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Review article

Gold Nanoclusters in Cancer Photothermal Therapy: Mechanisms, Theranostic Applications, and Clinical Translation Over the Last Decade

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ABSTRACT

This last decade has seen the rise of gold nanoclusters (AuNCs) as a new, revolutionary class of photothermal agents for cancer therapy. The AuNCs (<2 nm) have a high surface area-to-volume ratio and exhibit efficient electron-to-phonon coupling. AuNCs possess favorable renal clearance properties due to their extremely small hydrodynamic diameters. This review article provides a structured summary of advancements made in the areas of AuNC synthesis, ligand-shell engineering, environmentally friendly fabrication methodologies, and large-scale manufacturing methods during the years of 2015-2025. It also focuses on the role atomic precision and surface chemistry play in the photothermal performance, biodistribution, protein corona formation, and nano–bio interactions of AuNCs; in addition, we highlight the mechanistic details associated with non-radiative relaxation pathways, energy gap modulation, and optimizing photothermal conversion efficiency. It also provides proof of concept that AuNCs are suitable as multifunctional theranostic platforms that integrate both fluorescence and photoacoustic imaging into combination strategies of chemo-photothermal and immune-photothermal therapy, with immune checkpoint blockade to elicit a systemic immune response against tumor cells. The study demonstrates rapid renal elimination and low accumulation of AuNCs over long-term duration, while addressing some of the historical concerns associated with traditional inorganic nanoparticles. Finally, the translational barriers facing AuNCs were highlighted, including regulatory standardization, reproducibility, and cost-effectiveness. The future with artificial intelligence (AI) will support AuNCs synthesis Thus, AuNC-based photothermal therapy is an exciting new advancement in nanomedicine and is predicted to be on a fast track for use in precision oncology from the lab through to integration into clinical practice by 2030.

Keywords: Gold nanoclusters (AuNCs), Nanotheranostics, Photothermal conversion efficiency, Photothermal therapy, Precision oncology

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1. INTRODUCTION

Cancer remains a major worldwide challenge for modern medicine. Current treatment modalities, chemotherapy and radiotherapy, are limited by their systemic toxicity and lack of sufficient efficacy. By the mid-2020s, the overall trend in the field of oncology is moving from “one-size-fits-all” to “precision medicine.” Photothermal Therapy (PTT) is leading the way as a minimally invasive form of heat therapy that generates localized via the use of near-infrared (NIR) light to melt malignant tissue while preserving healthy tissue [1,2,3]. Selectively, over the past 10 years, Gold Nanoclusters (AuNC) have emerged as a promising photothermal agent, given their ultra-small size relative to other gold-based photothermal agents such as gold nano-rods and nano-shells. AuNCs are composed of a few hundred atoms and have core dimensions of <2 nm. The transition from larger gold structures to AuNCs results

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in a transition from continuous energy bands to discrete electronic levels; hence, AuNCs behave similarly to molecules due to their high photoluminescence, high photostability, and high surface-to-volume ratio [4].

The last 10 years have witnessed a transformative leap in understanding AuNCs. Previous research focused on synthesis and basic biocompatibility. However, modern breakthroughs have integrated this progress into multimodal theranostic platforms. By leveraging the spontaneous fluorescence of AuNCs for image-guided surgery, clinicians can now visualize and treat tumors simultaneously, while benefiting from their high photothermal conversion efficiency. In addition, the small size of AuNCs allows them to target the areas of cancer tissue that are the most susceptible to treatment due to their ability to pass through the renal filtration threshold, and thus, be eliminated from the body via the kidneys; thereby, alleviating concerns over possible heavy metal toxicity of these nanoparticles [5, 6]. Continuing to look ahead toward creating a new era of intelligent cancer treatment with AuNCs combined with immunotherapy and artificial intelligence-based dosing/administration regimens, this review will provide an overview of the key milestones achieved over the past 10 years, the current status of clinical translations of cancer treatment using AuNCs, and a path forward for future generations of gold nanotherapeutics

