

Translational Potential of Gold Nanoparticles in Cancer Diagnosis and Management

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ABSTRACT:

Conventional cancer therapies are often hampered by poor specificity, systemic toxicity, and multidrug resistance. Gold nanoparticles (AuNPs), with their tunable optical properties, high biocompatibility, and functional versatility, offer a promising nanotechnological approach for improving cancer diagnostics and therapeutics. This review aims to provide a comprehensive, forward-looking synthesis of the translational applications of AuNPs in cancer theranostics, emphasizing mechanisms, clinical progress, regulatory considerations, and future potential. A systematic literature search was conducted across PubMed, Scopus, Web of Science, and Google Scholar for English-language publications from 2010 to 2025 using the keywords "gold nanoparticles," "cancer theranostics," "nanomedicine," and "photothermal therapy." Out of 468 retrieved articles, 172 met the inclusion criteria and were analyzed in depth for their translational relevance, functionalization strategies, imaging performance, and clinical outcomes. AuNPs support multimodal imaging (CT, MRI, SERS), targeted drug delivery, and photothermal therapy. Functionalization strategies such as PEGylation and ligand attachment improve tumor targeting and pharmacokinetics. Hybrid systems and AI-guided nanodesigns enhance specificity, while preclinical and early-phase clinical trials affirm safety and efficacy in cancers. AuNPs are reshaping cancer management by integrating precision diagnostics, controlled therapy, and real-time monitoring into unified platforms. Continued interdisciplinary collaboration and regulatory alignment will be crucial for their full-scale clinical translation.

Keywords: Clinical Trials; Multimodal imaging; Nanomedicine; Photothermal therapy; Surface plasmon resonance (SPR); Theranostics.

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1. Introduction

Nanotechnology has revolutionized biomedical science by enabling precise manipulation of materials at atomic and molecular scales, opening new avenues for targeted diagnostics and therapy [1]. Among the diverse nanomaterials investigated, gold nanoparticles (AuNPs) have gained prominence in cancer theranostics owing to their localized surface plasmon resonance (LSPR), optical tunability, and exceptional biocompatibility [2, 3].

LSPR facilitates efficient light absorption and scattering at tunable wavelengths, allowing AuNPs to function as photothermal agents for tumor ablation and as contrast enhancers in modalities such as photoacoustic imaging, optical coherence tomography (OCT), and surface-enhanced Raman scattering (SERS) [4–7].

Equally important is their versatility in surface functionalization—AuNPs can be conjugated to monoclonal antibodies, folate, peptides, or nucleic acids to enable receptor-mediated endocytosis and selective tumor targeting [8–10]. Their small size and modifiable

charge further promote tumor penetration through passive diffusion, pH-triggered activation, or macropinocytosis [11–13].

Beyond foundational applications, recent trends integrate AuNPs into AI-guided nanocarriers, hybrid nanostructures, and plasmonic nanorobots for multimodal imaging, stimuli-responsive drug release, and real-time monitoring. These advances mark a convergence of nanoscience with precision oncology [14–17].

This review aims to synthesize the current advances in gold nanoparticle design and application, emphasizing translational progress toward clinical integration, critical regulatory challenges, and emerging intelligent nanotheranostic systems.

2. Materials & Methods

2.1. Search Strategy

A comprehensive literature search was conducted using PubMed, Scopus, Web of Science, and Google Scholar databases. Keywords included "gold nanoparticles," "cancer theranostics," "targeted drug delivery," "multimodal imaging," and "photothermal therapy," combined with Boolean operators (AND/OR). Only peer-reviewed English-language studies from 2010 to 2025 were considered.

2.2. Study Selection

Out of 468 retrieved articles, 172 studies met the inclusion criteria: Focused on AuNP synthesis, functionalization, or application in cancer diagnosis or therapy; Presented original data from *in vitro*, *in vivo*, or clinical investigations; Discussed translational or regulatory aspects of AuNP-based systems. Exclusion criteria: poor methodological rigor, non-cancer-related studies, or lack of full-text availability.

