REVIEW ARTICLE

Gold Nanoparticle-Mediated Photodynamic Therapy: Emerging Strategies for Targeted Cancer Treatment

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Abstract

Photodynamic therapy (PDT) is a comparatively gentle form of cancer treatment that uses a photo-sensitizer, light, and molecular oxygen to reactive oxygen species, inducing targeted destruction for the tumor cells. The combination of nanotechnology, especially gold nanoparticle (AuNPs), has much higher accuracy and treatment effect of PDT. The focus of this review is to extend the state-of-art of wearable AuNPs-based PDT, focusing on their physico-chemical benefits and potential for enhanced cancer treatment. A systematic review of the literature was conducted toward assessing the relevance to PDT of AuNPs with an emphasis on their surface plasmon resonance, biocompatibility, and functionalization capabilities. These included AuNPs-based systems, including PEGylated spheres, gold nanorods, and prostate-specific membrane antigen (PSMA)-targeted conjugates that were investigated as potential vehicles to effectively carry photosensitizers (PS) and mediators. The review also discusses the stimulated combination of photothermal therapy (PTT) and PDT. Preclinical *in vitro* and *in vivo* studies have shown that AuNPs-coupled PDT can improve tumor-specific accumulation, enable a selective cytotoxicity while simultaneously reducing non-specific side effects. The modification of AuNPs enabled effective PSs delivery and accumulation in tumors. Combining PTT and PDT also improves the therapeutic effect, implying the potential of overcoming some common defects in traditional PDT. In spite of promising preclinical results, clinical translation is still impeded by limitations related to LPP, suboptimal biodistribution, and nanoparticle clearance. Overcoming these challenges with sophisticated nanoparticle engineering and clear regulatory pathways might render AuNPs-mediated PDT a potent, targeted, personalized cancer therapy.

Key words: Cancer treatment, gold nanoparticles, lightactivated therapy, nanocarriers, photodynamic therapy

INTRODUCTION

Cancer, which is an evident collection of diseases characterized by the uncontrolled growth of aberrant cells that tend to dominate neighboring tissues and spread to distant organs.[1-3] It occurs as a result of genetic, epigenetic, and cellular processes gone awry, which are often influenced or initiated by environmental, lifestyle, occupation, and infectious factors. Unlike a benign tumor,

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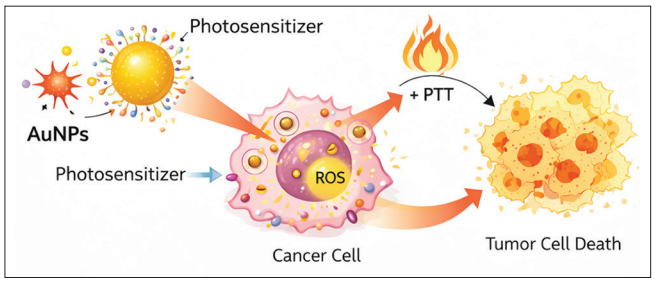
Graphical abstract



malignant cancer can invade and metastasize, which can be fatal when not discovered and treated at an early stage.[4,5] Consistent with GLOBOCAN 2020, an estimated 19.3 million new cancer diagnoses and ten million cancer-related deaths occurred registered worldwide. The incidence of cancer is projected to exponentially increase in the forthcoming years, with an estimated 28.4million new cases and 16.3 million deaths by 2040 -a rise of about 47% from the numbers reported in 2020.[6,7] This increase is mainly due to an ageing population, urbanization, and the increasing prevalence of risk factors including tobacco consumption, poor diet, physical inactivity,8220251502 and environmental pollution.[7-9]

The most diagnosable cancers in the world are breast cancer colorectal cancer (10.0%), prostate (7.3%) (11.7% in all), lung (11.4%), and stomach (5.6%). Lung cancer is still in the lead cause of cancer-related deaths, consisting of approximately 18% all causes of cancer death, followed by colorectal, liver, and stomach cancers.[6] Cancer is thus not any more acknowledged now only as a single disease but also as an assembly of hundreds of different disease types, each exhibiting explicit molecular features and responses to therapy. The World Health Organization defines that 30–50% of cancer cases can be prevented by lifestyle changes and early detection in medical practices.[10] Nonetheless, disparities in medical care access, diagnosis, and treatment persist that further contribute to outcomes, especially in emerging low- and middle-income countries where about 70% of cancer deaths occur. In past decades, cancer research has experienced a paradigm shift from treatments with broad cytotoxicity toward more specific and tailored approaches. Precision medicine, a concept of adjusting therapy based on genomics, epigenomics, and molecular markers, has produced encouraging findings in increasing survival of cancer subjects and the quality of their life.[11,12] Immunotherapies, monoclonal antibodies, and cancer vaccines are landmark discoveries with the potential to change the therapeutic framework. Due to rising global cancer incidence, there is a need to direct resources toward deeper research, improved healthcare facilities, and increased public awareness for prevention as well as early detection. An interdisciplinary, patient-focused strategy is necessary to decrease the mortality rate and to control cancer as delayed but more treatable disease.[13-15]

