Review Article

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Applications of nanomedicine-integrated phototherapeutic agents in cancer theranostics: A comprehensive review of the current state of research

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Abstract: Innovative approaches such as photodynamic therapy (PDT) and photothermal therapy (PTT) have made nanomedicines a promising frontier in cancer theranostics. The combination of nanocarriers with photothermal agents and photosensitizers (PSs) has shown excellent promise for the diagnosis and the treatment of cancer, primarily at the cellular, vascular, and tumor microenvironment level. Using nanocarriers in PDT has revolutionized precision and efficacy, allowing the drug to reach cancer cells faster and offering high enhancing PS accumulation. These agents are activated by light of specific wavelengths, leading to localized cytotoxicity, offering highly selective cancer therapy. Nanomaterials such as gold and silver nanoparticles have enabled remarkable progress in cancer hyperthermia using PTT. The unique optical properties of these nanoparticle-based nanomedicines make them ideal candidates for converting light energy into heat, selectively ablating the cancer cells. In this review, nanomedicine-integrated phototherapeutic agents are discussed and the most important recent developments in PDT and PTT are examined, as well as how nanoparticle-based formulations improve diagnosis and treatment. In addition, nanocarriers used in cancer phototherapy and their mode of action are discussed. Nanocarriers are useful for drug delivery as well as for imaging and diagnostic purposes during cancer treatment. In this review, we explore the role of nanoparticles in improving phototherapy precision and selectivity while minimizing collateral tissue damage. It specifies a comprehensive impression of the current research on cancer therapy, underscoring its potential to revolutionize the treatment paradigm by highlighting the current state of research.

Keywords: phototherapy, photodynamic therapy, photothermal therapy, nanomedicine, cancer, photosensitizers, photothermal agents

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1 Introduction

Cancer, one of the leading global causes of death in both men and women, remains a formidable global health challenge, necessitating continual exploration of novel therapeutic strategies to complement and surpass traditional treatment modalities [1,2]. The cancer treatment strategies include chemotherapy, photodynamic, photothermal, and hormonal therapies; however, a large number of patients remain at a high risk of disease recurrence or resistance [2,3]. Multidrug resistance (MDR), a developing issue in the treatment of cancer, further worsens the issue. Among the burgeoning avenues, the use of nanomedicines has emerged a transformative paradigm, offering an unprecedented precision and efficacy in cancer diagnosis and therapy [4].

Nanotechnology-based drug therapies have been extensively explored in recent years to address this issue, and the findings have shown remarkable potential in overcoming the drug resistance, with several nanocarrier-based pharmaceuticals being studied in the clinical settings [5]. Cancer nanomedicines aim to address the inherent limitations of traditional cancer diagnostics and therapy [6]. An integral part of cancer theranostics is the combination of cancer diagnosis and cancer treatment [4,7]. Many substances that can be incorporated into and released from theranostics, such as diagnostic and therapeutic ingredients [8]. The delivery can be triggered by an internal or external stimulus. Internal stimuli originate from the body, including pH, redox potential, oxidative stress, enzyme activity, and temperature [9]. An external stimulus is one that comes from outside the body, such as light, ultrasound, and magnetic fields. In addition to these factors, biomaterials that are able to respond to them have some advantages as well [9]. There are applications for nanoparticles in theranostics. Using nanoparticles, diagnostic materials, such as dyes, can be delivered to target tumors to allow imaging to be performed [10]. In addition, cancer drugs can be delivered to cancer cells using these devices [11]. By amalgamating the unique properties of nanoparticles with the principle of phototherapy, nanomedicines provide a versatile platform for targeted intervention, minimizing the systemic toxicity and maximizing the therapeutic outcomes [12]. The emerging area of nanotechnology has brought nanotherapeutics, and this technique has shown tremendous promise in treating cancer.

The conventional treatment of cancer, while often effective, is fraught with several limitations including nonspecificity, off-target effects, and resistance [13]. In response to these challenges, phototherapy has been proven to be an innovative and promising approach. Over the past few years, phototherapy has acquired regulatory approval for the treatment of many disorders, including cancer [14]. Solid tumors and other disorders are shown to be treated using phototherapy. Phototherapy is a photoactive technique that combines the use of PSs with particular light wavelengths. The global regulatory authorities have approved several photosensitizing medications and light applications for the therapy of cancer and microbial infections [15–17]. Hence, it garnered substantial interest from researchers worldwide, and as a result, it is now a more commonly used medical tool for the diagnosis and treatment of cancer. In the realm of phototherapy, two modalities, namely, photodynamic therapy (PDT) and photothermal therapy (PTT), have emerged as focal points of exploration. The PDT harnesses the cytotoxic effects of light-activated PSs to induce localized cell death, while PTT employs nanomaterials to convert light into heat causing cancer cell ablation.

Both modalities have benefited from the use of nanotechnology to increase their specificity and potency [18,19]. Target cells are killed by activated PSs by producing radicals or reactive oxygen species (ROS) in PDT and heat generation in PTT [16,20]. The integration of these phototherapeutic strategies with nanomedicine introduces a nuanced precision that addresses the shortcomings of conventional treatments. The intersection of nanomedicine, PDT, and PTT not only presents an opportunity to revolutionize cancer diagnosis and treatment but also challenges our understanding of the intricate interplay among light, nanoparticles, and cellular responses. However, despite the advantages and alluring properties of nanomedicines, there are still some hurdles associated with their therapeutic use, leading to an assert that they have not yet realized their full potential [17,21].

In clinical practice, targeting therapy through heightened permeability and retention (EPR) is not constantly effective, while the strength of the consequence alters depending on the type and the site of tumors, their blood perfusion status, and the properties of macromolecular anticancer agents [22,23]. Nanomedicine-based therapeutic regimes displayed better potential in targeting the cancer cells. Nanomedicines can specifically accumulate in solid tumors due to the EPR effect, which can improve the bioavailability of therapeutics at the target site [24,25]. This review aims to specify a comprehensive examination of the current landscape of nanomedicine-based phototherapy for cancer treatment, with a specific emphasis on the synergistic interplay between PDT and PTT. The intricate design of nanocarriers is tailored for these phototherapeutic applications, exploring their unique physicochemical properties that enhance drug delivery, imaging, and therapeutic efficacy. In addition, it aims to emphasize the recent progress in nanomedicine-based phototherapy with a comprehensive account of the current state of research that has been carried out using *in vitro* and *in vivo* studies in the treatment of cancer. We navigate through the evolving field of targeted delivery systems, addressing the critical balance between biocompatibility and therapeutic efficiency.

2 Photodynamic therapy using PS

2.1 Mechanisms underlying PDT

The PDT is a marginally invasive procedure of destroying cancer cells that employs a blend of light energy, a PS, and molecular oxygen present inside the cells. When all the three factors come into play, the photoproduction of ROS takes place resulting from the *in vivo* administration of the

PS in that specific site showing cytotoxic effects on tumor cells [26]. To activate the PS, a certain wavelength of light is needed. The PS is less toxic to the cells until it is activated by light; however, upon activation, it leads to the formation of ROS, which renders toxicity to the tumor. PDT is a two-stage process, which is initiated upon the administration of a PS selectively in the cancerous tissue, followed by the use of an irradiation of a particular wavelength showing maximum absorption by the photoactive drugs [27].

During the photochemical process, the PS molecule absorbs incident light, changing it from the ground state (S_0) to an excited singlet state (S_1) for a short period (~ns), which then undergoes intersystem crossing to a relatively more stable (~ms) excited triplet state having a longer lifetime. From this triplet state (T_1), the PS molecules return to the ground state (S_0) by undergoing a type I or type II photodynamic reaction. In the type I reaction, there is a transfer of electrons from the PS to the biological substrate, resulting in the production of ROS such as $O_2^{\cdot-}$ and $^{\cdot}OH$ [28]. However, in type II PDT, the transfer of energy occurs between PS and adjacent $^3O_2$ directly for the production of cytotoxic $^1O_2$ (Figure 1). The reactive species then activate several downstream biological events, including direct cytotoxicity, inflammation, and vascular events (Figure 2). Nevertheless, PDT involves oxygen in both these processes. The rate of type I PDT is less affected directly by the concentration of O_2; however, in type II PDT, PS in the triplet state transfers energy to nearby $^3O_2$ directly for the generation of cytotoxic singlet oxygen ($^1O_2$). This route needs the contribution of intratumoral O_2 concentration for the formation of ROS. In both situations, the ROS is generated to target the cancerous cells in a localized manner [29–31].

2.2 Light sources for PDT

The PDT procedure represents an extremely promising approach for treating certain types of cancerous or precancerous lesions because of its efficiency and selectivity [32,33]. To accomplish the technique, light, oxygen, and a PS must exist simultaneously at a subcellular level [34]. In response to light with a particular wavelength, PS converts the nearest molecular oxygen/oxygenic species into highly cytotoxic ROS that initiate tumor necrosis [35]. The majority of PSs are nontoxic in the dark, so PDT action strikes simply when and where PS-containing tissues are illuminated, therefore ensuring high selectivity toward cancerous tissues [36].

The preference of light source in PDT rests on the target spot, PS used, and light dose to be delivered. The conventional PDT utilizes short-range UV-Vis light (400–700 nm) to excite the PS; however, it fails to achieve deep tissue penetration [37]. The absorption wavelength of the PS should be taken into consideration while selecting the wavelength of the light source. Generally, optical fiber-based devices are utilized to deliver the light adjacent to the target. The distribution of the treatment light is also affected by the optical properties of the tissue [16]. It is expected that during treatment, highly pigmented areas absorb the light, while the majority of light gets scattered by the localized tissue. Light-emitting diodes with various illumination spectra choices have been widely used for this purpose; however, poor coupling efficacy with the optical fiber distribution restricts their application [38]. On the other hand, lasers use optical fiber coupling to provide high optical power to a distal irradiation area [39]. Light-transmitting devices have been constantly explored in the clinical setting as an opportunity to deliver light directly

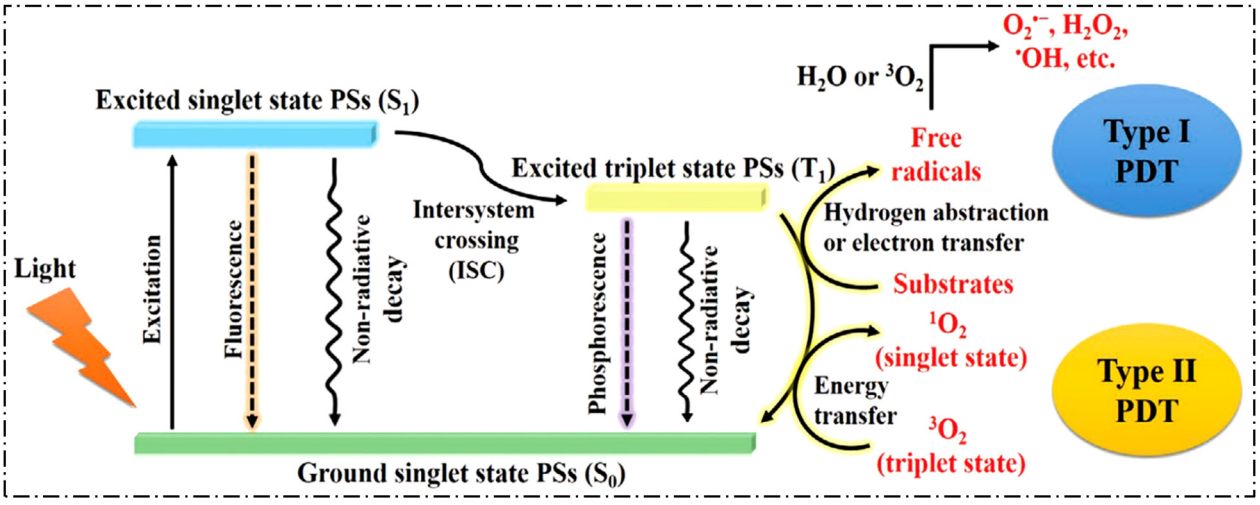

Figure 1: Type I and type II photochemical reactions in PDT. The PS changes from its ground state to an excited state after absorbing light and the activated PS generates free radicals (type I reaction) or oxidative substrates (type II reaction). Reprinted with permission from ref. [31], Copyright 2019, American Chemical Society.