2.3. Data Extraction

Data were systematically extracted for each study, including AuNP type and size, surface modifications, cancer model, therapeutic/imaging application, and translational relevance. Screening and data extraction were performed independently by two reviewers; discrepancies were resolved by consensus.

2.4. Ethical Compliance

The authors directly conducted no animal or human studies; all data were derived from published literature.

3. Results & Discussion

3.1. Binding Mechanisms of AuNPs in Cancer Theranostics

The effectiveness of gold nanoparticles (AuNPs) in cancer diagnosis and therapy stems from their ability to selectively accumulate in tumor tissues via both active and passive

mechanisms. Functionalization with targeting ligands enhances specificity, while physicochemical properties enable cellular penetration and uptake [18].

3.2. Active Targeting Mechanisms

Surface functionalization of AuNPs plays a critical role in enhancing their tumor specificity and cellular internalization. Conjugation with monoclonal antibodies such as anti-EGFR and anti-HER2 enables receptor-specific binding, thereby improving selectivity in imaging and targeted drug delivery [19, 20]. Folic acid-functionalized AuNPs exhibit strong affinity for overexpressed folate receptors on cancer cells, resulting in increased tumor uptake [8].

In addition, AuNPs modified with pH-responsive groups can sense the acidic tumor microenvironment, undergoing conformational changes that promote cellular entry [11]. Functional ligands such as peptides and aptamers further facilitate uptake by engaging specific cell-surface receptors and activating ligand-mediated endocytosis pathways, including clathrin-dependent internalization or caveolae-mediated transport [21].

3.3. Passive and Nonspecific Mechanisms

Nanoparticle accumulation and cellular uptake are also governed by several passive mechanisms that significantly influence the biodistribution of AuNPs within tumor tissues. The Enhanced Permeability and Retention (EPR) effect enables nanoparticles ≤ 100 nm to passively accumulate in tumors owing to leaky vasculature and inefficient lymphatic drainage [12].

Electrostatic interactions further contribute to nonspecific uptake, as negatively charged AuNPs are strongly attracted to the positively charged surfaces of cancer cell membranes, facilitating their adsorption [9]. Larger or aggregated nanoparticles are commonly internalized through macropinocytosis, an actin-dependent process characterized by membrane ruffling and vesicle engulfment that bypasses receptor specificity [22].

In contrast, very small AuNPs (<10 nm) may enter cells directly via passive diffusion or by traversing nonspecific membrane pores, thereby promoting enhanced cytoplasmic accumulation [23].

3.4. Surface Plasmon Resonance and Photophysical Principles of AuNPs

Gold nanoparticles (AuNPs) exhibit distinctive optical and photothermal properties due to their localized surface plasmon resonance (LSPR), a collective oscillation of conduction electrons induced by incident light. This resonance gives rise to strong light absorption, scattering, and local electromagnetic field enhancement, which underlie their biomedical use in biosensing, bioimaging, and photothermal therapy [24–26].

Figure 1 schematically depicts this phenomenon, where incident light interacts with a metallic nanoparticle, leading to electron displacement and surface charge separation that result in resonance excitation.

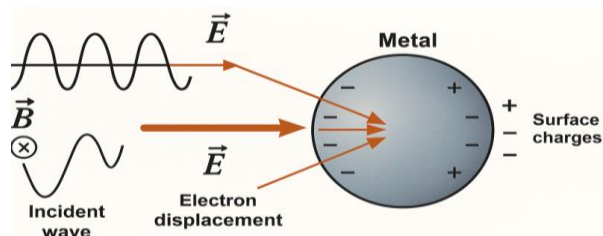


Figure 1. Schematic representation of electromagnetic wave interaction with a metallic nanoparticle showing surface plasmon resonance.

