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Gold Nanoparticles in Biomedicine: Advancements in Cancer Therapy, Drug Delivery, Diagnostics, and Tissue Regeneration

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(Received: 10/12/2023 Revised: 15/01/2024 Accepted: 18/02/2024)

KEYWORDS

Gold nanoparticles

Biomedicine

Cancer therapy

Drug delivery

Diagnostics

Tissue regeneration

Localized surface

Laser Ablation

ABSTRACT

This review article provides an overview of the applications of gold nanoparticles (AuNPs) in biomedicine, focusing on their use in cancer therapy, drug delivery, diagnostics, and tissue regeneration. The unique optical properties of AuNPs allow for photothermal therapy (PTT), while their flexible surface chemistry enables functionalization with targeting ligands and therapeutics. Extensive research has demonstrated the effectiveness of AuNP-mediated photothermal ablation in various tumor models using near-infrared (NIR) laser irradiation. Active tumor targeting has been achieved through the engineering of AuNP platforms with ligands such as transferrin, folic acid, and hyaluronic acid. Combining AuNPs with chemotherapy and immunotherapy has shown synergistic therapeutic benefits. Moreover, AuNPs have been extensively explored as carriers for drugs and genes. By employing stimuli-responsive polymers, lipids, and mesoporous silica, researchers have achieved precise control over the release of cargo within cells. In the field of diagnostics, the plasmonic properties of AuNPs have been leveraged for photoacoustic imaging, and successful clinical translation has been demonstrated in the mapping of sentinel lymph nodes. Furthermore, AuNP constructs have overcome the challenges associated with the blood-brain barrier (BBB), enabling effective delivery to the central nervous system (CNS). In regenerative medicine, functionalized AuNPs have exhibited remarkable potential in stimulating processes such as osteogenesis, myogenesis, angiogenesis, and tissue regeneration when combined with growth factors. Additionally, they have been found to accelerate wound healing through immunomodulation and promotion of revascularization. Furthermore, the use of AuNP-based hydrogels and scaffolds provides crucial structural support in tissue engineering applications. The versatility of AuNP platforms offers promising solutions to challenges in the fields of oncology, drug delivery, diagnostics, and regenerative therapies. Ongoing optimization efforts hold significant promise for translating these strategies from the laboratory to clinical applications.

1. Introduction

Gold nanoparticles (AuNPs) have received immense research interest over the past two decades due to their unique optical, electronic and chemical properties arising from surface plasmon resonance [1-3]. When the particle size is reduced to the nanoscale, AuNPs exhibit bright colors due to strong light absorption and scattering attributes [4-6]. This phenomenon is attributed to collective oscillations of conduction band electrons induced by an electromagnetic field, known as localized surface plasmon resonance (LSPR). The LSPR wavelength depends on

factors including AuNP size, shape, inter-particle distance and local dielectric environment, enabling tunable optical responses from visible to NIR regions simply by manipulating these parameters.

Beyond optical behaviors, AuNPs demonstrate exceptional biocompatibility and surface chemistry amenable to functionalization with a vast array of ligands, drugs and targeting moieties [5-7]. This renders them highly versatile platforms for biomedical applications. Their stability, non-toxicity and ease of conjugation to biomolecules have accelerated exploration across theranostics. Numerous studies over the past decade have established AuNPs as promising agents for cancer therapy, drug and gene delivery, molecular imaging, diagnostics and regenerative medicine [8-12]. Cancer remains a leading cause of death worldwide, necessitating continued development of targeted, personalized treatment strategies.

Photothermal therapy (PTT) utilizing AuNPs has emerged as a promising non-invasive modality. Upon irradiation with NIR light, AuNPs efficiently convert photon energy into localized heat through LSPR, inducing irreversible damage to cancer cells within the illuminated region. This selectivity circumvents off-target effects associated with chemotherapy and radiation therapy. Surface functionalization further enhances targeting and intracellular uptake within tumors [10-12]. Combining PTT with chemotherapy achieves synergistic effects through enhanced drug release and immunogenic cell death induction. Drug delivery poses major challenges including instability, rapid clearance, lack of tumor selectivity and insufficient intracellular concentrations achieved by conventional modalities [13-15]. AuNPs address these limitations through rational design of multifunctional platforms. Stimuli-responsive polymers, lipids, mesoporous silica and biomimetic interfaces stabilize payloads yet enable controlled intracellular release activated by tumor microenvironment cues like acidic pH or enzymes. Ligand-mediated active targeting further boosts accumulation within disease sites.

