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# Recent advances in gold nanoparticle-based targeted photodynamic and photothermal cancer therapy

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Cancer, the second leading cause of death worldwide, remains a major threat to human health. Current treatment options include surgery, radiation therapy, and chemotherapy and these options have significantly improved patient survival. However, they are often associated with severe side effects and high-risk of recurrence. Consequently, there is an urgent need for more effective and less invasive therapeutic strategies. Light-mediated tumor ablation techniques, such as photodynamic therapy (PDT) and photothermal therapy (PTT), have emerged as promising non-invasive approaches with notable potential in cancer management. Recent advances in nanomedicine, particularly the integration of photosensitizers (PS) with nanoparticles, have further enhanced the diagnostic and therapeutic efficacy of these modalities. Among various nanomaterials, gold nanoparticles (AuNPs) have attracted considerable attention due to their tunable optical properties, biocompatibility, and ability to mediate both PDT and PTT through controlled light irradiation and localized hyperthermia. In this review, we highlight recent progress in AuNP-based strategies for targeted photodynamic and photothermal therapies, discuss their current clinical status, and outline key challenges that must be addressed to facilitate successful translation from laboratory research to clinical practice.

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## 1. Introduction

Given that cancer is the second leading cause of death globally, it is one of the most prevalent and worldwide health issues.[1] Conventional cancer therapies, however, have significant disadvantages and often don't provide adequate outcomes.[2,3] Patients often need considerable time to recover from side effects after standard cancer treatment.[4] Furthermore, the majority of techniques are not very successful in killing cancer cells, and cancer chemotherapy may lead to problems with the heart, kidneys, bladder, neurological system, and lungs, among other organs.[5] Recently, there has been a lot of interest in using nanotechnology to detect and treat tumor illnesses;[6] this is because nanotechnology may provide novel approaches for investigating and regulating a wide range of biological and medical processes;[7] as a result, there are great hopes for developing novel methods to revolutionize cancer detection and therapy.[8] Many types of nano-objects of biological importance are now being used, such as liposomes, micelles, polymer nanoparticles, and metal nanoparticles.[9,10] Out of them, nanoparticles have the greatest potential for use in many medical applications.[11] This is shown by their practical usage as delivery agents, image-enhancing sensors, and diagnostic agents.[12] Furthermore, when combined with other therapies, the usage of nanoparticles may improve their effectiveness.[13]

A novel treatment approach for cancer with nanotechnology proposes gold nanoparticles, which are potential nanoproducts for cancer treatment. Due to their distinct optical and physicochemical characteristics, gold nanoparticles (AuNPs) have enormous potential for use in theranostics, medicine, and diagnostics. These nanoparticles may be functionalised for use in biological applications; their size and shape are often adjustable.[14,15] Gold nanostructures are used as drug carriers in therapies to reduce off-target effects and enable focused delivery to illness locations.[16] AuNPs' surface chemistry has proven beneficial in attaching targeting molecules, imaging tags, and medicinal compounds for various purposes, particularly as a delivery mechanism.[17,18] Photothermal therapy (PTT), a well-known use of AuNPs, has become a significant therapeutic area for cancer treatment because of its noninvasiveness, low cost, and minimal side effects.[19] AuNPs' surface electrons are stimulated and resonate when exposed to near-infrared radiation (NIR); this results in the rapid conversion of NIR light into heat and, eventually, a rise in the cancer cell's temperature to between 41 and 47 °C because of surface photo resonant peaks.[20] As a consequence, the cell sustains irreparable damage, including denaturation of proteins and membrane disruption.[21] According to Alle *et al.* (2020), one benefit of using AuNPs in PTT is that they may be easily administered to the local tumor location while limiting non-specific dispersion. They can be

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tuned to build a multifunctional cancer PTT and medication delivery system.[22]

Using AuNPs in photodynamic therapy for cancer treatment is an additional therapeutic benefit. PDT has been identified as a potential early-stage tumor when surgery is not feasible and contributes to cancer patients' longer lives.[23] PDT is an affordable, repeatable procedure that aids the tumor's long-term care.[24] PDT produces singlet or reactive oxygen species, which are hydrophobic light-sensitive chemicals that destroy cancer cells it is known that AuNPs increase PS photosensitizing capabilities, maybe due to the metal's localized surface plasmon resonance (LSPR). As a result, AuNPs may raise the PS PDT efficiency.[25] Research revealed that AuNPs might stimulate a PDT and PTT impact that effectively killed cancer cells.[20]

This review will focus on the advancements of gold nanoparticles in targeted photodynamic and photothermal therapy; thus, this review article is divided into seven pieces. Section 1 provides a concise explanation of the study's beginning. Section 2 covers the essential principles of photodynamic therapy and photothermal therapy. The role of nanotechnology in photodynamic therapy and photothermal therapy is explained in Section 3, while gold nanoparticles are covered in Section 4. The use of gold nanoparticles in photothermal and photodynamic treatment is covered in Section 5. The study also briefly discusses the clinical trial status of gold nanoparticle (AuNPs)-mediated photodynamic therapy (PDT) and photothermal therapy (PTT) in Section 6. The challenges associated with gold nanoparticles for medication delivery systems are covered in Section 7. The future perspectives are briefly described in Section 8.

## 2. Essential principles of photothermal therapy and photodynamic therapy

Phototherapies are a fast-growing class of cancer treatments that use different wavelengths of light to cause photothermal or photochemical changes in a target tissue.[26] The two most popular phototherapies are PDT and PTT. To create deadly reactive oxygen species (ROS) or increase the ambient temperature, they use light and either endogenous or exogenous absorbers.[27] PDT and PTT can supplement traditional cancer therapies because of their unique action methods. Both phototherapies have overcome compensatory signaling pathways and chemotherapeutic resistance at the cellular level.[28–30] PDT and PTT may improve tumor medication delivery.[31–33] Furthermore, PDT and PTT reduce off-target toxicity because they provide greater spatiotemporal control than systemic treatments. Modern endoscopic and fiberoptic light delivery methods allow for the minimally invasive irradiation of a wide range of solid tumors, including those in anatomically delicate locations that may not be amenable to surgery.[27,34] Lastly, compared to radiation treatment, phototherapies use nonionizing radiation, which lowers the chance of developing secondary cancer.[27,34]

### 2.1 Photothermal therapy (PTT)

PTT is a potentially useful therapeutic method that uses photothermal materials to generate heat from light energy.[35] This heat may specifically destroy cancer cells. By varying the photothermal materials' concentration and size, as well as the intensity and duration of light exposure, it is possible to regulate the heat produced by these materials accurately; this targeted therapy, which may be carried out using non-invasive light sources, may lessen the risk of damage to healthy tissues, making the treatment less invasive.[36,37] PTT also offers several benefits, such as high specificity and selectivity, which enable accurate targeting of cancer cells.[38] To improve treatment results, it may be used with various therapeutic modalities.[39,40] Two essential elements for a successful PTT process are a photothermal nanoagent (PTA) that may induce photothermal effects and near-infrared light (NIR) that has good tissue penetration.[41] During PTT, PTA is initially given intravenously or by other means, and since solid tumors have an elevated penetration and retention effect (EPR), PTA preferentially builds up in the tissue of the tumor. The tumor tissue is then exposed to a high-penetration NIR laser. PTA quickly raises the tumor's