3.4.1. Theoretical Foundations of SPR

The spectral position of the plasmon resonance depends on particle size, shape, composition, and surrounding dielectric medium. Smaller spherical AuNPs exhibit resonance peaks in the visible region (~520 nm), while larger or elongated structures (e.g., nanorods) redshift into the near-infrared (NIR) range (650–900 nm), optimal for deep-tissue penetration [27–29].

Modern computational models, including the finite-difference time-domain (FDTD) and discrete dipole approximation (DDA), enable precise predictions of field enhancement and resonance modulation in hybrid and anisotropic nanostructures [30,31]. SPR-based biosensors and plasmonic nanoparticles are advancing diagnostics, cancer therapy, and nanoscale optical circuitry for quantum communication and optoelectronics [32].

3.4.2. Shape- and Structure-Dependent Plasmonics

Morphology plays a pivotal role in tuning the optical responses of AuNPs. Shape-engineering allows precise tailoring of resonance to the NIR "biological window," improving both optical absorption and penetration for clinical imaging and ablation (Table 1) [33–38].

3.4.3. Plasmonic Coupling and Electromagnetic Enhancement

When AuNPs approach nanoscale proximity, plasmonic coupling occurs, producing intense near-field enhancement and redshifted spectra—a core mechanism in surface-enhanced Raman scattering (SERS) and photoacoustic imaging [39–41]. Controlled aggregation or anisotropic spacing enables single-molecule detection and improved sensitivity.

3.4.4. Translational Perspective

The application of SPR-based AuNPs extends beyond physics to clinical diagnostics and therapy. Their resonance-driven heating allows minimally invasive tumor ablation, while their photostability supports real-time intraoperative imaging. However, clinical translation requires reproducible synthesis, standardized optical calibration, and scalable GMP manufacturing. Recent AI-driven design models are helping predict resonance shifts and optimize photothermal conversion efficiency, accelerating the bench-to-bedside transition [42–45].

3.5. Imaging and Diagnostic Applications of AuNPs

Gold nanoparticles have become essential in cancer imaging due to their LSPR-induced light scattering, X-ray absorption, and photoacoustic conversion abilities. Their surface can be engineered for multimodal imaging, integrating two or more contrast modalities within a single platform [46].

Table 1: Comparative Attributes of Gold Nanoparticle Morphologies in Cancer Therapy.

Type of AuNP	Shape/Morphology	Tunable Optical Range	Key Applications	Clinical Relevance
Gold nanospheres	Spherical	Visible–NIR	Imaging, drug delivery, SERS	Biosensing and in vivo contrast enhancement
Gold nanorods	Rod-shaped	650–900 nm	PTT, deep-tissue imaging	Evaluated in breast/prostate cancer PTT
Gold nanoshells	Silica core + Au shell	Visible–NIR	CT, PTT	FDA Phase II for prostate tumor ablation
Gold nanocages	Hollow/porous	~800 nm	Drug delivery, molecular imaging	Preclinical pancreatic & HER2 ⁺ breast cancers
Gold nanostars	Branched/star-like	Broad NIR	SERS, PTT	Image-guided multiplex therapy
Hybrid AuNPs	Core–shell/composite	Design-dependent	Theranostics, optoelectronics	Emerging smart nanocarriers

Table 2: Comparative Overview of AuNP-Assisted Imaging Modalities.

Imaging Modality	AuNP Type	Key Features	Application
CT	PEGylated nanospheres	High X-ray contrast	Tumor boundary visualization [48]
MRI	Magnetically labeled AuNPs	Dual contrast (T1/T2) with AuNP stability	Soft tissue imaging [59]
OCT	Nanoshells	Enhanced scattering	Subdermal tumor assessment [45]
PAI	Nanorods/Nanocages	Strong NIR absorption	Deep-tissue tumor detection [46, 70]
SERS	Aggregated nanostars	Ultrafast, label-free signal enhancement	Multiplexed biomarker detection [41]
Dark-Field Microscopy	Antibody-functionalized AuNPs	High scattering for surface visualization	Cell-level cancer detection [7]

The AuNP-assisted imaging modalities are described in Table 2 and emphasized [47].