Molecular imaging plays a pivotal role in cancer management through noninvasive screening, diagnosis, surgical guidance and treatment monitoring. AuNP constructs have been translated to the clinic for photoacoustic lymph node mapping due to strong optical absorption. Beyond photo acoustics, AuNP-based MRI, CT and optical imaging probes continue optimization [7-9]. Regenerative medicine aims to replace or regenerate damaged tissues and organs. AuNPs interact favorably with cells, modulate inflammation and stimulate tissue-specific progenitor cells when functionalized with bioactive signals. They accelerate wound healing, bone formation, angiogenesis and nerve regeneration in both 2D and 3D environments. AuNP-integrated scaffolds and hydrogels provide structural support with tunable mechanical properties [11-14]. This review summarizes recent advances utilizing AuNP platforms across major biomedical domains including cancer therapy, drug delivery, molecular imaging and regenerative applications. The intrinsic properties of AuNPs coupled with rational material design strategies have generated multifunctional constructs addressing key challenges. Continued progress will further optimize AuNP-based strategies, translating promising preclinical findings into clinical impact across diverse diseases [8-11]. Reproducible, scalable and cost-effective synthesis underpins widespread clinical translation of AuNP technologies. Conventional methods utilize reduction of gold salt precursors (HAuCl4) in the presence of capping/stabilizing agents. Sodium citrate reduction is a classic technique yielding spherical AuNPs of 15-150 nm diameter. However, citrate-capped particles exhibit limited stability, necessitating additional surface functionalization for biomedical applications. Alternative reducing agents include sodium borohydride, ascorbic acid and tannic acid, enabling tunable shape control. Tannic acid reduction yields triangular/hexagonal AuNPs under optimized conditions [12-14].

Surfactants like cetyltrimethylammonium bromide (CTAB) generate rod-shaped gold nanorods (AuNRs) and nanowires with plasmon bands spanning visible to NIR

regions amenable to PTT and imaging. Green synthesis avoids toxic chemicals, harnessing plant extracts as reducing/capping agents. Aqueous leaf/fruit extracts containing polyphenols, terpenoids and other biomolecules reduce gold ions to form AuNPs. Such protocols achieve excellent monodispersed, stability and cytocompatibility [13-16]. Microbial reduction utilizing fungi/bacteria represents another ecofriendly approach. High-yield, size-selected synthesis remains challenging but critical for clinical translation. Phase transfer, microfluidic and gamma irradiation methods address this through precise control over nucleation/growth kinetics [17-19].

Combining bottom-up and top-down lithography enables fabrication of complex nanostructures with plasmonic hotspots. Continued scale-up coupled with quality assurance standards will accelerate translating AuNP platforms from research to the clinic. This comprehensive review article delves into the recent advancements in the use of AuNPs in biomedicine, focusing on their applications in cancer therapy, drug delivery, diagnostics, and tissue regeneration. By exploiting the unique optical properties and surface chemistry of AuNPs, researchers have harnessed their potential for PTT and targeted drug delivery. The combination of AuNPs with chemotherapy and immunotherapy has demonstrated synergistic therapeutic effects [20-22]. Moreover, AuNPs have shown promise in diagnostics, particularly in photoacoustic imaging and mapping of sentinel lymph nodes. In the field of regenerative medicine, functionalized AuNPs have exhibited remarkable potential in stimulating tissue regeneration and wound healing. The review highlights the versatility of AuNP platforms and their potential for clinical translation, providing valuable insights for researchers and clinicians seeking to utilize these nanomaterials for improved biomedical applications.