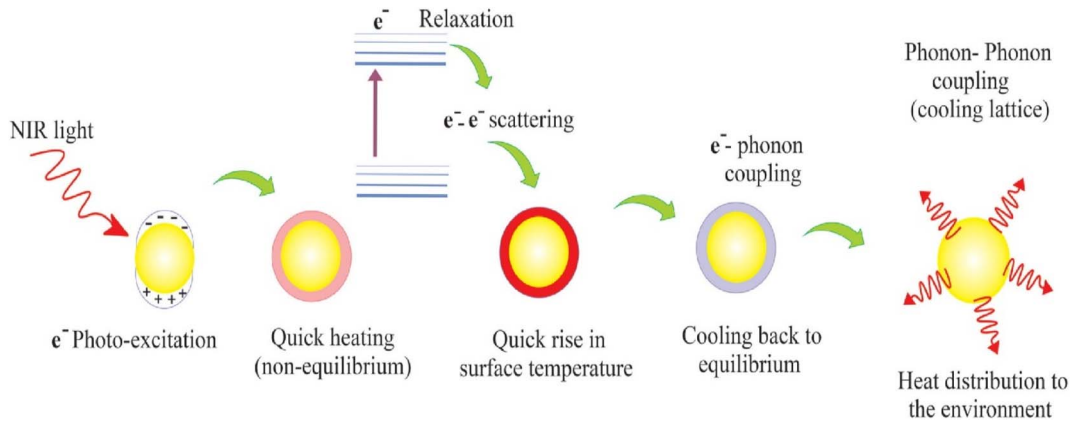


Fig. 1 Mechanism of photothermal therapy. A schematic of the mechanism of action of photothermal therapy, reprinted from ref. 53, copyright 2022, Elsevier.

local temperature to a point where tumor cells perish by absorbing certain NIR wavelengths and converting them into heat energy *via* nonradiative decay.[42,43] The photothermal conversion efficiency of PTAs is a major factor in PTT efficacy. To get the best PTT results, it is thus essential to produce PTAs with significant NIR light absorption and high photothermal conversion efficiency. Additionally, PTAs with strong biocompatibility, the capacity to accumulate in tumor tissues specifically, and biodegradability are necessary for clinical use.[44,45] Fig. 1 shows the mechanism of action of photothermal therapy.

### 2.2 Photodynamic therapy

PDT is a unique kind of light therapy that depends on the interaction of three essential elements: light, molecular oxygen (MO), and photosensitiser (PS)[46] (Fig. 2). Lamps, lasers, and light-emitting diodes are the three main light sources used by PDT. The choice of light source is influenced by the target's location, the photosensitizer's absorption spectrum, and the necessary dosage.[47] Because the oxygen molecules in the surrounding environment work as electron carriers, the non-toxic photosensitising substance that was applied to the target region gets activated when it is subjected to the appropriate amount of light.[48–50] This leads to the production of toxic reactive oxygen species (ROS), which break down cell membranes and cause necrosis or apoptosis in target tissues and microorganisms.[51,52]

## 3. Nanotechnology

Nanotechnology is the study of atomic, molecular, and supramolecular molecules to find properties that could be used to enhance human health. Modern biology and medicine are evolving with nanotechnology to produce novel materials at the nanoscale that may be used in biological systems.[55–57] Nanotechnology employs concepts and methodologies at the nanoscale to understand biosystems.[58] Because of their special qualities, nanoparticles are employed in medical applications.[59,60]

One of the primary benefits of using nanoparticles for cancer diagnostics is their increased ratio of surface area to volume in comparison to bulk materials[61–63] this property makes it possible to identify certain cancer compounds by densely coating the surfaces of nanoparticles with antibodies, small molecules, and other moieties.[63–65] Nanoparticles have several fortunate benefits. They have multiple uses, including delivering hydrophobic compounds, actively and passively targeting disease cells, and extending the time a drug is in circulation.[66–68]

### 3.1 Role of nanotechnology in photothermal therapy

Targeting the malignant region with a photothermal substance to selectively heat it and produce thermal damage to the tumor is known as photothermal therapy, a safe and efficient cancer treatment. These photothermal agents may be natural chromophores, metal nanoparticles, or light-absorbing dyes like porphyrin coupled with a transition metal, naphthalocyanine, or indocyanine green. Electromagnetic radiation, such as microwaves and radiowaves, damages cells in the thermal treatment of malignancies by denaturing proteins and membranes, ultimately leading to cell death. Since tumor cells are heat-sensitive, photothermal treatment selectively targets them without affecting healthy cells.[69] Drug-carrying

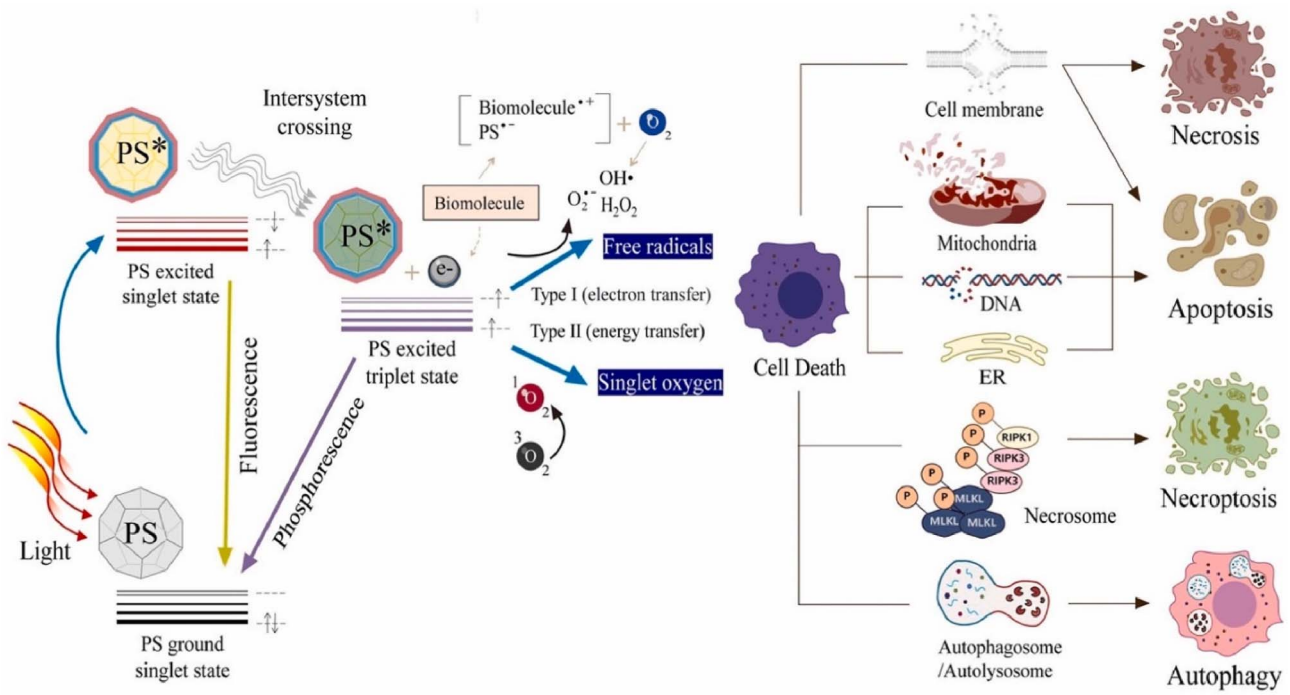


Fig. 2 Mechanism of photodynamic therapy. A schematic of the mechanism of action of photodynamic therapy, reprinted from ref. 54, copyright 2021, Springer Nature.

