthy tissues, particularly in anatomically complex regions. The issue of biodegradability and long-term safety also looms large for many nanomaterials, especially metallic or carbon-based ones, which are not easily degraded and may accumulate in organs like the liver and spleen, raising concerns about chronic toxicity. Lastly, regulatory challenges, including demonstrating reproducibility, safety, pharmacokinetics, and large-scale manufacturing standards, make clinical translation arduous. Overcoming these hurdles will require multidisciplinary collaboration, advanced biomaterials, and regulatory innovation to ensure safe and effective cancer treatments.

7. Future Perspectives

The future of nano-based photothermal therapy (PTT) and photodynamic therapy (PDT) holds immense promise, with emerging strategies aimed at enhancing their precision, efficacy, and clinical applicability. One of the most exciting directions involves the integration of PTT and PDT with other therapeutic modalities, such as immunotherapy, gene therapy, or CRISPR-based genome editing. These combinatorial approaches offer synergistic effects, potentially overcoming tumor resistance and improving long-term treatment outcomes. For instance, PTT/PDT-induced tumor cell death can enhance the release of tumor-associated antigens, thereby priming the immune system for an anti-tumor response when combined with checkpoint inhibitors or adoptive T-cell therapies.

Another promising avenue is the modulation of the tumor microenvironment (TME) to increase treatment specificity. Researchers are designing smart nanoparticles that are activated in response to unique TME conditions such as acidic pH, elevated enzyme levels, or hypoxia. These stimuli-responsive nanoplatforms can release their therapeutic payloads selectively at tumor sites, minimizing damage to healthy tissues. The application of artificial intelligence (AI) is also becoming pivotal in the development of nano-based therapies. AI and machine learning algorithms can assist in predictive modeling, nanoparticle design optimization, patient stratification, and personalized treatment planning, thereby accelerating the translation of nanomedicine from bench to bedside.

Furthermore, the emergence of personalized medicine is pushing the field toward the design of patient-specific nanoplatforms. Leveraging individual genomic and proteomic profiles can enable the customization of nanoparticle formulations, enhancing therapeutic outcomes while reducing adverse effects. These advancements collectively signal a transformative era in cancer nanomedicine.

CONCLUSION

Nano-based photothermal and photodynamic therapies represent a transformative approach in cancer treatment, combining precision, minimal invasiveness, and multifunctionality. Although several challenges persist, ongoing technological innovations and interdisciplinary collaborations are accelerating the transition from bench research to clinical applications. With careful consideration of safety, efficacy, and regulatory frameworks, these modalities hold substantial potential to become integral components of next-generation oncology.

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CITE AS: Kato Jumba K. (2025). Nano-Based Photothermal and Photodynamic Therapy in Cancer Treatment: From Bench to Bedside. EURASIAN EXPERIMENT JOURNAL OF BIOLOGICAL SCIENCES 6(3):6-13