2. Research areas to be addressed

This research aims to address several key areas in the field of AuNPs in biomedicine. These areas include the optimization of AuNP synthesis methods to enhance biocompatibility and stability, investigating the mechanisms underlying AuNP-mediated PTT and its efficacy in different tumor types, developing targeted AuNP platforms with improved tumor specificity and reduced off-target effects, exploring novel strategies to enhance cargo loading and controlled release from AuNP-based drug delivery systems (DDs), advancing AuNP-based diagnostic techniques for improved sensitivity and specificity in bioimaging and biosensing applications, evaluating the long-term safety and potential toxicity of AuNPs in biomedicine, integrating AuNPs with other therapeutic modalities such as chemotherapy, immunotherapy, and gene therapy to enhance treatment outcomes, investigating the regenerative potential of functionalized AuNPs in tissue engineering and wound healing applications, translating AuNP-enabled strategies from preclinical studies to clinical trials for validation and evaluation of their efficacy in human patients, and exploring novel applications and emerging research areas for AuNPs in biomedicine, such as targeted drug delivery to the CNS and theranostic applications combining therapy and diagnostics.

2.1. Literature review

AuNPs have emerged as promising tools in cancer therapy, offering unique properties for various applications. Saw et al. (2022) [8] investigated the use of photosensitizer-decorated confeito-like AuNPs in combination with a nano scaled PAMAM dendrimer spacer for improved photothermal-photodynamic treatment efficiency. Their study demonstrated enhanced therapeutic effects in cancer therapy. Another study by Lorenzoni et al. (2022) [9] explored the use of organ selenium compounds as functionalizing agents for AuNPs in cancer therapy, highlighting their potential in enhancing therapeutic outcomes. In the field of drug delivery, Ziaei et al. (2023) [10] developed in situ forming alginate/gelatin hybrid hydrogels containing doxorubicin-loaded chitosan/AuNPs nanogels for local therapy of breast cancer, demonstrating the potential of this system for targeted and controlled release of therapeutic agents. Hu et

al. (2022) [11] designed a guanosine-based hydrogel integrating the photothermal effect of PDA-AuNPs through a dynamic borate bond for PTT of cancer, showcasing the versatility of AuNPs in constructing innovative therapeutic platforms. The combination of AuNPs with other therapeutic modalities has also been explored. Faid et al. (2022) [12] investigated the enhanced photothermal heating and combination therapy of AuNPs on a breast cell model, demonstrating the potential of AuNPs in synergistic treatment approaches. Mi et al. (2022) [13] utilized biologically synthesized AuNPs using Cirsium japonicum var. maackii extract and evaluated their anti-cancer properties on AGS gastric cancer cells, highlighting the potential of natural extracts in AuNP synthesis and cancer therapy. Many articles have also provided comprehensive insights into the current trends and advancements in AuNP-based cancer therapy. Alle et al. (2022) [14] discussed the current trends in engineered AuNPs for cancer therapy, covering various aspects such as synthesis, functionalization, and therapeutic applications.

Deng et al. (2023) [15] focused on aptamer-conjugated AuNPs and their diagnostic and therapeutic roles in cancer, highlighting the potential of targeted AuNP systems in precision medicine. Furthermore, studies have explored the use of AuNPs in combination with imaging techniques and gene therapy. Dong et al. (2022) [16] developed an intracellular miRNA-triggered surface-enhanced Raman scattering imaging and dual gene-silencing therapy system using AuNPs, demonstrating the potential of AuNPs in theranostic applications. Hu et al. (2023) [17] hybridized carbon-based dot-capped AuNPs with manganese dioxide for enhanced photodynamic cancer therapy, showcasing the versatility of AuNPs in combination with other nanomaterials for improved therapeutic outcomes. Huang et al. (2023) [18] reviewed the construction of AuNPs for drug delivery and their application in cancer immunotherapy, highlighting the potential of AuNPs in enhancing immune responses and improving cancer treatment efficacy.