2. SYNTHESIS AND SURFACE ENGINEERING: THE LAST DECADE

The application of gold nanoclusters (AuNCs), in clinical settings, involves manipulating their atomic composition and surface chemistry through atomic engineering techniques over the past decade from the use of traditional colloidal chemistry. In this branch of research, the quantity of nanoparticle gold atoms is altered, along with the ligand that stabilizes them, to optimize their performance as a means to convert light energy into heat while remaining biocompatible or safe for use on human subjects. [7,8]

2.1. Top-Down vs. Bottom-Up Synthesis

The preparation of AuNCs (<2 nm) requires strategies that prevent uncontrolled growth into larger nanoparticles. Bottom-up nanoparticle synthesis typically starts with the reduction of metallic precursor ions to form zero-valent atoms while, the top-down represent the inverse story [9] (Table 1).

Bottom-Up Synthesis: This is the normal method of obtaining gold nanoparticles, wherein the chemical reduction of gold precursors (Au+3 or Au+) is done in solutions containing stabilizer compounds. More recently, there has been further development of direct in situ growth of nanoparticle nanostructures on supporting materials via prior growth of a gold film, which will permit for rapid formation of small gold nanoparticle nanostructure complexes onto virtually any support [10].

Top-Down Design: In this way, smaller nanostructures are formed from larger ones, such as big materials or films, through chemical etching [10]. A particular methodology called BUTTONS (Bottom-Up Then Top-Down Synthesis) has applied. In this technology, larger gold nanostructures are first synthesized and then etched to produce nanoparticles [10].

2.2. Ligand Shell Engineering: From Thiolates to Proteins

The ligand shell is the interface between the inorganic gold core and the biological space, producing stability and pharmacokinetics [7].

Thiolate Protection: Thiol ligands play a central role in stabilizing the cores of gold, and preventing aggregation by passivating the surface [11]. Glutathione (GSH) is a typical hydrophilic ligand used to generate a typical number of clusters (e.g., Au_{18}, Au_{25}, and Au_{39}) [12]. Protein Templating: Protein-enveloped systems, like using albumin or lactoferrin, which provide high stability and function [13]. These proteinaceous envelopes protect the luminescent gold core and affect macromolecular dynamics to improve bio-targeting of AuNCs [11]. Ligand Exchange and Size-Focusing: This method substitutes original thiols with alternative ligands to influence thermodynamic stability or selectively dissolve unstable aggregates, enhancing the synthesis of atomically clusters [11].

Table 1. Comparison of bottom-up and top-down nanomaterial synthesis approaches, highlighting differences in mechanism, control, scalability, and representative methods.

Feature	Bottom-Up (Chemical Reduction)	Top-Down (Etching/Ablation)
Primary Mechanism	Assembly from ions/atoms [9].	Fragmentation of bulk materials [10].
Control	High precision in surface chemistry [10].	Stronger control over particle position [10].
Scalability	High in colloidal suspension [10].	Limited by clean-room requirements [10].
Method Examples	Seeded growth, Chemical reduction	Chemical etching, E-beam lithography

2.3. Green Chemistry: Eco-Friendly Ways to AuNC synthesis

This method of using biological agents (plants/microbes) instead of a physicochemical-based approach to reduce environmental impact has gained popularity because they are considered environmentally safe [14, 7].

Phyto-synthesis: Herbally based extract contain compounds called secondary metabolites (polyphenols, flavonoids) which possess both reducing and blocking capabilities [14]. Some commonly used plant materials containing these types of compounds are Clerodendrum trichotomum leaf extracts or mandarin peel extract, both yielding spherical nanoparticle products that can be utilized in anti-cancer therapy [15].

Eco-Friendly Advantages: There are several eco-friendly advantages to using this method, such as lower costs and energy efficiency when compared to traditional methods; because of avoiding toxic chemicals during preparation, healthy tissue damage from chemical agents is minimized [14].

2.4. Stability and Scaling: Challenges in Industrial Production

Transitioning from lab-scale synthesis to industrial manufacturing includes complex problems in scalability and reproducibility [16].

Quality Control: Important parameters such as size distribution, targetability, and functionality must be reproducible to ensure safety and efficacy [16]. There is a lack of matched guidelines for nanoformulations, which creates problems in obtaining final approval to manufacture nanoparticles [16].

