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REVIEW

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Understanding gold nanoparticles and their attributes in ovarian cancer therapy

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Abstract

Ovarian cancer is one the deadliest disease wherein the survival rate is very low. Despite of advances in medical sciences, researches are still at the stage of infancy where patients are succumbing to this malignancy. Multidrug resistance, toxicity, mode of treatment related issues like catheter related complication poises a number of challenges to scientists worldwide. Novel therapy is now thus being focussed to sensitive the cells more towards the treatment. Gold nanoparticles (Au NPs), known for their high biocompatibility, and strong optical and magnetic responses, have emerged as promising agents for both the diagnosis and treatment of ovarian cancer. Owing to physical characteristics, AuNPs may be used as adjuvants in bioimaging, radiotherapy and fluorescence imaging. As a result, these characteristics substantially support AuNPs in biological domains. In addition to their therapeutic potential, Au NPs exhibit strong surface plasmon resonance (SPR) properties, enhancing imaging techniques for early detection of ovarian tumors. Furthermore, chemical properties such as Magnetic Resonance and Imaging Properties, X-ray imaging property, Two-photon or multiphoton imaging, and Optical coherence tomography (OCT) imaging properties enhance the use of Au NPs in diagnosis. This paper highlights the properties, targeting potential and diagnosis and treatment of ovarian cancer by Au NPs has been discussed.

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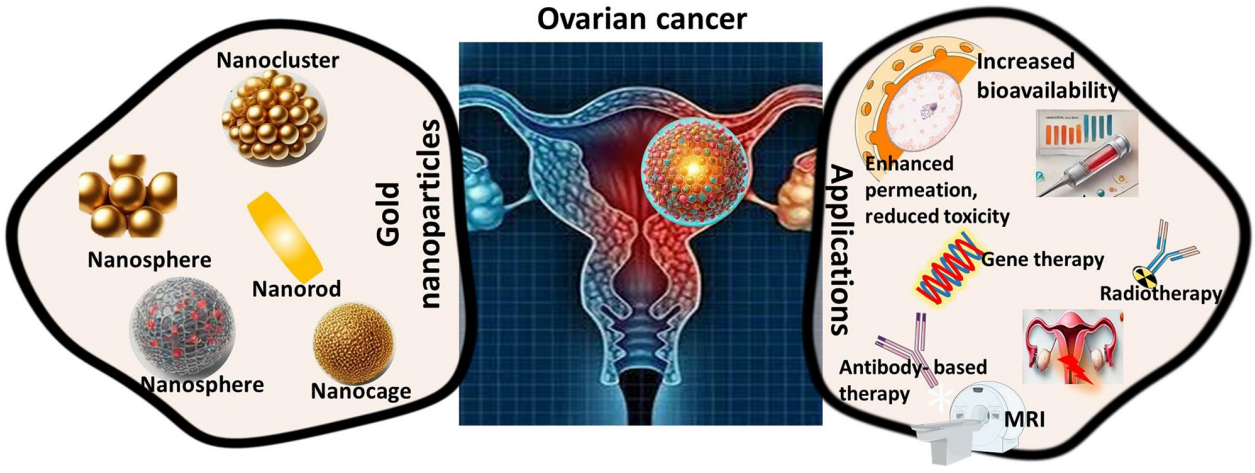
Graphical abstract



Keywords Ovarian cancer, Chemotherapy, Gold nanoparticles, Targeted drug delivery, Toxicity, Theranostics

Introduction

Ovarian tumour is considered as most aggressive female reproductive tract diseases. This cancer entails complex molecular and genetic factors that make it extremely lethal and resistant to conventional therapies. It often goes undiagnosed at early stages leading to more damage in the majority of the women. Nearly, 13–27% of patients diagnosed with ovarian cancer usually survive for five years post-diagnosis. The high mortality rate emphasizes the urgency for targeted therapies, better diagnosis, prognosis, and treatment for ovarian cancer [1–3].

The current screening methods have limited effectiveness in detecting this cancer. While vaginal ultrasound and the biomarker CA-125 are primary tools for its detection, they have not been successful in significantly reducing the high mortality rates associated with the disease [4].

The exact cause remains unclear, but several factors are known to increase its likelihood. Lifestyle choices, such as obesity, cigarette smoking, and a sedentary lifestyle influence the risk. Additionally, exposure to environmental agents like herbicides, talc and pesticides has been associated with a heightened risk. However, environmental factors and such lifestyle play a minimal role in ovarian cancer development. The disease is most prevalent in postmenopausal women, with incidence rising with age, often resulting in advanced stages of the disease and low survival rates. The strongest risk factor is a family history of ovarian cancer, particularly due to mutations in the BRCA1 and 2 genes. Some research also indicates that repeated ovulation may contribute to the increased risk of developing ovarian cancer. Furthermore, the loss of the tumor suppressor gene p53 is another significant molecular mechanism, as approximately 55% of ovarian cancer cases are associated with a deficiency in this gene [5].

As per the surveillance by the national cancer institute, the rate of new cancer cases was 10.2/1 Lakh women/year [6].

The incidence and prevalence of ovarian cancer vary significantly worldwide due to various factors. In developed countries, the prevalence is influenced by an increase in certain surgical interventions. In the United States, ovarian cancer accounts for 4% of cancer-related deaths in women, while breast cancer represents 15%.

Ovarian cancer is often asymptomatic, which makes early detection challenging. Despite advancements in screening technology, surgical methods, and chemotherapy, most cases are diagnosed at advanced stages. This is primarily due to the absence of a single, reliable, and specific screening method for early-stage detection. Advanced stages of ovarian cancer (stages III and IV) are linked to a poor prognosis and significantly reduced survival rates compared to cases diagnosed at stage I. However, survival rates can vary depending on the histotype of the disease.

Patients with advanced ovarian cancer may benefit from neoadjuvant therapy or primary tumor debulking surgery. Selecting one of these strategies requires a careful and intricate decision-making process. For patients with metastatic disease that can be surgically resected and who are well-suited for surgery, surgical debulking is generally recommended. Neoadjuvant chemotherapy, on the other hand, could be a better choice for patients who do not qualify for surgery or who are unlikely to achieve total surgical cytoreduction. It is recommended that this

decision be guided by consultation with a gynecologic oncologist before starting neoadjuvant chemotherapy. Laparoscopy can also be a useful technique for determining whether optimum cytoreduction can be accomplished [7].

Conventional cancer treatment strategies like surgery, radiotherapy, and chemotherapy lead to side effects, and multidrug resistance, and do not provide sustained remission hence, they fail to provide satisfactory results [8–11]. There is an urgent need for a paradigm shift in cancer treatment strategies. In oncology, nanotechnology has emerged as a promising field. With the help of nanotechnology, cancer cells can be selectively targeted without affecting healthy cells this also reduces the chances of toxic side effects [12–17]. Nanoparticles can improve the sensitivity and accuracy of detecting cancer in the early stages. It also detects biomarkers associated with cancer leading to better intervention [18–20]. Among various carriers, Au NPs have drawn notable attention because their very high biocompatibility causes fewer adverse reactions [21, 22]. It exhibits Localized Surface Plasmon Resonance (LSPR) properties which makes it an excellent agent for photothermal therapy [23]. Gold nanoparticles (Au NPs) are considered one of the best options for enhancing the sensitivity and accuracy of cancer detection because of their exceptional biocompatibility, which reduces the likelihood of adverse reactions in biological systems [24–27]. This makes them safer and more suitable for medical applications compared to many other nanomaterials. Additionally, their unique properties, such as ease of surface functionalization, strong optical characteristics, and stability, make them highly effective for detecting cancer biomarkers. By improving detection sensitivity, Au NPs contribute significantly to early diagnosis, which is critical for timely and effective cancer intervention. Gold nanoparticles can be used for precision medicine as their surface can easily be modified by various biomolecules like peptides, antibodies, and drugs which helps in targeted cancer therapy [28]. The section below discusses the causes, statistics, and mortality of ovarian cancer while discussing the use of nanotechnology and gold nanoparticles further [4, 5, 7, 29].

Nanotechnology in cancer therapy

Nanotechnology possesses great promise for improving the diagnosis and overcoming treatment challenges while tackling present issues. This ground breaking technique in cancer treatment channels its distinct optical, magnetic, and electrical properties to develop more sophisticated and highly accurate therapies. To make treatment more effective, nanoparticles can be designed to deliver high concentrations of drugs in a controlled manner to the tumor cells. Due to their small size, they can reach the parts of the body that are hard to access and treat tumors more effectively [30, 31]. Nanotechnology offers a promising solution to one of the most significant challenges in cancer treatment by specifically targeting cancer stem cells, thereby preventing the recurrence of cancer or the development of resistance to therapies [14]. Numerous drugs based on nanoparticles have been authorized by the US Food and Drug Administration (FDA) for targeted cancer treatment in the past. One of the examples is Onivyde, a PEGylated Liposomal Carrier for Irinotecan, which has been licensed by the FDA for the treatment of metastatic pancreatic adenocarcinoma. It has been discovered that irinotecan, which inhibits topoisomerase I, accumulates in tumors where it can be released gradually and has a longer-lasting anti-tumor impact [35].

Promising findings from clinical studies on nano-formulations indicate their potential in cancer therapies [32–34, 36]. However, to enhance their effectiveness, several challenges need to be addressed. Nanoparticles spare the healthy cells and tissues, successfully penetrate physiological barriers, and demonstrate prolonged retention within tumor tissues; however, blood proteins form a layer over them making it hard for them to recognize and reach cancer cells. Such issues must also be tackled to make these formulations more effective. Various nanoparticles have been explored extensively since the past decade, such as liposomes, solid-lipid nanocarriers, dendrimer, and metal nanoparticles such as gold and silver nanoparticles. There is always a perpetual necessity for more effective therapy which should be highly efficacious with minimal to no side effects. Gold nanoparticles present a scope for meeting the never-ending therapeutic demand of cancer patients. The section below provides information regarding gold nanoparticles and their role in ovarian cancer therapy.

Gold nanoparticle (Au NPs)

Gold nanoparticles (Au NPs) have shown significant promise in advancing the diagnosis and treatment of ovarian tumors, owing to their unique physicochemical properties and versatility in biomedical applications [10]. One of the key advantages of Au NPs is their ability to enhance targeted drug delivery. By precisely directing therapeutic agents to malignant ovarian cells, Au NPs increase drug efficacy while minimizing side effects on healthy tissues [25, 37].

The Au NPs can be developed by a controlled crystallization technique that highly resists oxidation, providing a uniform size distribution ratio [38, 39]In addition to drug delivery, Au NPs offer substantial benefits in imaging and early diagnosis due to their strong surface plasmon resonance (SPR). This optical property improves the contrast in imaging techniques like MRI and CT scans, facilitating better visualization of tumors and enabling earlier detection. Early diagnosis is crucial in ovarian cancer, as it is

often asymptomatic in its initial stages and typically diagnosed at an advanced stage [33, 40].

Au NPs hold the potential to enhance the specificity, efficacy, and safety of cancer therapies while reducing systemic toxicity and overcoming drug resistance. The ongoing development of Au NPs is expected to play a key role in the future of oncological treatments. The optical properties of Au NPs are primarily driven by surface plasmon resonance (SPR), a phenomenon that causes the nanoparticles to scatter and absorb light much more strongly than most organic molecules. This makes Au NPs highly effective as contrast agents in optical imaging [41]. By attaching ligands to the surface of Au NPs surface, they can be stabilized; further bioconjugation can be facilitated by bonding linkers to the periphery of Au NPs; and their application range can be expanded by directly immobilizing functional ligands. These are the main goals of surface modification of AuNPs [42–44].

Physical properties

Surface plasmon resonance (SPR)

A defining feature of Au NPs is their SPR, which arises from the collective oscillation of free electrons on the nanoparticle surface when excited by specific wavelengths of light. After a laser beam strikes gold (Au) at a specific angle and distance, SPR takes place at the surface, gradually lowering the intensity of the reflected light. After a laser beam strikes gold (Au) at a specific angle and distance, SPR takes place at the surface, gradually lowering the intensity of the reflected light.