Nanoparticles have gained significant attention in biomedicine due to their unique properties and potential applications in drug delivery, diagnostic imaging, and cancer therapy. This literature review aims to summarize recent developments in the field and highlight key trends and future perspectives. Pasparakis et al. [21] shows an overview of the use of gold and silver nanoparticles in biomedicine. The review discusses their synthesis, functionalization, and applications in drug delivery, imaging, and therapeutics. Lan et al. [22] focus on multifunctional nanocarriers for targeted drug delivery and diagnostic applications in lymph nodes metastasis. The review discusses various types of nanocarriers, including liposomes, polymer nanoparticles, and inorganic nanoparticles, and their potential for imaging and therapy of lymph node metastasis.

Abed et al. [23] review the preparation, anti-cancer activity, and drug delivery applications of platinum nanoparticles. Many reviews show the unique properties of platinum nanoparticles and their potential as therapeutic agents. Zhang et al. [24] discuss the use of algal polysaccharides-based nanoparticles for targeted drug delivery applications. Researchers show the potential of these nanoparticles for targeted drug delivery and provide insights into their future prospects. Das et al. [25] shows the convergence of nanoparticles and artificial intelligence for targeted drug delivery in cancer therapy. The review discusses the current progress and challenges in the field, including the use of nanocarriers, imaging agents, and molecular targeting strategies. Mamidi et al. [26] show an overview of carbonaceous nanomaterials incorporated biomaterials. The review discusses the synthesis, characterization, and applications of carbon-based nanomaterials in various biomedical fields. Gupta et al. [27] review polysaccharide-based theranostic systems for combined imaging and cancer therapy. The review focuses on recent advances in the design and development of polysaccharide-based nanocarriers for targeted drug delivery and imaging. Sharma et al. [28] discuss recent advances in metal-based nanoparticles for nucleic acid

delivery in therapeutic applications. The review highlights the potential of metal nanoparticles, such as gold and silver, for efficient delivery of nucleic acids, including DNA and RNA, in gene therapy. Gupta et al. [29] show the multimodal potentials of AuNPs for bone tissue engineering and regenerative medicine. The review discusses the unique properties of AuNPs and their applications in bone regeneration, including drug delivery, imaging, and scaffold fabrication. Rabaan et al. [30] focus on multifunctional nanoparticles for cancer theranostics. The review discusses recent trends and developments in the design and fabrication of nanoparticles for simultaneous diagnosis and therapy of cancer. Kaushik et al. [31] discuss nanocarrier cancer therapeutics with functional stimuli-responsive mechanisms. The review highlights recent developments in stimuli-responsive nanocarriers for cancer therapy, including pH-responsive, temperature-responsive, and enzyme-responsive systems. He et al. [32] review advances in nanomedicines for lymphatic imaging and therapy. The review focuses on the design and development of nanoparticles for lymphatic imaging and targeted therapy.

Govindan et al. [33] shows an advanced multifunctional magnetic nanostructure for cancer diagnosis and therapy integrated into an artificial intelligence approach. The review discusses the use of magnetic nanostructures for imaging, drug delivery, and hyperthermia therapy in cancer treatment. Brindhadevi et al. [34] discuss carbon nanomaterials as DDs for cancer therapy. The review provides an overview of different types of carbon nanomaterials, including carbon nanotubes, graphene, and carbon dots, and their applications in drug delivery.

Kumari et al. [35] present a comprehensive review on the journey from 3D to 4D printing in nanomedicine and healthcare. The review discusses the advancements in 3D and 4D printing technologies and their applications in nanomedicine, including DDs, tissue engineering, and personalized medicine.

2.2. Synthesis methods of AuNPs

AuNPs have gained significant attention in various fields due to their unique properties and potential applications. The synthesis of AuNPs involves the preparation of nanoscale gold particles with controlled size, shape, and surface properties. Several synthesis methods [20-36] have been developed to produce AuNPs, each offering distinct advantages and limitations. In this article, we will explore seven commonly used techniques for the synthesis of AuNPs.

2.2.1. Chemical Reduction Method

The chemical reduction method is one of the most widely employed techniques for synthesizing AuNPs. It involves the reduction of gold ions in a solution using a reducing agent. Common reducing agents include sodium borohydride ($NaBH_4$), citrate, and ascorbic acid. The reduction reaction leads to the formation of AuNPs with sizes ranging from a few nanometers to tens of nanometers. This method is relatively simple, cost-effective, and allows for the control of nanoparticle size by adjusting the reactant concentrations and reaction conditions.