3.5.1. Advantages of AuNP-Based Imaging [48]

AuNPs offer several intrinsic imaging advantages, making them highly suitable for biomedical visualization. Their spectral tunability, achieved by adjusting the surface plasmon resonance peak, enables optimization for deeper tissue imaging, particularly within the near-infrared (NIR) window, where light penetration is maximal. In contrast to conventional fluorescent dyes, AuNPs exhibit remarkable photostability and resist photobleaching, enabling reliable longitudinal imaging. Their surfaces can be readily bioconjugated to targeting molecules, such as antibodies and peptides, enabling receptor-specific localization and improving imaging precision. Moreover, AuNPs support true multimodality, integrating complementary imaging and therapeutic platforms including CT, SERS, and photothermal therapy (PTT). This high bioconjugation capability further allows the attachment of ligands for receptor-directed imaging, as illustrated in Figure 2, facilitating highly selective visualization of tumor tissues.

3.5.2. Translational Integration

Recent clinical initiatives (e.g., AuroLase® Therapy, Nanospectra Biosciences) have demonstrated the safety and feasibility of gold-silica nanoshells for prostate and head–neck cancers. Real-time tumor delineation using Raman-enhanced imaging is also under Phase I evaluation for intraoperative use.

To ensure regulatory success, toxicokinetic profiling, immunogenicity studies, and long-term clearance analysis are mandated under FDA and EMA guidelines. Integration of machine-learning image reconstruction with quantum-enhanced photonics is anticipated to refine sensitivity and diagnostic precision.

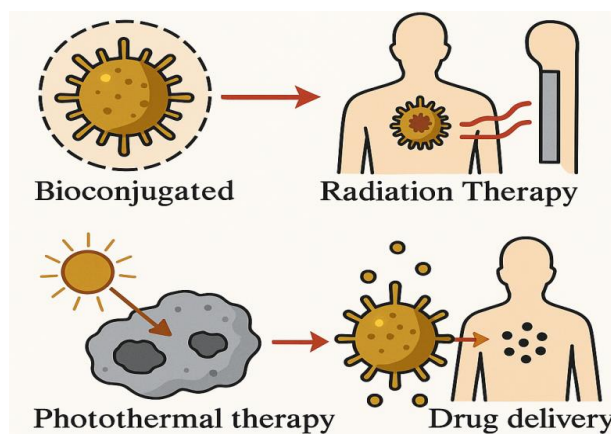


Figure 2. Biomedical imaging and theranostic applications of gold nanoparticles.

3.6. Advanced Theranostic Insights and Clinical Integration

Gold nanoparticles (AuNPs) have evolved from passive imaging enhancers into multifunctional theranostic nanoplatforms that unify diagnosis and therapy, enabling real-time monitoring of treatment outcomes. Their optical tunability, surface engineering flexibility, and biocompatibility support applications in photothermal therapy (PTT), targeted delivery, and molecular imaging (Figures 2 and 3).

Clinical translation of AuNPs has advanced steadily from animal models to human evaluations. PEGylated gold nanorods have demonstrated efficient, localized hyperthermia in early-phase human studies of breast, prostate, and colon cancers [49]. Similarly, nanoshell-based therapy has progressed to FDA-monitored Phase II trials, where gold–silica nanoshells (AuroLase®, Nanospectra Biosciences) achieved precise tumor ablation with minimal collateral damage [50].

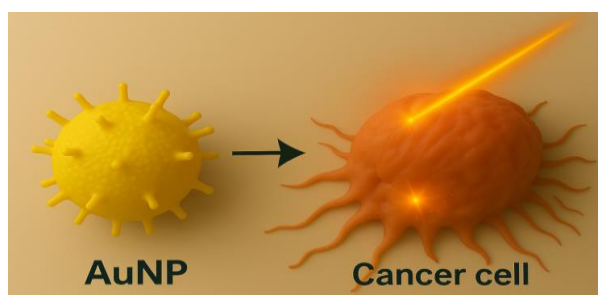


Figure 3. Photothermal-mediated cancer cell ablation using AuNPs.