Batch-to-Batch Consistency: Classical production almost suffers from poor reproducibility and limited control in the cluster initialization when the scaled up [16].

Up-to-date Solutions: Technologies such as microfluidics and supercritical fluid methods **a**re being used to solve the defects relating to scalability challenges and maintain critical quality attributes [16].

3. PHYSICOCHEMICAL PROPERTIES DRIVING PTT EFFICIENCY

The effectiveness of gold nanoclusters (AuNCs) in PTT is managed by a central departure from the physics of larger plasmonic nanoparticles. While gold nanorods and nanoshells rely on Localized Surface Plasmon Resonance (LSPR), a collective oscillation of conduction band electrons, AuNCs (<2 nm) reside in the quantum regime. Understanding the electronic transition rules and relaxation pathways in this regime is important for increasing the photothermal conversion impact [17].

3.1. Electronic Structure and Molecular-Like Transitions

An example of AuNCs is when the size of the core drops below the size of the Fermi wavelength (≈2nm), they lose the ability to support a continuous density of states and the density of states collapses into energy level structure. As a result, AuNCs possess molecular character that can be defined by HOMO-LUMO (Highest Occupied Molecular Orbital to Lowest Unoccupied Molecular Orbital) transitions rather than by LSPR [18]. Excitation of plasma electrons from their ground states (S0) into higher excited singlet states (Sn) occurs upon photon absorption by AuNCs. The relative rate of the two mechanisms of non-radiative and radiative transitions near the "ground state" and "higher excited states" respectively dictate the pathways to and the balance of the resultant fluorescence to heat [19].

Non-Radiative Relaxation: The objective for proper PTT is to maximize the process of non-radiative relaxation through the use of direct electron-phonon interactions. The non-radiative relaxation occurs first through the transfer of energy from the electronic excitation to the thermal (phonon) energy of the crystal lattice (phonons), then to the thermal energy of the solvent by the process of phonon-phonon collisions [20].

"**Gap**" **Law**: The energy gap law states that as the energy gap between adjacent energy states decreases, the rate of non-radiative relaxation increases. This is a major design consideration since modifying AuNCs to have various defect states and creating specific surface ligand interactions on the surface of the AuNCs will promote dissipation of non-radiative thermal energy at a higher rate than fluorescence [21].

3.2. Optimizing Photothermal Conversion Efficiency (η)

The photothermal conversion efficiency, denoted η the metric of merit for any PTT agent. It represents the fraction of absorbed light energy converted into heat. It is quantitatively determined using the energy balance of the system, often derived from the Roper model:

$\eta = hS(T_{max}-T_{surr})-Q_{dis} / I(1-10^{-A\lambda})$

Where:

h is the heat transfer coefficient.
S is the surface area of the container.
T_{max} is the equilibrium temperature under irradiation.
T_{surr} is the ambient temperature.
Q_{dis} represents heat dissipated from the solvent/container.
I is the laser power density.
Aλ is the absorbance of the AuNCs at the excitation wavelength.

Current studies indicate that AuNCs can complete η values rivaling or exceeding those of traditional dyes and plasmonic particles due to their low scattering cross-sections (which lower light loss) and efficient electron-phonon relaxation (Table 2).

Table 2. Comparative photothermal efficiencies η of AuNCs vs. standard agents

Nanomaterial Type	Absorption Peak (nm)	η (%)	Mechanism of Enhancement	Ref
Indocyanine Green (ICG)	780	15 - 25%	Standard organic dye (control)	[22]
Au Nanorods (AuNR)	808	22 - 50%	LSPR (Shape dependent)	[23]
BSA-AuNCs	650 - 700	60 - 65%	Protein-constrained vibration	[24]
GSH-AuNCs (Aggregated)	808	30 - 45%	Aggregation-Induced Heating	[25]

4. BIOLOGICAL INTERPLAY AND THE NANO-BIO INTERFACE

The line between synthetic nanomaterials and biological systems, this determines the ultimate clinical success of PTT agents. For AuNCs, their ultra-small size (<2 nm core) and high surface-to-volume ratio create a determined biological interplay compared to traditional, larger plasmonic nanoparticles.