Plasmon resonance occurs when light stimulates a noble metal, causing conduction electrons to oscillate collectively. Surface plasmon resonance (SPR) occurs at the metal surface, while localized surface plasmon resonance (LSPR) occurs in nanoparticles. LSPR in AuNPs enhances the local electromagnetic field and extinction coefficient prompting surface-enhanced spectroscopy (SES). This optical extinction is over 1000 times stronger than typical organic molecules [45], making AuNPs suitable for photodynamic therapy, photothermal therapy and colorimetric assays in tumor diagnosis and treatment. Factors such as shape, size, composition, and microenvironment affect the SPR [46, 47].

Size and shape effects

The optical properties of Au NPs vary with size and morphology. Spherical Au NPs smaller than 20 nm primarily absorb light, while larger particles (20–80 nm) exhibit increased scattering. Changes in the interparticle distance or surrounding refractive index also cause colour changes, such as from red to blue-purple, due to SPR shifts [48]. Au NPs used in PTT are typically nanoshells or nanorods, their cellular absorption may be restricted when they are placed into a biological context [49]. On contrary, gold nanostars demonstrated outstanding biocompatibility, efficient PTT, minimal toxicity, and plasmon tunable in the NIR range [50].

High surface-to-volume ratio

The reduced size of gold nanocarrier increased the surface-to-volume ratio, enhancing surface energy and interaction potential. Such property further facilitated the modifications with ligands, while enhancing the biocompatibility [51]. In comparison to free drug molecules, Au NPs' high surface area to volume ratio enables substantial prodrug or drug loading capabilities, which can drastically reduce the lowest effective doses. The PEG linker decreased the nonspecific binding of serum proteins to the conjugated particle's surface and enhanced particle stability in the cell culture conditions. Doxorubicin hydrochloride (DOX) has been shown to have increased efficacy following its conjugation to natural gum, which stabilized the AuNPs [52].

Photothermal conversion

Au NPs can transform the absorbed light into heat through SPR, making them ideal for applications like photothermal cancer therapy [53]. Tumor vascular variety blood vessels have perforated pipe walls than normal tissue blood vessels, which causes tumor tissue inside the blood supply to clog. Because of this, the tumor tissue's cooling ability is worse than that of normal tissue, and the heat generated during the heat energy process is more likely to accumulate inside the tumor, where its temperature can easily reach 46 °C above and the surrounding normal tissues can only be heated to 41 °C or so. Furthermore, normal cells can tolerate temperatures as high as 47 °C, but tumor cells are naturally less heat-resistant. Tumor cells typically have a fatal temperature of 42.5–43 °C. Photothermal conversion has a bright future in cancer cell imaging and PTT since tumor cells are often less heat-resistant than normal cells, with the former typically having a fatal temperature of 42.5–43 °C and the latter able to survive temperatures as high as 47 °C [54]. A study evidenced the photothermal effect by Au NPs under the influence of visible light in vitro [55].

Fluorescence properties

It is already known that radioactive decay occurs as fluorescence emission, while on the other hand, the nonradiative decay rate occurs as energy transfer, intersystem transitions, thermal radiation and various others. Fluorescence resonance energy transfer (FRET) is the main cause of fluorescence quenching of AuNPs in these nonradiative decay forms. The FRET between fluorescence molecules and AuNPs decreases significantly with distance, and when the distance is less than 5 nm, the energy of the excited fluorescent group will be transferred to

the AuNPs entirely, causing fluorescence quenching. The quenching and return of the fluorescence can be used to represent the interaction among the particles, making it suitable for diagnostic purposes [56]. Typically, AuNPs in amalgamation with fluorescent molecules are linked using various linkers, which interact with the material to alter its structure, changing the distance between the AuNPs and fluorescent molecules. One of the linkers used for the detection of lung cancer cells was recognition sequences [53, 57].

Chemical properties

Surface modification

The surface of gold nanoparticles can be easily functionalized in a way to accelerate its use in multiple fields [58]. Various approaches such as bioconjugation with antibodies, protein and DNA [59], electrostatic interaction via citrate capping [60], covalent attachment via thiolation [61], and polymeric coating using chitosan or PEG [62] can be followed. These interactions enable the selective distribution of gold nanoparticles into cells as well as biosensing and bioimaging applications because of the great affinity of gold NPs for functional groups.

Catalytic properties

Despite having low catalytic activity in bulk, gold nanoparticles demonstrate exceptional catalytic activity [63] particularly in redox reactions like the catalytic low-temperature oxidation of carbon monoxide [64], the hydrogenation of 4-nitrophenol [65], oxidation of alcohols [66], or selective epoxidation reactions. Because gold is a Lewis acid, Au NPs are also frequently described as effective catalysts for processes based on alkyne activation. Although it has been reported that catalytic property directly depends on the size of Au NPs [23].

Ease of coupling

AuNPs have the ability to establish strong chemical interactions with groups that contain S and N, which sets them apart from many other nanoparticles. This enables AuNPs to bind to a broad range of organic ligands or polymers that serve a particular purpose. These surface alterations give AuNPs exceptional drug transport, targeting, and biocompatibility properties. For the transport and aggregation of tumor tissue, smaller AuNPs in combination with the photosensitizer have been investigated. The interesting feature of AuNPs is that they may be used for dual therapy of PDT and PDT [67].

Magnetic resonance and imaging properties

Au NPs serve as excellent MRI contrast agents when combined with other elements like gadolinium or iron oxide. Their dual-modal imaging abilities (e.g., MRI and CT) and specific tumor targeting enhance their efficacy in diagnosing cancers [23].

In clinical settings, magnetic resonance imaging (MRI) is a popular imaging technique where a magnetic field pulse causes the protons in water molecules to align. The radiowaves that are produced when the proton relaxes to its ground state are then collected and recreated as volumetric pictures.

T1-weighted or T2-weighted sequences are used in MRI depending on the type of tissue to be examined. However, the method is time-consuming in comparison to other optical imaging methods like CT but provides excellent contrast for soft tissues Numerous T1 and T2 contrast agents have been manufactured for molecular imaging, producing positive and negative contrast, respectively [68]. AuNPs, thus used as carriers for paramagnetic metal complexes like gadolinium or can be combined with superparamagnetic materials such as Fe_3O_4 particles [69].

X-ray imaging property

Due to their ease of synthesis, low toxicity and functionalization, and detection, AuNPs are a popular option among metal nanoparticles. For real-world uses in medicine, AuNPs with regulated optical, geometrical, and surface chemical characteristics have been thoroughly investigated. One of the key benefits of AuNPs is their versatile functionalization, which makes it easier to transport AuNPs to different cell types for bioimaging targeted delivery, gene/drug delivery, and other therapeutic and diagnostic uses [70].

Images obtained at various intervals following intravenous injection demonstrate that the tiny AuNPs are eliminated by the kidneys rather than being concentrated in the liver and spleen. These experiments on animals show that AuNPs are effective X-ray contrast agents, providing unique pharmacokinetic and physical benefits over conventional Iodine-based agents. Compared to conventional iodine-based agents, they are non-toxic, offer greater contrast, and allow for longer imaging periods [71].

Two-photon or multiphoton imaging [72]

Two-photon imaging (TPI) uses two near-infrared (NIR) photons to excite a fluorophore within the visible range enabling reduction in scattering of tissue background and improving imaging depth. TPI is widely used in high-resolution 3D imaging which in the presence of AuNPs exhibits stable surface plasmon resonance (SPR) and photobleaching resistance. Thus, AuNPs enhance their two-photon absorption coefficient, making them 10–100 times greater than organic fluorophores [73]. Studies show that the two-photon signal from a single AuNR during in vivo imaging is 58 times stronger than that

from a single rhodamine molecule. Gold nanostars can also be tuned to the NIR region, displaying strong two-photon luminescence in vitro and in vivo [74].

Optical coherence tomography (OCT) imaging property

Tomography creates three-dimensional structures from segmented images of objects. Without exposing patients to radiation, such as from X-rays, optical tomography techniques can offer a non-invasive diagnostic. The foundation of OCT is light interference, where a beam is divided in half, one of which passes through the sample while the other serves as a reference. The spatial information about the tissue's microstructure may be found in the time-of-flight data of a photon that is passed through or get reflected from tissue [75]. A 2D picture including details about the interior tissue architecture is created by the ensuing interference. OCT is particularly helpful for imaging biological tissues like the skin, eyes, or breast since it profoundly penetrates the object of interest [76]. The chemical environment, including the ozone concentration and pH, in the tissue samples could be detected and imaged using AuNP-assisted OCT. As OCT contrast agents, a researcher proposed gold triangular nanoprism core in polyaniline shell nanoparticles, which is pH-responsive, with a reaction time of less than 1.0 s, and distinct extinction and dispersion characteristics in basic and acidic conditions. This method may be applied to 3D imaging of biological samples' pH distribution, including the acidic areas of tumors [77].

Targeting characteristics of Au NPs

Gold nanoparticles (Au NPs) are actively explored for therapeutic administration and cancer therapy because of their outstanding features. They can be functionalized to affect particular tissues, cells, or intracellular components. Both active and passive selective drug targeting is possible due to the unique characteristics of gold nanoparticles [78–81].

Active targeting plays a crucial role in delivering drugs, genes, and theranostics to specific sites, effectively minimizing exposure to healthy tissues. This approach enhances therapeutic efficiency while reducing side effects. By significantly increasing the amount of drug delivered to target cells compared to free drugs or passively targeted nanosystems, active targeting offers a notable advantage. After nanoparticles accumulate in the tumor region, their efficiency can be further enhanced through active targeting. This involves decorating the nanocarrier surfaces with ligands that bind to receptors overexpressed on tumor cells [82, 83]. This strategy not only improves the affinity of nanocarriers for cancer cell surfaces but also enhances drug penetration. The concept was first demonstrated in 1980 using antibodies grafted onto liposome surfaces, paving the way for the development of various other ligands, such as peptides, nucleic acids, and aptamers [84]. Chung and coworkers synthesized PEGylated Au NPs which were further functionalized with various amounts of transferrin. Transferrin proteins are overexpressed on cancer cells these Au NPs were designed to target tumor cells via an active targeting method. They found precision in drug delivery with this approach [85]. In another study, Bhattacharya and colleagues synthesized gold nanoparticles by reducing $HAuCl_4$ with $NaBH_4$. Folic acid was attached to Au NPs in a single step. Cell targeting was enhanced by using PEGs of different molecular weights such as PAM2 with molecular weights of 2000 and 10,000, PAM4 with a molecular weight of 20,000, and PSH2 with a molecular weight of 2000. Nanoconjugates formed by attachment of PEG and FA to the Au NPs were analyzed using advanced analytical techniques like UV-visible spectroscopy, TEM, TGA, and infrared spectroscopy, among others. Radioactive folic acid ^{3}FA was used to study its binding and release from nanoconjugates. They observed the highest binding observed in Au-PAM4-20 K and decreased in the order: Au-PAM2-10 K, Au-PAM2-2 K, and Au-PSH2-2 K. FA was released fastest from Au-PSH2-2 K hence order of release rate was observed to be reverse of the binding order. Au-PAM4-20 K-FA nanoconjugates were tested on seven different cancer cell lines to study cancer cell targeting. Among ovarian cancer cell lines, the FR expression was highest in OV-167 cells and decreased in the order: SKOV-3, OV-202, and OVCAR-5. Similarly, in several cancerous expression cell lines, FR expression was highest in OPM-1 and lowest in RPMI. Cancer cell with higher FR expression was effectively targeted by FA-tagged Au NPs. Hence, FA-Au NPs can be used to exploit the overexpression of folate receptors on cancer cells to provide targeted drug delivery, tumor imaging and tumor ablation [86]. Numerous studies configured targeting ligands in association with Au NP for cancer treatment. Various targeting agents with gold nanoparticles have been shown in Fig. 1.

Peptide-based Au NPs

Peptides, short polymers of amino acids, can be precisely synthesized and characterized chemically to meet specific design requirements. Although they typically exhibit lower receptor affinity compared to antibodies and numerous other proteins, peptides are becoming increasingly popular as targeting moieties due to their simplicity and rapid uptake kinetics [82, 87, 88]. Studies have demonstrated the use of peptides to target Au NPs for cancer imaging. However, there are relatively few examples of peptide-based Au NPs being utilized for cancer therapeutics, highlighting an area with significant potential for further exploration [89].