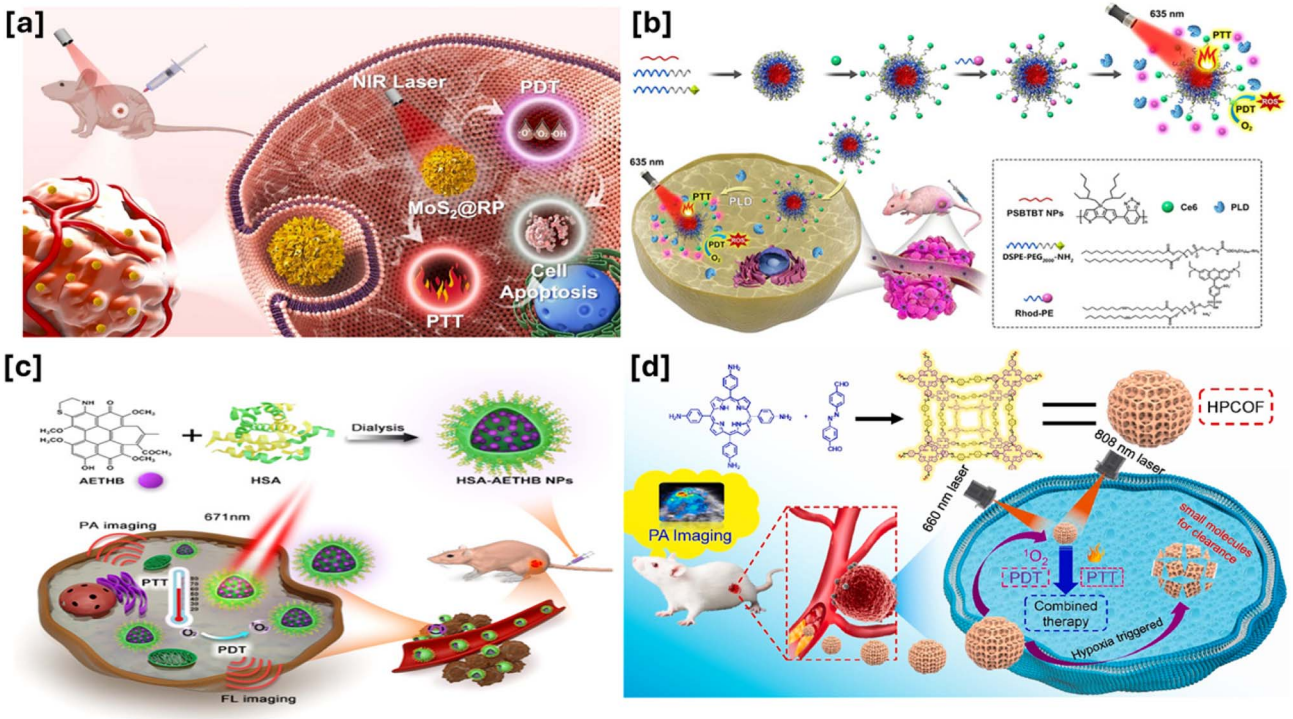


Fig. 3 The role of nanotechnology in photothermal and photodynamic therapy. [a] Schematic synthesis of $MoS_2$@RP heterostructure for synergistic PDT/PTT of ccRCC, reprinted with permission from ref. 81, Copyright 2024 Elsevier; [b] schematic representation of PSBTBT-$Ce_6$@Rhod NPs-mediated PLD-activatable tumor images and combined PTT/PDT therapy reprinted with permission from ref. 82, Copyright 2021 ACS; [c] schematic illustration of the preparation of HSA-AETHB NPs and PTT/PDT synergic therapy of tumors. Reprinted with permission from ref. 83, Copyright 2019 American Chemical Society; and [d] schematic illustration of the preparation of HPCOF and photoacoustic imaging-guided combined therapy under 660 nm and 808 nm laser irradiation. Reprinted with permission from ref. 84, Copyright 2024 Elsevier.

nanoparticles, for example, are photothermal agents because they absorb light and produce heat.[70] The NIR region has high absorption of gold nanoparticles, carbon nanotubes (CNTs), and nanorods between 650 and 900 nm.[71] Nanoparticles in a size range of 10–100 nm have the ability to transform light into heat, which means they can give less energy needed to destroy tumor cells.[48,72] In addition to the death of cells mediated by heat, heating metal nanoparticles, such as gold nanoparticles, results in bubbles and cavitation around the nanoparticle, often producing mechanical stress that eventually damages cells.[73] Because the targeted tumor cells in nanoparticle-mediated photothermal treatment are optically sensitive, a lower threshold laser is needed to increase the heat around the infected cells to a level sufficient to cause cellular damage. When anti-EGFR antibody-linked gold nanoparticles were utilized in photothermal cancer treatment, researchers discovered that the resulting 70–80 °C thermal abrasion was what killed the cells.[69]

### 3.2 Role of nanotechnology in photodynamic therapy

Due to its ability to administer PS precisely to specific locations with little harm to normal tissues, PDT's use of nanotechnology has opened up new therapeutic options for cancer.[74] Much research has been done recently on integrating NPs and PSs to address the underlying problems with traditional PDT.[75] Because of their innate hydrophilicity, NPs may greatly increase PSs' solubility in water, increasing their cellular absorption.[76] Because NPs may get past immune system barriers and prolong the release of conjugated PSs, they shield them from unintended destruction.[77] Moreover, because of their high surface area-to-volume ratio, they can hold a lot of anticancer medications in cancer tissue.[68] Because of the EPR effect, small NPs may easily enter cancer cells.[78] Excellent biocompatibility, highly changeable surface chemistry, and versatility in loading different drugs and targeting agents for different goals are other advantages of NPs that have led to their acceptance as a PDT alternative.[79] Through the EPR effect, NPs have enhanced the pharmacokinetic characteristics of PDT, including high volumes of distribution, excellent clearance values, and increased bioavailability in cancer cells.[80] As a result, NP-based drug delivery methods in PDT are gaining traction quickly. The role of different types of nanoparticles in photothermal and photodynamic therapy is shown in Fig. 3, and various Nanotechnologies used in Photodynamic Therapy and Photothermal Therapy are listed in Table 1.