4.1. Mechanism of Cellular Uptake: Endocytosis and Beyond

Nanomaterials enter the cell through energy-dependent vesicular transport processes (e.g., through clathrin-mediated endocytosis) when contacting the plasma membrane [26]. For example, functionalized gold nanoparticles use both size and architecture to determine the endocytic pathway for internalization via receptor-mediated mechanisms [27]. A significant difference between traditional uptake mechanisms and AuNCs is the scale of these materials, as they are less than one nanometre in diameter. Although AuNCs (e.g., BSA-capped AuNCs) take on endocytic pathways similar to their precursor protein, smaller AuNCs with thinner capping layers can have atypical behaviours, including the ability to avoid classical endosomal entrapment. As a result, they may be found homogeneously throughout the cytoplasm and are capable of penetrating the nucleus [28]. The ability of AuNCs to target intranuclear structures makes them an effective tool for PTT.

4.2. The Protein Corona: How Biological Fluids Alter AuNC Individuality

When AuNCs are administered by intravenous route, they are immediately introduced into a highly complex biological fluid rich in proteins. In this situation, the spontaneous adsorption of biomolecules onto the surface of AuNCs occurs, which ultimately leads to the formation of a "protein corona" that alters the physicochemical properties, cellular interactions and ultimately therapeutic effects of the nanomaterial [29]. The formation of both a hard and soft corona may totally mask the synthetic targeting ligands, thereby preventing active targeting, which is necessary for the precision therapy to be effective. This issue has prompted new surface engineering developments to be developed around the use of stealth chemistries. Research has shown that capping AuNCs with specially designed dihydrolipoic acid (DHLA)-based ligands that have been modified with polyethylene glycol (PEG) or zwitterionic motifs significantly reduces the likelihood of crown protein formation by thermodynamically disfavoring non-specific protein adsorption [30]. Additionally, cutting-edge techniques are being utilized to develop dynamic control over this interface using supramolecular chemistry. For example, host-guest interactions can be used to disrupt the presence of the protein corona in

specific microenvironments. As a result, researchers can successfully and accurately control the cellular uptake of these nanoparticles in the desired target tissues [31].

4.3. Biodistribution and Renal Clearance: Solving the Bioaccumulation Puzzle

The most important barrier to the clinical translation of inorganic nanomaterials is bioaccumulation for a long time. Old gold nanoparticles (10–100 nm) are rapidly seized by the mononuclear phagocyte system, resulting in retention in the liver and spleen for long time. AuNCs solve this bioaccumulation puzzle through their ultra-small dimensions. The kidneys have a glomerular filtration barrier that acts as a very strict size exclusion filter and has an approximate hydrodynamic diameter threshold of about 5.8 nm. Since the footprint (size) of tightly capped gold nanoparticles (such as glutathione capped flakes) is less than this threshold, they can be cleared from the kidney quickly and easily, which allows for rapid elimination of the flakes in urine. This ability to rapidly eliminate the flakes reduces the risk of long-term heavy metal toxicity as well as providing a favourable pharmacokinetic profile for systemic clinical application [32, 33].

5. THERAPEUTIC SYNERGIES: MORE THAN JUST HEAT

The primary mechanism of PTT is raising the local tissue temperature (e.g., > 42°C) to cause cellular necrosis or apoptosis. Heat as a single way of therapy is rarely sufficient to remove heterogeneous solid tumors completely. The power of ultra-small AuNCs clinically is in their ability to service as multifunctional hubs. By leveraging PTT characterizations, it can be matched with advanced diagnostics, immunology, and pharmacology to achieve synergistic outcomes [34].

5.1. Theranostics: Integrating Fluorescence and Photoacoustic Imaging

The paradigm of theranostics, the integration of therapeutics and diagnostics on a single platform, is ideally represented by AuNCs. Because of their ultra-small size (<2 nm), the continuous conduction band of gold is quantized into discrete energy levels. This quantum confinement results in natural luminescence and strong electron-phonon coupling, making them outstanding dual-modal contrast agents [35].