Cancer static occurs a former cause of death worldwide, with developing incidence rates creating an immense public health problem.[7] Despite advancements in standard therapies: surgery, chemo- and radiation regimes, these treatment approaches were again bound to harsh side effects, little tumor specificity, and potential relapse. In this setting, photodynamic therapy (PDT) has been developed as a promising adjuvant or complementary treatment modality mainly due to its functionally long-lasting nature, high specificity, and possibility of being used repeatedly without cumulative side effects.[16-18] PDT relies on the interaction of three integral components; a photosensitizing agent, an activated wavelength of light, and the availability of molecular oxygen in tissues.[19,20] Photosensitizers (PSs), once irradiated with light, are responsible for producing reactive oxygen species (ROS), that is, $^1O_2$ that leads to the cellular oxidative damage directing toward apoptotic killing. This specific mode of action makes PDT a method that can specifically kill cancer or diseased cells and leaving the adjacent healthy tissue intact.[21,22]

PDT was first approved for dermatological and oncological indications, although this modality has since grown to encompass a wide array of clinical applications such as infectious diseases, ophthalmology, dermatology/biofilm disruption, and antimicrobial therapy. In cancer therapy, PDT has been used for the treatment of skin, lung, esophagus, bladder, and head and neck tumors with potential applications also in deep-seated and drug-resistant cancers.[17,23] In addition, recent advances in the development of nanotechnologies, targeted drug delivery systems, and next-generation PSs have greatly improved PDT efficiency and specificity. Nanotechnology is spending cancer treatments in the modern world country, nanotechnology allows for diagnostics, along with healing would mean against many other available enhancement programs. Novel results in addressing these therapeutic challenges revolutionize the strategies to diagnose, image, and treat cancer.[24,25]

Nanotechnology, which is defined as the use of materials on the nanometer scale (1–100 nm), enables the development of multifunctional nanoparticles that can target tumor cells in a specific manner, deliver drugs in a controlled and sustained release fashion to achieve an enhanced therapeutic outcome, and reduce off-target effects.[26,27] Unique features of nanoparticles, such as large surface area to volume ratio, size and shape tunability, and ability to be functionalized with ligands, antibodies, or drugs, make them promising candidates for the treatment of cancer. Numerous nanocarrier systems, including liposomes, dendrimers, polymeric nanoparticles, micelles, carbon-based nanostructures and metallic nanoparticles, have been developed for their ability to enhance the pharmacokinetics and biodistribution of anticancer agents.[28,29] In addition, the development of nanotechnology also has supported the expansion of theragnostic applications in integrate diagnostic-therapeutic

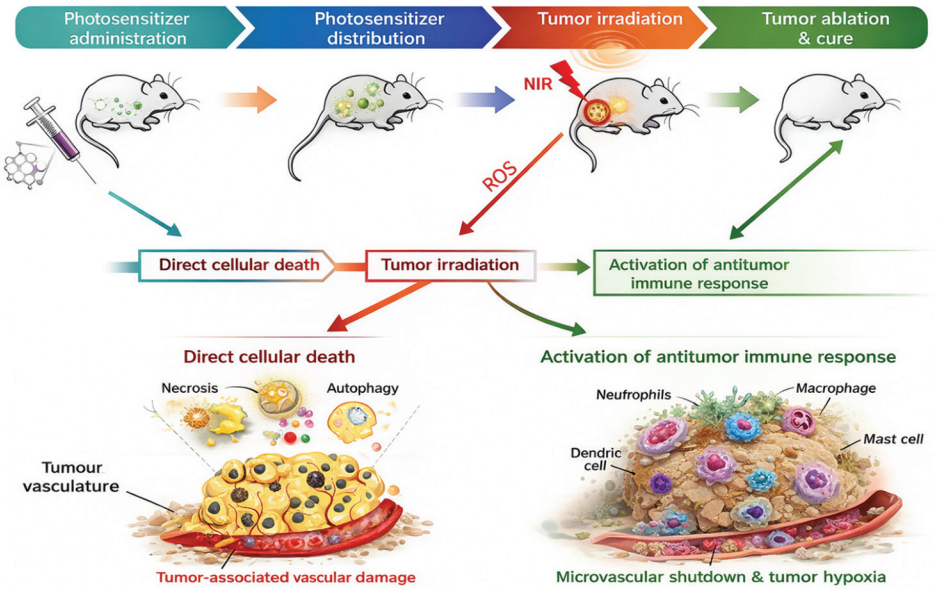


Figure 1: Principles of photodynamic therapy (according to Dąbrowski *et al.*,[41])