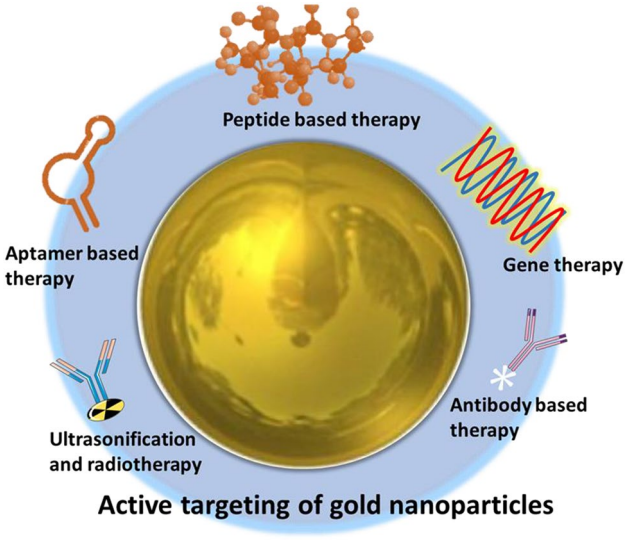


Fig. 1 Representation of targeting agents in association with gold nanoparticles in cancer therapy

In another study, researchers explored the use of a peptide in combination with miRNA to enhance cancer treatment. This approach aimed to harness the targeting precision of peptides along with the gene-regulatory functions of miRNA, creating a dual mechanism for improved therapeutic effectiveness. The study involved the design and synthesis of a gold nanoplatform (GNF), that was loaded with miR-145, a microRNA often downregulated in various cancers, including epithelial ovarian cancer. For targeted delivery, the GNF was functionalized with the FSH33 peptide, which is known to specifically target ovarian cancer cells. This resulted in the creation of the GNF-miR-145 nanosystem. The GNF-miR-145 system was selectively absorbed by ovarian cancer cells, including the A2780 and SKOV3 cell lines, and demonstrated significant therapeutic effects. It notably inhibited the viability and migration of these cancer cells, as well as their ability to proliferate and grow without anchorage, a characteristic of cancerous growth. Additionally, the GNF-miR-145 nanosystem decreased the release of VEGF, a key factor in tumor growth and angiogenesis, and reduced the size of ovarian cancer spheroids. This was achieved through damage to the cell membranes, which not only diminished cell viability but also possibly triggered apoptotic cell death. These findings offer important progress in the development of miRNA-based therapies, particularly through the use of nanoparticles as selective delivery vehicles. This approach not only holds the potential for advancing cancer treatment but also provides useful insights for future in vivo evaluations and clinical applications [90].

Antibody decorated Au NPs

Nanoparticle surface coatings serve several important purposes, including enhancing stability by protecting against opsonization (the process of tagging nanoparticles for immune clearance) and biofouling (the unwanted accumulation of biological molecules). These coatings often contain specific moieties, such as peptides or antibodies, that allow nanoparticles to bind selectively to biological targets, such as cancer cells. The intracellular fate of nanoparticles depends on their ability to specifically bind to cell surfaces and accumulate within the cell's interior [91].

While many studies have focused on the behaviour of individual components of hybrid nanoparticles (such as the inorganic core), it is well understood that hybrid nanoparticles, although stable in serum or solution, may lose their structural integrity in complex biological environments, particularly after cellular uptake. Once inside the cell, nanoparticles undergo intracellular trafficking, where they are exposed to significant changes in the chemical environment. The pH within endosomal pathways gradually decreases, and the presence of proteolytic enzymes and reactive oxygen species can negatively (or positively) impact the stability of organic components, leading to the gradual decomposition of inorganic materials, like iron oxide. Additionally, elevated intracellular levels of biomolecules, such as glutathione (GSH), can disrupt chemical bonds, including thiol bonds to the gold surface or disulfide linkages, further affecting the nanoparticle's stability. The relative fates of the nanoparticle core versus the organic components after cellular uptake or in vivo administration remain poorly understood. However, this knowledge is crucial for the development of multicomponent nanoparticles for biomedical applications. Understanding these processes could lead to improvements in therapeutic efficacy, imaging contrast, nanoparticle clearance, and minimizing off-target toxicity in vivo.

In a study by Han et al., the luminescent properties of 5 nm gold nanoparticles (Au NPs) were exploited to investigate the intracellular trafficking and fate of these nanoparticles, which were functionalized with an organic layer composed of polyethylene glycol (PEG) and an epidermal growth factor receptor (EGFR)-targeting antibody. The results showed that the intracellular uptake of the targeted Au NPs having a size of 5 nm led to strong two-photon luminescence, characterized by broad emission and short lifetimes, which were distinct from the fluorescence of the nanoparticle-conjugated antibody. This allowed for selective imaging of these components using two-photon luminescence and two-photon excited fluorescence lifetime microscopy. The study found that the nanoparticle coating was detached from the nanoparticle surface inside the cell, leading to the formation of

nanoparticle clusters that emitted strong luminescence. Furthermore, the researchers observed a spatial separation between the gold core and the antibody coating within the cells. Using data from two-photon microscopy, electron microscopy, in vitro assays and 2P-FLIM analysis, the researchers proposed a model to describe the interactions of functionalized 5 nm Au NPs with live cells [92].

Aptamer based Au NPs

Aptamers are short, single-stranded RNA or DNA oligonucleotides derived from a random nucleic acid library through a process called systematic evolution of ligands by exponential enrichment (SELEX). These molecules fold into specific secondary or tertiary structures, enabling them to bind to molecular targets with high specificity and precision, comparable to antibodies. However, aptamers offer several advantages over antibodies: they can be synthesized more easily, are non-immunogenic and cost-effectively, making them an attractive alternative in various biomedical applications [93–95].

A study successfully developed and characterized AS1411 aptamer-conjugated gold nanoparticles (Au NPs) loaded with a therapeutic drug. These nanoparticles were evaluated for particle size, zeta potential, and in vitro drug release. Cell viability assays demonstrated that in normal cells, aptamer-conjugated nanoparticles were primarily removed via exocytosis or efflux mechanisms, as corroborated by flow cytometry and confocal microscopy. This phenomenon is likely due to the low nucleolin levels typically present in normal cells. In contrast, cancer cells, which overexpress nucleolin, internalized the nanoparticles more effectively. However, within cancer cells, some internalized nanoparticles were entrapped in endosomes or underwent lysosomal degradation, as indicated by LysoView™ staining. Flow cytometry analysis further assessed cellular uptake in both normal and cancer cells by tracking the compound's native fluorescence. The results showed that C8 when conjugated with AS1411-Au NPs, exhibited significantly higher uptake in cervical cancer cells compared to normal cells. This finding underscores the enhanced selectivity of AS1411-Au NPs for cancer cells, particularly the cervical cancer cell line, which could improve the therapeutic index of C8. Among the tested cell lines, HEC-1-A cells displayed higher C8 internalization, suggesting greater specificity of the AS1411-Au NPs conjugates for cervical cancer cells. Differences in fluorescence intensity observed between flow cytometry and confocal microscopy experiments were attributed to varying incubation times. Overall, this study provides strong evidence that aptamer-conjugated nanoparticles, such as AS1411-Au NPs, offer great potential for targeted drug delivery in cancer therapy. Their selectivity and efficacy position them as promising therapeutic agents, particularly for treating gynecologic cancers [96, 98].

Targeting by gene therapy

Research has shown that miRNA expression varies across different types of cells, including among the intrinsic subtypes of cancer, which are distinguished based on the expression of specific receptors. MicroRNAs (miRNAs) are small, non-coding RNA molecules that regulate mRNA translation and stability at the post-transcriptional level. In mammals, miRNA binding sites are typically located in the 3′ untranslated regions (3′ UTRs) of target mRNAs, where their binding either halts translation or triggers mRNA degradation, leading to gene silencing. It is well-established that dysregulated miRNA activity can alter the expression of oncogenes or suppress tumor suppressor genes. Certain miRNAs, termed oncomiRs, are linked to specific cancers by promoting oncogenic events when dysregulated. Depending on their role, miRNAs can be overexpressed (oncomiRs) or downregulated (anti-oncomiRs), and both scenarios are associated with cancer development. Therefore, maintaining appropriate miRNA levels within cells is crucial, either by silencing overexpressed miRNAs or delivering miRNA mimics. However, a significant challenge remains the lack of an efficient and reliable miRNA delivery system [99]. A study by Chaudhari et al. demonstrated that gold nanoparticles (Au NPs) functionalized with miRNA (miR-206) were effectively delivered to cancer cells, resulting in cell cycle arrest at the G0-G1 phase and the downregulation of NOTCH3 (target of miR-206) expression [100]. NOTCH3 resists Fas-ligand induced apoptosis signaling in the smooth muscle cells. Thus, it was confirmed in this study, that Au NPs mediated gene therapy fostered the process of apoptosis.

Targeting by external stimulus

Combination therapies have emerged as a promising approach to address the limitations of conventional cancer treatments. Increasing attention has been directed toward using ultrasound (US) to enhance the intracellular delivery of chemotherapeutic agents, particularly in preclinical studies. Additionally, nanoparticles (NPs) have been shown to improve the effectiveness of US-based therapies. Kip et al. utilized the US-responsive properties of nanocone-shaped gold nanoparticles (Au NPs) in a combined US and cisplatin (CP) treatment strategy. This triple-combination therapy, incorporating US, Au NPs, and low-dose CP, successfully overcame drug resistance in ovarian cancer cells in vitro, highlighting its potential to minimize chemotherapy-induced side effects [101].

In a study, the surface of gold nanoparticles (Au NPs) was modified with thioglucose, capitalizing on the fact that cancer cells have a higher metabolic rate and glucose

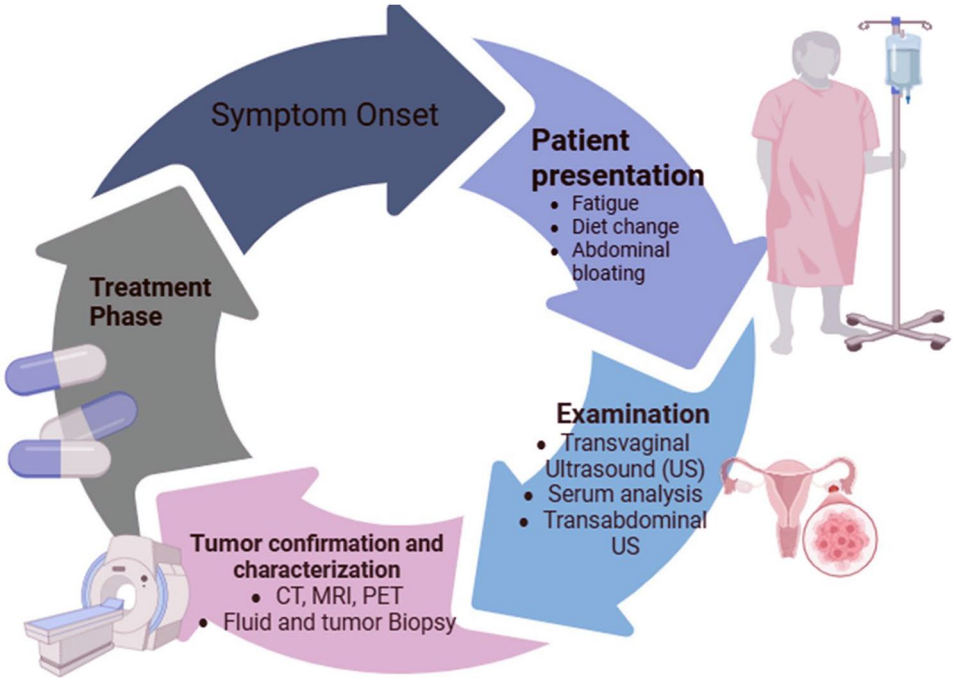


Fig. 2 Representation of diagnosis pathway of ovarian cancer from the onset of symptom to treatment

uptake compared to normal cells. This selective glucose uptake enabled the specific internalization of thioglucose-coated Au NPs by cancer cells. In vivo experiments showed that Glu-Au NPs accumulated in cancerous tissues at levels 10 times higher than in normal ovarian and uterine tissues [102]. Geng et al. explored the potential of thioglucose-bound Au NPs as a sensitizer for radiotherapy in ovarian cancer. When SK-OV-3 cells were treated with Au NPs alone, radiation alone, or a combination of both, the Au NPs enhanced the antiproliferative effect compared to radiation alone. The interaction between X-ray radiation and Au NPs led to increased production of reactive oxygen species (ROS) [103].