2.2.2. Microemulsion Method

The microemulsion method utilizes a microemulsion system consisting of water, oil, and a surfactant. Gold precursors are dissolved in the water phase, and a reducing agent is added to initiate the reduction reaction. The surfactant molecules act as stabilizers, preventing the aggregation of AuNPs. This method offers excellent control over the size and shape of the nanoparticles and allows for the synthesis of monodisperse AuNPs with high stability [17-22].

2.2.3. Solvothermal Method

The solvothermal method involves the synthesis of AuNPs in a high-pressure reactor at elevated temperatures. Gold precursors are dissolved in a suitable solvent, and a reducing agent is added. The reaction is carried out under high pressure, typically ranging from a few atmospheres to several hundred atmospheres [25-32]. The high pressure and temperature conditions promote the rapid nucleation and growth of AuNPs. This method enables the synthesis

of AuNPs with controlled size and shape, including nanorods, nanospheres, and nanocubes.

2.2.4. Green Synthesis

Green synthesis methods utilize natural sources, such as plant extracts, microorganisms, or biomolecules, as reducing and stabilizing agents for the synthesis of AuNPs. These methods are considered environmentally friendly alternatives to traditional chemical synthesis methods. Plant extracts contain various bioactive compounds that can reduce gold ions and facilitate the formation of AuNPs [15-18]. Green synthesis methods offer the advantages of being cost-effective, sustainable, and biocompatible, making them suitable for biomedical applications.

2.2.5. Electrochemical Method

The electrochemical method involves the reduction of gold ions at the electrode surface under an applied electric potential. A gold electrode is immersed in an electrolyte solution containing gold precursors, and a voltage is applied to initiate the reduction reaction [15-21]. The size and shape of the AuNPs can be controlled by adjusting the applied potential, electrolyte composition, and reaction time. The electrochemical method allows for the synthesis of AuNPs with high purity and control over their size and shape.

2.2.6. Laser Ablation (LA) Method

The LA method utilizes a high-energy laser pulse to ablate a gold target submerged in a liquid medium. The laser pulse generates a plasma plume, which rapidly cools down and leads to the formation of AuNPs. This method offers precise control over the size and shape of the nanoparticles by adjusting the laser parameters, such as energy, wavelength, and pulse duration. The LA method is suitable for the synthesis of AuNPs in various liquid media, including water, organic solvents, and surfactant solutions.

2.2.7. Template-Assisted Method

The template-assisted method involves the use of a template or scaffold to guide the synthesis of AuNPs with specific shapes and sizes. The template can be a solid substrate, such as a porous membrane or a polymer matrix, or a soft template, such as micelles or vesicles [22-28]. The gold precursors are introduced into or onto the template, followed by a reduction step to form AuNPs. The template is then removed, leaving behind the desired AuNPs. This method allows for the fabrication of AuNPs with complex structures, such as nanotubes, nanowires, and hollow nanoparticles.

3. Application of AuNP

3.1. Applications of AuNPs in Wound Dressings

Wound dressings incorporating AuNPs have emerged as promising alternatives to conventional gauze for accelerating tissue repair. AuNPs exert antimicrobial effects on pathogenic bacteria implicated in chronic wounds like MRSA and Pseudomonas aeruginosa through oxidative stress induction. Researchers functionalized cotton gauze with chitosan-capped AuNPs via a green synthesis method. *In vitro* tests showed the AuNP-gauze exhibited potent bactericidal activity comparable to commercially available silver nanocomposite dressings, while avoiding cytotoxicity against human cells [22-27].