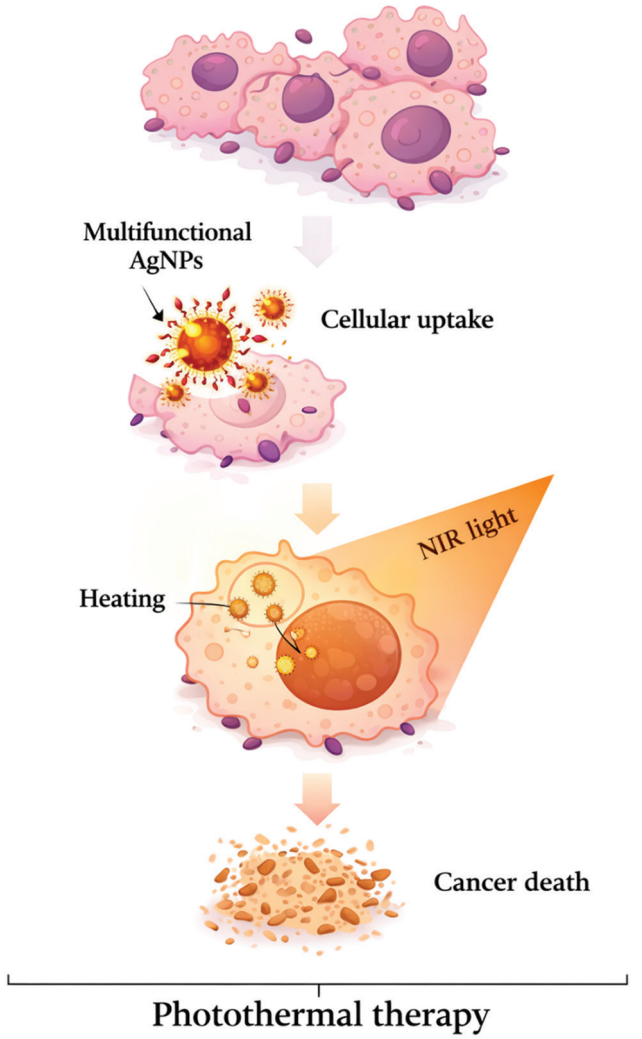


Figure 2: Breast cancer cells (Adopted from Dheyab *et al.*,[68])

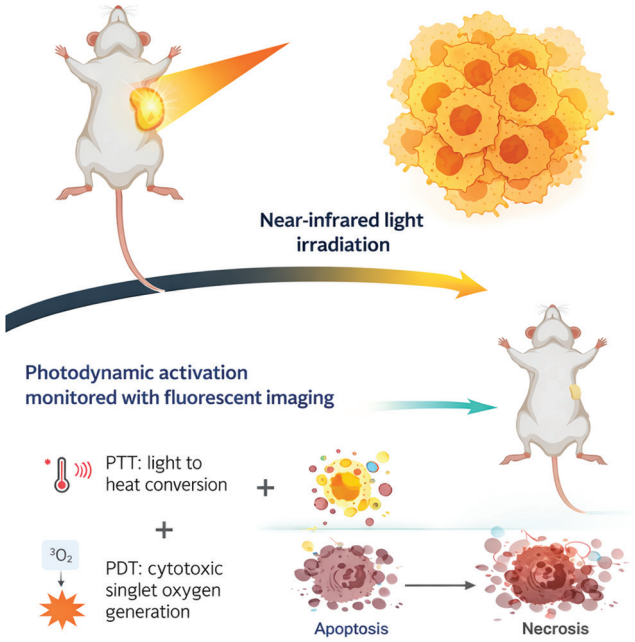


Figure 3: Phototherapy of tumors (as defined by Bhamare *et al.*,[78])

work station into an individual nano procedure for real-time monitoring treatment response.[30,31]

In recent years, nanotechnology has played a key role in increasing the efficacy of PDT. Among the numerous studied nanomaterials, gold nanoparticles (AuNPs) are one of the developed highly recommended candidates due to their unique optical, electronic, and physicochemical properties. AuNPs also possess biocompatibility, abundant surface functionalization, and strong surface plasmon resonance (SPR) that could