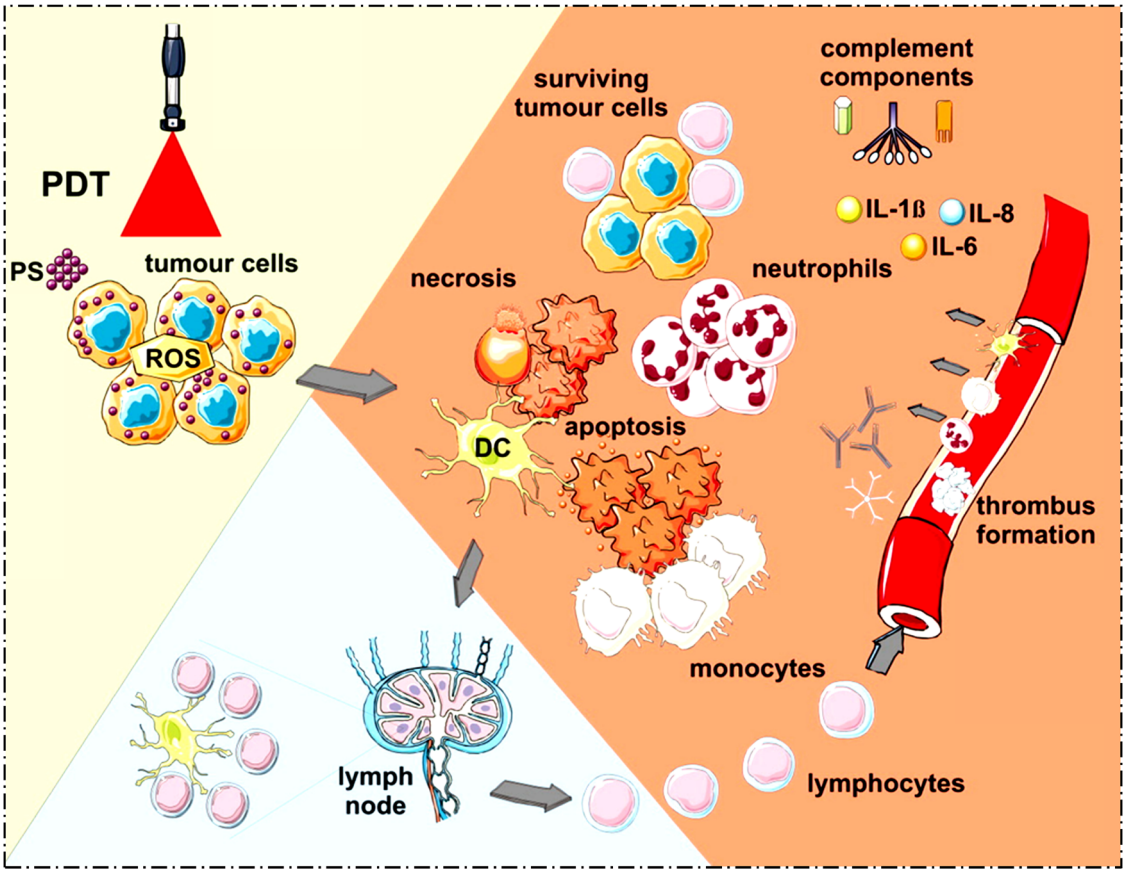

Figure 2: Apoptosis, necrosis, and related biological cascades initiated by intracellular ROS produced upon the excitation of PS in PDT. Reprinted with permission from ref. [31], Copyright 2019, American Chemical Society.

to the PS, although this has often resulted in more invasive methods of delivery [40]. There are limitations to both of these improvements when it comes to tackling deep-seated lesions and metastases. Thus, alternative approaches may include introducing molecules, nano-objects, or materials that function as internal lights [41].

2.3 Role of oxygen in PDT

Oxygen is actively involved in the photosensitization process that yields oxygen-derived ROS, and hence, its presence is necessary to obtain a preferred effect. Under hypoxic conditions, PDT treatment is challenging for most solid tumors, and there are chances of recurrence, as the hypoxic cells are resistant to the therapy [42]. To enhance the performance of O_2 delivery, nanomaterials and O_2 carriers such as perfluorocarbon, hemoglobin (H_b), and metal-organic frameworks (MOFs) are often combined to develop a new O_2 delivery system [43–45]. Moreover, nanoparticles coated with pH-sensitive polymer enable the controlled production of molecular oxygen as a function of external stimuli (temperature and pH). Several nanostructures of manganese oxide (MnO_2) have been utilized to release tumor hypoxia through the decomposition of endogenous hydrogen peroxide (H_2O_2) and producing O_2 within the cancer cells [46]. Recently, a nanosystem-mediated PDT capable of improving oxygen to accelerate $^1O_2$ release, resulting in tumor inhibition was described [24]. Similarly, nanosized carriers such as micelles and vesicles allow homogeneous delivery of O_2 in the tumor [47,48]. The H_b-loaded NPs exhibited considerable support for ROS production during ROS-enhanced therapy. MOFs have also been explored as oxygen carriers, which showed good potential as sorbent materials for oxygen molecules [45,49,50]. Due to this role, nanoformulations of zirconium (IV)-based MOF (UiO-66) were encapsulated inside red blood cells (RBCs) [45]. The released O_2 can increase the $^1O_2$ production and intensify the PDT outcomes for hypoxic conditions.

2.4 Features of PS

PS are the high-level conjugated molecular systems that transfer their energy from the incident light into another nearby molecule. During this photochemical reaction, a

series of ROS are formed that can cause damage to the cells [42]. An ideal PS should fulfill several requirements such as being easy to obtain in the pure form, less toxicity in the dark with minimal side effects, and having a high quantum yield with maximum light absorption capacity in the far-red/NIR region [51]. Nevertheless, it should be cost-effective, dissolve easily in the body fluids, and get quickly eliminated from the body. Moreover, the biomolecules (H_b) absorb light in a shorter range (<650 nm), considerably decreasing the amount of light that can enter deep tissues. Therefore, NIR light is opted to expose the PS to improve deeper tissue penetration [52]. According to their structural makeup, PS can be divided into organic and inorganic types. The organic PS are categorized into three stages: the first stage corresponds to the porphyrin derivatives, which are usually hydrophobic. Variations of the porphyrin's structure yield the second-generation PS such as phthalocyanines (chlorine e_6; Ce_6) with improved tumor discrimination. However, the use of these PS is limited owing to the photoinduced degradation and dark phototoxicity. Therefore, investigations aiming to find PS with better tumor accumulation properties as the third-generation PS (nanocarrier-assisted PS) are underway [53]. Despite their versatility and innovative nature, nanocarriers offer distinct advantages and characteristics for drug delivery [54]. They are promising choices for improving the accuracy and efficiency of drug therapy in diverse medical applications because of their nanoscale size, controlled release kinetics, biocompatibility, individualized drug delivery, and long-term stability [55]. In addition to controlled release kinetics, nanocarriers provide other key features. The precision of these systems allows them to deliver drugs sustained for a prolonged period of time, making them ideal for persistent drug delivery [56]. A nontoxic approach is used throughout these systems, which minimizes any adverse effects on the body [56]. The immune response is reduced by this characteristic, which makes nanocarriers a safe method for delivering drugs. Several factors that can affect nanocarrier biodistribution, which can be divided into nanoscale properties, physiological factors, blood circulation times, tumor microenvironments (TMEs), and administration routes [57]. Recent research published by Sultan *et al.* demonstrated that targeted delivery formulations for cancer treatment have made significant progress [58]. This study was intensive on the characterization of chitosan nanoparticles surface linked to rituximab with cisplatin (mAbCCNP) and with cisplatin-loaded chitosan nanoparticles with cisplatin (CCNP). There were notable physicochemical differences among these formulations, with CCNP exhibiting a zetapotential (ZP) value of 30.50 ± 5.64 mV and a particle size of 308.10 ± 1.10 nm, while mAbCCNP had a ZP value of 26.90 ± 9.09 mV and a slightly larger particle size of 349.40 ± 3.20 nm. It is important to note that CCNP and mAbCCNP showed controlled delivery kinetics of cisplatin, which indicates they have potential as effective delivery systems [58].

These PS bear unique optical absorption features and high quantum yield in the triplet-excited state allowing them to generate their own ROS. Particularly, nanomaterials of inorganic origin showed inherent chemical constancy and attracted much attention in modulating the second-generation PS [59]. The photosensitive materials exhibited energy bands, which deliberated them with light-activated ROS generation. Owing to their phototoxicity, TiO_2 nanoparticles may cause glioblastoma cancer cells to undergo programmed cell death. The mechanistic investigations showed the formation of electron-hole pairs as a result of the shift of electrons from the valence band to the conduction band of TiO_2 under UV light irradiation, which might additionally interact with the adjacent O_2 and H_2O molecules to produce ROS [60]. In this direction, several PS based on inorganic nanomaterials such as the Si nanoparticles, $SnWO_4$ nanoparticles, and CdSe quantum dots (QDs) have been utilized as PS in the PDT [27,61–63].

2.5 Comparative studies between the PS and nanoformulated PS

Traditionally, dye molecules and aromatic hydrocarbons have been used as PSs, such as xanthane-derived dyes (Rose Bengal and eosin) and methylene blue [64]. During the electronic transitions between different excited states of the dye, ROS is produced and monitored by electron transfer to oxygen [64]. In a light reactive species, there can be at least two excited states: a singlet and a triplet. As a consequence of radiation absorption, photosensitive species typically undergo electronic transitions between the ground state (S_0) and singlet excited states (S_1 or S2), although a subsequent transition to a triplet excited state (T_1) may also occur, which is forbidden in principle. Intersystem crossing is the term used to describe such a phenomenon. It is possible to cross intersystems when there is an applicable energy change between the excited states and there are heavy atoms present in the PS [65]. Two mechanisms may occur when the electrons are in a triplet state: (i) they can be shifted to other species, forming free radicals, which can react with oxygen to produce ROS, including superoxide radical anions (O_2), H_2O_2, and hydroxyl radicals (OH), as described earlier; and (ii) they can be transported to triplet oxygen ($^3O_2$) to form singlet oxygen ($^1O_2$), as described earlier. As with both mechanisms, ROS production

is more efficient when the intersystem crossing is more probable.

The PS summarizes different structures with descriptions of their chemistry and physical properties, as well as their combination into nanoparticles/nanostructures [66]. In general, porphyrins are hydrophobic compounds composed of four interconnected transformed pyrrole subunits [67]. In addition to absorption of visible light, they are well known for having high levels of conjugation [68]. These molecules can also contain metallic atoms, resulting in natural chromoproteins like hemoglobin and chlorophyll. These compounds have high quantum yields (F) and a rich chemistry, resulting in relatively high ROS production [69]. It is actually possible to modify the original porphyrin structure, which can impact its optical properties such as its absorbance spectrum. A major drawback of these filters is photobleaching, low absorption in the IR or NIR spectral window, and poor selectivity [70]. Developments in nanotechnology have provided new opportunities and implementations. The majority of biomolecular interactions occur in nanostructures, which have a size of 1–100 nm. In particular, PSs have been conjugated or incorporated into nanostructures to enable their use in nanomedicine [71]. In addition to multifunctionality, second-generation PSs have the potential to deliver drugs directly to tumor cells with increased efficiency and selectivity in terms of intracellular delivery [36]. Recently, PSs have been conjugated with different nanostructures, including inorganic nanoparticles, micelles, and vesicles, especially liposomes, that have already been commercially developed [36]. Four generations of PSs use porous carriers like mesoporous silica and MOFs. In these structures, there is the possibility of incorporating a large number of sensitizer molecules [72]. Pharmacological formulations of PSs are also referred to as third- and fourth-generation PSs from a pharmaceutical perspective.