Diagnosis of ovarian cancer by gold nanoparticles

Cancer-related mortality rates are disproportionately high in low- and middle-income countries, largely due to challenges such as late-stage diagnoses, limited access to advanced clinical evaluations, and high costs associated with pathological services. Traditional cancer treatments, including chemotherapy, surgery, and radiotherapy, though essential, often result in significant side effects, and harm healthy tissues, and may not fully eradicate the cancer. These limitations have driven the exploration of innovative approaches to cancer diagnosis and therapy, with nanotechnology emerging as a promising solution. In particular, gold nanoparticles (Au NPs) have gained attention for their unique physicochemical properties such as biocompatibility, surface modification, and capability to be engineered for specific applications, including imaging, drug delivery, and targeted therapy. Au NPs can be functionalized with various biomolecules to improve their specificity for cancer cells, thus enhancing the efficacy of diagnostic and therapeutic interventions. Several studies have demonstrated the utility of Au NPs in ovarian cancer, particularly in the realms of molecular imaging and biomarker detection. The stage from diagnosis and treatment of ovarian cancer is represented in Fig. 2 [77].

In a study, Qu and his colleagues used Au NPs to target ovarian cancer by using molecular imaging techniques. Glypican-3 (GPC-3) proteins are over-expressed on the surface of cancer cells. The fluorescence-labeled Au NPs were conjugated with GPC-3-targeting peptides (GPC3@Au NPs). The nanoparticles bind to GPC-3 expressing cancer cells and emit fluorescence which can help visualize their location within cells. GPC-3-expressing HeLa cells were incubated with both functionalized (GPC3@Au NPs) and unmodified Au NPs. Strong fluorescence was observed in the cells exposed to GPC3@Au NPs as shown in Fig. 3 while low fluorescence was observed with bare Au NPs. This suggested that GPC3@Au NPs were effectively taken up by the cancer cells due to efficiently targeted binding by the GPC-3 peptide. The study confirmed that the GPC3-functionalized fluorescent Au NPs significantly enhanced imaging contrast by using laser scanning confocal microscopy. A clearer and more detailed visualization of the cancer cells was obtained. Though GPC3@Au NPs were effectively taken up by the

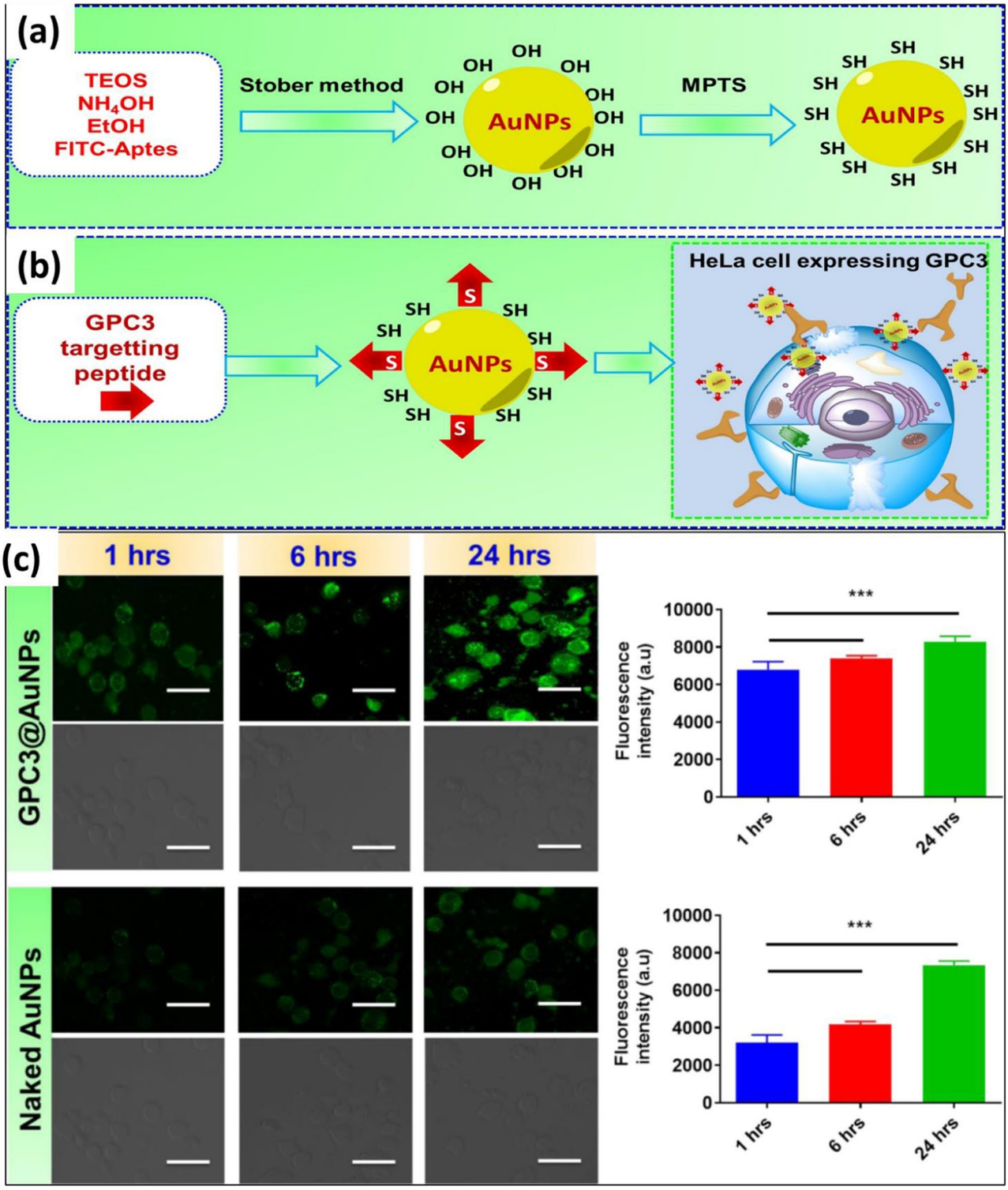


Fig. 3 Schematic representation of (**a**) Au NPs-doped gold nanoparticle synthesis and (**b**) their functionalization with the GPC-3 ligand peptide. (**c**) Confocal microscopic images of HeLA cells post treatment with GPC-3 functionalized Au NPs and naked Au NPs and their respective fluorescent intensity. Reproduced with permission from [104]

cells they did not reduce cell viability. Hence this technique can be safely used as an imaging tool [104].

Moreover, functionalization with targeting ligands such as folic acid (FA) has proven effective for enhancing the targeting of ovarian cancer cells, which commonly overexpress folate receptors. In another study, photoluminescent gold nanoclusters AuNCs were made stable and biocompatible with the help of bovine serum albumin (BSA). Folate receptor α (FRα) is overexpressed in ovarian cancer cells to target them nanoclusters were functionalized with folic acid (FA) creating FA-BSA-AuNCs. This increases the ability of nanoclusters to accumulate in cancer cells and them ideal for imaging. They compared the uptake of FA-BSA-AuNCs in NIH, OVCAR-3 cancer cells to non-targeted BSA-AuNCs. When cells were incubated with non-targeted BSA-AuNCs red fluorescent spots were observed inside the cells and dark outline around the nuclear region which meant AuNCs had penetrated the cell but not the nucleus. Whereas, greater internalization and enhanced bioimaging ability were observed when cells were treated with FA-functionalized AuNCs. FLIM Analysis (Fluorescence Lifetime Imaging Microscopy) was performed, and bright, uniform fluorescence was observed throughout the cell's cytoplasm in the case of FA-functionalized nanoclusters. This further confirmed that functionalization with FA enhanced uptake, targeted treatment and image-guided diagnosis. Thus, the potential of nanotechnology to create precise, efficient tools for detecting and treating cancer was confirmed by cellular uptake study by epi-fluorescence microscopy and fluorescence lifetime maps (FLIM) technique. These results confirmed an enhanced uptake by the targeted system while the non-targeted one remained in the perinuclear region (Fig. 4) [105].

FA-conjugated Au NPs were shown to accumulate preferentially in cancer cells, improving the specificity and efficiency of imaging and therapy. Studies by Kumar et al. further highlighted the potential of folate-functionalized Au NPs for in vivo diagnostic applications, showing that these nanoparticles could be used for cancer detection through radioactive labeling with 99mTc, providing insight into the biodistribution of the nanoparticles in animal models. Folic acid and HYNIC were attached to the carboxylic end of UA, transforming it to thiol (SH) characteristics at the Br end. Modified ligands folic acid FA-UA-SH and HYNIC-UA-SH were attached to the gold nanoparticles. To ensure that the average size remains < 10 nm tween 80 was used. Gold nanoparticles were labeled with radioactive ^{99m}Tc to aid in cancer detection using the HYNIC approach. The efficiency of ^{99m}Tc labeled Au NPs was tested on FR-positive KB cancer cells. It was observed that the Au NPs were able to inhibit [3 H] folic acid binding and hence had an affinity for folate receptors. Biodistribution studies in SCID mice with KB transplanted cancerous cells showed that the ^{99m}Tc-labeled nanoparticles accumulated 1.39%ID per gram in the tumor and 5.4%ID per gram in the kidney 3 h after infusion. This study highlighted that surface modification with folic acid nanoparticles can direct towards folate receptors but more work is needed to make sure there is no off-target accumulation. Nevertheless, in vivo pharmacokinetics aligned with the design goals of the researchers hence these particles can be used in future diagnostic applications [30].

The ability of Au NPs to concentrate at tumor sites opens the door for enhanced imaging modalities and targeted therapies, particularly in cancers with known overexpression of specific receptors like FRα. Additionally, the development of sensors using Au NPs for detecting ovarian cancer biomarkers has gained traction in recent years. For example, Viswanathan and co-researchers developed an electrochemical immunosensor to detect MUC16 antigens which are found elevated in ovarian cancer patients using AuNEE. AuNEE is a group of gold electrodes created by the gold coating within the voids of a polycarbonate layer. The structure of AuNEE was stabilized by a thin layer of cysteamine it also served as the foundation for the attachment of antibodies specific to MUC16 by network formation with EDC-Sulfo-NHS. The bioassay process involves the addition of an immunoliposome coated with an antibody of MUC16 and loaded with ferrocene carboxylic acid on the GNEE. When MUC16 is present it binds to the antibody present on the liposome and AuNEE creating a "sandwich" with AuNEE on the bottom and the liposome on the top. Redox-active ferrocene (COOH) carboxylic acid was discharged from the immunoliposome which corresponded to the levels of MUC16 it was quantified by differential pulse voltammetry. The concentration-response bend disclosed MUC16 concentration strength in a range of 0.001–300 U per ml. The minimal identification limit was found to be 5×10^{-4}U per ml ($S/N = 3$). Real and spiked serum samples were tested by this sensor and its accuracy was compared to that of the ELISA test. It demonstrated positive results paving the way for further development [107].