Table 1: *In vitro* and *in vivo* studies on AuNPs mediated photodynamic therapy

Model type	Nanoparticle type	Photosensitizer	Targeting ligand	Key outcome	References
In vivo	AuNPs coated with polydopamine	Chlorin e6 (Ce6)	RGD peptide	Dual PDT/PTT showed strong tumor suppression in 4T1 mice model. High ROS generation and good biocompatibility.	[67]
In vitro and *in vivo*	Hollow AuNPs	IR820	None	Dual-modal PDT/PTT using NIR laser enhanced phototoxicity and suppressed tumor growth in MCF-7 xenografts.	[68]
In vivo	Mesoporous silica-coated AuNPs	Methylene blue	Anti-EGFR antibody	Improved tumor targeting and minimal side effects in A431-bearing mice; effective photodynamic activity.	[69]
In vitro and *in vivo*	AuNPs functionalized with PEG and FA	Ce6	Folic acid	High tumor accumulation in HeLa xenografts with >70% growth inhibition. Enhanced selectivity and ROS production.	[70]
In vivo	Core–shell Au@ SiO_2 NPs	Rose Bengal	Transferrin	Targeted PDT suppressed glioma tumor by 65%. Improved BBB penetration and tumor uptake in U87 model.	[71]
In vivo	PEGylated AuNPs	Indocyanine Green (ICG)	FA and PEG	Strong tumor inhibition in HCT116 xenograft mice. Biocompatible, dual-mode imaging+therapy.	[72]
In vitro and *in vivo*	AuNPs–liposome hybrid	Ce6	Anti-HER2 antibody	Enhanced accumulation in HER2+tumors. PDT triggered apoptosis and immune response in mouse model.	[73]
In vivo	AuNPs with mesoporous silica shell	Chlorin e6	None	Controlled ROS release via pH-sensitive shell. Effective tumor shrinkage *in vivo* with no systemic toxicity.	[74]

PEG: Poly (ethylene glycol), BBB: Blood-brain barrier, AuNPs: Gold nanoparticles, NIR: Near-infrared, PDT: Photodynamic therapy, PTT: Photothermal therapy, ROS: Reactive oxygen species

serve to enhance light absorption, localized heat production, and ROS generation.[32,33] These properties render AuNPs as favorable vehicles or synergistic agents for PSs delivery and phototherapy. Furthermore, AuNPs allow the targeted delivery of PSs by surface conjugation with tumor ligands, peptides, or antibodies, which enhance tumor-associated selectivity and decrease nonspecific induced damages on normal tissues. AuNPs can also serve as carriers of multimodal therapies, for the combination of PDT with photothermal therapy (PTT), chemotherapy, or imaging enhances synergistic and more effective treatments for cancers.[34,35] This review discusses the latest progress fashion in the fabrication and application of AuNPs for PDT, including synthetic methods, functionalization strategies, modes of action, and clinical applications. It emphasizes the benefits of AuNPs facilitated PDT compared to conventional PDT, recent progress in the development of multifunctional nanoconjugates, and challenges that need to be addressed for clinical translation.[36]

Principles of PDT

PDT is a non-invasive treatment modality, which relies on the interactions of three basic components: A PS, light with an appropriate wavelength, and molecular oxygen to yield cytotoxic ROS able to kill cells preferentially within targeted areas. PDT has experienced many medical treatments in the field of oncology, dermatology, and antimicrobic therapy due to its spatial and temporal precision, low invasion, and ability to induce immunological responses. The mechanism of PDT is illustrated in Figure 1.[37,38]

Mechanism of PDT

The basic mechanism of PDT is a photochemical process through PS excitation in the presence of light. The therapeutic effect of PDT is strictly mediated by the interaction of three main components [Table 1]:

PS

PSs are molecules that become activated upon exposure to light and selectively concentrate in diseased tissues, such as tumoral or infected areas.[14] The PS absorbs light, plays transitions from the ground state (S_0) to a 1st excited singlet state (S_1), and then relaxes to a longer-lived lowest excited triplet state (T_1) through intersystem crossing. This triple state triggers further photochemical reactions. An ideal PS ought to be safe in the dark, specifically accumulate into target tissues and have high absorption in this therapeutic window (600–800 nm) for effective. Penetration of tissue.[39]

Light activation

A light source of a specific wavelength corresponding to the absorption spectrum of the PS that is used to sensitize

(activate) the PS. Common light sources are lasers, LED's, and fiber optic depending on the location of the intended use. The light dispersion in tissue relies on the wavelength, such that red or near-infrared (NIR) light (650–800 nm) has deeper penetration and is applicable for interior tumors.[40]

Molecular oxygen

Oxygen in tumor tissue is necessary for PDT efficacy. Once activated, the triplet-state PS energy is transferred to ground-state molecular oxygen ($^3O_2$), leading to the formation of ROS, mainly singlet oxygen ($^1O_2$). There, it is still classified as a Type II reaction. Alternatively, in case of Type I reactions, the light-excited PSs react with cells or cellular components to generate free radicals or superoxide anions for which further extend with oxygen and generate other ROS.[22]

AuNPs: Properties and synthesis

AuNPs have emerged as versatile nanomaterials due to their unique physicochemical properties and numerous applications in diagnostics, therapeutics, and PDT.