Other studies have immobilized AuNPs within collagen, gelatin or silk fibroin-based matrices to impart antimicrobial properties. NIR irradiation of such constructs containing 13 nm PEGylated AuNPs led to localized photothermal damage of embedded MRSA bacteria within 15 minutes without affecting surrounding keratinocyte cell viability, supporting application as laser-activated antibacterial dressings [17-22]. AuNPs have also been incorporated into nanofiber scaffolds for synergistic effects. Electro spun polyurethane mats containing GNPs demonstrated 99.9% elimination of planktonic MRSA and P. aeruginosa in 3 hours, while promoting keratinocyte and fibroblast attachment/proliferation indicating biocompatibility.

Beyond antimicrobials, AuNPs promote wound healing through anti-inflammatory actions. AuNPs modulated nitric oxide and interleukin-6 levels released from lipopolysaccharide-stimulated macrophages *in vitro*, and reduced edema when incorporated into chitosan films applied onto dermal wounds in mice [22-24]. Underlying

mechanisms involve quenching of reactive oxygen/nitrogen species by AuNPs. The nanoparticles have also been observed to support fibroblast migration, angiogenesis and re-epithelialization in animal wound models when delivered within collagen or fibrin scaffolds [25-29].

3.2. Applications of AuNPs in Pharmacy

While AuNP delivery platforms were discussed previously, further pharmaceutical uses include solubility/stability enhancement and diagnostic/therapeutic efforts. Gold nanoclusters containing as few as several tens of gold atoms exploit quantum confinement effects to exhibit bright, tunable fluorescence emissions without toxicity concerns [22-26]. Their compact size enables direct solution/solid phase bioconjugation with biomolecules without perturbing recognition. Ligand-functionalized gold nanoclusters showed possibility as fluorescence reporters for protease activity profiling within biological fluids and tissues.

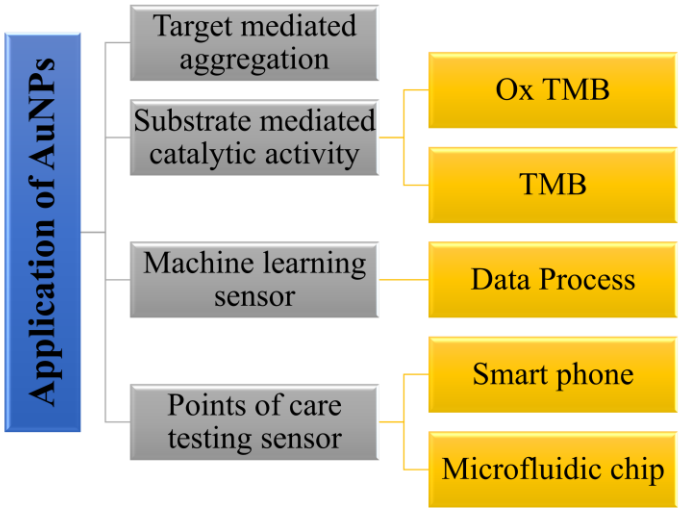

Figure 1: Emerging Developments in Pathogen Detection Utilizing Gold Nanoparticle-Based Colorimetric Sensors

At larger scales, AuNPs boost solubility/dissolution of poorly soluble actives. Researchers prepared gold nanospheres stabilizing amorphous solid dispersions of the antidiabetic agent glimepiride, resulting in over 80-fold solubility/dissolution rate enhancement without compromising drug stability. Mechanistic understanding identified partial drug coating on AuNP surfaces coupled with wetting effects on the surrounding crystal lattice as causative. Figure 1 indicates the latest advancements in pathogen detection through the utilization of gold nanoparticle-based colorimetric sensors [27-33]. Figure 1 shows the recent developments and breakthroughs in the field, emphasizing the growing importance of these sensors in detecting and identifying pathogens.

Sensors AuNPs have been widely utilized in various sensor applications, including optical, electrochemical, and surface-enhanced Raman scattering (SERS) sensors. Their unique properties, such as tunable surface plasmon resonance and large surface area, allow for the detection of target analytes with high sensitivity and selectivity. AuNPs can be functionalized with specific biomolecules, such as antibodies or DNA probes, to create biosensors capable of detecting a wide range of analytes, including proteins, nucleic acids, and pathogens [15-22].