Fluorescence Imaging: In contrast to bulk plasmonic gold nanoparticles (which cause fluorescence quenching), atomically precise AuNCs exhibit unique, controllable fluorescence properties. Recent breakthroughs have extended the fluorescence signal into the second near-infrared window (1000-1700 nm) of the NIR-II spectrum. NIR-II fluorescence imaging provides unprecedented spatial resolution and penetration depth because of minimized photon scattering and tissue autofluorescence, enabling real-time visualization of AuNC biodistribution and accurate surgical demarcation of tumor margins [36].

Photoacoustic Imaging (PAI): PAI finds an intermediate solution between the high contrast of optical imaging and the deep penetration of ultrasound waves. Upon the absorption of pulsed NIR laser radiation, AuNCs exhibit fast non-radiative relaxation, resulting in localized thermoelastic expansion, which can be detected as ultrasonic waves by transducers. Since the amplitude of PA signals is directly proportional to the efficiency of photothermal conversion, AuNCs provide a strong diagnostic signal, which can be used for non-invasive three-dimensional tumor mapping to determine the timing and dosage of the therapeutic PTT laser pulse [37].

5.2. Immuno-PTT: Stimulate the Abscopal Effect via Hyperthermia

One of the major shifts have been seen lately in nanomedicine is the understanding that AuNC-mediated PTT can actually work like a tumor vaccine right where the tumor is. When thermal ablation is applied, it's not just about destroying cells; certain temperature settings can break them apart, triggering a whole series of immune reactions. This is what can be called Immunogenic Cell Death (ICD). It modified the tumor from being an immunologically cold place to a hot place, which is highly deal

Release of DAMPs: Hyperthermia induces the release of Tumor-Associated Antigens (TAAs) and Damage-Associated Molecular Patterns (DAMPs), such as calreticulin (CRT) present on the cell surface, and the production of ATP and HMGB1.

Dendritic Cell Activation: These signals employ and mature antigen-presenting cells, particularly dendritic cells (DCs), which engulf the TAAs and move to the draining lymph nodes.

The Abscopal Effect: It happens when dendritic cells (DCs) in lymph nodes present antigens released from thermal treatments to naive T-cells. This process prevents the widespread proliferation of cytotoxic CD8+ T lymphocytes. Once activated, these T-cells travel throughout the body, working to eliminate distant metastatic lesions that haven't been irradiated. This is what we call the abscopal effect. Recent research has highlighted that when you combine gold nanoclusters (AuNCs) with immunoadjuvants or use them alongside Immune Checkpoint Blockade (ICB) therapies, like anti-PD-1/PD-L1 antibodies, it significantly boosts T-cell infiltration. This combination also helps to overcome the immunosuppression often seen in tougher "cold" tumors.

5.3. Combination Therapy: AuNC-Mediated Chemo-Photothermal Systems

Multidrug Resistance (MDR) continues to be one of the main reasons that chemotherapy treatments fail. Chemo-photothermal combination therapy is a method of using the localized heat generated by gold nanoparticles (AuNCs) to make tumor cells more sensitive to the effects of chemotherapeutic agents, which allows them to have synergistic effects on each agent with an overall combination index of less than one. Mild hyperthermia can increase fluidity of the cell membranes of tumor cells (resulting in greater uptake of the drug into the cell) and temporarily down-regulate the expression of ATP-binding cassette (ABC) transporters that are involved in the efflux of the drug. In addition, AuNCs can serve as ideal structural scaffolds for the stimulus-responsive delivery of drugs to tumor cells:

Mesoporous Frameworks: An example of this type of scaffold is mesoporous magnetic gold "nanocluster" assemblies. The systems can be loaded with a drug such as doxorubicin (DOX) and the heat generated by the systems upon near-infrared (NIR) irradiation will disrupt the non-covalent interactions of the drug with the carrier, causing localized burst-release of the drug in the tumor microenvironment [39].

DNA-AuNC Composites: Advanced formulations utilize DNA tetrahedrons wrapped in gold nanomaterials to carry intercalated chemotherapy drugs. The heat generated by the gold core not only induces thermal ablation but also promotes a "proton sponge" effect, facilitating rapid lysosomal escape and ensuring the drug reaches the nucleus efficiently [40].