3 PTT using PTA

3.1 Mechanisms underlying PTT

The PTT is a method of heat ablation in which the PTA utilizes light energy of a longer wavelength. Therefore, PTT is capable of damaging the pathologic cells selectively at more penetration depth. In this procedure, the conversion of photon energy to thermal energy takes place [73]. However, an excess dose of irradiation may cause tissue burning and inflammation in the adjacent tissues. The mechanism of cancer cell death depends on the temperature generated as necrosis occurs at ≥50°C, whereas apoptosis ensues between 43 and 50°C. It is therefore necessary to maintain the temperature for apoptosis as necrosis is associated with a risk of cancer metastasis [74]. The strategies applied for selective PTT using PTA are shown in Figure 3.

Recent investigations are now being directed toward using heat to lessen the undesirable side effects and increase the effectiveness of PTT [75]. Nanoparticles play a crucial role in PTT because of their characteristic properties making them exceptional PTA [76]. They not only have unique shape, size, and optical properties but also possess good photothermal efficiency that allows easy tumor penetration [77]. The improvement in radioactive absorption and scattering properties of metal nanoparticles (Au, Ag, and Cu) due to their distinctive surface plasmon resonance (SPR) phenomenon makes them suitable for PTT [77,78]. The nanoparticles derived from these metal ions show high densities of free electrons, which is revealed during the plasmon resonance in the visible region suitable for PT applications [79]. The SPR phenomena appear from the collective oscillation of free charge carriers in nanoparticles steered by the electromagnetic field of incident light. It has garnered great attention for its role in heightened optical phenomena and optoelectronic control [80,81]. Nevertheless, their outstanding radioactive scattering nature plays a pivotal role in imaging-guided PTT.

3.2 Features of PTA

Based on their highly effective photothermal conversion efficiency (PCE), PTA can outpace any absorption disturbance from the biological chromophores [82]. The currently used laser in PTT is NIR light (biological window = 750–1,350 nm), resulting in deeper tissue penetration. This wavelength range can be divided into two subwindows: the NIR-I (750–1,000 nm) and the NIR-II (1,000–1,350 nm). The NIR-II has a deeper tissue penetration, and fewer biological interferences as compared to the NIR-I, which has a short tissue penetration depth. Nanosized photothermal agents in this situation can not only achieve larger tumor accumulation than small molecules but also offer numerous imaging routes and advantageous features [82].

4 Advantages and drawbacks of phototherapy

When compared to conventional treatments, phototherapy has several advantages. First, by altering the irradiation site, intensity, and power, phototherapy may accurately

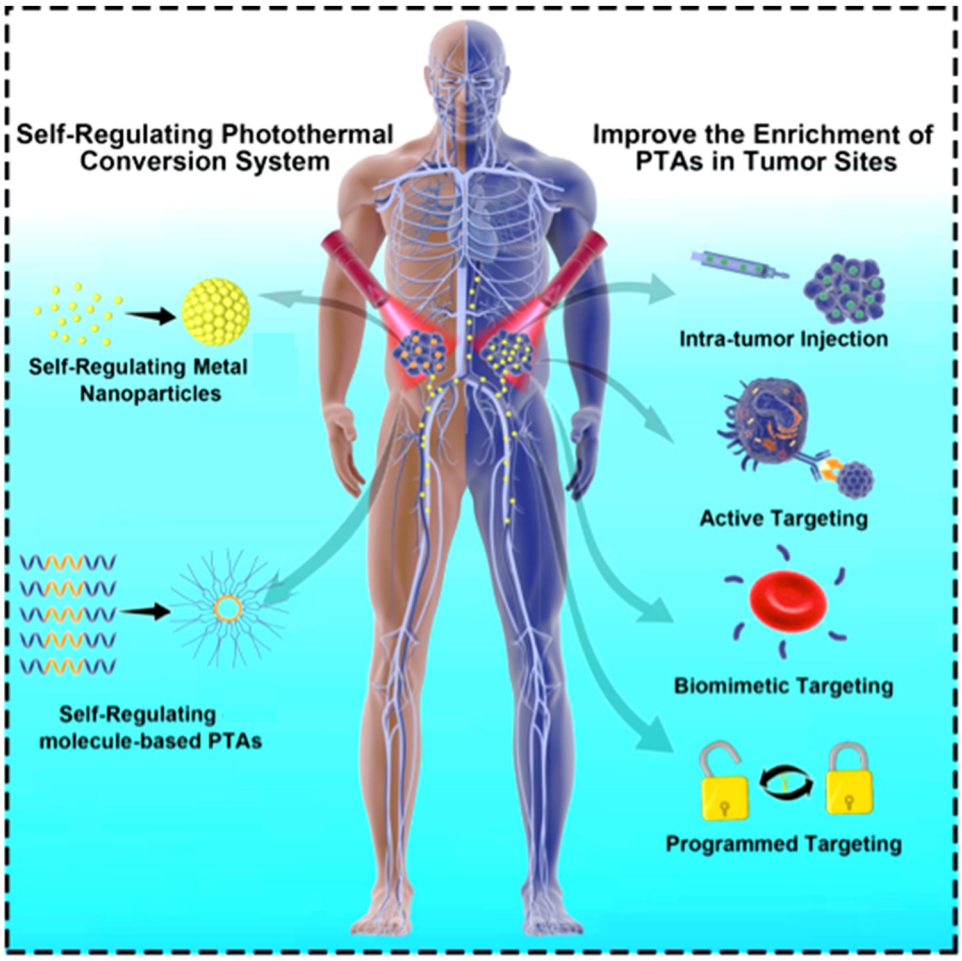

Figure 3: Strategies to improve selective PTT using PTA; adapted from ref. [74], under Creative Commons License.

manage the area, time, and effectiveness of the treatment. It is simple to swiftly modify the treatment plan as per clinical requirements. An effective treatment plan is ensured by the constrained irradiation area, low risk of adverse effects, and high energy output. Phototherapy has shown an increase in the life span and a decrease in the size of tumor in murine model [59]. Nevertheless, despite these benefits, single-mode phototherapy has limited therapeutic use. Tumor relapse, one of the major problems, which cost thousands of lives every year, cannot be solved by phototherapy, although it has shown promising therapeutic results in solid tumors in animal models.

In addition, tissues underlying the tumor also suffer some sort of damage as a result of the heat produced during PTT. Eventually, since lasers can only penetrate small and superficial tumors, the range of phototherapy is constrained. As a result, phototherapy does not result as well in clinical settings as it does in animal studies. The PDT is also associated with several practical issues including those related to light penetration depth, delivery and localization of PS, photodynamics, and photochemistry of PS, all of which are important factors for the precise generation of ROS. These issues are being investigated to develop a mechanistic approach that may solve the majority of PDT-related issues, starting at the molecular level to their biological consequences. As a result, the studies are being focused on how cellular death and vascular blockage can work well, and how ROS can stimulate the immune system following PDT. Finally, antioxidants, inorganic salts, and nanoparticles are utilized to enhance the ROS generation and eventual improvement of the therapeutic efficacy [83].

There are some hurdles identified in clinical practices associated with phototherapy for cancer. The immunological responses, hemolysis, and thrombogenicity are the major hurdles, which should be considered in clinical settings. Although cancer phototherapies can have several advantages such as minimal invasiveness and use of non-ionizing radiations; however, major concerns revolving around PDA and PTT are their ability to prevent cancer

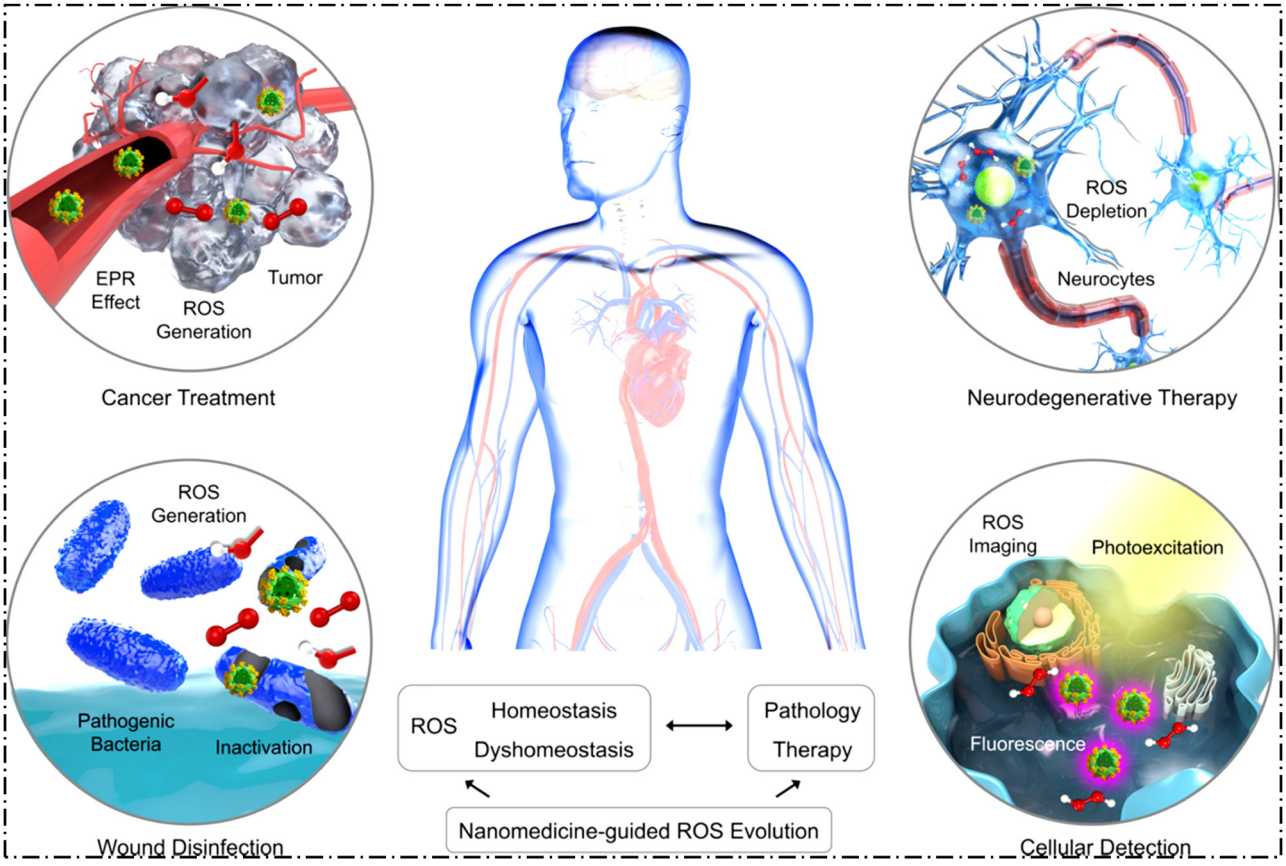

Figure 4: Applications of nanomedicine in the generation or depletion of ROS and their therapeutic and diagnostic implications. Reprinted with permission from ref. [31] Copyright 2019, American Chemical Society.

relapse and limiting collateral damage to healthy tissues. It is therefore important to carefully investigate the specificity and selectivity of nanocarrier-based phototherapy in the treatment of cancers for maximized laser tissue penetrations.

5 Nanocarrier-assisted phototherapy

5.1 Nanocarrier-assisted PDT

The nanomaterial-based delivery technologies have been applied recently in the PDT that can alter biodistribution as well as the pharmacokinetics (PK) and pharmacodynamics (PD) of PS. The nanostructured materials generated using nanomedicines pose as an intriguing replacement for the conventional PDT since they allow PS to be transported and absorbed well, thereby improving their anticancer potential. Nanoparticle holds unique physiochemical and photoconverting properties that can convert exogenous NIR light into self-illuminating substances that can cause tumor tissues to produce their light. The advantage of taking nanoscale particles (1–100 nm), particularly known as upconverting luminescent nanoparticles (UCNPs) is that they can show anti-Stokes luminescent, which can tune the NIR light (spectral range in 710−1,100 nm) into visible light and thus to trigger PS *via* FRET. In this context, several PS have also been employed with UCNPs to build composite nanoplatforms for deep PDT [39].

Photogenerated ROS targets the tumor tissue through a photosensitization process leaving behind the surrounding tissue unaffected [84]. Based on the remarkable therapeutic outcomes, nanomaterial-based PDT has emerged as a favorable therapy for a variety of cancer forms (Figure 4). Previous investigations revealed that the nanocarrier-modified materials exhibited considerable interest in assembling next-generation PS owing to their intrinsic chemical stability. Other benefits of inorganic nanomaterials include their unique energy band, which enables them to produce ROS when exposed to light for further therapeutic usage [85].