In addition to thermal modalities, AuNPs offer significant advantages in radiation therapy. Their high atomic number enables enhanced photon absorption, improving local dose deposition while reducing injury to surrounding healthy tissues [51]. Targeted delivery platforms have also benefited from advances in ligand functionalization and stealth coatings, which collectively improve tumor accumulation and extend systemic half-life [52].

Regulatory progress continues to support their translational trajectory, with multiple AuNP conjugates currently advancing through IND-regulated Phase I/II safety studies. These milestones collectively indicate a clear movement toward clinical feasibility and the emergence of AuNP-based nanomedicines as viable theranostic tools [53].

3.6.1 Next-Generation and Emerging Architectures

Gold nanoparticles (AuNPs) have evolved from passive imaging enhancers into multifunctional theranostic nanopatforms that integrate diagnosis and therapy, enabling real-time monitoring of treatment responses. Their optical tunability, flexible surface engineering, and inherent biocompatibility support a wide range of biomedical applications, including photothermal therapy (PTT), targeted drug delivery, and molecular imaging (Figures 2 and 3).

Clinical translation of AuNPs has progressed steadily from animal studies into human evaluations. PEGylated gold nanorods have shown effective and localized hyperthermia in early-phase clinical investigations involving breast, prostate, and colon cancers [49]. Likewise, nanoshell-based therapeutics have advanced to FDA-monitored Phase II trials, where gold–silica nanoshells (AuroLase®, Nanospectra Biosciences) achieved precise tumor ablation with minimal collateral damage [50].

Beyond photothermal approaches, AuNPs also enhance radiotherapy outcomes. Due to their high atomic number, they increase photon absorption and improve local radiation dose deposition while reducing injury to adjacent normal tissues [51]. Advances in ligand functionalization and stealth coatings have further strengthened targeted delivery strategies by enhancing tumor accumulation and extending systemic circulation time [52].

Regulatory developments continue to reflect the maturing clinical landscape of AuNP-based technologies. Several AuNP conjugates are currently undergoing IND-regulated Phase I/II safety evaluations, marking a significant transition toward clinical feasibility and supporting their emergence as versatile and effective theranostic tools [53].

3.6.2 Translational Challenges and Practical Solutions

By coupling nanodesign with advanced AI-driven characterization and predictive toxicology, researchers can bridge the gap between bench innovation and regulatory acceptance (Table 3) [59-61].

3.7. Drug Delivery Platforms Using Gold Nanoparticles

Gold nanoparticles offer a modular framework for precise, controllable drug delivery. Their nanoscale dimensions, surface functionality, and optical responsiveness facilitate targeted payload release, improving therapeutic index while minimizing systemic exposure [62].

Table 3: Comprehensive details of translational challenges and emerging solutions.

Key Challenge	Current Barriers	Emerging Solutions
Immune Clearance & RES Uptake	Rapid opsonization and macrophage sequestration reduce circulation time.	Zwitterionic coatings, biomimetic cell-membrane cloaking, and polysaccharide shells significantly decrease immune recognition.
Biodistribution & Tumor Penetration	Heterogeneous vasculature and dense extracellular matrix hinder uniform delivery.	3-D organoid tumor models and microfluidic "tumor-on-chip" systems enable realistic evaluation and optimization of penetration profiles.
Scalability & Reproducibility	Difficulties in achieving consistent particle size and ligand density under GMP conditions.	Microreactor-based synthesis and machine-learning QC analytics improve batch uniformity and process control.
Regulatory Standardization	Fragmented global guidelines; lack of long-term toxicity data.	ISO/TR 10993-22 (2021) and FDA nanotechnology guidance now provide clearer pathways for nanomedicine evaluation; early regulatory consultation is recommended.