These sensors find applications in areas such as medical diagnostics, environmental monitoring, food safety, and forensic analysis. AuNP-based biosensors have been employed for the rapid and sensitive detection of disease biomarkers, facilitating early diagnosis and personalized treatment strategies as shown in Table 1.

Table 1: The applications of AuNPs in sensors, biomaterials, and cancer disease

Applications	Description
Sensors	AuNPs have been utilized in various sensor applications, including optical, electrochemical, and surface-enhanced Raman scattering (SERS) sensors. They can detect target analytes with high sensitivity and selectivity, making them suitable for applications such as biosensing, environmental monitoring, and disease diagnosis.
Biomaterials	AuNPs can be incorporated into biomaterials to enhance their properties and functions. They have been used in tissue engineering scaffolds, DDs, and wound dressings. AuNPs can improve biocompatibility, promote cell adhesion and proliferation, and provide controlled release of therapeutic agents.
Cancer Diagnosis	AuNPs have been employed in various cancer diagnostic techniques, such as imaging and biosensing. They can be functionalized with targeting ligands or contrast agents for tumor-specific imaging, enabling early detection and accurate diagnosis. AuNP-based biosensors offer rapid and sensitive detection of cancer biomarkers for diagnostic purposes.
Cancer Therapy	AuNPs have shown promise in cancer therapy, particularly in photothermal therapy (PTT). By absorbing NIR light, AuNPs generate localized heat, selectively destroying cancer cells while sparing healthy tissue. They can also be loaded with anticancer drugs and targeted to specific tumor sites for enhanced therapeutic efficacy.

3.3. Applications of AuNPs in Bone and Tissue Engineering

Over 800 million people worldwide suffer from osteoporosis according to the International Osteoporosis Foundation (IOF). Delivery of osteogenic signals recognizing this massive unmet need has prioritized AuNP exploitability in orthopedics. AuNPs functionalized with BMP-2 induced BMPR-Smad signaling and ectopic bone formation comparable to free growth factor when injected intra-muscularly in rats. AuNP-modified polymer scaffolds enhanced vascularization, re-reendothelialization and arterial healing compared to bare constructs in rat abdominal aorta interposition grafts [15-21]. Together, these studies demonstrate AuNP multifunctionality in regulating cell–material interactions and stimulating native tissue regeneration processes. While requiring further optimization, AuNP-integrated scaffolds present translatable strategies to address high unmet clinical needs in orthopedics and beyond. Augmenting cellular instructive biomaterials through facile bioconjugation paves avenues toward engineering implantable living tissues from biomimicry principles [18-22]. AuNPs can enhance bone and tissue regeneration in orthopedic applications through several key mechanisms. First, they can be functionalized with bioactive molecules like bone morphogenic proteins (BMPs) to promote osteogenesis, enabling localized and sustained delivery of osteoinductive cues. Second, incorporating AuNPs into scaffold materials reinforces their mechanical properties, providing structural support for new tissue growth [25-29]. AuNPs also stimulate the release of pro-angiogenic growth factors, promoting angiogenesis and facilitating nutrient exchange necessary for tissue regeneration. Moreover, the antioxidant effects of AuNPs reduce inflammation, creating a favorable microenvironment for regeneration and healing responses. Functionalized AuNPs can recruit endogenous stem cells to defect sites and guide their differentiation into specific cell lineages to reconstruct damaged tissues [26-29]. Additionally, AuNPs offer the advantage of imaging guidance, allowing noninvasive tracking of scaffold degradation, cell homing, and tissue in-growth through various imaging modalities. By harnessing these properties through rational materials design, AuNPs present opportunities for regenerating challenging orthopedic tissues using AuNP-enabled scaffolds, hydrogels, and growth factor carriers [28-32]. The

stimulation of pro-angiogenic growth factors from platelets and stem cells by AuNPs occurs through multiple mechanisms, including platelet activation and aggregation, stem cell differentiation, oxidative signaling, plasmonic heating, and scaffold functionalization. These mechanisms collectively contribute to the promotion of angiogenesis and support the regeneration process in orthopedic applications.