Exclusive physicochemical properties of AuNPs

AuNPs have optical, electronic, and catalytic properties that depend on their size and shape. A characteristic property is the SPR, which represents the collective oscillation of conduction electrons on the incidence of light, leading to intense absorption and scattering in the visible-NIR region. This property can better utilize them in imaging, sensing, and PTT therapy. What's more, their high surface area to volume ratio makes it possible for them to bind a variety of biomolecules, and good biocompatibility and chemical stability make them suitable for biomedical applications. Their morphology in the form of spheres, rods, stars, and cages also affects their optical and biological properties.[42,43]

Methods of synthesis

Chemical synthesis

Most commonly, the reduction of gold salts (usually $HAuCl_4$) using reducing agents such as sodium citrate (Turkevich method) or sodium borohydride. This allows controlling both the particle size and shape; however, post-synthesis surface modification is often still necessary for biological use.[44,45]

Green synthesis

Furthermore, the green approach used plant extracts, polysaccharides, or microorganisms as reducing and capping agents. The more concept reduction of toxicity and improvement in biocompatibility enhance a need of the method that it may be applicable in medical treatment. Flavonoids and polyphenolics phytochemicals, usually serve as stabilizing agents.[46,47]

Physical methods

These, among others, are laser ablation, ultraviolet irradiation, and thermal decomposition. Despite the high purity of particles they generate, they are not so widely-used because of their higher energy consumption and less scalable operation.[48,49]

Surface modification and functionalization strategies

The functional surface modification of AuNPs can enhance the colloidal stability and facilitate site-specific biological interactions. Generic approaches include Ligand Exchange, exchanging weakly bound surface ligands with thiol-terminated molecules (e.g., poly(ethylene glycol) [PEG], peptides). Covalent conjugation involves the binding of biomolecules (such as antibodies, aptamers, and drugs) through amide, ester, or click chemistry, whereas electrostatic interactions enable the reversible binding of oppositely charged species. Functionalization plays an important role for enhancing targeting ability, circulation time, and medicinal cargo carrying capacity, which promotes the clinical application of AuNPs in nanomedicine.[50-52]

PTT and its combination with PDT

PTT is crowed because it takes the advantage of located heating capacity of AuNPs under NIR light irradiation and during SPR process, which is significant to local hyperthermic treatment of tumor cells. They produce heat caused coagulation of cells and denature proteins in the tumor, which gradually causes cell damage, shrinkage, and death. In contrast, PDT is based on light activation of a PS resulting in ROS generation and cellular damage and killing. When PTT and PDT are applied together, a synergetic effect is launched: PTT promotes the blood flow and oxygen supply in tumor tissues, which increases the efficiency of PDT; On the other hand, ROS generated by PDT can sensitize heat outcomes to cancer cell factor, enhancing PTT effect. This synergism has a superior tumoricidal effect than either modality alone.[53,54]

Dual mode treatment using AuNPs

Au NPs are effective carriers and simultaneously the active agents in PTT/PDT dual mode. The surface of these nanoparticles can be functionalized with PSs and so allows the possibility of a simultaneous or sequential PDT-PTT treatment through a single light source or different wavelengths.[18] Nanostructures, including Au nanorods, nanoshells, and nanostars, exhibit extremely high efficiency owing to their tunable SPR in the NIR range. Hybrid vehicles such as core-shell, AuNPs-polymer composites, and liposome formulations may be designed for the co-delivery of PSs, targeting ligands, and therapeutic drugs. As light-triggered therapeutically turn-on agents, the dual-functional systems can provide accurate control and higher tumor selectivity with improved bioavailability of the agents.[55,56]

Benefits of combined PDT and PTT on cancer cells

There are multiple therapeutic benefits by combining PDT with PTT on AuNPs incorporation. This combination maximizes cancer cell death via two cooperatively working mechanisms of thermal damage and oxidative stress with reduced light dose and drug concentration, which causes the parallel minimize in healthy tissues deterioration. Furthermore, the synergistic response can also address issues related to tumor hypoxia that suppress PDT efficacy and reduce the probability of resistance by cancer cells. The combined treatment also induces immunogenic cell death (ICD) that may drive anti-tumor immune responses. In summary, the unified PDT and PTT with AuNPs offers a positive direction for improved targeted and non-invasive antitumor therapies.[57,58]