Another significant advancement is the work by Raghav et al., who developed an impedimetric immunosensor using gold-silver core-shell nanoparticles for CA125 detection. Antibodies that specifically bind to CA125 antigen were immobilized onto these nanoparticles. When CA125 binds to an antibody on the nanoparticle changes in electrical resistance. Sensors provided measurable changes in its signal as CA125 levels increased from 1 to 150 IU per ml $r^2 = 0.994$ as against the maximum straight response of 1–100 IU per ml showed for impedimetric biosensors to date. The sensor is highly specific with minimal interference (2–5%) with other

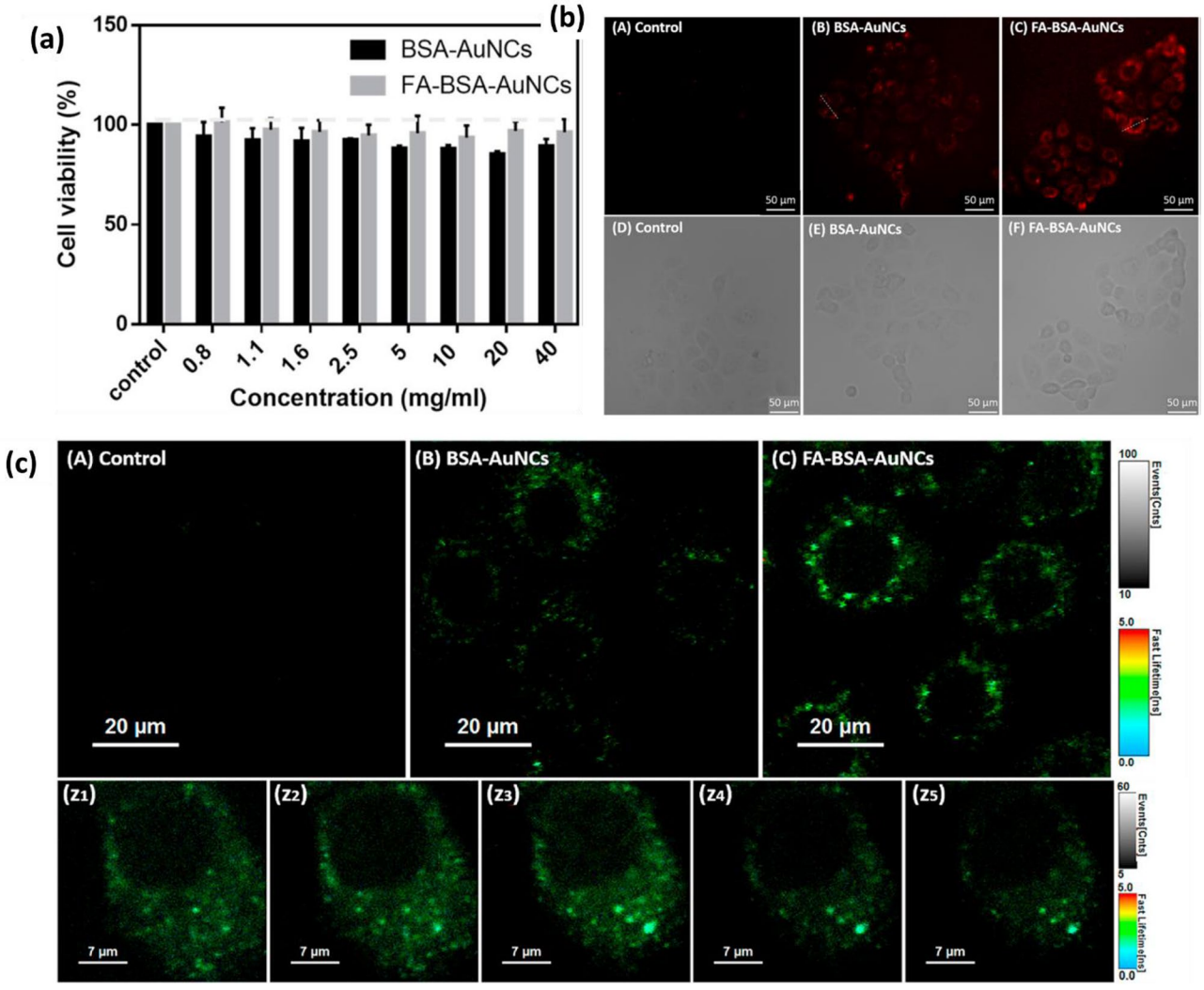


Fig. 4 Representation of potential features of nanotechnology as precise and efficient tool in cancer therapy. (**a**) Cell viability assay after treatment of NIH: OVCAR-3 cells with FA coated and uncoated nanoparticles. A superior biocompatibility via FA targeted therapy was demonstrated in comparison to non-targeted ones. (**b**) Red dots inside the AuNC-incubated cells (Fig. 5(B–C)) show that a substantial portion of AuNCs were able to pass through the cell membrane and gather inside the cytoplasm, mostly in the perinuclear area. The nuclei are shown by the black zone that the red emission of AuNCs outlines, demonstrating that AuNCs cannot penetrate the nuclear membrane. FA based therapy again showed better internalization. (**c**) the fluorescence lifetime maps confirms the uptake by FA conjugated gold nanoparticle [128]

serum components. 90% of its functionality is retained for 20 days. It takes only 20 min for a cancer diagnosis. Hence, this method provides a stable, more sensitive and faster way to detect CA125 for ovarian cancer diagnostics [108].

Furthermore, Srivastava and fellow researchers presented a novel method to detect two tumor markers as diagnosis using a single tumor marker may give a false or missed diagnosis. The sensor consists of two types of DNA-AgNCs that emit different colors. When they are functionalized with an aptamer specific to CEA they emit a green color (gDNA1-AgNCs-apta1) while a red color is emitted when they are functionalized with an aptamer specific to CA125 (rDNA2-AgNCs-apta2). When Au NPs are close to DNA-AgNCs aptamer complex they cause fluorescence quenching due to the process called surface plasmon-enhanced energy transfer. Au NPs tend to aggregate but the presence of DNA-AgNCs bound to their specific prevents this aggregation. When CEA or CA125 are present they bind to their respective aptamer as a result Au NPs move away from the complex the aggregation of Au NPs continues leading to a diminished quenching effect and recovery of fluorescence. The presence and concentration of each marker can be determined by the corresponding color's fluorescence since each aptamer has a specific color signal. Each examination needs only 1–2 uL of serum sample. The sensor is effective for early and accurate diagnosis of cancer because it is highly sensitive, with detection limits as minimal as 7.5 pg per mL for CEA and 0.015 U per ml for

CA125 [109]. They also underline the importance of surface functionalization and the integration of nanotechnology into medical devices, which could transform the landscape of cancer diagnosis and treatment.

In another study, a colorimetric nano-biosensor was developed using Au NPs to detect platelet-derived growth factor (PDGF), a biomarker that is significantly upregulated in the plasma of ovarian cancer patients. The system's functionality was validated through spectroscopy analyses, with the nanoparticles further characterized using X-ray diffraction (XRD) and scanning electron microscopy (SEM). The detection mechanism relied on the interaction between PDGF-specific aptamers and Au NPs. When mixed with a sample containing PDGF, the aptamers bound to the target, causing the aggregation of Au NPs, which resulted in observable changes in both absorbance as well as color. At higher PDGF concentrations, the color of the Au NPs solution shifted from pinkish to light purple. The biosensor exhibited a linear response to PDGF concentrations ranging from 0.01 to 10 μg/ml under optimal conditions. Notably, the sensor was sensitive enough to detect PDGF at concentrations as low as 0.01 μg/ml. Furthermore, the technique was successfully tested in artificial serum, which mimics the complex composition of biological fluids. These results highlight the practical potential of the Au NP-aptamer-based system for cancer diagnosis. The developed biosensor demonstrated key advantages, including high reliability, selectivity, and reproducibility, making it a promising tool for the early detection of ovarian cancer [97].

In a study by Albertini et al., gold nanoparticles (Au NPs) functionalized with an arginine–glycine–aspartic acid-like peptide were developed for cancer diagnosis and therapy. The study reported remarkable tumor-targeting efficiency. In a subcutaneous tumor model in mice, the accumulation of peptide-decorated nanoparticles was approximately four times higher than that of uncoated particles and 1.4 times higher than PEGylated particles two hours post-administration. Similarly, in an intracranial tumor model, the peptide-decorated nanoparticles showed 1.5 times the accumulation of uncoated particles and five times that of PEGylated particles within the brain at the same time point. These findings highlight the promising potential of this peptide-functionalized carrier for both diagnostic and therapeutic applications in cancer [89].

Application of Au NPs for treatment of ovarian cancer

Recently, the trend of enhancing the payload of anticancer agents using nanotechnology has introduced a new approach to drug delivery, offering significant potential in biomedical research. This shift has led to the emergence of multifunctional gold nanoparticles (Au NPs) as promising theranostic agents for cancer treatment. These nanoparticles are capable of effectively delivering larger amounts of drug molecules to the targeted disease site, making them a valuable tool in cancer therapy (Table 1).

A study by Zhang et al. demonstrated the potential of biogenic gold nanoparticles for anticancer and antioxidant applications. Using a green synthesis approach, they combined Au NPs with kaolin clay, derived from the root extract of Ephedra, to enhance the stability and biocompatibility of the nanoparticles [110]. Environment-friendly methods were used to create Au NPs, making them more biocompatible and less toxic. Kaolin clay enhanced the stability of nanoparticles. The developed nanocomposite had both antioxidant and anticancer potential. The antioxidant potential of Au NPs/Kaolin composite was determined by the DPPH colorimetric assay. A 100% antioxidant activity was observed at 1000 μg/ml. This indicated the good radical scavenging ability of nanoparticles. Cell viability was measured by MTT assay. Ovarian cancer cell lines (PA-1 and SK-OV-3) and normal human umbilical vein endothelial cells (HUVECs) were chosen to evaluate the cytotoxicity of nanocomposite. IC50 value for PA-1 cells was found to be 250 μg/ml and 119 μg/ml for SK-OV-3 cells. This showed that nanocomposite effectively reduced the growth of cancer cells. The level of inflammatory factors like TNF-α, IL-6, and IL-1β in a mouse with adenomyosis were studied before and after treatment with the Au NPs/Kaolin composite. A marked decrease in these factors suggested that it had effective anti-inflammatory properties. The proteins such as p-p38, p38, p-JNK, JNK, p-ERK8, and ERK involved in the MAPK/ERK signaling pathway were analyzed in tamoxifen-induced adenomyosis mice. It was observed that the nanocomposite inhibited the MAPK/ERK pathway.

In another study by Lee et al., a novel approach for targeted drug delivery was developed using hyaluronic acid (HA)-coated Au NPs (HA-AuDEN-DOX) loaded with the chemotherapeutic drug doxorubicin (DOX). Au NPs were encapsulated with dendrimer which was further coated with Hyaluronic acid (HA) to increase its specificity towards CD44. Due to mitochondrial dysfunction, cancer cells have high levels of glutathione (GSH). The Au-thiol bond between DOX and the nanocarrier breaks to GSH releasing DOX to the nanocarrier as shown in Fig. 5. It was observed that without GSH only 1.1% of DOX was released while with GSH 54.8% of DOX was released. Hence it was concluded that a high GSH environment typically present in cancer cells favors the release of DOX. Also, the acidic environment of tumor cells triggered the release of 75.9% DOX in the presence of GSH. Using confocal laser scanning microscopy (CLSM), it was observed that Au NPs had better

Table 1 Illustration of applications of gold nanoparticles in the treatment of ovarian cancer