5.2 Nanocarrier-assisted PTT

Various nanoparticles based on inorganic, organic, and composite materials have been explored till date for their photothermal applications. These materials exhibit distinct features such as easier to synthesize, robust NIR absorption, and improved photostability [86]. Nevertheless, their clinical applications are hindered owing to their poor biodegradability, although organic nanoparticles, dyes, and polymers have shown better biocompatibility and biodegradability [25]. However, poor photostability and tedious synthetic methods are still associated with organic PTAs, which limit their uses in phototherapy. Therefore, new organic–inorganic composite materials are being developed to overcome such drawbacks, which are achieved through chemical conjugation and display better photoelectric properties in PTT [87].

Several forms of nanoparticles have been investigated for photothermal applications including the ferromagnetic nanoparticles, single-walled carbon nanotubes, multiwalled carbon nanotubes (MWCNTs), and polymer-based materials [88,89]. However, their use is still limited as PTA owing to their low biocompatibility, water insolubility, and elevated toxicity. Recently, gold nanoparticles (AuNPs) have shown good promise as PTA in PTT. Colloidal AuNPs have been reported to have localized plasmon surface resonance (LPSR), resulting in photoacoustic (PA) and hyperthermic properties useful for selective cancer targeting and medical applications in imaging [90]. By tuning the shapes of AuNPs (nanorods, nanocages, and nanostars) and size, the LPSR photochemical properties can be tuned. Consequently, the photothermal and PA properties of the material can be changed by using varied light wavelengths in the NIR area [91].

The AuNPs showed several advantages over other nanoparticles as they can be delivered efficiently into the local tumor site, activated through NIR laser with the possibility for deep penetration, and can be tempered for complicated cancer PTT and drug delivery systems [92]. Commonly used light-based therapeutic candidates in targeted cancer PTT are gold-silica nanoshells (GSNs). These GSNs (AuroShells) bear a diameter of ~150 nm, maximally absorb the NIR light and convert it to heat [93]. Once, the nanoparticles accumulate in the tumor tissue, they undergo photothermal heating under the influence of NIR laser, resulting in hyperthermic cell death, while healthy tissue remains unaffected. The mechanism associated with cell death, mainly necrosis, is the high-energy irradiation that leads to a change in protein and lipid structure. On the other hand, apoptosis, which is typically brought on by low-energy radiation, has no impact on immune or inflammatory responses [94]. Therefore, with the use of AuNPs, a unique photothermal mechanism for selective cancer therapy can be envisaged.

6 Types of nanocarriers used in phototherapy

The PDT and PTT individually employ light as radiation, which helps achieve their therapeutic outcomes [95,96]. These therapeutic approaches gained much attention recently owing to the noninvasiveness of light and partial adversative consequences associated with these treatments. The nanoscale-based carriers could be helpful to simplify the collective treatment and can be utilized to achieve necessary developments in the area of photo-chemotherapy and photo-radiotherapy, improved PK, co-loading multiple agents, reducing toxicities, and sustained release [97–100]. The nanoscale-based carriers are the materials that possess nano-dimensions and which are capable of carrying several imaging agents and drug molecules. These systems could be in the form of metal nanoparticles [97], polymers [98], graphene or graphene-based materials [99], as well as non-metals, such as silica nanoparticles [100]. These nanomaterials have numerous applications in the field of novel drug delivery systems, gene delivery, imaging, and phototherapy [101–103].

The target-based mechanism of nano-entities depends on the improved EPR effects that are supposed to take place when the tumors influence a specified size, and allow the formation of blood vessels that repeatedly seem to be leaking [104]. The accumulation of substantial elements is further enhanced by the absence of lymphatic drainage in certain cancers. The EPR effect is frequently raised as an inactive pointing in divergence to active targets that employ targeting vectors, such as peptides or antibodies [105]. The EPR outcome was confirmed in several preclinical trials; however, the trial results on human volunteers have been extensively uncertain. One of the reasons for the conflict might be the multiplicity of tumors of the same type. There are various factors such as tumor interstitial fluid pressure, degree of angiogenesis, and lymph angiogenesis, which might vary from tumor to tumor, resulting in relatively diverse consequences [104–107]. PTT is generally inadequate to exterminate the tumor completely, and combining it with chemotherapy can be more efficient than the individual therapy. The use of nanoscale-based carriers can permit the integration of both therapies effectively. The nanocarrier systems utilized for photo-based thermal therapy and chemotherapy are divided into three major classes: (i) gold (Au)-based materials, (ii) carbon/carbon-based materials, and (iii) other inorganic materials.

6.1 Gold (Au)-based nanomaterials

The gold (Au) nanodimensional materials have been utilized in diverse biomedical applications owing to their good biocompatibility and the feasibility to fabricate the nanostrcutures in adaptable shapes and sizes [108,109]. The main advantage of AuNPs is their special SPR, which is quite effective in biomedical applications [110]. These optical characteristics and absorbance of photon-based light in Au nanoparticles might possibly be shifted to the anticipated wavelength. The AuNPs generally display two SPR emission modes, the first is initiation from the transverse mode (~520 nm) and another is from the longitudinal mode [111]. The position can be contingent on the characteristic ratio and could be shifted toward the NIR region [112]. Principally in the field of phototherapy photon-based absorption, ~800 nm wavelength is required for deeper tissue penetration [113]. The fabrication and functionalization of AuNPs and their utilization in imaging, diagnostics, and medicine have been reported previously [114]. The biomedical applications of AuNPs owing to their immunological properties have also been described [115]. The biomedical applications of AuNPs include early-stage diagnosis of tumors and their treatment. The shape and morphology-dependent fabrication of AuNPs were achieved successfully for the precise tumor analysis and treatment. The expected properties of AuNPs ought to be scientifically and intensely understood [116]. The applications of AuNPs can be divided into two major categories: physical and chemical, as shown in Figure 5.

6.2 Carbon/carbon-based materials

A variety of carbon and carbon-based materials such as carbon-dots, carbon nanotubes, and fullerenes have been considered for biomedical applications [117–119]. Both graphene and carbon nanotubes are low-dimensional sp^2-hybridized carbon-based materials that exhibit unique physical and chemical characteristics making them useful in a wide range of applications including nanomedicine [120]. Among them, carbon nanotubes and nanoscale graphene showed maximum absorption of NIR light and are consequently being considered as nanoscale carriers for PTT and as drug delivery vehicles for the intracellular transfer of genes, proteins, and chemotherapeutic drugs [121]. The carbon nanotubes are classified into single-walled and MWCNTs and are being considered owing to their high surface area, resulting in unmatched biodistribution effects and PK [122]. The carbon nanotubes, like other carbon-based materials, require to be functionalized to improve their dispersion in aqueous media and allow

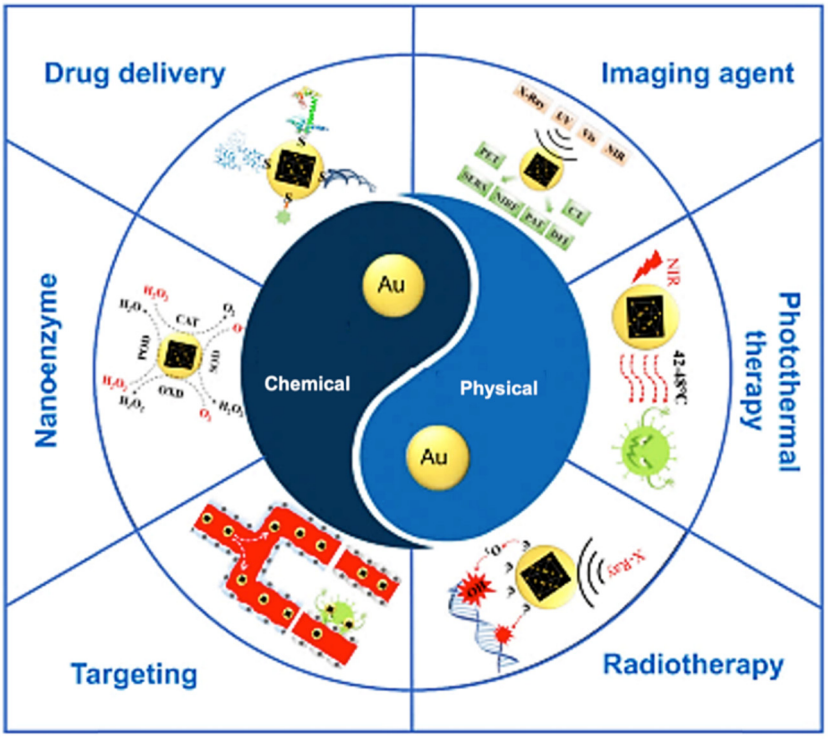

Figure 5: Applications of AuNPs in the tumor diagnosis and its treatment, adapted from ref. [116] under Creative Commons license.

them to be attached to the target-based vectors. A recent study on carbon nanotube structure is reported where QDs-based MWCNT nanocomposites were fabricated successfully for photothermal applications [123]. The effect of intratumoral injection of the prepared nanocomposites was examined in the A549 cell line-induced tumor-bearing nude mice, and the results revealed successful tumor inhibition.

The nanosized graphene and graphene oxide chemically functionalized with other materials have also been considered efficient carriers for the delivery of drugs including the bio-inert materials owing to their high loading efficiency [124]. In addition, nanosized graphene oxides act as photothermal agents, which can absorb NIR light in its compact form. In most of the cases, an ~808 nm NIR laser is employed for the photoactivation. The PEGylation of the graphene nanosized particles is generally anticipated to improve the circulation time, further enhancing the tumor uptake and delivery of anticancer drugs [125]. The transferrin-coated nanosized graphene oxide was also able to penetrate the blood–brain barrier (BBB) and attack glioblastoma tumors. This specified that the transferrin simplified the permeation of nanoparticles over the BBB [126].

The following categories can be used to categorize photothermal agents in general [127]: i) organic dyes, including indocyanine green and heptamethine cyanine; ii) organic nanoparticles, such as porphyrin–lipid conjugate porphysomes and organic semiconducting polymeric nanoparticles; iii) gold nanomaterials; iv) single-walled/multiwalled carbon nanotubes and graphene oxide, and v) other inorganic nanoparticles such as metal oxide and QDs [128]. Photothermal agents such as organic nanomaterials are frequently biocompatible and biodegradable. However, they suffer from inherent constraints such as poor photothermal stability, poor PCE, and complicated synthesis [87]. The intrinsic optical properties of inorganic nanomaterials typically provide excellent NIR light absorption, high photothermal competence, and high photostability compared to organic nanomaterials. Among the benefits of localized SPR (*e.g.* gold nanomaterials), narrow emission spectra, and structural characteristics are the ease of synthesis and the ability to modify surfaces with functionalization, such as carboxylic, hydroxyl, and epoxy groups (*e.g.*, carbon nanomaterials) [129].

6.3 Other inorganic and organic materials

These include the nanomaterials, where their physicochemical properties can be ascribed to the presence of inorganic materials such as metals [130]. The term inorganic nanoparticles is comparatively newer as this class was established a few decades ago and their biomedical applications have only been identified recently [131,132]. The inorganic nanoparticles consist of two parts: a core, which comprises metals such as in AuNPs, QDs, and iron oxide nanoparticles, and a shell, which comprises organic polymers or metals that shield the core from chemical interactions or assist as a substrate for coupling with biomolecules [133–135]. The utilization of inorganic nanoparticles offers numerous advantages such as the target-based release, improved stability, and increased solubility of the drugs. The additional advantage that is relatively significant is that the remarkable penetrability of nanoparticles makes them particularly useful for the treatment of cancer [136]. In general, organic phototherapy agents are lipophilic; thus, co-precipitation is a simple method of achieving biological applications [137]. However, for water-soluble phototherapy agents such as cyanine dyes, it is challenging to encapsulate them into nanoparticles by co-precipitation approach [137,138]. At present, the preparation of water-soluble phototherapy agents into liposomes could be a better alternative [139]. In addition, liposomes can be designed to release drugs thermally when photothermal agents are trapped within them, which is a common strategy for designing smart phototherapy materials. Organic dyes and photothermal nanoagents can be used to improve the photothermal effect, including metallic nanoparticles, nanocarbons, and metal oxide nanomaterials [140,141]. An effective PTT system has been constructed with several kinds of organic materials. In addition to their superior PCE, graphene quantum dots (GQDs) also have an incomparable morphology and are simple to functionalize [142]. The chemotherapeutic drugs can be delivered inside cancer cells by pH-sensitive GQDs [143]. Upon laser irradiation and acidification of the intracellular environment, the nanocarriers released doxorubicin (DOX) [144].