Apoptosis, necrosis, and autophagy

There is also a demonstration that AuNPs facilitated PDT container brings about multiple types of cancer cell death, mainly apoptosis, necrosis, and autophagy. Apoptosis, that is, programmed cell death, is characterized by condensed chromatin, DNA fragmentation, and blebs formation in the membrane. PDT leads to intrinsic (mitochondrial) or extrinsic (death receptor) apoptotic signaling through the destruction of cellular components and the stimulation of caspases. When oxidative damage becomes overwhelming or apoptotic signaling is insufficient, necrosis from cell swelling and membrane rupture, accompanied by inflammation, may take place. In addition, PDT retains trigger autophagy, a catabolic process in which damaged organelles and proteins are degraded within autophagosomes. Although autophagy may be cytoprotective at first, sustained or excessive activation results in autophagic cell death. The interaction between these paths is subject to PDT dose, PS localization, and tumor type.

ROS generation and oxidative stress

The cytotoxic effects of AuNPs-induced PDT are mostly still dependent on the production of ROS, such as $^1O_2$, O_2^-, and •OH. When light is irradiated, the PS directly conjugating or being encapsulated into AuNPs photochemically reacts in the presence of molecular oxygen to generate ROS dominantly against lipids, proteins, nucleic acids, and cellular membranes. This oxidative stress attenuates the integrity of mitochondria, causes strand breaks in DNA, and leads to the induction of pro-apoptotic pathways. The high local concentration of ROS also causes cellular disruption on lysosomal and endoplasmic reticulum functions, which further increases the stress response of cells. The improved photostability and directed PS delivery by AuNPs result in ROS production at localized sites, resulting in elevated PDT specificity and decreased systemic side effects.[22,59]

Effects on tumor microenvironment

AuNPs-based PDT not only directly kills cancer cells but also has a great influence on the tumor microenvironment TME). ROS-mediated damage bargains with the stability of tumor vascularity and communicates to vascular shutdown, hypoxia- and nutrient-deprivation that hinder growth and metastases. PDT can also affect the immune response by ICD, which triggers the exposure of Damage-associated molecular patterns (e.g., calreticulin, HMGB1, and adenosine triphosphate [ATP]). These molecules are able to attract and activate antigen-presenting cells, which can improve antitumor immunity. In addition, PDT remodels the extracellular matrix and damages tumor stromal cell support, destroying the protective architecture of the tumor. The multi-mode effects of AuNPs-based PDT on TME not only lead to immediate tumor killing but also long-term anti-tumor recurrence.[60,61]

In vitro experiments with AuNPs-based PDT

AuNPs facilitated PDT has gained wide investigations in the selective tumor ablation, both *in vitro* and *in vivo*. Major *in vitro* studies include those of Broadbent *et al*.,[55] and Zhang *et al*.[62] which presented The PEGylated AuNPs are functionalized with a phthalocyanine PS (C11Pc) and the EGFR-targeting peptide AEYLR. These nanoconjugates exhibited highly selective phototoxicity toward the EGFR-positive A549 lung cancer cell line but not to the EGFR-different negative HEK293 cells, resulting in desirable efficiency and selectivity due to covalent attachment of PS and its low non-specific desorption. In a similar study, Stuchinskaya *et al*.[63] successfully used antibody-conjugated AuNPs with zinc–phthalocyanine for PDT of HER2-positive breast cancer cells. The 4-component nanoconjugate effectively induced singlet oxygen generation and specifically killed the HER2-overexpressing cancer cells, demonstrating that AB-MAT-PDT-enhanced NDH proves to be useful for PDT enhancement.

In an attempt to advance this strategy further, Liu *et al*.[64] demonstrated a combined PDT/PTT *in vitro* as well as *in vivo*. They developed HAuNRs co-loaded with a new originated PS, chlorin e6-C-15-ethyl ester (HB), and modified them by cyclic RGD peptide for tumor targeting. Under the excitation of single-wavelength 660 nm laser, these nanorods efficiently generated ROS and hyperthermia. For the dual-modality therapy, it also showed excellent biological performance, including high tumor accumulation, good selectivity, and negligible systematic toxicity with a tumor inhibition percentage of 77.04% on ECA109 esophagus cancer-bearing mice. Additional *in vitro* work by Imanparast *et al*.[65] involved 6-mercapto-1-hexanol modified AuNPs to co-deliver protoporphyrin IX and folic acid for improved percutaneous coronary intervention (PCI). As a result, PpIX/FA-MH-AuNPs showed enhanced selective cytotoxicity and

decreased drug incubation time, indicating PCI as an effective method to avoid the endolysosomal trapping.