S.no.	Particle size	Type of nanocarrier	Chemo-therapeutic agent	Cell lines	The outcome of the study	Reference
1	$Fe3O_4$ NPs: 33 nm Au NPs: 13 nm Nanocomposite: 30–40 nm	Au NPs/L-arginine/Fe3O4 magnetic nanocomposite	—	SK-OV-3, SW-626, and PA-1 HUVEC	Au NPs/L-arginine/Fe3O4 is a promising nanocomposite for treating ovarian cancer	[115]
2	80 nm	Poly-amino-coated DH-GNR nanocomposite	Doxorubicin	SKOV3, Bcl-2	DH-GNR will be of great potential in the treatment of ovarian cancer	[132]
3	< 10 nm	Tc-99 m labelled ultrafine gold nanoconjugates	—	KB cell	Tc-99 m Au NP can be used for the diagnosis of FR-positive cancers	[106]
4	Diameter–100 nm Length 400 nm	Gold nanoelectrode	—	—	Imunoliposome and gold nanoelectrodes can be used for the detection of ovarian cancer	[107]
5	5 nm	PEG and FA attached Au NP	—	OV-167, SKOV-3, OV-202, OV-202, OPM-1, RPMI, OVCAR-5	Au NPs can be used to target cancer cells	[86]
6	Fe_3O_4-20–25 nm Au- 6–8 nm	Dumbbell-shaped Apt-Au-Fe_3O_4 nanoparticles	—	SKOV-3	Apt-Au-Fe_3O_4 nanoparticles show high potential for photo-controlled targeted cancer treatment	[44]
7	Less than 12 nm	Gold-silver core-shell nanoparticles-based impedimetric immunosensor	—	—	gold-silver core-shell nanoparticles-based impedimetric immunosensor detects CA125 for ovarian cancer diagnosis	[108]
8	178.6 nm	Au@MSN-Ter/THPP@CM@GelMA/CAT biomimetic nano@microgel	—	SKOV3 cells, OVCAR3	biomimetic nano@microgel could be a promising candidate for in situ ovarian cancer therapy	[115]
9	30 nm	DNA-silver nanoclusters	—	—	Diagnosis of dual cancer marker	[109]
10		Au NPs	—	OVCAR5, OV167, OV202,A2780, SKOV3	Targeting MICU1 could enhance the therapeutic efficacy of Au NPs against cancer cells	[116]
11	Au NP: 39.31 ± 9.33 Au NP-cisPt: 125.52 ± 17.62 HA-cisPt-Au NP: 144.71 ± 3.78	HA-CisPt-Au NP,	cisplatin	NIH/3T3, MCF-7 and U-87	HA-cisPt-Au NP formulation has significant potential to treat cancer	[117]
12	20 nm	Au NP	—	TAF18, HUVEC, CP20-EGFP and OV90-EGFP	Au NP can inhibt proliferation of cancer cells	[118]
13	10–15 nm	Au NPs/Kaolin bio-nanocomposite	Tamoxifen	PA-1 and SK-OV-3	The Antioxidant potential and Anti - human ovarian cancer effects of Au NPs/Kaolin bio-nanocomposite was revealed	[106]
14	100 nm	citrate capped gold nanoparticles	—	—	This technology might potentially be used as a universal means of ovarian cancer screening testing, allowing patients to obtain early and actual treatment	[133]
15	195 ± 6 nm for Au NPs, and 230 ± 19 nm for GPC3@Au NPs	GPC3@Au NPs	—	HeLa	Au NPs -based system for the in vitro molecular imaging of ovarian carcinoma cells was studied	[104]
16	12.3 nm	HA-AuDEN-DOX	Doxorubicin	SK-OV-3	A promising application of HA-AuDEN-DOX for the treatment of ovarian cancer with CD44 overexpression was studied	[111]

Table 1 (continued)

S.no.	Particle size	Type of nanocarrier	Chemo-therapeutic agent	Cell lines	The outcome of the study	Ref-er-ence
17	16.6 nm	Au NPs green-mediated by ECurcumae Kwangsiensis Folium leaf aqueous extract	Curcumae Kwangsiensis Folium leaf aqueous extract	W-626, PA-1, and SK-OV-3, HUVEC	The Au NPs green-mediated by Curcumae Kwangsiensis Folium leaf aqueous extract can be used as novel chemotherapeutic drugs in humans soon	[112]
18	100 nm	US + AuNCs + Cis	Cisplatin	A2780cis	Triple combination therapy exhibited superior therapeutic activity with higher number of Cis inside the cisplatin-resistant cells	[101]
19	25 ± 12 nm	BSA-AuNCs	—	NIH: OVCAR-3	FA-BSA-AuNCs employed as efficient fluorescent contrast agents and promising candidates for image-guided cancer diagnosis and therapy applications	[105]
20	~ 30 nm	Fe3O4@Thymbra spicata/Au nanocomposite	—	SW-626, PA-1,SK-OV-3 and HUVEC	Fe3O4@Thymbra spicata/Au NPs nanocomposite shows excellent antioxidant properties and can be used as novel chemotherapeutic drugs in humans soon	[113]

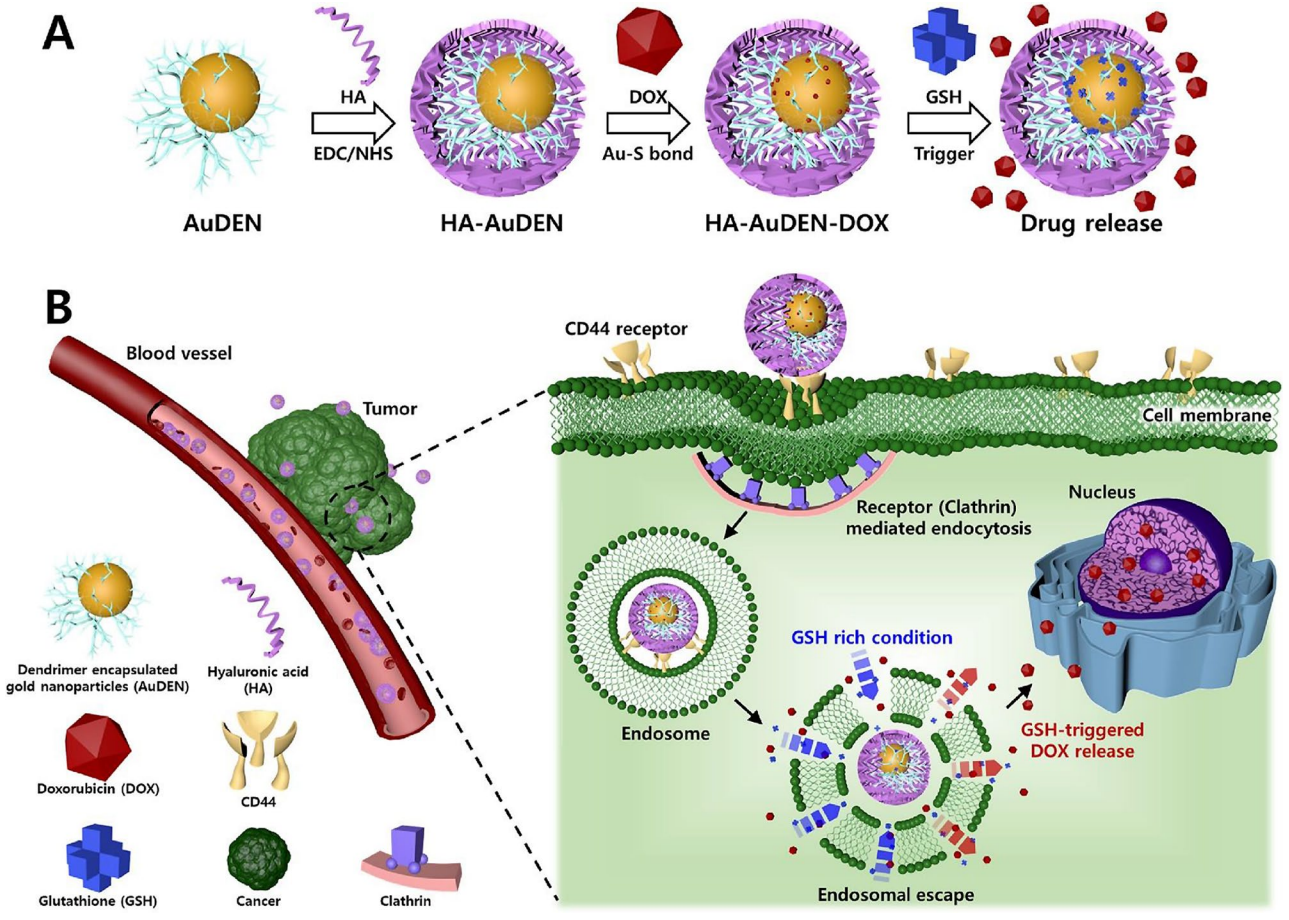


Fig. 5 Representation of synthesis protocols for HA-AuDEN-DOX; **B**, Drug delivery mechanisms of HA-AuDEN-DOX. Reproduced with permission from [85]

internalization in SK-OV-3 ovarian cancer cells compared to free DOX. In vivo, anticancer efficacy was studied in a mouse with ovarian cancer xenograft (SK-OV-3 cells) (SK-OV-3 cells) the effect of HA-AuDEN-DOX was compared with free DOX and PBS(control). Tumor volume was reduced by 64.6% and the treatment control ratio was found to be 66% after treatment with HA-AuDEN-DOX. Ki67 proteins were used as a biomarker to gauge the cell proliferation rate. 24.7% Ki67 index was found when treated with HA-AuDEN-DOX while 72 with free DOX and 100% with PBS. This study highlighted the efficiency of this modified Au NPs in targeted anticancer drug delivery [111].

Chen et al. explored the green synthesis of Au NPs using Curcumae kwangsiensis Folium leaf extract, which exhibited potent anticancer and antioxidant activities [112]. Cytotoxicity of this nanoformulation was studied on ovarian cancer cell lines (SK-OV-3, SW-626, and PA-1) as well as a normal cell line (HUVEC). Low cytotoxicity was observed in normal cells indicating it selectively targeted tumor cells. Significant anticancer activity was observed by performing an MTT assay. IC50 value of various tumor cell lines indicated Au NPs effectively inhibited the growth of cancer cells. Antioxidant capacity was evaluated by DPPH assay. IC50 of 153 mg/ml was obtained on treatment with Au NPs and 202 mg/mL for BHT. This implied that Au NPs had a better antioxidant activity effect than BHT. This study highlighted that Au NPs formulated using green chemistry have the potential to show excellent anticancer and antioxidant properties.

Kip et al. investigated a combination therapy approach, using gold nanocones (AuNCs), ultrasound (US), and cisplatin to enhance ovarian cancer treatment. Cell lines used in this study were A2780 and cisplatin-resistant A2780cis. Individually Cis-only and ultrasound therapy was less effective but triple combination therapy showed the lowest cell viability. Ultrasound facilitated the accumulation and retention of both Au NPs and cisplatin ICP-MS method was used to study this accumulation. The triple therapy reduced colony formation to 2.8% in A2780 cells and 17.4% in A2780 cis cells as shown in Fig. 6. The highest accumulation was found in the sub-G1 and G1 phases of the cell cycle in the triple therapy. Cisplatin alone was less effective in inducing apoptosis. This study highlighted the efficiency of combination therapy in overcoming drug resistance and enhancing cisplatin's cytotoxic effect [101].

Ding et al., used ultrasonic irradiation for coating Au NPs decorated *Thymbra spicata* extract modified-magnetite nanocomposite to treat ovarian cancer. Iron oxide has been studied widely owing to multiple properties like biocompatibility, superparamagnetism and ease of synthesis. Herein, modification with Fe_3O_4 has capped the Au ions and improved their stability without aggregation. MTT assay was performed for 48 h on different cell lines such as SK-OV-3, SW-626, PA-1, and HUVEC. IC50 value indicated Fe3O4@Thymbra spicata/Au NPs nanocomposite selectively targeted cancer cells without affecting healthy cells. The results from the DPPH assay showed that the nanocomposite was effective in protecting the cells from oxidative stress (Fig. 7). Due to the dual property of the nanocomposite i.e., selective cytotoxicity and strong antioxidant capacity, they have the potential to be used as an effective anticancer treatment [113].

Xu and his co-researchers developed an eco-friendly and cost-effective method to create a magnetic nanocomposite by modifying L-arginine with iron oxide nanoparticles to enhance further the functionality of this composite, Au NPs were added to its surface. L-arginine was used as a coordinating agent to bind the Au NPs onto the Fe_3O_4 nanocomposite surface and act as a stabilizer for the gold nanoparticles. Through the DPPH assay, the researchers tested the antioxidant properties of the nanocomposite to neutralize free radicals. The IC50 value of the Au NPs/L-arginine/Fe3O4 nanocomposite was found to be 180 mg/mL, while IC50 of butylated hydroxytoluene (BHT) (standard antioxidant compound) was found to be 125 mg/mL which showed that although the nanocomposite had antioxidant properties it was less potent than BHT. They also investigate the cytotoxic (cell-killing) and anti-neoplastic characteristics of the Au NPs/L-arginine/Fe3O4 nanoparticles on different cell lines such as HUVECs (normal cell line) and SK-OV-3, SW-626, and PA-1 (Ovarian tumor cell line) over 48 h which revealed that the IC50 values for the nanomposite were: 213 mg/mL for PA-1 cells, 162 mg/mL for SW-626 cells, 149 mg/mL for SK-OV-3 cells. The IC50 values suggested that the Au NPs/L-arginine/Fe3O4 nanocomposite can be effective in killing ovarian cancer cells to different extents, with a more pronounced effect seen in the SK-OV-3 cell line relative to the others. The characteristics of particles were identified by different techniques such as FE-SEM, EDX, TEM, XRD, FT-IR, ICP-AES, and VSM. This indicated that the nanocomposite could be promising for the cure of ovarian malignancy [114].