Several inorganic nanomaterial-based drugs are in the clinical phase and are being tested for their application in the treatment of various cancer forms, and a few of them are summarized in Table 1.

QDs are semiconductor nanoparticles with inimitable photonic/optical possessions, owing to their quantum effect and size effect [151]. These are ideal for drug delivery applications owing to various intrinsic properties such as high loading capacity of drugs, no adverse drug reactions reported, good biocompatibility and low toxicity, prolonged residence time as shown in the *in vivo* studies, appropriate particle size and shape ideal for the delivery of drugs, and improved stability [152]. The QDs are signified by inorganic nanoparticles such as CdS, CdTe PbS, and ZnS; however, the frequently used QDs system contains the inner

semiconductor core consisting of CdSe, which is covered with the ZnS outer shell [153]. Owing to their inimitable properties such as resistive behavior to photo-based bleaching, powerful and stable fluorescence for a longer period, high sensitivity, and precision, QDs are considered a novel class of biosensors, which can be utilized for the early-stage detection of cancer [154]. In a previous study, QDs were prepared, and the emission spectrum of scanning multiphoton microscopy was utilized to investigate the tumor cell eruption in animals and the cells labeled with QDs intravenously inoculated into mice. It was reported that the QDs and spectral imaging permitted the instant recognition of five diverse types of cells with multiphoton laser excitation [155]. In conclusion, nanoparticles from organic or inorganic materials are promising carriers for the delivery of drugs in cancer therapy and can be further utilized for clinical applications. The nanoparticle-based drug delivery system proves to be superior to the conventional systems for the reason that they can reduce the general side effects, which the patients undergo during chemotherapy, by delivering the same cytotoxic levels of drugs at the tumor site.

7 Phototherapeutic nanomedicines for the diagnosis and treatment of cancer

7.1 For cancer imaging

In line with the recent advancements in the individualized cancer treatments, more advanced imaging techniques for cancer diagnosis must be developed. Further, the relevant clinical studies appear to be trending toward the effective integration of diagnosis and treatment of cancer. Phototheranostic nanomedicines are especially well suited to bridge the gaps between the diagnosis and therapy of cancer. To improve medical imaging quality, numerous contrast materials have also been developed using NPs. Imaging technologies such as fluorescence imaging, MRI, PA imaging, computed tomography, and positron emission tomography have been effectively playing crucial roles in cancer therapy in conjunction with advanced nanoplatforms. Fluorescence imaging, which utilizes the excitation characteristics of fluorophores, has advanced rapidly in recent years as the most cost-effective imaging technique. Because many phototherapeutic agents are fluorescent, NPs containing these components (for example, NIR dyes, SPNs, and QDs) may perhaps be used as fluorescence contrast compounds for cancer imaging in real-time greater spatial resolution fluorescence imaging [42,156,157]. Examples of phototheranostic nanoplatforms developed so far are summarized in Table 2.

In contrast to the NIR-I fluorescence imaging, NIR-II fluorescence imaging is favored for having a higher spatial and temporal resolution, which inhibits autofluorescence in the corpora. As a result, researchers sought to include NIR-II fluorescent dyes in phototherapeutic NPs to achieve the desired NIR-II fluorescence [167]. For MRI to work, water protons' magnetic dipoles must be able to align when subjected to a strong magnetic field. In previous studies, the related physical principles, picture capture, and processing have been explored [167,168]. Similarly, MRI is recognized among imaging modalities for its dominance in soft tissue contrast and ability to offer more information on tissue function, structure, blood perfusion, and many more. Because of their magnetic inhomogeneity, super-paramagnetic iron oxide nanoparticles (SPIONs), which have been approved by the FDA, can be used as MRI contrast agents for medical diagnostics and rehabilitation [169]. Table 2 summarizes the application of various nanomaterials in targeted cancer therapy and imaging by incorporating gold and AgNPs into the phototherapeutic nanosystems. Metal ion–chelated MRI contrast agents have also garnered a lot of interest recently. As a result, gadolinium(III)-based contrast agents (GBCAs) are utilized in over 40% of all MRI examinations, accounting for approximately 40 million GBCA administrations annually. The function of phototherapeutic nanostructured materials for MRI is achieved

Table 1: Inorganic nanoparticle-based formulations in clinical stages utilized for the treatment of cancer

S. No.	Formulations	Nanoparticles used	Applications	Clinical phase	Ref.
1	NK105	Micellar nanoparticles	Breast cancer	Phase II	[145]
2	AuroLase	AuNPs	Neck cancer and lung cancer	Phase I	[146]
3	Docetaxel PNP	Polymeric nanoparticles	Advanced solid malignancies	Phase I	[147]
4	Carbon dots or C-dots	PEG-coated SiO_2 NPs	Melanoma	Phase I	[148]
5	CYT-6091	AuNPs	Breast cancer and pancreatic cancer	Phase I/II	[149]
6	Combidex	Iron oxide nanoparticle	Imaging of tumor	Not available	[150]

Table 2: Treatment and diagnosis of cancer using phototherapeutic nanoplatforms

S. No.	Types of nanoplatforms	Nanomaterials features	Treatment	Application	Techniques	Ref.
1	Inorganic nanoparticles	Featuring optical, thermal, and electrical conductivity, as well as magnetic and catalytic properties, SPR and photothermal materials may exhibit long-term circulation *in vivo* and toxicity issues	Cancer imaging and therapy	Drug carriers, imaging tools, therapy agents, and functional coatings that are effective against cancer	Photodynamic therapy and hyperthermia	[150]
2	Lipid-based nanoparticles	Biocompatible, biodegradable, and amphiphilic drug colloidal carriers	Enhancing the antitumor activity of several chemotherapeutic agents	Drug delivery in nanocarriers controlled and modified, preventing degradation of hydrophilic and hydrophobic drugs	ME cold dilution	[158]
3	Protein nanoparticles	Biocompatible, biodegradable, and low immunogenic structures; FDA-approved drugs; easy functionalization	Breast cancer with metastatic spread	Treatment and imaging of cancer	Genetic recombination	[159]
4	ZnO QDs conjugated with gold NPs	Unique physicochemical properties, porous structure, and biodegradability	Delivery of drugs targeted at tumors	Platform for delivery of PDT, PTT, imaging, PA imaging, radiotherapy, and phototherapy	Electrochemical	[160]
5	Mesoporous ZnO nanofibers (ZnOnFs)	Biocompatible, biodegradable, and unique physicochemical properties	Breast cancer	Targeted and sustained delivery of bioactive and chemotherapeutic anticancer drugs; specific toxicity *via* reactive oxygen species generation	Electrospinning	[161]
6	AuNPs	High photostability and photoluminescence in a one-dimensional, SPR effect	Therapy for breast cancer	It has excellent plasmonic materials, with adjustable energy regulation, bio-receptor immobilization, improved analyte loading, and strong catalytic properties	Photothermal	[162]
7	Silver nanoparticles (AgNPs)	A one-dimensional, unique physicochemical property, including optical, thermal, and electrical conductivity, as well as resistance to viruses, fungi, and bacteria	Antitumor agents	Bioreceptors are immobilized, the analyte is loaded better, and the catalytic properties of the enzyme are strong	Imaging in biomedicine	[163]
8	AuNPs/graphene oxides	The SPR effect, the strong absorption of NIR light, the high surface area, and the high photostability and photoluminescence of the material	Therapy for breast cancer	Photothermal imaging and drug carriers that immobilize bioreceptors, improve analyte loading, and demonstrate good catalytic properties	NIR-activated PTT	[164]
9	Ag–Au nanostructure	Effects of SPR and photothermal radiation	Therapy for breast cancer	Immobilization of bioreceptors, radiology, phototherapy, and improved presence of analytes in PA imaging and Raman spectroscopy imaging	NIR PTT	[165]
10	Polymeric nanoparticles	Easy to modify and biocompatible	Cancer therapy	Intelligent drug responses, functional coatings	Chemotherapy	[166]

by chelating Gd(III) into phototherapeutics or nanocarrier materials [170].

The PA imaging is a novel hybrid imaging technology that combines optical and ultrasonic imaging to increase the image depth to many centimeters [171]. The short-pulsed laser first stimulates the intrinsic or exogenously supplied light absorber at the target spot, which then partially transforms the energy into heat *via* vibrational relaxation during the PA imaging process. Thermoelastic expansion creates sound waves, which an ultrasonic transducer captures for three-dimensional reconstruction. Consequently, the PA images are produced based on the arrival timings of sound waves at the transducer. Unlike photons, phonons are not widely distributed in biological tissues. Furthermore, the scattered photons produced during PA imaging may aid in the creation of PA waves [172]. Therefore, PA imaging utilizes both high-resolution acoustic imaging and high-contrast optical imaging and has been used clinically to detect prostate and breast cancer [173], and tumor metastases [173,174]. It also finds applications in therapeutic monitoring and endoscopic gastrointestinal imaging [175]. PA imaging can be performed without contrast media, for instance, endogenous Hb and melanin, which may produce PA signals; however, most biological tissues have intrinsically low contrast due to weak NIR absorption. External PA imaging compounds with higher adsorption coefficients and tumor selectivity, notably NPs absorbing light in BWs, have been developed to expand their usage in disease diagnostics [176].

Gold nanoclusters are typical PTT agents for PA imaging [177], and other than this, CNTs [178], reduced graphene oxide [179], UCNPs [180], QDs [181], small-molecule dyes [182], SPNs [183], and melanin [184] are also developed. PA agents efficiently convert light to heat for the PTT. For example, GNRs have outstanding and tunable optical characteristics making them suitable for PA imaging [185,186]. Recently, a new type of tiny GNRs was disclosed in a study, which was found to improve the PA contrast when compared to regular-sized GNRs [186]. The seedless technique was employed to manufacture micro GNRs with absorption in the NIR-II region, having smaller size than the conventional ones with the same aspect ratio (length/width). Miniaturized nanorods are remarkably more stable and can create a robust PA signal when illuminated by a nanosecond pulsed laser than the conventional GNRs. Smaller GNRs improved drug delivery by 30% and elicited greater PA signals in tumor-bearing mice. The theoretical and numerical analysis concluded that the PA signal affects GNR absorption and surface-to-volume ratio.

Owing to the advantages, such as their adaptability to change, high biocompatibility, and relatively low cost, organic PA agents, particularly small molecule dyes, have received much attention [187,188]. Their weak photostability, however, precludes future utilization. SPNs have also gained much interest as a different type of PA agent due to their great photostability and carefully controlled optical characteristics [184,189]. A recent study concentrated on developing SNP-based NIR-II absorbing compounds as PA agents to lessen the tissue absorption and light scattering while performing PA imaging [183]. Notably, PA cavitation could be employed to cause mechanical damage to target tissues, which would have a therapeutic effect. To overcome the challenges of treating glioblastoma, a dendrimer-based NP with high red absorbance and efficient BBB penetration in tumor tissues was developed [190]. Adenosine receptor on the BBB may promptly be activated by the presence of 4-[2-[[[6-amino-9-(*N*-ethyl-*α*-D-ribofuranuronamidosyl)-9*H*-purin-2-yl]-amino] ethyl] benzene propanoic acid hydrochloride (CGS) on the surface of NPs to promote self-accumulation in the tumor (Figure 6). In addition, the NPs used PA to convert pulsed laser light into a shockwave, creating a targeted antitumor impact [42]. More importantly, NP-mediated PA could reveal the tumor depth, shape, and vascular architecture.