3.7.1. Mechanisms of Drug Loading and Release

AuNPs incorporate drugs through multiple physicochemical mechanisms:

Covalent Conjugation: Drugs tethered via amide, thiol, or ester bonds ensure stability and can be released through enzymatic or pH triggers; **Electrostatic Adsorption:** Ionic interactions enable reversible attachment of charged molecules.

Hydrophobic & π - π Stacking: Facilitates encapsulation of poorly soluble chemotherapeutics.

pH-Responsive Linkages: Hydrazone or imine bonds cleave selectively in acidic tumor environments, enabling site-specific release [63–65].

These interactions can be combined to achieve dual-stage or sequential release profiles.

3.7.2. Surface Engineering for Precision Targeting

Surface modifications modulate biocompatibility, targeting, and pharmacokinetics (Table 4).

3.7.3. Emerging and Dual-Function Platforms

Emerging and dual-function platforms continue to expand the versatility of gold-based nanotechnology. Monodisperse AuNPs improve reproducibility and pharmacokinetic predictability [66]. Dual-function theranostic systems integrate imaging agents with chemotherapeutic compounds, allowing real-time tracking of treatment responses. AI-optimized loading ratios, supported by neural network-based prediction models, help determine optimal drug-to-nanoparticle configurations while reducing the need for extensive experimental iterations [69].

Additionally, neutron-activation imaging offers a minimally invasive approach for in vivo mapping of drug distribution [70].

3.7.4 Clinical Translation Barriers and Prospects

Despite laboratory success, scaling, stability, and regulatory complexities impede rapid clinical adoption. Manufacturing challenges persist, as GMP-grade synthesis requires strict control over particle size with less than 10% variation, although continuous-flow

microreactors are helping address this limitation. Stability remains another critical factor, with long-term colloidal stability and prevention of aggregation during storage necessitating optimized formulations; lyophilization with cryoprotectants such as trehalose has shown promise in maintaining particle integrity. Regulatory evaluation also presents challenges, as drug-nanoparticle conjugates are classified as combination products, requiring dual-path approval encompassing both device and drug components.

Safety and clearance profiles further complicate translation, with biodistribution studies demonstrating slow hepatic clearance of larger AuNPs; the development of biodegradable or ultrasmall (<5 nm) constructs may help mitigate risks associated with long-term accumulation. Collectively, these insights underline that the future of AuNP-mediated drug delivery lies in rational hybridization, AI-assisted process control, and early regulatory engagement.

4. Conclusion

Gold nanoparticles (AuNPs) represent one of the most mature and versatile nanotechnological platforms bridging diagnostics and therapeutics in oncology. Their localized surface plasmon resonance (LSPR), tunable morphology, and modifiable surface chemistry enable a unified approach to imaging, targeted drug delivery, and photothermal therapy. This review consolidates physicochemical principles with translational advancements, emphasizing regulatory milestones, manufacturing challenges, and the integration of AI-assisted nanodesign and hybrid theranostic architectures. Although issues such as immune clearance, biodistribution control, and large-scale reproducibility persist, emerging solutions—including zwitterionic coatings, organoid modeling, and microreactor synthesis—are rapidly narrowing the gap between experimental promise and clinical reality. Looking forward, AuNPs are poised to contribute to personalized and adaptive oncology, where real-time diagnostic feedback and intelligent therapy converge within a single nanosystem.

Table 4: Surface engineered strategies, mechanisms, and targets of AuNPs.

Mechanism	Trigger / Control	Advantages
PEGylation	Passive stealth	Increases circulation, minimizes immune uptake [67]
Ligand Functionalization	Receptor-specific	Improves uptake via receptor-mediated endocytosis [68]
Natural Polymer Coating	Environmentally responsive	Enhances mucoadhesion and biocompatibility [19]
Biomimetic Cloaking	Self-recognition	Camouflages AuNPs from RES; prolongs half-life [69]

Achieving this vision will depend on multidisciplinary collaboration among materials scientists, pharmacologists, clinicians, and regulatory experts to ensure safe, standardized, and ethically compliant translation of gold-based nanotheranostics.

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Conflict of interest

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