### 3.3 Drug targeting mechanisms in nanotechnology

Passive targeting and active targeting are the two types of medication targeting mechanisms. The underlying causes of increased permeability and retention (EPR) based medication targeting in passive targeting include the tumors' faulty lymphatic drainage and quickly expanding leaky vascularization, which helps to retain nanoparticles and submicron particles.[98] For this particular kind of cancer treatment,

Table 1 Various nanotechnologies used in photodynamic therapy and photothermal therapy

| Nanocomposite | Modality & protocol | Cancer type | Outcomes |
|---|---|---|---|
| PEGylated GO modified by folic acid, rhodamine B | PTT and PDT 808 nm, 1.8 W $cm^{-2}$ | *In vivo* Ehrlich tumors cells | Using the theranostic function, temperature change *via* GO/FA-ICG to 40 °C suppressed tumour growth[85] |
| Multifunctional graphene oxide | PTT and PDT 808 nm, 660 nm, 2 W $cm^{-2}$ | MCF-7 cells | When photothermal and photodynamic therapy were combined, the cancer cells were eradicated more effectively than when they were treated separately[86] |
| Hollow silica nanoparticles loaded with hydrophobic phthalocyanine (Pc@HSNs) | PTT and PDT 730 nm, 1.5 W $cm^{-2}$ for 10 min | Tumor-bearing mice (*in vitro* and *in vivo*) | Both in vitro and in vivo studies shown that the dual phototherapeutic activity of Pc@HSNs may eliminate cancer cells or tumour tissues[87] |
| Mesoporous silica composite nanoparticles (hm-$SiO_2$($AlC_4$Pc)@Pd) | PTT and PDT 660 nm 0.5 W $cm^{-2}$ for 7 or 10 min | HeLa cells (*in vitro*) | Results *in vitro* demonstrated that combination PDT/PTT therapy using hm-$SiO_2$($AlC_4$Pc)@Pd had a higher cell-killing efficacy than either PDT or PTT treatment alone after exposure to a 660 nm CW-NIR laser[88] |
| Poly(cyclotriphosphazene-*co*-tetraphenylporphyrin-*co*-sulfonyldiphenol) nanospheres (CP-TPP) | PTT and PDT 808 nm laser (1.5 W) and 630 nm LED (50 mW $cm^{-2}$) for 8, 15, and 20 min | HeLa cells (*in vitro*) | Cell viability was lower than that of individual PDT or PTT at doses of CP-TPP/Au/PEG nanospheres between 10 and 100 μg $mL^{-1}$ (ref. 89) |
| Self-assembled zinc phthalocyanine nanoparticles | PTT and PDT 650 nm 0.7 W $cm^{-2}$, 10 min | HeLa cells (*in vitro*) | Nearly 93% of the HeLa cells were killed by the synergistic PTT and PDT at a particle concentration of 20 μM after ten minutes of laser therapy[90] |
| Carbon nanohorn/phthalocyanine hybrid | Synergistic PTT and PDT 650 nm laser (3 W $cm^{-2}$) | HeLa cells (*in vitro*) | The cell viability test indicates that the combination of PTT and PDT exhibits much greater cell-killing efficacy *in vitro*[91] |
| Phycocyanin–polypyrrole nanoparticles | Synergistic PDT and PTT 620 nm (100 mW $cm^{-2}$) and 808 nm (2 W $cm^{-2}$) for 10 and 5 min | MDA-MB-231 human breast cancer cells and HEK-293 human embryonic kidney cells | The obtained nanoparticles effectively killed MDA-MB-231 cells in a dual way upon laser illumination[92] |
| Black phosphorus quantum dots (BPQDs) | Synergistic PTT and PDT 625 nm light (80 mW $cm^{-2}$) for 10 min 808 nm laser (2 W $cm^{-2}$) for 2 min | Hep G2 cells | The results demonstrate that combined phototherapy significantly promotes the medicinal effectiveness of cancer therapy compared to PTT or PDT alone[93] |
| Nanographene oxide | Synergistic PTT and PDT 808 nm, 655 nm, 2 W $cm^{-2}$, 3 min | Hela and NIH/3T3 cells | The combined effect of PDT and PTT treatment of the cells led to a much higher rate of cell death in comparison to PDT-only or PTT-only therapy[94] |
| Pluronic-based graphene oxide-methylene blue nanocomposite | Synergistic PTT and PDT 660 nm LED light and 808 nm NIR light at 0.5 W $cm^{-2}$ | Cervical cancer (SiHa) cells | The results indicated that the nanocomposite had the potential to treat cancer *via* non-invasive phototherapy effectively[95] |
| Nano-graphene oxide | Synergistic PTT and PDT 808 nm (320 mW $cm^{-2}$; 15 min) and 980 nm (320 mW $cm^{-2}$; 18 min) | B16F0 cells | Experiments conducted *in vitro* shown that B16F0 melanoma cancer cells may be effectively destroyed by phototherapy when exposed to 980 nm light, thanks to the combination of GO-mediated PTT and PDT effects[96] |
| Iron oxide carbon dot ($Fe_3O_4$-CDs) nanoparticles | Synergistic PTT and PDT 660 nm laser (0.5 W $cm^{-2}$) and 808 nm laser (2 W $cm^{-2}$) | HeLa cells | Because of the complementary PTT and PDT using a near-infrared laser, conducted both *in vitro* and *in vivo* demonstrated that GP-PGA-$Fe_3O_4$-CDs@BPQDs were extremely biocompatible and had outstanding tumor-inhibition effectiveness[97] |

nanoscale drug carriers such as liposomes, dendrimers, and inorganic nanoparticles are being thoroughly researched in terms of drug delivery.[99] Owing to their small size, these nanoparticles preferentially aggregate at the tumor site *via* their enhanced permeability receptor action, allowing them to pass through hyper-permeable blood capillaries.[100] The interaction of a ligand-containing drug carrier with target cell surface receptors is the main mechanism of the active targeting technology. This process facilitates intracellular drug accumulation by receptor-mediated endocytosis and tumor accumulation of the drug.[101] Typically, ligand-functionalized nanoparticles may actively target one or more specific receptors that are overexpressed in tumor cells. As a result, endothelial cells and tumors are identified using cellular targets in an active targeting technique.[102,103] Drug targeting mechanism are shown in Fig. 4.

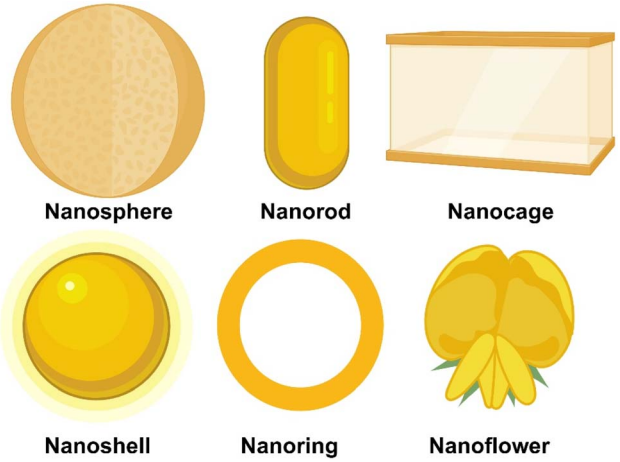


Fig. 5 Different types of gold nanoparticles for photothermal and photodynamic therapy. Created in BioRender. Dhilip Kumar, S. (2025) https://BioRender.com/7k1a6dq.