The NPs were injected into murine models through their tail veins and after the brain inoculation phase, animals were subjected to pulsed laser energy to initiate PA treatment. The brain glioblastoma arteries prevalent in the tumor periphery were overexpressed with the protein v3 integrin and were the target for the developed nanoparticles. The connection between the agonist, CGS, and the A2A adenosine receptor (A2AAR) on the vascular endothelial cells was made feasible by increasing the local concentration of NPs. The BBB was made permeable by the CGS present on the NPs for a sufficient period to allow a large number of NPs to enter the glioblastoma. Since the v3 integrin is also widely expressed in tumor cells, the NPs directly targeted the glioblastoma once they crossed the BBB. The developed NPs absorbed the light energy from the pulsed laser application to create a PA shockwave, causing local mechanical injury to the tumor cell. The PA image produced by the pulsed laser application is displayed in Figure 6 on the bottom left-hand side. This image contained data about the shape of the vasculature and the depth of the tumor [190].

7.2 For cancer stem cells (CSCs)

Genetic mutations are one of the root causes of cancer at the molecular level. Cells can resist many common cell cycle processes, most notably cell cycle arrest, due to mistakes in DNA instructions. Still, CSCs can develop tumors.

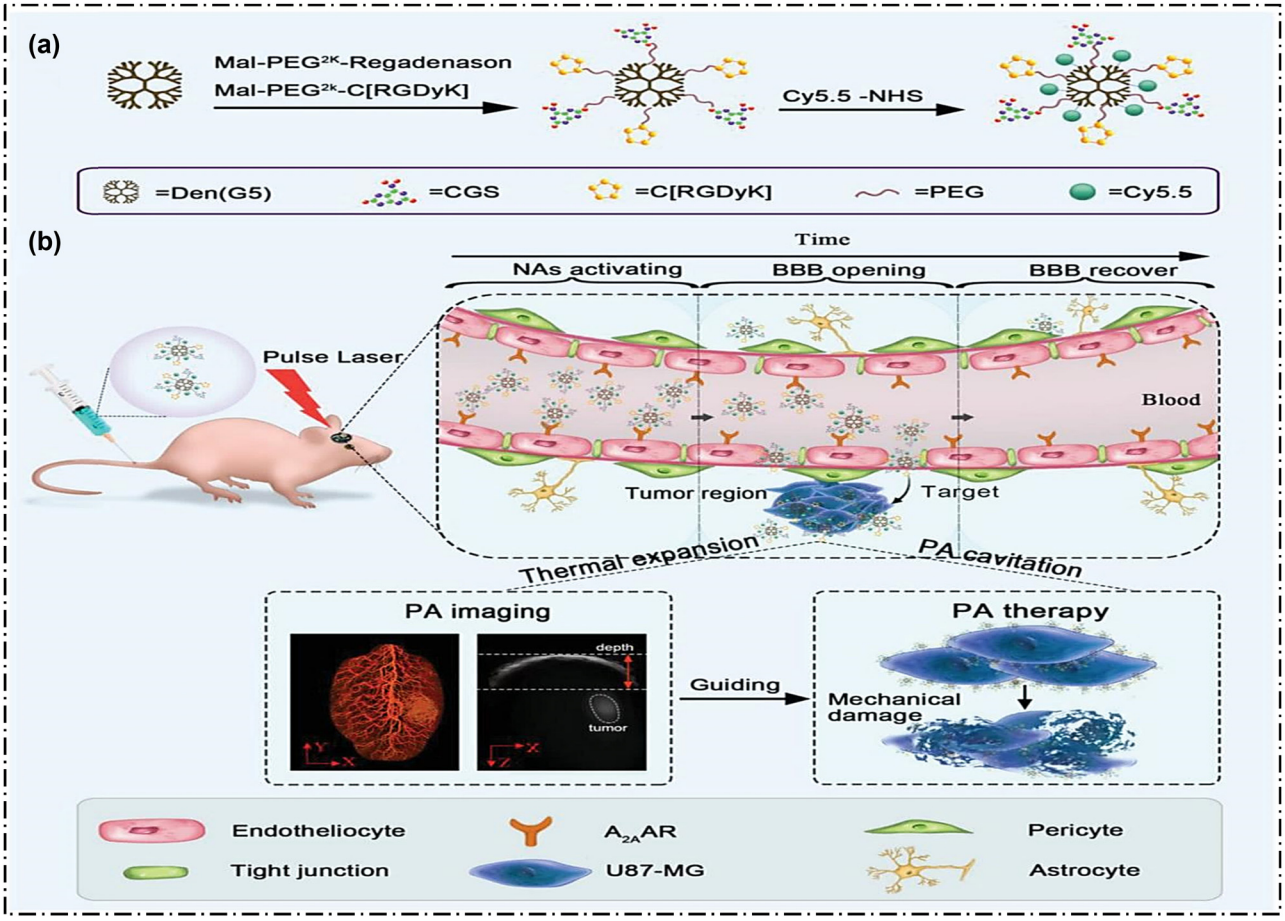

Figure 6: (a) Preparation of the Den-RGD/CGS/Cy5.5 nanoparticles and (b) utilization of Den-RGD/CGS/Cy5.5 in PA precision glioblastoma therapy. Reprinted with permission from ref. [190], Copyright 2019 WILEY-VCH Verlag GmbH & Co.

These CSCs originate from healthy stem cells that have changed genetically, epigenetically, and de-differentiated from somatic tumor cells. These cells make up around 1% of the tumor tissues. In addition, it has been shown that these CSCs, which exhibit great propensities for self-renewal and multiplication, are in charge of the development, upkeep, spread, and recurrence of tumors. The CSCs possess several distinct characteristics that enable them to endure standard cancer treatments including radiotherapy and chemotherapy [191]. As a result, other recently developed therapeutic modalities, such as phototherapy, have served as an alternative strategy for the treatment of CSCs [192]. In a previous study, ionizing radiation (IR) and PTT treatment of patient-derived xenografts were combined, and the results showed that mild hyperthermia (42°C) *via* AuroLase therapy could sensitize the breast cancer stem cells (bCSCs) to IR [193]. This might be because PTT altered the expression of heat shock protein (HSP) in bCSC and reduced their ability to repair double-stranded breaks in the DNA due to the IR radiation. In addition, another study was performed to assess the PTT's ability to prevent metastasis following initial tumor treatment by inhibiting bCSCs *via* highly crystalline iron oxide NPs [194]. It was reported that the PTT mediated by nano agents had the potential to increase the destruction of CSCs, enhance breast cancer survivorship, and offer an alternative therapy for patients with metastatic cancer who can no longer be treated.

7.3 For cancer immunotherapy

Various approaches for cancer immunotherapy, particularly immune checkpoint inhibition and development of anticancer vaccines, have now been investigated extensively [195–198]. Yet, a long journey awaits before the single-cancer immunotherapy could be used to cure both primary and distant cancers. This is mostly because it is difficult to find the most appropriate biomarkers and because each patient is different from the other. Combining two or more therapies to achieve a synergistic

therapeutic outcome is a promising strategy to further enhance the therapeutic effect [199], in which the phototherapy-synergized cancer immunotherapy has been identified as a key approach [200,201]. The activation of immune cells' memories and the promotion of the antitumor immune response have both been linked to the phototherapy. Understanding the PDT/PTT-assisted tumor immunotherapy mechanism is important as it could lead to an immune cell cascade impact in the TME [202]. PDT/PTT would cause a wide variety of antigens to be produced from tumor lesions, which could then enter the bloodstream. It is vital to consider, nevertheless, that the amount of laser radiation also affects the immune system cells and damages the nearby tissues. It is preferable to execute PTT at a relatively low temperature (41–47°C) by adjusting the laser irradiation dose as hyperthermia (>50°C) generated by PTT can potentially cause inflammatory disease and heat damage to neighboring normal tissues [196,203]. To lessen the impact of these immunosuppressive substances, immunosuppressive inhibitors must typically be administered [196]. Several new combinatorial techniques have been adopted using phototheranostic nanomedicines for the phototherapy-synergized cancer treatment resulting in promising immunotherapeutic outcomes.

7.3.1 PTT-synergized cancer immunotherapy

Synergistic outcomes were observed when the PTT was combined with cancer immunotherapeutics. Tumor ablation induced by the photothermal heating during PTT-mediated cancer immunotherapy may make it easier for the immune cells to reach the TME, which is crucial for an antitumor immune response. It is also important to note that the best temperature range for PTT cancer immunotherapy is between 39 and 45°C, as higher temperatures can hasten cell necrosis, which can impair the production of HSPs and other immunostimulatory factors [204]. PTT-synergized immunoadjuvant treatment, among other approaches, could promote lymphocyte recruitment, resulting in improved cancer immunotherapeutic efficacy [205–207]. For instance, IFN promotes MHC I expression in antigen-presenting cells (APCs), while also having a detrimental impact on cancer cell growth and angiogenesis. As a result, a pertinent study using CpG-encoded structured DNA-conjugated GNP nanogels was conducted to boost splenocyte IFN production during PTT [207].

The cargo-free photothrombotic nanomedicine for PTT-synergized immune adjuvant therapy was created using an innovative method to encapsulate PTT agent ICG inside the immune adjuvant OVA in addition to the inorganic NPs [208]. As shown in Figure 7, the OVA-ICG nano vaccines were

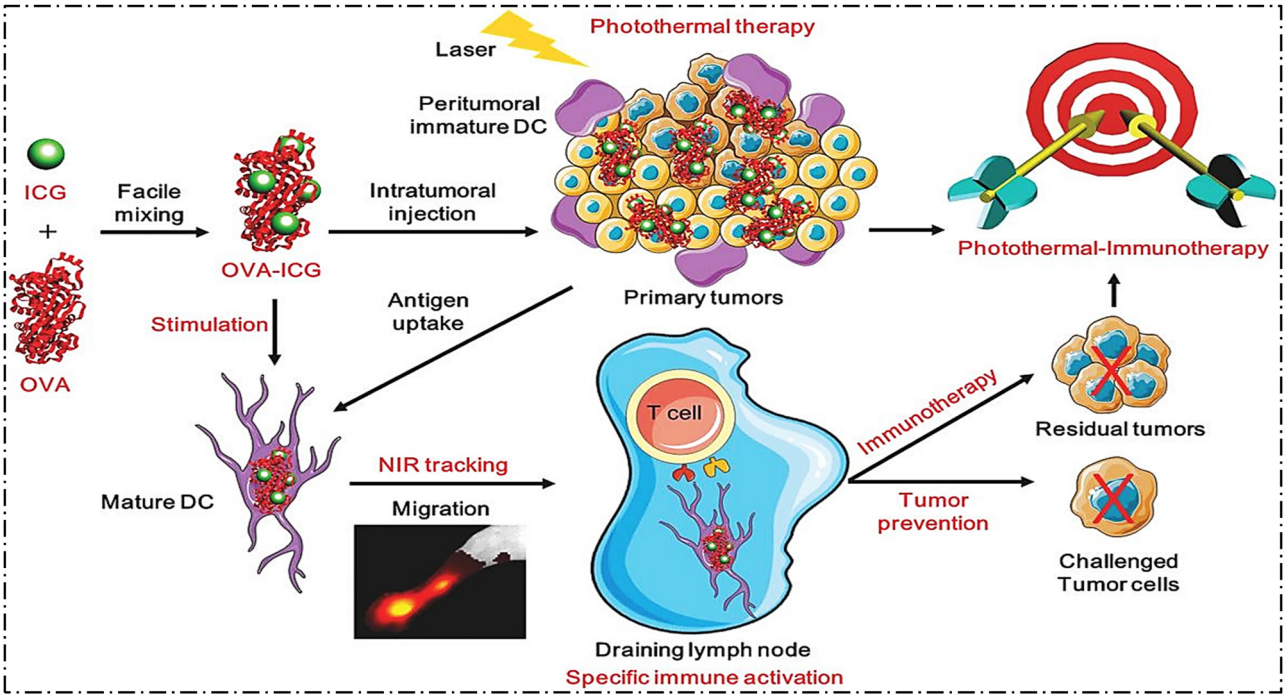

Figure 7: Preparation of OVA-ICG nanovaccines and their role in DC stimulation/tracking, photothermal-immunotherapy, and tumor prevention. Reprinted with permission from ref. [208], Copyright 2018 WILEY-VCH Verlag GmbH & Co.

produced with high antigen-loading efficiency (80.8%) and ICG-loading content (19.2%) through simple mixing of ICG and OVA [42]. In addition, the formulation OVA-ICG did not affect the PCE of ICG. According to the findings, immature DC 2.4 cells were stimulated to secrete IL-6 and TNF-a *in vitro*, indicating a successful immunostimulant. OVA-ICG injection followed with 808 nm laser irradiation reduced the melanoma tumors *in vivo*.