6. TOXICITY AND BIOCOMPATIBILITY ASSESSMENT

The clinical use of AuNCs is contingent upon their safety in order to use them in vivo. AuNCs have been shown to behave molecularly as opposed to the large particle or bulk gold nanoparticles, this has a major effect on how they will interact with cellular machinery.

6.1. *In Vitro* vs. *In Vivo* Toxicity: A Decade of Data

Data has progressed over time from simple cell-viability assays at the cellular level (in vitro) to using larger animal models (in vivo). Though gold is considered to be an inactive metal, other materials will be used to help stabilize AuNCs, and these ligands will determine whether or not the AuNCs are toxic.

***In Vitro* Findings:** Most experiments using MTTS or LDH have shown >90% cell viability when tested at concentrations of 500 µg/mL. If toxicity was observed in these cases, it was usually found to be due to reactive oxygen species (ROS) or from lysosomal membrane integrity loss as a result of a positively charged surface of the AuNCs (43).

***In Vivo* Findings**: Expected changes in health for rodents include no significant change in size/weight and no change in behaviour compared with control/untreated animals; however, stealth coatings will be necessary to prevent removal by the RES (44).

6.2. Long-term Safety Profiles and Metabolic Pathways

The renal elimination point is the holy grail of AuNCs. AuNCs, due to their size (~3 nm), are smaller than the glomerular filtration threshold (~6 nm), so they are excreted via urine rather than stored in the liver. Table 3 shows the key pharmacokinetic parameters and their clinical implications for AuNC-mediated photothermal therapy. The data highlights the relationship between ultra-small hydrodynamic diameters and efficient renal clearance, which minimizes systemic retention and off-target toxicity in reticuloendothelial organs.

Table 3: Safety and Metabolic Metrics of Gold Nanoclusters (AuNCs) in Photothermal Therapy (PTT) Applications (2016–2026).

Feature	Observation (2016–2026)	Impact on PTT	Ref
Size/Hydrodynamic Diameter	Typically, <5 nm	Enables rapid renal excretion.	43
Biodistribution	Primary accumulation in the kidneys/Tumor	Low off-target toxicity in Liver/Spleen.	44
Half-life (t1/2)	2–6 hours (ligand dependent)	Sufficient time for PTT activation post-injection.	45
Clearance Pathway	Primarily Renal (Urine)	Minimizes long-term "Gold-storage" syndrome.	46

Fig. 1 shows a diagram of the metabolic pathway and biocompatibility of Gold Nanoclusters (AuNCs). (A) Intravenous injection and protein corona formation: Schematic illustrating the administration of AuNCs into the bloodstream. Upon entry, the nanoclusters interact with serum proteins to form a "protein corona," which modulates their biological identity and subsequent distribution. (B) Size-dependent glomerular filtration in the kidney: Renal clearance of AuNCs is governed by their hydrodynamic diameter. Small nanoclusters (< 6 nm) pass through the glomerular filtration barrier and are excreted via urine. In contrast, larger aggregates (> 6 nm) are not filtered and remain in the systemic circulation or are sequestered by the reticuloendothelial system (RES). (C) Comparative histology of major organs: Representative H&E-stained histological sections of the heart, liver, spleen, lung, and kidney obtained 30 days post-photothermal therapy (PTT). The lack of morphological changes or inflammatory cell infiltration across all major organs indicates the long-term biosafety and minimal systemic toxicity of the AuNCs.

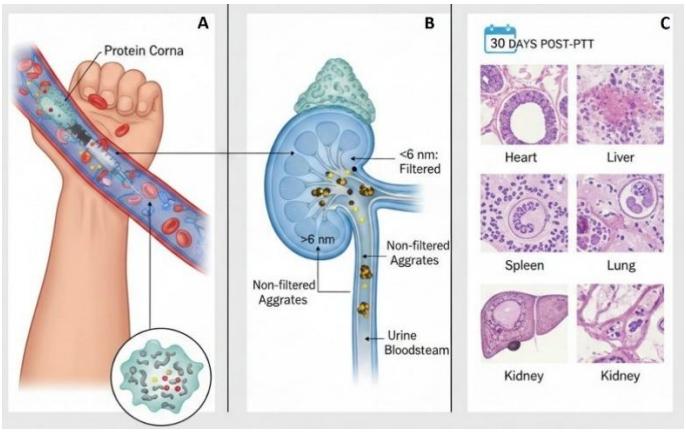

Fig.1. Schematic representation of the metabolic pathway and biocompatibility of Gold Nanoclusters (AuNCs). (A) Intravenous injection and protein corona formation, (B) Size-dependent glomerular filtration in the kidney, (C) Comparative histology of major organs.