Ma and his team coated gold nanorods with silica and were loaded along a photosensitizer called porphine, which generates ROS under near-infrared light. Catalase enzyme which converts endogenous hydrogen peroxide in tumors into oxygen is incorporated into the nano@microgel. This boosts ROS generation for PDT, increasing the oxygen supply within the tumor. Tosyl Ethylenediamine (Ter) ligand helps direct the nanoparticles to the ER of cancer cells and is attached to the surface of these nanoparticles.

The size of gold nanorods (Au NR) increased after coating. Naked Au NR showed a size of 56 nm which increased to 178 nm after forming PDT-generating and

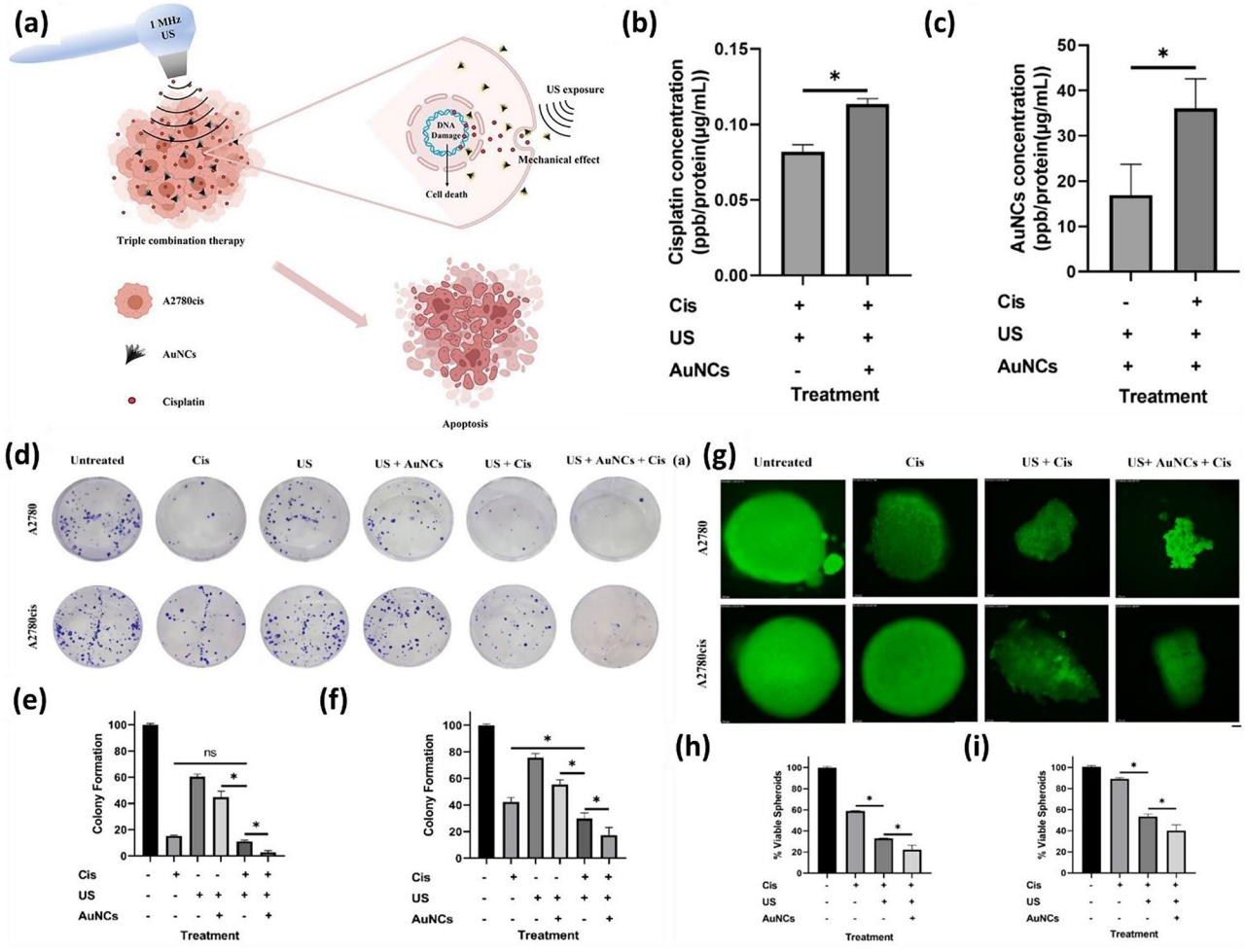


Fig. 6 (**a**) Graphical representation of treatment of ovarian cancer cells under the influence of ultrasonic waves and Au NPs. (**b** and **c**) ICP-MS analysis on A2780 cis ovarian cells showing higher accumulation of Pt ion via triple combination therapy. Under the influence of Au NPs, cis got accumulated. (**d**, **e** and **f**) The US, Au NPs and Cis triple combination treatment effectively inhibited each cell's capacity to form colonies, and our findings demonstrated that the with low dosage drug concentrations, triple combination therapy exhibited a long-term therapeutic impact on resistant cells, suppressing about 83% of colony growth. (**g**, **h** and **i**) The triple combination therapy has same effect on 2D and 3D model of drug resistant ovarian cancer spheroid. Statistically, 10% more spheroid was treated with combination treatment as compared to US and Cis alone [129]

ER- targeting biomimetic gold nanorod-mesoporous silica core-shell nanoparticles (Au@MSN-Ter/THPP@CM NPs) (shown in Fig. 8). To provide stable, extended retention within tumor nanoparticles and catalase are encapsulated by GelMA. AuNR absorbs NIR light and converts it to heat causing damage to tumor cells. Two ovarian cell lines OVCAR3 and SKOV3, were used to evaluate nanoparticle cytotoxic effects. WST-1 assays were used cell viability was assessed after treatment with Au@MSN-Ter/THPP@CM NPs. It reduced cell viability in both cell lines. NPs preferentially target ovarian cancer cells over normal human dermal fibroblasts. The combination of PDT-PTT causes ER stress causing cell death. Additionally, they help to recognize and attack cancer cells by exposing CRT (calreticulin) on the surface of the cell and also releasing raised mobility group box 1 (HMGB1) from the core of the cell (nucleus) in SKOV3 cells, both of which act as signals to the immune system. These findings showed that upon intratumoral injection of the Au@MSN-Ter/THPP@CM@GelMA/CAT microsphere, the Au@MSN-Ter/THPP@CM NPs were mostly retained in the tumor tissue. However, Au@MSN-Ter/THPP@CM NPs injected into the tail vein similarly showed accumulation in the major organs like the kidney, liver, and lungs. Additionally, the results of 15 days of therapy with various formulations and lasers on the tumor weight of sacrificed mice demonstrated that Au@MSN-Ter/THPP@CM@GelMA/CAT and Au@MSN-Ter/THPP@CM NPs could both considerably reduce the tumor weight when exposed to double lasers. Furthermore, Au@MSNTer/THPP@CM@GelMA/CAT and Au@MSN-Ter/THPP@CM@GelMA/CAT NPs with double lasers both had tumor weights that were noticeably lower than those of the Au@MSN-Ter/THPP@CM@

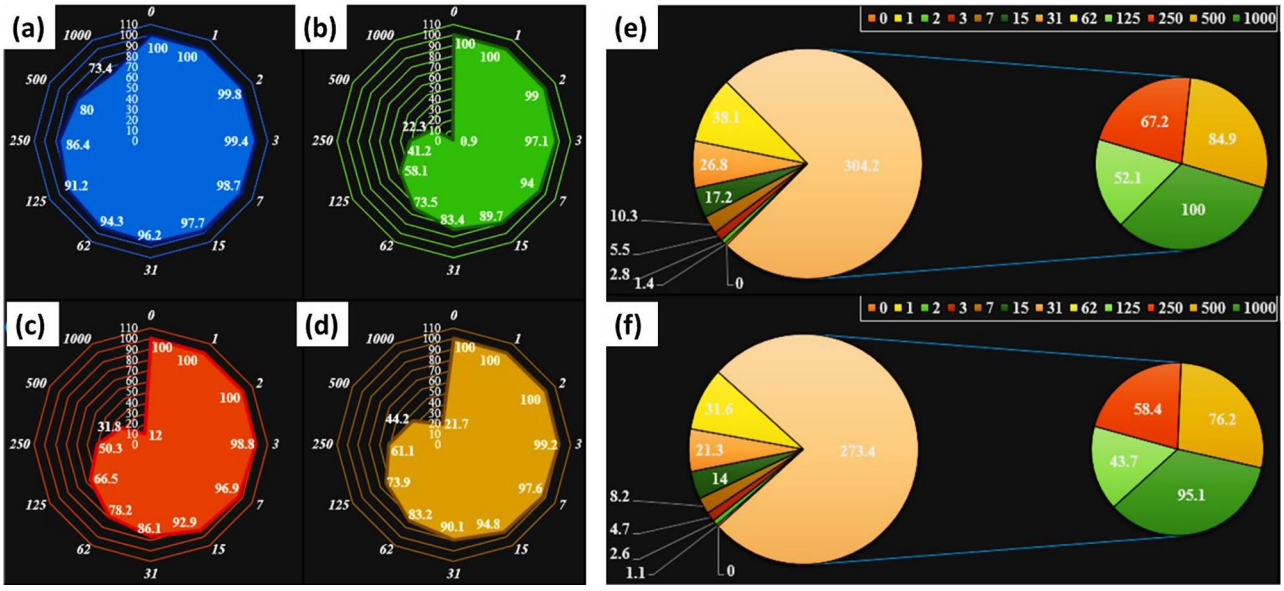


Fig. 7 (**a**–**d**) Representation of anticancer property of iron oxide functionalized Au NPs in normal cells (**a**: HUVEC), PA-1 (**b**), SW-626 (**c**) and SK-OV-3 (**d**). Antioxidant assay or free radical inhibition study using functionalized nanosystem (**e**) and butylated hydroxy toluene (**f**) [130]

GelMA/CAT only treated group, with the Au@MSN-Ter/THPP@CM@GelMA/CAT with lasers treated group showing the lowest tumor weight result. This recently developed biologically inspired nano@microgel may be a futuristic applicant for on-site ovarian malignancy treatment (Fig. 8) [115].

Au NPs have the potential to kill cancer cells but sometimes cancer cells show unexpected resistance to it. In this study, Arvizo and his colleagues investigated how ovarian cancer cells show resistance to apoptosis when exposed to positively charged Au NPs. Mitochondrial calcium uniporter is a channel responsible for controlling the entry of calcium ions (Ca^{2+}) into mitochondria it is regulated by MICU1. OVCAR5, OV167, as well as OV202, were grown in DMEM, A2780 was raised in RPMI, and SKOV3-ip was raised in McCoy's medium. MICU1 plays a protective role by managing calcium levels and preventing mitochondrial dysfunction, which would otherwise trigger apoptosis in cancer cells. Positively charged Au NPs led to cell stress and death when they are introduced into malignant ovarian cancer cells, by increasing the concentration of calcium ions in the cytoplasm. MICU1 regulates calcium influx into the mitochondria, thereby maintaining mitochondrial stability and preventing apoptosis. They used pharmacological inhibitors and siRNA to decrease MICU1 activity. The mitochondrial membrane depolarizes leading to its dysfunction and the initiation of apoptosis when MICU1 is silenced. Anti-apoptotic protein Bcl-2 reduces making cells more prone to apoptosis. Caspase-3 activity gets enhanced signifying activation of apoptotic pathway. Cell death cascade is further triggered by the release of Cytochrome c. This study highlighted that by targeting MICU1, it may be possible to sensitize cancer cells. When MICU1 is inhibited, the presence of Au NPs enhances these pro-apoptotic effects, leading to more effective cell death in cancer cells [116].