Immune checkpoint inhibitors were also combined with the PTT, and the results have been promising so far [209–212]. In one such study, PEGylated SWNCTs were developed and utilized as PTT agents to heat the tumor cells [212]. Tumor cells generated immunostimulatory mediators such as tumor-associated antigens, HSPs, and inflammatory cytokines upon exposure to an 808 nm NIR laser light. These immunostimulatory mediators caused dendritic cells to mature, which then attracted the tumor-specific CD8+ T lymphocytes. In addition, by including anti-CTLA-4 blocking therapy in the therapeutic process, the suppressive function of Treg cells was effectively suppressed, improving the ratios of CD4 and CD8 cells to Treg cells. Notably, CD20 tumor-infiltrating B lymphocytes may favorably influence the facilitation of tumor-specific antigen presentation. As anticipated, the animals receiving PTT-synergized immune checkpoint inhibitor therapy showed improved tumor growth inhibition.

7.3.2 PDT-synergized cancer immunotherapy

Similar to PTT, PDT may also trigger potent antitumor immune responses through a related mechanism. To actualize the PDT-synergized immunoadjuvant therapy, immunoadjuvants (such as GM-CSF, OVA, and CpG) were initially linked to the photothermal nanosystems. In addition, certain immunogenic substitutes for the aforementioned immune adjuvants have been reported by various studies to support the PDT's ability to elicit an immunological response. For instance, proapoptotic cells often produce the Ca^{2+}-binding protein, calreticulin (CRT), which in the lumina of the endoplasmic reticulum may move to the cell surface acting as a phagocytic signal as the cell undergoes apoptosis [213,214]. To enhance the anticancer effects of phototherapy, UCNP-based antigen-capturing nanosystems (UCNP/ICG/RB-mal-NPs) were developed, and the findings suggested that the tumor-derived protein antigens, in particular, CRT and phototherapy-treated tumor cells, could be stopped and kept, thereby improving the APC tumor antigen absorption and presentation [215]. Another new class of immune adjuvants called synthetic long peptides (SLPs) with immunotherapeutic effects have been developed as cancer vaccines for various cancer forms. The SLP and bremachlorin-mediated PDT were combined in a study to improve the percentage of CD8+ T cells and the effectiveness of immunotherapy [216]. Over 30% of primary and distant cancer forms were successfully treated by the SLP-PDT vaccination, and it outperformed the single SLP vaccine (20%) and PDT (0%), indicating that systemic immunity can be acquired.

The therapeutic nanosystems for PDT-synergized immune checkpoint inhibitors are also being studied [217–221]. With the help of siRNA silencing, PD-L1 was found to be downregulated in the POP micelle, a multifunctional micelleplex nanoplatform [217]. The proinflammatory cytokines and the attraction of cytotoxic CD8+ T cells were made feasible by the efficient induction of the adaptive immune response. Although PDT or PD-L1 siRNA silencing alone only suppressed around 73 or 65% of the relevant tumor development, respectively, PD-L1 immune checkpoint blockade therapy combined with PDT was able to completely eradicate the tumor. Indoleamine-2,3 dioxygenase (IDO), an intracellular enzyme that is overexpressed in the TME of many malignancies, has recently been identified as another intriguing immune checkpoint modulator [222]. Tryptophan can be converted to kynurenine in the presence of IDO, which causes cytotoxic T cells to become "starved" and activates T regulatory cells. As an alternative strategy for immune checkpoint inhibition, numerous IDO inhibitors have been discovered [223]. PpIX-1MT-NPs were reported to have self-assembled using the amphiphilic chimeric peptide PpIX-1MT [224]. To create the molecular structure of PpIX-1MT, 1-methyltryptophan (1-MT), an inhibitor of IDO, was first linked to the *C*-terminal of a peptide that activates caspase-responsive peptide. The PS PpIX was then further linked to the *N*-terminal of the peptide *via* a PEG segment and palmitic acid. According to the findings, the 1-MT release behavior of PDT-induced apoptotic cells treated with PpIX-1MT-NPs in the presence of caspase-3 was consistent and quick, reaching up to 83% over 50 h (Figure 8) [42]. The flow cytometry results indicated that the immune response was activated during PDT because the exposure to CRT was increased after PDT. Meanwhile, the serum and spleen showed a superior ratio of CD8+ T cells/CD4+ T cells. In a CT26 metastatic murine model, the researchers further demonstrated the efficacy of the therapy of primary and secondary CT26 tumors.

PS and other drugs have low tumor penetration, although the PDT can boost immune function and is a viable method for combining various treatments. Thus, their therapeutic efficacy was underutilized. To implement the use of PDT and immunotherapy together, as study was performed where a hyaluronidase-sensitive size-reducible vehicle (mCAuNCs@HA) coated with RBC membranes (RBCm) was developed. In this

approach, the PS pheophorbide A (PheoA), ROS-responsive prodrug PXTK, and anti-PD-L1 peptide were loaded onto the inner NPs, which had the ideal size of 150 nm, when the original vehicle got to the cancer cells. By combining PDT, immunotherapy, and chemotherapy, this technique could remarkably improve antitumor and antimetastatic efficiency owing to its increased penetration capacity [42].

8 Recent developments in nanomaterials for cancer theranostics

The ever-evolving nature of cancer, TME, and other complexities such as biological barriers, and multi-drug resistance limits the efficacy of antitumor drugs and has made cancer research a topic of extensive investigation. Over the last two decades, a steep rise in the cancer-related research, particularly in the development of theranostic nanoparticles for effective cancer treatments, has been observed. The idea of integrating nanomaterials with phototherapies including PDT and PTT is an innovative emerging strategy in cancer nanotheranostics. This might be owing to the advantages associated with PTT such as noninvasiveness, high specificity, strong anticancer activity, and fewer side effects to the normal tissues. The combination of nanotechnology with phototherapy results in synergistic anticancer effects; however, despite all the advantages associated with phototherapeutics, their ability to cause phototoxicity is still a challenge [225]. The nanomaterials used in the phototherapy for cancer theranostics can be divided according to their mode of action.

8.1 Deep tissue penetrating nanomaterials

Recently redox-responsive polyethyleneimine/tetrahedral DNA/DOX nanocomplexes (NCs) were prepared to achieve deep tumor tissue penetration and overcome the issues of MDR. In xenografted drug-resistant tumor murine models of breast (MCF-7/R) and ovarian (SKOV3/R) cancer, the prepared NCs displayed greater tumor penetration and therapeutic potential [226]. Reverse nanomicelles of azobenzene-functionalized interfacial cross-linked loaded with 5-fluorouracil (5-FU) were developed, which could balance the aggregation

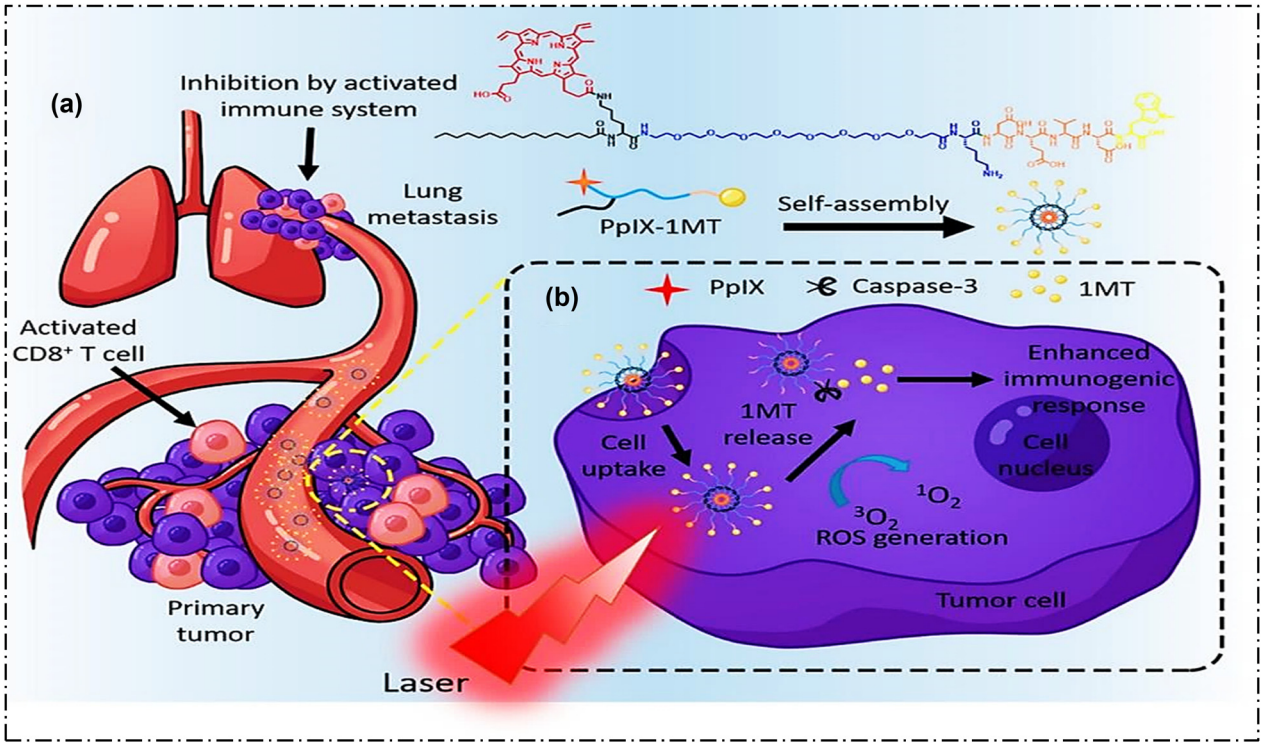

Figure 8: (a) The EPR effect allows the chimeric peptide PpIX-1MT to concentrate in the tumor, activates CD8+ T lymphocytes through cascade activations, and reduces the initial tumor and lung metastasis; (b) *In situ* PDT in the primary tumor resulted in caspase-3 synthesis, 1MT release from PpIX-1MT nanoparticles, and death of tumor cells. Reprinted with permission from ref. [224], Copyright 2018, American Chemical Society.

and penetration of 5-FU in the tumor [227]. A black phosphorous QDs-based DNA-gel nanoparticle (NP) formulation allowed particles to penetrate the cells and was found safe for cancer treatment [228]. Biodegradable amphiphilic gelatin-wrapped NCs comprising DOX and copper sulfide-loaded dendrimers showed dual cell-tissue penetrability and effective deep-tissue penetration in chemo-phototherapy [229]. A biomimetic upconversion nanosystem delivered glucose oxide (GOx) to tumor areas *via* homotypic targeting to selectively starve cancer cells and generate H_2O_2. This starvation-phototherapy cascade was regarded as a smart and simple multimodal cancer therapy [230].

The IR-780 and GOx-based polylactic-co-glycolic acid nanospheres penetrated in 3D tumors and selectively accumulated in mitochondria at the same time, suggesting a synergistic treatment approach of phototherapy and enzyme-induced starvation therapy under dual-imaging guidance, making these nanospheres a promising nanocarrier for cancer theranostic applications [231]. Nano-scintillator-mediated X-ray-induced PDT could cure deep-seated cancers [232]. Two-photon lasers and X-ray irradiators increased the tissue penetration for deep PDT [233]. X-ray-excited theranostics help overcome the light penetration and tissue attenuation issues [234]. Due to its deep tissue penetration capabilities, NIR light-detonated phototherapy has garnered much attention in the treatment of cancer. Because of low tissue autofluorescence and deep tissue penetration, NIR imaging proved to be a promising MDR monitoring method. MDR cancer molecular NIR imaging required stable biomarker probes with excellent specificity and affinity [235]. Gliomas are very infiltrative and difficult to remove; however, a biomimetic catalase-integrated albumin phototheranostic nanoprobe could accurately guide glioma excision [236]. A recent approach, wherein organic phototheranostic nanomedicines with optimized NIR biological transparent window (700–900 nm) were found to be desirable for multimodal cancer therapy [237]. A novel polymer encapsulated sorafenib and chlorin e6 NPs were designed for efficient tumor treatment by accumulating in the tumor as a result of the EPR effect postintravenous administration *in vivo* [238]. For the diagnosis and treatment of cancer, novel IR808 dye-sensitized glutathione cladded Au-Bi bimetallic NPs were prepared to enhance the inhibition effect of tumors. The *in vitro* and *in vivo* results proved its excellent ablation effects on cancer cells [239]. Another recent magneto-thermodynamic strategy for deep-seated tumors was reported in the literature, wherein this novel design triggered free radical generation and exhibited significant therapeutic efficacy for orthotopic liver tumors in a rat model [240].