6.3. Important Metabolic Findings from 2016-2026

1. Hepatobiliary vs Renal: Small GSH-capped AuNCs have over 70% renal clearance within 4 hours of administration, so they do not cause long-term hepatic burden [45].
2. Protein Corona: Upon entering the circulation, AuNCs attract plasma proteins to form a corona, which determines the metabolic fate and organ distribution of AuNCs [45].
3. Genotoxicity: Long-term studies (10 years) of AuNCs dosed at a therapeutic level for PTT show no evidence of significant DNA fragmentation or chromosomal damage [46].

7. BARRIERS TO CLINICAL TRANSLATION

The preclinical efficacy of AuNCs as PTT agents has been established for nearly 10 years, yet significant bench-to-bedside barriers still exist. These barriers fall into three categories: regulatory, technical, and economic.

7.1. Regulatory Hurdles and FDA/EMA Standards

Currently, nanomedicines/therapeutics undergo evaluation by institutional authorities such as the U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA) under existing pharmaceutical and biological guidelines [47]. However, AuNCs pose unique challenges for regulators since their behaviour is driven by nanoscale-specific properties—like size-dependent biodistribution and surface interactions—rather than traditional regulatory frameworks [48].

Case-by-Case Evaluation: Since there are no harmonized nanospecific regulations, regulators tend to evaluate products on a case-by-case basis which can produce unpredictable approval timelines [48].

Safety Thresholds: Before transitioning to clinical development, AuNCs need to have demonstrated sufficient biocompatibility and also effective clearance through the kidneys (generally less than 6

nm) to prevent long-term accumulation in organs belonging to the mononuclear phagocyte system (e.g., liver, spleen) [49].

7.2. Reproducibility and Batch-to-Batch Consistency

A key technical issue inhibiting AuNCs manufacturing at a large scale while maintaining **atomic precision**.

Synthesis Sensitivity: Classic wet-chemical reduction techniques typically experience high levels of variability due to broad sensitivity of reaction conditions such as temperature and mixture agitation speed.

Continuous Flow Approaches: To address inter-batch variance, we are seeing the transition in this field to use of microfluidic and millifluidic reactors. These systems provide both precision control over the timing of the reaction and superior heat transfer which are critical for enabling consistent size distributions and surface characteristics of nanoparticles produced in mass quantities [50].

Green Synthesis Challenges: While "green" (eco-friendly) synthesis is becoming increasingly utilized to enhance biocompatibility, the intrinsic variability of biological reactants is a major obstacle to standardizing nanoparticle production [51].

7.3. Cost-Benefit Analysis vs. Conventional Therapies

To gain acceptance for expanded use of AuNCs in photothermal therapy, there needs to be an established advantage over traditional procedures (e.g., surgical options, chemotherapeutics, radiation). Non-invasive types of AuNC-based therapies will likely lead to fewer infections due to clinical intervention precautions and avoid lasting negative results from physical or physiological trauma associated with any of the above standard of care techniques [52]. The cost of researching and developing the necessary AuNC materials to find the right size/shape/chemical composition for a specific treatment is currently prohibitive leading to higher costs than would be found for low-cost generic chemotherapeutics (Table 4) [53].