## 4. Gold nanoparticles

Due to its crucial resonance features, gold nanoparticles are gaining interest as potential uses in cancer treatment. Gold nanoparticles' wavelengths, emission frequencies, and aggregation state strongly depend on their size, shape, surface, and aggregation state. These particles occur in different sizes and forms, including nanoporous gold disks, nanoporous gold cages, nanoflowers, nanoshells, nanospheres, and nanorods, as illustrated in Fig. 5. Each nanoparticle has a distinct wavelength representing its electrons' maximal excitation. Gold nanoparticles can absorb and scatter incident light simultaneously, and "photon confinement" produces powerful electromagnetic fields that cause a variety of visual phenomena on the particle surface.[108]

Numerous varieties of gold nanoparticles have been investigated recently. Factor like wavelength energy absorbance

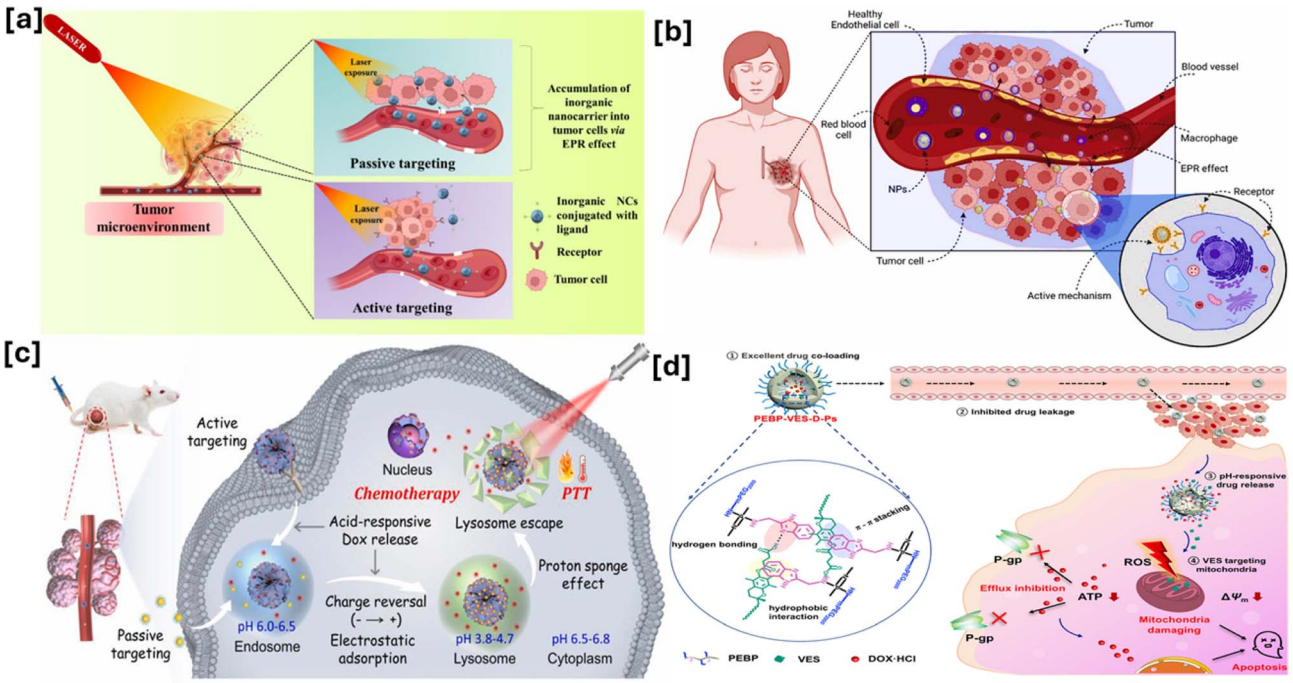


Fig. 4 Drug targeting mechanism [a] schematic representation of PTT-mediated passive targeting and active targeting of tumor cells *via* inorganic NCs in the management of melanoma, reprinted with permission from ref. 104 Copyright 2024 Elsevier; [b] description for delivery of the NPs into the body followed by the tumor-specific accumulation of the NPs because of the EPR effect (passive targeting), reprinted with permission from ref. 105, Copyright 2023 Elsevier; [c] dual-targeted delivery of Dox-DNFs and BSA-AuNPs for combinational chemo-photothermal therapy of cervical cancer, reprinted with permission from ref. 106, Copyright 2023 Elsevier; and [d] structural composition and the proposed mechanism of action of VES/DOX·HCl co-delivered nanovesicle PEBP-VES-D-Ps based on amphiphilic poly[$(PEG)_x(BIMA)_y$-phosphazene]$_n$ (PEBP) for MDR reversal, reprinted with permission from ref. 107, Copyright 2021 Elsevier.

should be considered when comparing the photothermal heating capability of each kind of particle. Each form of gold nanoparticle has unique benefits and characteristics; it is impossible to determine which type is most appropriate for treating cancer, given these differences in size. Consequently, choosing gold nanoparticles with benefits for every application is crucial. However, the observed patterns support the size impact of photothermal heating and are consistent with experimental results.[109] A comparative study on various gold nanoparticles-mediated photothermal and photodynamic therapy is listed in Table 2.

### 4.1 Gold nanoparticles for photothermal therapy

Due to its special qualities, gold nanoparticles have been a well-liked treatment agent for PTT.[110–112] In addition to their biocompatibility and low cytotoxicity, gold nanoparticles' easily modified surfaces and regulated physicochemical characteristics make them useful for various medicinal applications. PTT has profited from gold nanoparticles' adjustable absorption capabilities.[113,114]

Because gold nanospheres readily produce heat when exposed to laser light at the wavelength of their surface plasmon resonance, they have been studied as PTT agents.[115] For instance, 40 nm gold nanospheres were used to treat oral cancer cells *in vitro* using photothermal treatment.[116] Gold nanostars measuring 30 nm were created by Liu *et al.* and demonstrated deep infiltration and high accumulation in malignancies.[117] After 4 minutes of 980 nm laser irradiation at 50 °C, thermal ablation was caused by the superior photothermal action of gold nanostars. On the other hand, gold nanostars may melt and become nanospheres due to the heat generated by light.[118] Consequently, it was proposed to use silica to modify the surface of gold nanostars to increase their photostability.[119]

Gold nanorods have two surface plasmon resonance peaks. The key element influencing the absorption characteristic of gold nanorods is their aspect ratio.[120] A multifunctional nanoparticle was developed by Yi *et al.*[121] They created gold nanorods whose greatest absorption was measured at 670 nm, the excitation laser's wavelength. After four minutes of laser irradiation, the temperature rose to 45 °C, causing tissue injury. As a result, the interesting characteristics and unique capabilities of gold nanorods make them appropriate for PTT agents. Gold nanoparticles in PTT are shown in Fig. 6.

### 4.2 Gold nanoparticles for photodynamic therapy

PDT is a potential treatment for the management of malignant conditions like cancer if PS is selected carefully. It is usually characterized by a low rate of illness, excellent tolerability, minimally intrusive techniques, recurrent usage, minimum impairment, and often outpatient care.[122–124] Much research is being done to develop gold-containing nanocomposite PS with unique properties that may overcome some of the limitations of PDT applications and boost productivity to overcome the shortcomings of presently utilized PS Particularly in hydrophobic formulations, gold nanoparticles provide an excellent biocompatible PS carrier.[125–127] Furthermore, PS. molecules may be conjugated or encapsulated on the gold nanoparticle's surface. For example, gold nanoparticles were adsorbed with hypericin (Hyp) photosensitiser (PS) to increase the cellular absorption of hypericin in breast cancer.[128] In order to increase $ZnPcS_4$ bioavailability and phototoxicity in two and three-dimensional tumour models, the compound was encapsulated in AuNP and paired with targeted antibodies.[129] Every choice has benefits and drawbacks. Following light irradiation, the PS molecules on the NP surface might eventually cause tumor death by separating from the nanocarrier spontaneously or enzymatically and adhering to the prokaryotic membrane. The gold nanoparticle may interfere with PS's photoactivity, but PS within the NP is more protected from deterioration than PS at the surface from the environment of living things on route to the tumor.[130]