Furthermore, Mokoena *et al*.[66] investigated the coupling of cannabidiol with AuNPs-based PDT in combination with hypericin. This combination regimen mediated apoptosis in MCF-7 breast cancer cells through vacuolization, ATP depletion, lactate dehydrogenase leakage, and up-regulation of apoptotic proteins Bax, p53, and release of cytochrome c. A published study further supported that PDT assisted with phytochemicals might be an effective force against cancer. Together, these studies highlight the potential of AuNPs as PDT/PTT PS and a nanoplatform for drug delivery in cancer therapeutics under targeted therapy with less interference to normal tissues and easier to implement in laboratory and animal models.

In vitro studies on AuNPs-mediated PDT

In vivo tests with AuNPs for PDT showed substantial improvements in targeted tumor drug delivery, biodistribution, and therapeutic responses. Cheng *et al*. utilized PEGylated AuNPs functionalized with silicon phthalocyanine 4 (Pc 4) for highly efficient tumor accumulation in nude mice, which decreased the delivery time of the drug from 48 h (free drug) to <2 h, and significantly improved photodynamic efficiency under exposure to a 672 nm laser.[35,75] Hwang *et al*.[76] summarized several AuNPs morphologies, including nanoshells and nanorods, employed for PTT (combined with PDT) applications. These systems demonstrated deep tissue penetration, low systemic toxicity, and tumor-selective ablation in rodent models by virtue of their tunable SPR peak in the NIR. More recently, targeted PDT against a canine orthotopic prostate cancer model was also successfully developed by Luo *et al*.[77] using PSMA-targeted AuNPs loaded with Pc158. The present study found selective tumor fluorescence, site-specific necrosis upon light exposure, and low off-target toxicity, suggesting that it is feasible to translate the approach from small to large animal models.

Challenges and limitations biodistribution and clearance of AuNPs

The pattern of *in vivo* distribution of nanoparticles depends on factors such as size, shape, surface charge, and coating materials, which collectively influence their biodistribution and clearance. The practical applicability of AuNPs-based PDT is much pinched by the bottleneck of its corresponding clinical models, e.g., tissue delivery and metabolism.[28] AuNPs are also rapidly captured by the mononuclear phagocyte system after systemic injection, such that AuNPs mainly accumulate in the liver, spleen, or kidneys instead of being homogeneously distributed or showing specificity toward tumor cells.[79,80] This extra-target accumulation may greatly decrease the therapeutic efficacy of PDT and bring potential long-term retention in non-target organs. The clearance of AuNPs is significantly size-, surface charge-, coating- and shape-dependent, e.g., smaller (size <5 nm) typically are renally cleared, while larger are cleared hepatobiliary. However, larger or aggregated AuNPs are removed from tissues slowly on the order of weeks to months, raising concerns for chronic toxicity as well as activation of the immune system/interference with organ function. Engineering of AuNPs with biodegradable coatings and optimization of their surface properties for long blood circulation time, and integration of active targeting ligands might enhance tumor site-specific biodistribution, as well as efficient excretion; however, the solution not only brings complexity but also the additional requirement on safety test.[34]

Toxicity and side effects

Although AuNPs are generally considered biocompatible and chemically inert, their surface chemistry, size, and dose may have a profound impact on their *in vivo* toxicological profile.[31] Untreated or inappropriately stabilized AuNPs can provoke oxidative stress, inflammation, and cytotoxicity, mainly within the liver, kidneys, and lungs. ROS production leads to event-like killing of the tumor, which is advantageous for PDT, though it may harm the surrounding healthy tissue if not strictly compartmentalized.[81] In some instances, the presence of AuNPs off-target organs has resulted in histological changes typical for pyogenic or fibrosing process. Furthermore, it was reported that if the nanoparticle surface is coated with surfactants, stabilizers, or targeting ligands, these nanoparticles could induce the immune response or hemolysis and aggregation of platelet may be occurred due to their composition as well as charge. Such effects are exacerbated by administration of multiple or high-dose regimens, thus posing concerns regarding chronic toxicity and immunogenicity. Thus, there is a crucial need for extensive toxicological testing, optimal dose determination, and safety evaluation over extended time periods in order to use AuNPs facilitated PDT in a clinical setting.[81]