Table 4. Comparative Cost-Benefit Analysis of AuNC-Based Photothermal Therapy Versus Conventional Cancer Treatments

Factor	Conventional Therapy (e.g., Surgery/Chemo)	AuNC-Mediated PTT
Invasiveness	High (Surgical excision)	Low (Non-invasive laser irradiation)
Selectivity	Low (Systemic toxicity in chemo)	High (Localized thermal ablation)
Capital Cost	Established hospital infrastructure	High (Laser equipment + nano-agent)
Patient Recovery	Long (Surgical healing/Chemo fatigue)	Rapid (Minimal off-target damage)

8. FUTURE HORIZONS AND FINAL REMARKS

Gold nanocluster (AuNC) research will change from an experiment for trial-and-error basis into a data and computation based predictive science after 2025. The use of Artificial Intelligence (AI) and precision diagnosis represent the Third Wave of nanomedicine.

8.1. AI-Driven Optimization of Nanocluster Geometry

The coming 10 years will be defined by **Machine Learning (ML)** and **AI** in the design of atomically precise clusters. Traditionally, identifying the optimal Au_nL_m (where n is the atom count and L is the ligand) was a slow, empirical process.

Predictive Modelling: An example would be using artificial neural networks to estimate Photothermal Conversion Efficiency (PCE) and kidney clearance rates based solely upon the geometric symmetry and electronic structure of a nanocluster [54].

Autonomous Synthesis: The use of self-driving laboratories (comprising both microfluidic reactors and AI feedback loops) is starting to allow for the production of AuNCs with an almost perfect batch-to-batch reproducibility, thereby addressing the reproducibility crisis [55].

8.2. Personalized Nanomedicine: Patient-Specific PTT

The future of PTT is about to change dramatically with a focus on Theranostic Personalization. Gone are the days of a one-size-fits-all approach to AuNCs. Instead, future therapies will incorporate individualized responses based on each patient's physiology.

Companion Diagnostics: Before being treated, patients will have a nanotracer scan done that will allow for mapping their glomerular filtration rate (GFR) to help identify the best possible AuNC dosing for a patient's ability to clear from their body. This will help further reduce any risk of long-term retention of AuNCs at even very low levels [56].

Adaptive Dosimetry: Real-time thermal imaging combined with the PTT laser will provide the ability to adaptively adjust the laser power to ensure that the tumor attains the desired ablation temperature (>42°C) while protecting healthy neighboring tissue in difficult anatomical locations [57].

8.3. Summary and Final Outlook for 2030

By 2030, AuNC-mediated PTT is anticipated to move from an experimental therapy to a routine neoadjuvant standard of care. In combination with immunostimulatory therapy (photoimmunotherapy), AuNC-mediated PTT will not only be effective for ablation of primary tumors but will also produce a systemic abscopal effect that will be useful for the treatment of metastatic disease. Therefore, in looking ahead to 2030, the experience derived from the "Decade of Progress" has shown that gold is no longer a long-term bioaccumulative risk; it is now a tool used in metabolism. The primary goal for 2030 is to complete phase II and III clinical trials and to successfully transition to atomically precise manufacturing [57].

9. CONCLUSION

In the last 10 years, gold nanoclusters (AuNCs) have gone from experimental curiosity to clinically-viable option. The ability to have "atomic precision" and renal clearance paths alleviates long-held anxieties about bio-accumulation of metals. My vision for 2030 is that advancements in AI-based design and photo-immunotherapy will allow AuNC-mediated PTT to be used as a personalized, neoadjuvant standard of care. By removing existing regulatory and manufacturing obstacles, these "metabolizable tools" will create a selective, non-invasive means for managing systemic cancer, changing the landscape of nanomedicine.

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Ethical Approval

This study is a literature review and does not involve any original research with human participants or animals performed by any of the authors. Therefore, ethical approval was not required.

CRediT authorship contribution statement

Jenan A. Ghafil: Conceptualization, Investigation (literature search and data extraction), Project administration, Writing - original draft, Writing - review & editing.

Bashar Ibrahim: Methodology (search strategy and inclusion criteria), Resources, Supervision, Validation, Investigation, Project administration, Writing - original draft, Writing - review & editing.

Nihad Taha Mohammed Jaddoa: Writing - original draft, Writing - review & editing.

All authors have read and agreed to the published version.

Availability of data and materials

Data sharing is not applicable to this article as no new datasets were created or analyzed during the current study. All information used is available in the cited literature.

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