According to many reports, when PS is combined with gold nanoparticles increases PS accumulation and ROS production, which is a key component of photodynamic treatment.[131] When PEGylated gold nanoparticles were used *in vivo* instead of traditional PDT drug delivery, Pc4 administration increased by around two times. The only noticeable negative effect of the therapy *in vivo* was the presence of Pc4 throughout the whole body of the mouse, including the kidneys and lungs. Tumor necrosis and size decreased one week after PDT due to the therapeutic impact.[132]

Researchers also examined the effectiveness of intravenously injecting mice with subcutaneously implanted murine melanoma (B78H1 cells) using C11Pc (phthalocyanine derivative)-conjugated AuNP. The AuNP–C11Pc combination was shown to aim for cancerous tissues more preferentially than the free C11Pc. Furthermore, it promoted an antiangiogenic reaction by severely damaging blood capillary and endothelial cells, generating a more widespread PDT response. On the other hand, the spleen and liver absorbed the AuNP–C11Pc compound, and it persisted in the liver for up to a week without seeming to lower PS.[133] Gold nanoparticles in PDT are shown in Fig. 6.

## 5. Application of gold nanoparticles in PTT and PDT

Gold nanoparticles' special qualities make them popular in various applications. Their multifunctionality, ability to deliver hydrophobic compounds, ability to actively and passively target disease cells, ability to extend the duration of a drug's circulation, and promotion of drug safety and tolerability are just a few of their advantages.[150]

Scientists are interested in using gold nanoparticles as drug carriers due to their optical, tunable, and surface plasmon resonance (SPR) characteristics. Controlling their dispersion is simpler because of the wide variety of core diameters (1 to 150 nm) in which they may be manufactured. Gold nanoparticles are readily mutable because of their negative charge on their surface. This implies that adding other biomolecules, such as medications, targeting ligands, and genes, will make them readily functional. Furthermore, gold nanoparticles are a great

 

Table 2 Comparative study on various gold nanoparticles-mediated photothermal and photodynamic therapy

| Type of gold | Laser treatment | Cell model | Application | Outcomes | Advantages |
|---|---|---|---|---|---|
| Gold nanorods | 808 nm laser ($0.5\ W\ cm^{-2}$), 60 s | Human liver cancer HepG2 cells | PTT | When more MMP-9 was added, the ensuing responsive AuNRs displayed much greater cellular uptake *in vitro*[136] | Experimentally, AuNRs are effective cancer treatments because they penetrate and retain tumour tissue better than normal tissue. The aspect ratio of AuNRs influences tumour retention. Despite the fact that smaller AuNRs are eliminated faster, high aspect ratio and small volume AuNRs are ideal for tumour-mediated transport employing the EPR effect. AuNRs circulate longer than nanospheres, and macrophages absorb them four times better[137,138] |
| Gold nanorods | 633 nm and 808 nm | Rats, 8 to 10 weeks in age | PDT & PTT | The combination of PDT + PTT therapy caused a significant reduction in tumor volume and large-area tumor necrosis[139] | |
| Gold nanocages | 805 nm | The breast cancer cell line SK-BR-3 | PTT | We have shown that Au nanocages with comparable optical characteristics may effectively act as agents for the *in vitro* photothermal killing of cancer cells[140] | Photothermal conversion is enhanced by gold nanocages, a novel nanoparticle. The average size is 20–50 nm. A galvanic replacement reaction with a silver template and gold salt creates a hollow gold–silver alloy structure with variable wall thickness. The nanocage's surface develops a gold coating due to the metals' differing chemical potentials, while silver ions dissolve into the aqueous $HAuCl_4$ solution. Gold nanocages' porous surface and hollow interior make them promising for medication delivery and encapsulation. Gold nanocages passively and actively distribute medications by upregulating cancer cell receptors and increasing EPR[141] |
| Gold nanocages | 580 and 630 nm $2.5\ W\ cm^{-2}$ | HeLa cells | PDT | We saw increased cell death when HeLa cells were exposed to 630 nm light and cultured with nanocomposites[142] | |
| Gold nanospheres | 808 nm at an output power of $32\ W\ cm^{-2}$ for 3 min | B16/F10 melanoma cells | PTT | NDP-MSH-PEG-HAuNS have the potential to mediate targeted photothermal ablation of melanoma[143] | The internalisation and membrane wrapping of spherical particles have been extensively explored. Continuous wrapping, low adhesion energy, and low membrane energy barriers make spherical particles easier to absorb than nonspherical ones[144] |

Table 2 (*Contd.*)

| Type of gold | Laser treatment | Cell model | Application | Outcomes | Advantages |
|---|---|---|---|---|---|
| Gold nanoshell | 820 nm, 35 W $cm^{-2}$ | Human breast carcinoma | PTT | When human breast cancer cells cultured with nanoshells were exposed to NIR light (820 nm, 35 W $cm^{-2}$), it was discovered that photothermally caused morbidity[145] | Gold nanoshells (AuNSs) are nanoparticles with a gold coating on an inorganic (metal) or organic (polymer or lipid) core. Their unique features make them popular in medicine delivery. First, their resonance optical properties enable deep tissue penetration and rely on size and shape. They also absorb light and convert it into heat for photothermal ablation of cancer cells. AuNSs may release drugs at precise places when subjected to near-infrared (NIR) radiation. By functionalising these particles with ligands, they can connect to sick cell receptors for precise targeting. AuNSs are ideal for passive drug delivery because they accumulate in tumours *via* the enhanced permeability and retention (EPR) effect. Encasing nucleic acids, protecting them from degradation, and releasing them precisely by NIR irradiation, AuNSs may be employed in gene therapy[146] |
| Gold nanoshell | 670 nm (PDT) and $\lambda = 810$ nm | Head and neck carcinoma | PDT | In NIR irradiance, we observed significant cell inhibition at PDT radiant doses 80–100 times lower than those necessary for comparable outcomes with dual-function nanosystems[147] | |
| Gold nanoflower | 808 nm (9 W $cm^{-2}$) for 5 minutes | HeLa cells | PTT | This kind of AuNF was shown to be non-toxic to HeLa cells when exposed to visible light, but NIR irradiation *in vitro* significantly increased photothermal ablation[148] | Gold nanoflower has low toxicity to cells, and a strong photothermal effect[148] |
| Gold nanoring | 1064 nm, 200 mW | Oral cancer cells | PTT & PDT | By using the Au NP sample to compare the inactivation threshold intensities of NRI between fs and CW laser illuminations, we can see that fs laser illumination is more effective in cancer cell inactivation through the PTT effect when compared with CW laser illumination[149] | Gold nanoring has a deeper tissue penetration[149] |

option for usage as drug carriers due to their non-toxic nature and biocompatibility.[151,152] For instance, conjugating the long-used cancer treatment drug methotrexate (MTX) with gold nanoparticles increased the drug's cytotoxicity against a variety of tumor cell lines as compared to MTX administered alone. When coupled with gold nanoparticles, MTX accumulated in the tumor cells more quickly and to a greater degree.[119]

AuNPs are used in clinical diagnostics and other biological research due to their SPR, magnetic resonance, and fluorescence capabilities. The use of surface plasmon resonance (SPR) with AuNPs is effective in several applications, including DNA hybridization, antibody characterization, and protein conformational studies.[153,154] When measuring biological processes at the cellular and molecular levels using magnetic resonance imaging (MRI), AuNPs' magnetic resonance characteristics come in handy. Quantifying the molecular alterations linked to the beginning and progression of pathological conditions aids in the early diagnosis and prognosis of illnesses like cancer.