Gotov and his developed hyaluronic acid (HA) wrapped, cisplatin combined gold-based nanostructures (HA-cisPt-Au NPs). Stability in the biological environment as well as slow clearance from the bloodstream were promoted due to negative charges on the surface of these NPs. CD44 sensors are highly expressed in malignant cells HA coating allows selective uptake by malignant cells by this receptor. The MTT assay in vitro cytotoxicity tests were conducted on MCF-7 and U-87 cell models, both with NIR and without NIR laser irradiation. Greater cytotoxic effects were shown by HA-cisPt-Au NPs compared to free cisplatin, particularly in MCF-7 cells. Laser activation of the Au NPs further increased the cytotoxicity of the nanoparticles. NIH/3T3 fibroblast cells (normal cells) exhibited lower toxicity with HA-cisPt-Au NPs, demonstrating the selective targeting ability of the Au NP. In vivo, antitumor efficacy was done on tumor-bearing mice. Compared to free cisplatin significant suppression in tumor growth was observed when HA-cisPt-Au NPs was combined with NIR laser. The formulation did not cause any significant change in body weight. The research highlighted the synergistic potential of combining chemotherapy (cisplatin) with photothermal therapy using gold nanoparticles [117].

Finally, Zhang and his team explored the use of Au NPs to intervene in the interaction within the TME of EOC. The citrate reduction method was used to synthesize

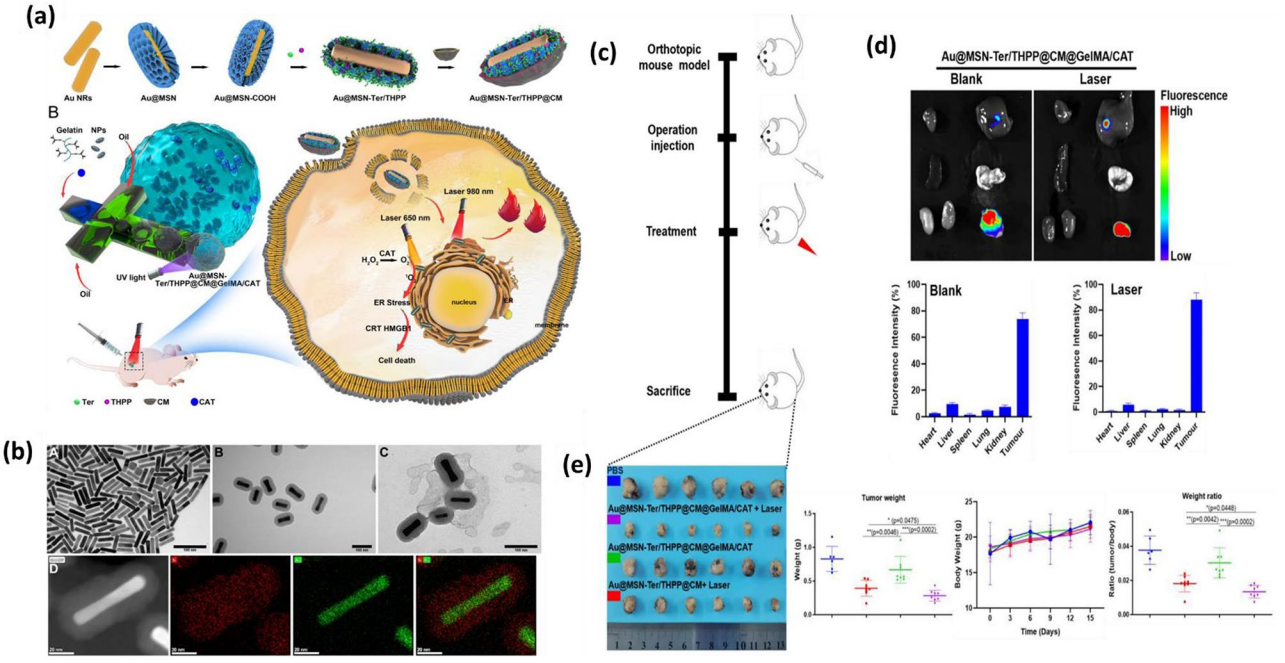


Fig. 8 (**a**) Graphical representation of preparation of PDT generating and ER targeting biomimetic gold nanorod-mesoporous silica core-shell nanoparticles and its effect on cell death. (**b**) TEM image of Au NRs, Au@MSN NPs, Au@MSN-Ter/THPP@CM NPs (above) and high-angle annular dark-field and elemental mapping image of Au@MSN NPs (below) NPs. (**c**) representation of animal study, (**d**) THPP fluorescent signal images of various organs captured by in vivo imaging system and e represents data of cancerous lesion images, weight of tumor, weight of mice's body and tumor to body weight ratio [104, 111, 128, 131]

20 nm Au NPs. Various advanced analytical techniques like UV-visible spectroscopy, Dynamic Light Scattering, and TEM were used to characterize prepared Au NPs. To study the interactions and signaling pathways that promote cancer cell proliferation they set up a culture system containing CC, TAF18(CAF), and HUVEC(EC). EGFP was used for its tracking and quantification. It was observed CAF and CC led to CC proliferation. The combination of both led to even more proliferation of CC. 25 µg/ml of Au NPs were added to the coculture this inhibited the proliferation of CP20-EGFP and OV90-EGFP. This indicated that Au NPs disrupted the interaction provided by TAF18 and HUVEC to CC in the TME. Even some morphological changes were observed in CC like smaller or more spread-out cells. This study highlighted that Au NPs can interrupt the crosstalk in TME among CAF, CC, and EC leading to reduced migration, invasion, and proliferation of CC [33].

Challenges and limitations

Despite being a promising approach, there are still several significant obstacles to overcome before AuNPs and platinum-based agents may be used together in anticancer treatment. First, further pre-clinical research is still needed to evaluate the safety of nanoparticles in vivo in the entire animal study. Second, therapeutic agents can reach both the targeted region and normal tissues since the combined therapy improves the absorption of both cisplatin and AuNPs. Optimizing the therapeutic dose and manner of delivery may be required to prevent unintended toxicity. Analyzing the pharmacokinetics of nanoparticles in vivo to evaluate their ADME processes is as crucial, much as researching pharmaceutical medications. Furthermore, some tissue-level toxicological investigations are necessary, such as those that examine hematological toxicity (blood), immunogenicity, nephrotoxicity (kidney), and hepatotoxicity (liver).

A combination of hyperthermic intraperitoneal chemotherapy (HIPEC) and cytoreductive surgery is another treatment strategy for advanced ovarian cancer. General surgeons adopted this technique, which was created to combine local chemotherapy administration with surgical radicality. A phase III trial reported an overall survival improvement of 13.3 months in patients with recurrent epithelial ovarian cancer (EOC) undergoing HIPEC, is the most referenced paper on HIPEC in EOC. However, there are several restrictions on validity, randomization and statistical analysis of the trial [119].

Future prospects

The overall survival rate of ovarian cancer patients has not improved over the past 30 years, and the illness has not been cured yet. While early research is now focusing on people with recurring illnesses, the main goal should

be to improve front-line therapy approaches to boost the cure rate. Additionally, the "one-fits-all" approach to treating cancer should be reconsidered, and prognostic indicators are necessary to enable tailored and focused treatments such as PARP.

inhibitors and immune checkpoint inhibitors on the front line.

As per the present report, gold nanoparticles operate as a molecular "brake" that stops the "run-away" activation of Akt/NF-κB pathways caused by cisplatin or other platinum-based agents, which results in acquired drug resistance and cell stemness. AuNPs' ability to make ovarian cancer cells more sensitive to modest doses of cisplatin may reduce the possibility of dose-limiting toxicity and increase the therapeutic's applicability for a variety of tumors that need more clinical research.

Numerous ligands specifically designed for ovarian cancer should be assessed, which after functionalization on Au NPs can induce apoptosis, reduce cell growth, and improve overall survival [120–127].

Conclusion

One of the deadliest gynecological cancers that affect women in the western world is ovarian carcinoma. A comprehensive surgical debulking is part of the primary management, which is followed by a combination chemotherapy regimen based on platinum and taxane. The majority of patients with advanced-stage illness eventually acquire platinum resistance, which results in minimal responsiveness to any therapies and shorter survival, even if initial responses frequently show sensitivity to platinum drugs. In order to effectively treat them, platinum and other drug related resistance must be overcome.

Nanotechnology has drawn a lot of interest in cancer treatment throughout the last 10 years. Because of the distinct magnetic, optical, or structural characteristics of the nanometer-sized Au particles, it offers a novel strategy and all-encompassing technology against cancer. In a preclinical animal model of ovarian cancer, 20–80 nm gold nanoparticles (AuNPs) decreased angiogenesis, metastasis, and proliferation. At the molecular level, AuNP therapy changed the profiles of many secretory cytokines, most of which are important for controlling signaling linked to stem cell maintenance. It is also postulated that a small dosage of AuNPs may be used to sensitize ovarian cancers to chemotherapy like cisplatin because of these special and noteworthy characteristics. Pretreatment with AuNPs even inhibited NF-κB/Akt signaling, reduced the stem cell pool, and downregulated the multidrug resistance gene to prevent cisplatin-induced chemoresistance acquisition.

Au NPs also show promise as multifunctional theranostic agents that can diagnose and treat cancer simultaneously. Peptides, aptamers and antibodies have been studied to target the cancer cells specifically. Overall, Au NPs hold transformative potential in ovarian cancer therapy.

In conclusion, studies on gold nanoparticles (Au NPs) for the early detection as well as cure of ovarian tumour demonstrate significant development and evolution in precision medicine. Au NPs boost and strengthen therapeutic moiety administration efficiency via focusing oncogenic cells specifically, which enables lower drug doses and mitigates adverse effects, potentially overcoming drug resistance. Their optical and magnetic properties allow for improved imaging, facilitating early diagnosis, and when combined with photothermal therapy. Though further research is essential to address clinical translation, biocompatibility, and long-term safety.

Abbreviations

HUVEC	Human Umbilical Vein Endothelial Cells
NP	Nanoparticle
Au NPs	Gold nanoparticles
FE-SEM	Field Emission-Scanning Electron Microscopy
PLA	Poly L Lysine
EDX	Energy Dispersive X-ray Analysis
TEM	Transmission Electron Microscopy
DOX	Doxorubicin
FT-IR	Fourier Transform-Infrared Spectroscopy
AuNR	Gold nanorod
ICP-AES	Inductively Coupled-Plasma Atomic Emission Spectroscopy
XRD	X-ray Diffraction
DH-AuNR	Doxorubicin and gold nanorod
PGA	Poly glutamic acid
NIR	Near-infrared
Tc	Technetium
FR	Folate receptor
UA	11-Bromoundecanoic acid
HYNIC	Hydrazinonicotinic acid chelate at the carboxylic acid
AuNEE	Gold nanoelectrode ensemble
PEG	Polyethylene glycol
PAM2	PEG-diamine
PAM4	PEG-tetramine
PSH2	PEG-dithiol
FR	Folate receptor
TGA	Thermogravimetric analysis
VEGF	Vascular endothelial growth factor
PTT	Photothermal Therapy
PMAL	Poly maleic anhydride-alt-1-decene
MSN	mesoporous silica
ROS	Reactive oxygen species
PDT	Photodynamic Therapy
ER	Endoplasmic reticulum
GelMA	Gelatin methacryloyl
ICD	Induction of Immunogenic Cell Death
CEA	Carcinoembryonic antigen
CA125	Carbohydrate antigen 125
DNA-AgNCs	DNA-silver nanoclusters
MICU1	Mitochondrial Calcium Uptake 1
XPS	X-ray Photoelectron Spectroscopy
DTT	Dithiothreitol
CAF	Cancer-associated fibroblast
EC	Endothelial cells
TME	Tumor microenvironment
EOC	Epithelial ovarian cancer
EGFP	Enhanced green fluorescent protein
CC	Cancer cell
PDGF	Target platelet-derived growth factor
GPC-3	Glypican-3 protein
CLSM	Laser Confocal microscopy

IHC	Immunohistochemical
UV–Vis	UV–Visible Spectroscopy
BHT	Butylated hydroxytoluene
US	Ultrasonic waves
BSA	Bovine serum albumin
TADF	Temperature activated delayed fluorescence
EPR	Enhanced Permeation and Retention
ADME	Absorption, distribution, metabolism and excreation

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