8.2 Target-specific nanomaterials

Conventional PDT is associated with problems in delivering the PS to tumor locations. A novel approach to overcome the problem is the development of a multifunctional drug delivery system of two or more NPs for efficient cancer therapy. Recently, photothermally active polydopamine NPs were formulated for loading chemotherapeutic drugs and targeting cancer cells. These NPs were first functionalized with polyamidoamine dendrimers followed by the conjugation with polyethylene glycol and folic acid targeting moieties, and finally, DOX was absorbed on the surface of the particles. The nanosystems demonstrated high NIR PCE [241]. For targeted PDT, nanosheets of the iodo-BODIPY-biotin conjugate as a PS showed a high NIR extinction coefficient, high singlet oxygen efficiency, and a surface-targeting ligand [242]. With high singlet oxygen generation and a short sensitivity time, NPs loaded with porphyrin sensitizers are the most widely used PS for PDT of ovarian cancer [243]. Among various recent theranostics, indocyanine/polydopamine-coated laponite nanosystems modified with polyethylene glycol-arginine-glycine-aspartic acid DOX-loaded nanoplatforms (ICG/LAP-PDA-PEG-RGD/DOX) showed high effectiveness PA imaging-guided chemotherapy of cancer cells overexpressing $\alpha_v\beta_3$ integrin.

Synergetic chemo-phototherapy under NIR laser irradiation was observed *in vivo* in a 4T1 tumor-bearing mouse model [244]. Fucoidan and photosensitive polypyrrole NP complexation was found to be an effective P-selectin-mediated delivery strategy with significant ROS/photothermal combinatorial therapeutic effects on lung cancer cells and tumors [245]. Apoferritin-conjugated cypate nanoprobes fabricated for NIR PA imaging and fluorescence imaging emerged as a versatile theranostic platform for solid tumor imaging and therapy [246]. When paclitaxel and the PS IR780 iodide were co-loaded into micelles with a particle size of ~150 nm, a multimodal method for the treatment of malignant tumors was identified. Outstanding stability and photothermal/photodynamic efficacy were exhibited by these nanomicelles [247]. Aptamer-targeted PDT where aptamers could act as ligands that recognize and bind specifically to tumor cells or their membrane proteins [248]. The imaging-guided theranostics and aptamer-targeted treatment platforms including PTT, chemotherapy, and PDT were also developed. These aptamer-targeted photodynamic systems for tumor therapy have excellent potential for the future. For improved PDT for cancer, TME-responsive and efficient NPs were developed [249]. A unique melanin nanoprobe (PMNs-II-813) and extremely specialized

prostrate-specific membrane antigen-specific molecular inhibitor were developed for targeted prostrate treatment [250].

Integrated dual targeting with controlled chemotherapy and PTT for cancer was recently achieved by Fe_3O_4@carbon (C)/ZnO-DOX-folic acid (FA) nano drug delivery systems, and the *in vitro* and *in vivo* results were promising [251]. Redox-responsive docetaxel (DTX)-loaded hyaluronic acid-cystamine-docosahexaenoic acid and choline e6 NPs were fabricated for the management of breast cancer with accurate cellular absorption and enough release of drugs in tumor tissues [252]. Dual-modal nano bipyramids for targeted cancer imaging and PTT are the latest entrants in this area, which have emerged as an effective platform for various biomedical applications [253]. The double targeting of nedaplatin-carboxyl-functionalized magnetic mesoporous silica-galactosylated chitosan NPs revealed that the NPs combined with PTT exhibited good anticancer effects [254]. The cerium oxide (CeO_2) catalase nanozyme-loaded hyaluronic acid nanovesicles were made with recycled CeO_2 to deal with the lack of oxygen at the tumor site, which makes it difficult for PS to act for a long time.

Targeted delivery of the PS Indocyanine green to the tumor was improved [255]. Magnetic molybdenum disulfide–chitosan/carboxymethylcellulose functionalized nanocomposites loaded with DOX ($mMoS_2$-CS/CMC-DOX) were prepared for excellent photothermal effects exhibiting tumor targeting properties than plain $mMoS_2$ [256]. Synergistic effects of combining PTT with immunotherapy were recently investigated to treat and target tumors [257]. Nanographene oxide covalently conjugated with FA, followed by the hydrothermal deposition of CuS nanoflowers was developed recently. The NGO-FA-CuS cytotoxicity toward cancer cells was enhanced, and the photothermal effects of the complex were found to be dependent on its concentration and power intensity of the laser source [258]. Targeted PDT for prostate-specific membrane antigen (PSMA) helped get more PSMA to tumors by making the tumors' blood vessels more permeable [259]. Combining photothermal and IR in the targeted treatment of triple-negative breast cancer using silver NPs is another recent development [260].

8.3 Photoactivatable nanomaterials

Recently, an organic semiconducting pro-nanostimulant with NIR photoactivable immunotherapeutic action for synergistic cancer therapy was revealed. In a mouse xenograft model, it stopped the growth of both primary/distant tumors and lung metastasis, which could not be achieved with phototherapy alone [261]. A photoactivable pro-therapeutic was designed and proposed for metastasis-inhibited cancer therapy. A semiconducting polymer nanoblocker was developed to inhibit intracellular protein synthesis upon NIR photoactivation to synergize PDT for metastasis-inhibited cancer therapy [262]. In yet another interesting study, a photoactivable prodrug-backboned polymeric NP system ($CNP_{PtCP/si(c\text{-}fos)}$) was developed for light-controlled delivery and synergistic photoactivated chemotherapy. Promising results for gene/drug co-delivery nanosystems were obtained for various cancer types [262]. A photoactivable RNAi system was developed, which fought cancer better when gene therapy and PTT were used together, in both *in vitro* and *in vivo* investigations [263]. A new strategy for drug/gene co-delivery was developed when controllable endo/lysosomal escaping versatile nanoplatforms such as photoactivated poly-prodrug NPs for effective light-controlled Pt(iv) and siRNA were fabricated for the treatment of various cancers [264]. Self-assembled nanostructures for protecting ruthenium moieties improved their stability, and these assemblies could get activated by red light, making them aptly suitable for *in vivo* cancer phototherapy [265]. A ROS-activatable thioketal connection between cabazitaxel and TKdC prodrug produced a colloidal-stable nanoassemble with low systemic toxicity and improved efficacy [266]. Photoactivable nanomicelles self-assembled from polyethylene glycol-stearamine conjugate with ROS-sensitive thioketal linker and co-loaded with DOX and pheophorbide A were developed for enhanced chemo-PDT [267].

8.4 Multifunctional nanomaterials

A multifunctional PMSA-targeted melanin-like polydopamine nanocarrier was developed for prostate cancer holding potential in early cancer theranostics [268]. In another recent study, a photothermally active polydopamine NP-based platform was designed for loading the chemotherapeutic drugs and targeting cancer cells as a promising approach to cancer therapy [241]. For the treatment of hypoxic cancer therapy, to increase drug loading and to control the release of radicals into the environment, a $CuFeSe_2$-based system was created by layering a MIL-100(Fe) shell with a polymerization initiator and phase change material. The remarkable biocompatibility and anticancer properties of this potential multifunctional nanomaterial were demonstrated by *in vitro* and *in vivo* investigations [269]. Combinatorial chemotherapy and PDT were developed to augment antitumor responses of α-PD1 through core-shell metal ion drug NPs [270]. The one-step strategy simplified the complex synthesis of multifunctional

NPs and created an "all-in-one" theranostic agent. In the development of an iodinated polyaniline NPs, integration of iodine doping with chemical oxidative polymerization for computed tomography imaging and PA imaging-guided PTT was carried out [271]. Cathepsin B-responsive multifunctional peptide-conjugated nanorods were fabricated for mitochondrial targeting [269]. A multifunctional, programmable DNA nanotrain with mitochondrion targeting was formulated that responded to azoreductase for highly effective photodynamic treatment and activatable hypoxia imaging [272]. Imaging-guided chemo-photodynamic combination treatment was observed with graphitic carbon nitride QDs [273,274]. Nanohybrids combining chemo-photo-gene therapy were developed for effective tumor growth reduction, and no adverse effects were observed [275]. The co-biomembrane-coated Fe_3O_4/MnO_2 multifunctional NPs were also fabricated recently for enhanced chemo-dynamic therapy [276]. The use of multifunctional nano-biosensors based on MOFs was reported for improved fluorescence imaging of intracellular miRNA-122 for simultaneous chemo-photothermal treatment [277].

9 Future perspectives

The benefits of PDT in treating some cancers and pre-cancers over traditional chemotherapy and radiation therapy have made this treatment a mainstream cancer therapy despite significant advancements over the last decade. A number of weaknesses need to be overcome before these nanostructures can be incorporated into clinical practice. The main issues are as follows:

- For large or deep-seated tumors, PDT is not recommended because light is unable to penetrate deeply into tissues. Therefore, PSs excited with NIR light will penetrate deeper into tissues than PSs excited with UV light or visible light.
- PDT is only useful for treating metastatic cancers because it is a local treatment.
- In most cases, patients considered with PDT report high sensitivity to light after treatment, requiring special precautions after PDT. Currently, efforts to address these constraints can be categorized into either of two approaches: finding increased efficacy in PSs or developing nanostructures that can improve PS localization.

First, intensive research aims to optimize the properties of PSs, either by preparing new compounds or by altering the core of existing compounds. Specifically, we will obtain PSs whose optical window absorption is greater, whose extinction coefficients are greater, whose singlet oxygen production is more efficient, and whose chemical and physical properties, especially solubility, are better. In addition, the targeting ability of the nanostructured system plays an important role in controlling the PS's location. Various targeting molecules attach to the surface of the nanostructured carrier system in order to realize active PS targeting, such as carbohydrates, proteins, peptides, and antibodies. Furthermore, after the nanostructures have completed their therapeutic functions, they should be removed from the body to minimize side effects. The majority of current NPs used in PDT are nonbiodegradable and may gather in the body if they are not excreted, which confines their clinical application. The development of biodegradable nanostructures with high phototherapeutic properties should be the focus of future research.

10 Conclusion

Resistance to chemotherapeutic drugs resembles the resistance for infectious diseases, which is mediated by the reduction of apoptosis-related proteins, an increase of DNA repair, drug inactivation, efflux protein overexpression, and miRNAs. Thus, research on cancer are now aimed to overcome this resistance. Nanotechnology is increasingly utilized to combat MDR in the treatment of numerous diseases including cancer by the use of passive or active targeting. Nanocarriers to pool siRNAs, nano-based chemotherapeutic drug combinations, and antibody-mediated target action have been explored in many malignancies. Nanomedicines surpass traditional drugs in having better biocompatibility, target selectivity/specificity, PK, and stability apart from reducing the systemic toxicity and MDR. Although the nanotechnology-based anticancer products have shown great promise in preclinical studies, advanced clinical studies are still underway. Application of nanotechnology in phototherapy and immunotherapy are the key advancements in recent decades. Integration of nanotechnology with phototherapy proved to be an ideal approach to achieve target specificity and deeper tumor penetration which could cure metastatic malignancies with low incidence of side effects. Therefore, it can be concluded that nanomedicine-based phototherapy can serve as a novel and effective approach for the theranostics of various cancer forms, and further advanced studies are warranted to establish their role in clinical settings.

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