Because they effectively quench fluorescence and absorb SPR, AuNPs are integral to PDT and are used to treat cancer and certain skin diseases. PDT employs PS and a laser as light-sensitizing agents. Singlet oxygen and very active free radicals produced by PS trigger necrosis or death in tumor cells after they have been exposed to it.[155]

Transfection agents have been created using AuNPs scaffolds for treating genetic diseases and cancer *via* gene therapy. AuNP-conjugated oligonucleotide complexes have been used as intracellular gene agents to regulate protein expression in cells.[156] The expression of luciferase has been inhibited by using RNA-conjugated gold nanoparticles.[157]

AuNPs are effective sensors for various analytes and compounds, such as proteins and sugars. The sensors are made to detect AuNPs and their different features in mind.[158] AuNPs are used *in vivo* for CT imaging as well as cell imaging. Their primary reason for usage is that they substitute for CT devices that rely on X-rays. They are used because of their improved body tolerance, easier attachment to the moiety, and higher absorbent coefficient. Due to their compact size and high concentration, AuNP exhibits excellent X-ray attenuation. This makes using imaging to detect cancer simpler[159] NIR light is employed for deep tumor imaging because tissue absorption is relatively poor for light with wavelengths >650 and <2000 nm. During whole-body scans, NIR-active probes called AuNPs are used to image cancer cells in human bodies. Tumor imaging uses AuNPs as a contrast agent when coupled with anti-EGFR antibodies.[160,161] AuNP may be used as a screening test kit to determine whether an individual has the COVID-19 virus. The RNA from the sample has been analysed using the AuNP-based kit, which operates at the molecular level, and it contributes to reliable viral identification.[162]

## 6. Clinical trial status of gold nanoparticles in cancer PDT and PTT

To accomplish the goal of oncotherapy in practical applications, particularly in clinical trials, it is often required to fully use the physical and chemical features of AuNPs. Table 3 lists the AuNPs currently being used in clinical studies.

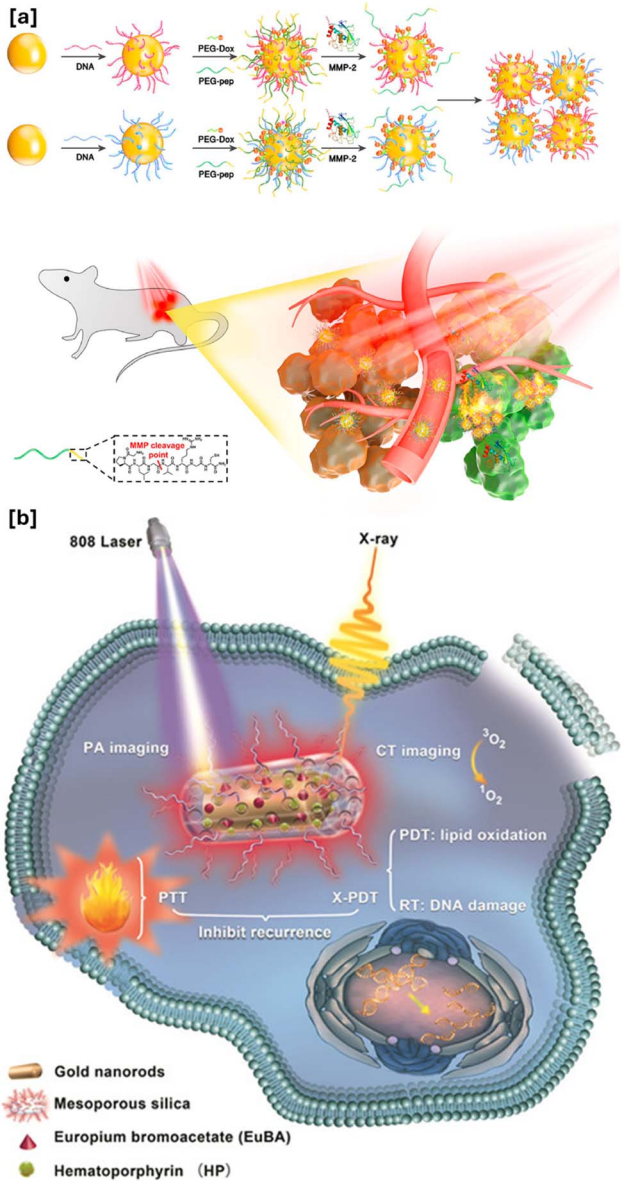


Fig. 6 Gold nanoparticles in PDT and PTT [a] schematic illustration of MMP-induced aggregation of AuNPs *in vivo* for enhanced PAI/PTT of tumor, reprinted with permission from ref. 134, Copyright 2019 Elsevier; and [b] illustration of the conjugation of a scintillator complex and gold nanorods for PTT/PDT synergic therapy of tumors. Reprinted with permission from ref. 135, Copyright 2020 American Chemical Society.

## 7. Challenges associated with gold nanoparticles for medication delivery systems

AuNP-assisted PTT and PDT seem promising, and it have shown encouraging benefits in cancer therapy. This approach can potentially be employed in cancer treatment and diagnosis.

Table 3 Summary of gold nanoparticles in clinical trials

| ClinicalTrials.Gov identifier | Name | Application | Phase | Status |
|---|---|---|---|---|
| NCT03020017 | Spherical nucleic acid (SNA) gold nanoparticle NU-0129: A | Glioblastoma gliosarcom | Early phase 1 | Completed |
| NCT04907422 | Gold nanoparticles | Carcinoma Ex pleomorphic adenoma of salivary glands | Observational | Completed |
| NCT07034248 | Gold nanoparticle | Breast cancer | NA | Not yet recruiting |
| NCT06870994 | Gold nanorod | Cutaneous metastatic melanoma | NA | Not yet recruiting |
| NCT00356980 | Colloidal gold | Unspecified adult solid tumor | Phase 1 | Completed |

Several obstacles must be addressed before these therapies can be used in clinical settings. The use of gold nanoparticles in clinical practice is limited due to the lack of clinical studies that thoroughly investigate many parameters and markers. The start of clinical studies may broaden and clarify the uses of nanoparticles in medicine and diagnosis. However, they must be conducted after thorough safety and toxicity assessments of these nanoparticles.[163]

Although there is a lot of interest in AuNPs, their therapeutic applications are limited by a few significant issues. Uncertainty about the toxicity profile of AuNPs *in vivo* is a major medical setback.[164] It could be difficult to minimize cytotoxicity while maintaining AuNPs' bioactivity and therapeutic qualities. Because of their low photothermal conversion efficiency, spherical AuNPs, for example, have limited promise despite their decreased toxicity.[165] However, according to different research, gold nanospheres and nanorods are more poisonous than other designs like flowers or stars. There is an urgent need for more varied and prolonged *in vitro* and *in vivo* research since the present *in vivo* data are inadequate and sometimes inconsistent.