Penetration depth and tumor accessibility of light

A crucial practical challenge in PDT application, including the AuNPs-ameliorated one, is the low penetration depth of light into biological tissues. PSs are activated by light through PDT primarily with the aid of specific wavelengths of light, most frequently NIR light (650–900 nm), to produce ROS and kill tumor cells.[82] However, even near-IR light gets extinguished within only 1–2 cm of tissue depth, and is therefore applicable to almost exclusively superficial tumors where those in the skin, oral cavity, or otherwise accessible mucosal surfaces. This creates a problem in case of deep-seated or under-vascularized tumors for which successful and efficient light delivery is often very difficult, requiring the use of invasive techniques like fiber-optic probes or interstitial laser delivery systems[5] that are not always feasible and pose an increased risk. In addition, tissue light

scattering/absorption by hemoglobin/melanin and water may decrease the efficacy of illumination. Such depths impose limitations on the application of AuNPs-mediated PDT and, thus, further improvements might include more sophisticated light delivery systems, photoactivatable prodrugs, or a combination of modalities, for example, PTT or ultrasound-triggered activation, to address depth-related restrictions.[40]

Stability and reproducibility issues

Physically and chemically stabilizing AuNPs for PDT application is a major manufacturing and regulatory hurdle.[58] Physicochemical characteristics (size, shape, surface charge, and ligand density) are very critical determinants for biotechnological applications of AuNPs. Slight fluctuations during the synthesis or functionalization processes can generate batch-to-batch discrepancies in drug loading ratio, colloidal stability, and targeting efficiency, which might have an influence on biodistribution, cellular uptake, and PDT efficacies. Moreover, AuNPs are vulnerable to aggregation in biological media or after storage, thereby losing their surface properties and decreasing bioavailability. In addition, *in vivo* instability could cause premature release of the PS or reduced targeting specificity.[83,84] In addition, the application of ill-defined or heterogeneous surface coatings makes quality control and scale-up for clinical use difficult. To address these challenges, extensive standardization of protocols for nanoparticle synthesis is required, as well as including stable surface stabilizers (e.g., PEGylation) and rigorous characterization with validated analytical techniques. Reproducibility is particularly important for regulatory approval, warranting GMP-compliant procedures and comprehensive physicochemical and biological controls.[85]

Regulatory matters and status of clinical trials

In spite of mounting preclinical support for AuNPs- mediated PDT, regulatory approval and clinical translation are challenging tasks. The heterogeneity of nanoparticle preparations in terms of size, coating, and surface modifications makes it difficult to standardize particles, including regarding GMP compliance. Regulatory bodies (e.g., FDA and EMA) demand extensive toxicology, biodistribution, pharmacokinetics, and long-term safety data.[26,34] Added to this is the proof of scalability, reproducibility, and commercial affordable production. A limited number of AuNPs-based formulations for other applications (such as AuroShell for PTT) have been involved in early-phase clinical trials, however, most PDT-targeted AuNPs to date are preclinical or in the translational phase. Collaborations between nanotechnologists, clinicians, regulatory specialists, and industry partners are required to achieve more rapid clinical implementation. Clear, adapted regulation for nanomedicine together with transparent reporting standards will be key factors to move these innovative therapies into routine clinical practice.[86]

CONCLUSION

Photodynamic therapy (PDT) based on gold nanoparticles (AuNPs) represents a promising "structure–function" paradigm in nanomedicine. PDT has emerged as a highly effective application of this concept, offering significant advantages in cancer treatment. This review has outlined the main results from *in vitro* and *in vivo* experiments, which showed that AuNPs are able to increase the delivery, accumulation, and PDT efficiency of PS. Various gold nanostuctures, including PEGylated spheres, nanoshells, and PSMA-targeted nanoconjugates, have displayed improved tumor targeting specificity, diminished off-target effects, and successful tumor ablation following NIR light irradiation. The multifunctional characteristics of AuNPs make their possible application in diagnostic imaging and therapy (theranostics) possible, so as to monitor the treatment dynamically and view the process in real time. Furthermore, their surface can be tailored for passive or active tumor targeting, drug co-delivery as well as responding to bio-environmental stimuli. To sum up, all of these features of AuNPs-driven PDT all remind us about a great perspective to employ them in the context of cancer treatment, with the combination use such as chemotherapy, PTT, and immunotherapy. In the future, efforts should continue to solve some of the current limitations, such as biodistribution, long-term safety, light penetration depth, and nanoparticle reproducibility. Moreover, additional attention should be paid to manufacturer's quality practice with good regulatory terms and well-designed clinical trials. Through continued innovation, together with interdisciplinary collaboration and regulatory clarity, AuNPs-based PDT has the great potential to emerge as a practical and individualized cancer therapeutic option for clinical practice in the near future.

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