As for potential accumulations, research has shown signs of sperm toxicity and residues of AuNPs in the heart, brain, and lungs, although as of yet, no long-term toxicity research has been conducted.[166] It's crucial to remember that current clinical studies for the treatment of various illnesses are brief and have

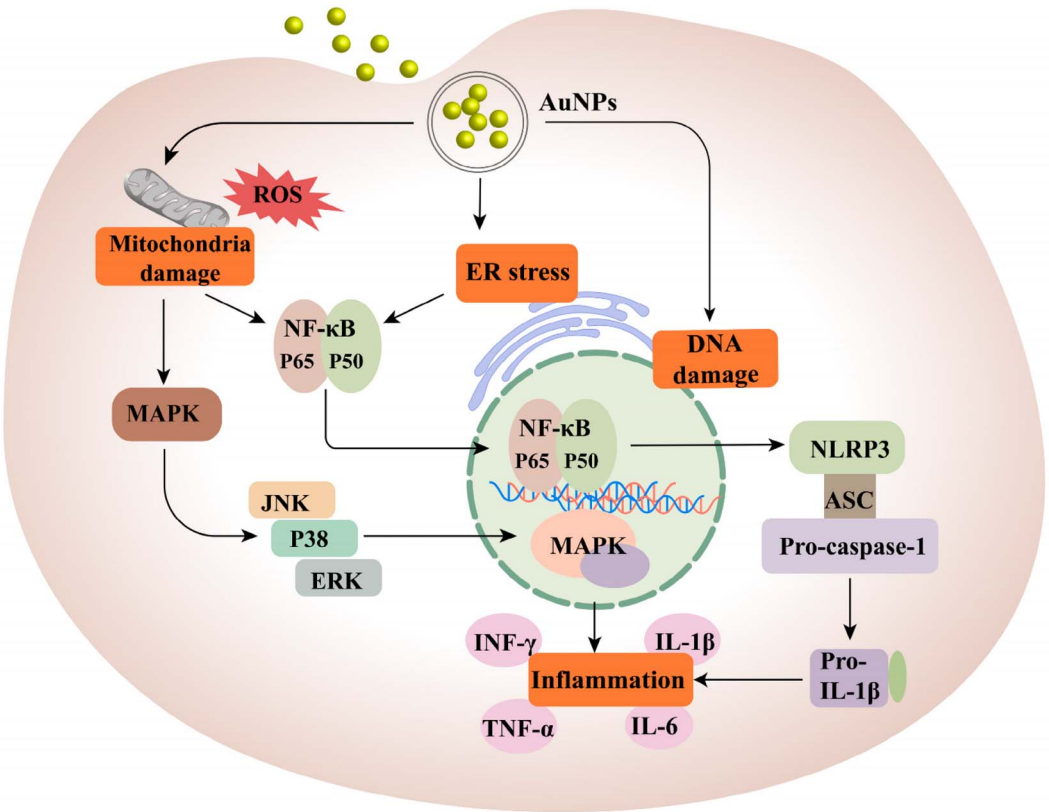


Fig. 7 Schematic overview of the mechanisms of AuNP interaction with the immune system. Reprinted with permission from ref. 168 under the terms and conditions of the Creative Commons Attribution (CC BY) license.

tiny sample numbers, even if they haven't shown any significant harm. Therefore, to comprehend the possible impacts of gold buildup in different organs, bigger, longer-term research are required.[167] Fig. 7 shows the mechanisms of AuNP interaction with the immune system.

## 8. Future perspectives and conclusions

Nanomedicine's adaptable qualities might overcome even the most difficult limitations when used with photo-based treatment. By multifunctionalizing and delivering PS molecules to certain tissues, nanomedicine may provide cancer therapy a breakthrough over traditional treatment approaches.[159] Improving PDT and PTT specificity requires a critical step: clinical phases may use nanoparticles with enhanced physicochemical characteristics. The delivery of PS is enhanced, and its solubility, circulation duration, and effectiveness are all increased when PS molecules are conjugated into NPs by active or passive targeting.[160,161]

Gold nanoparticles are advantageous for biomedical applications because of their optical qualities and ease of synthesis, enabling simple conjugation with biological moieties. Crucially, the surface and core characteristics of gold nanoparticles may be tailored for single and many uses, such as chemical sensing, molecular recognition, and imaging. As a result, PDT and PTT are appealing methods for treating tumor cells. It is possible to inject millions of functionalized gold nanoparticles into the circulation, where they attach to certain cancer cells and either support PTT or PDT for effective tumor excision by surgery.

Even with these advancements in gold nanoparticle technology, more affordable gold nanoparticle-based solutions are still needed to provide highly precise early cancer detection and therapy. Understanding nanoparticles' characteristics and composition affecting their absorption and distribution throughout the body is the first step towards creating such a nanosystem.

A number of operational challenges, including rigid process parameters and a toxic microbial environment, have also been encountered in the microbial synthesis of AuNPs. Thus, in order to meet the increasing industrial demands for AuNPs, researchers are looking at cost-effective synthesis procedures due to the limitations of current techniques of synthesis.[169] The photosynthesis of AuNPs is acknowledged as an essential activity due to its renewable and ecologically beneficial characteristics. However, the effectiveness of synthetic processes is being impacted by the use of economically relevant plants and foods as stabilising and reducing agents. To improve the efficiency of the biosynthetic process, it is crucial to look into the reduction and stabilisation potential of non-commercially valued plants, especially biowastes, for the synthesis of AuNPs.[170]

It is really interesting to precisely identify the bioactive compounds involved in the stabilization of AuNPs and the reduction of gold ions using both qualitative and quantitative approaches. That would be very helpful in creating AuNPs with the physiochemical properties that are needed for their possible uses. It would also demonstrate a greater comprehension of the actual reduction and stabilization process, as well as reaction synthesis, which has not yet been thoroughly investigated.

The synthesis circumstances significantly influence the physicochemical properties of biosynthesized AuNPs. Determining how process factors affect the dimensions and form of photosynthesized AuNPs is thus quite intriguing. In order to produce nanoparticles with the necessary dimensions and form—which will be very beneficial in selecting their appropriate prospective applications—it would be helpful to investigate the synthesis conditions on developing surface features of AuNPs. Since the size and form of nanoparticles have a significant impact on their future uses, the assessment of quantitative growth kinetics is very important. The growth kinetics of AuNPs produced using traditional techniques have been extensively reported in the literature. However, AuNP-mediated plant growth kinetics are still in the dark ages. Active nanoparticle targeting is theoretically also feasible, but more research is needed to figure out how to get past the immune system and reach the target. Therefore, it is essential to address several crucial aspects, including stability, long-term health impacts, repeatable and reliable production methods/assays, and cellular and immunological responses. This necessitates further study to refine the aforementioned strategies, especially in relation to PTT and active targeting. Furthermore, it is equally significant and vital to recognize it before using nanoparticle destiny in clinical trial applications. Therefore, more study in this area will be needed to address the ingestion of the nanoparticles, their subsequent location, any pertinent immune response, and, most crucially, their elimination from the human body.

## Author contributions

A. A. Obalola: methodology, data curation, formal analysis, investigation, writing – original draft, visualization, software. H. Abrahamse: co-supervision, funding acquisition, resources. S. S. Dhilip Kumar: conceptualization, project administration, supervision, visualization, software, writing–review & editing, funding acquisition. All authors read and approved the final manuscript.

## Conflicts of interest

The authors have declared no conflict of interest.

## Data availability

No primary research results, software or code have been included and no new data were generated or analysed as part of this review.

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