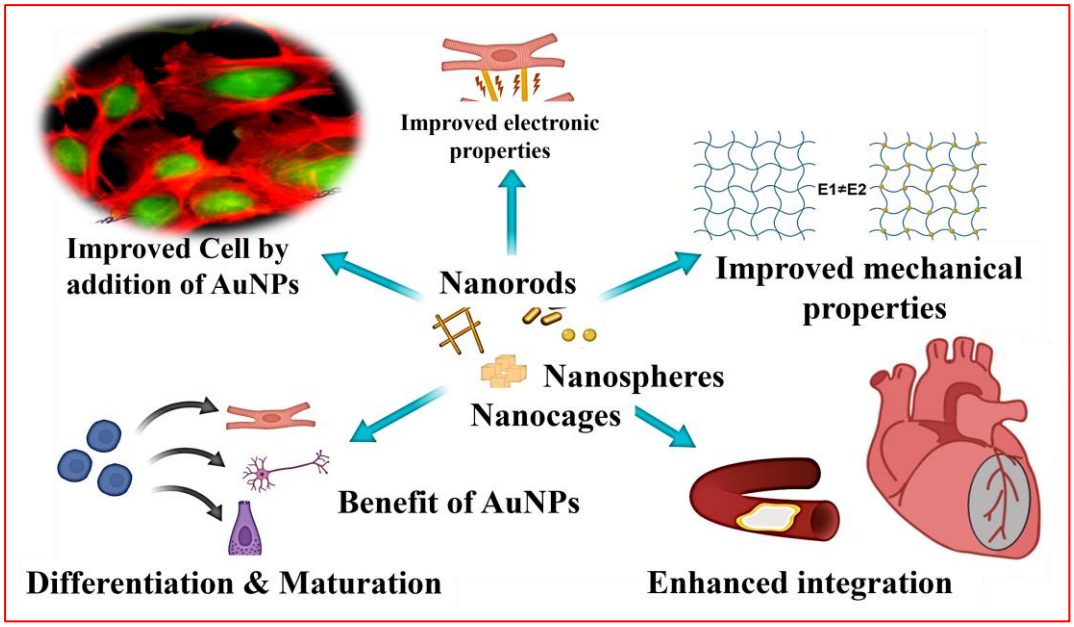

Figure 2: Integration of Gold Nanoparticle-Incorporated Scaffolds for Advancing Tissue Engineering and Regenerative Medicine

Figure 2 illustrates the integration of AuNP-incorporated scaffolds as a pivotal strategy in the field of tissue engineering and regenerative medicine. The schematic diagram showcases the integration of AuNPs within the scaffold matrix, highlighting their unique role in enhancing tissue regeneration and therapeutic outcomes. The incorporation of AuNPs offers numerous advantages, including their optical, electrical, and catalytic properties, which can be harnessed to promote cellular interactions, facilitate tissue growth, and regulate the controlled release of bioactive molecules. The blood-brain barrier (BBB) poses a significant challenge for delivery of therapeutic agents to the brain and CNS. It tightly regulates molecular exchange between the bloodstream and brain microenvironment through specialized endothelial cells joined by tight junction proteins. This restricts passive diffusion of over 98% of small molecule drugs and virtually all large molecules like biologics.

Looking ahead, investigating mechanisms underlying size/shape dependent transport kinetics, cell receptivity dynamics, and nanocarrier transcytosis versus paracellular shuttling may facilitate rational design of gold nanoparticle-based BBB permeators. Defining safe, controlled dosing parameters for transient BBB opening techniques requires diligent *in vivo* studies [31-35].

AuNP platforms modified with endogenous transport signals or biomimetic surfaces demonstrate promise to non-invasively administer therapeutics for brain conditions otherwise untreated. Further optimization of AuNPs holds the potential to revolutionize drug delivery to the CNS. However, several challenges must be addressed for successful clinical translation. First, the size limitation of nanoparticles restricts efficient receptor-mediated endocytosis across the BBB, with only particles smaller than 100 nm typically undergoing this process. Larger particles are not efficiently taken up. Second, AuNPs are rapidly cleared by the mononuclear phagocyte system after intravenous injection, limiting the available timescale for BBB transport before elimination from circulation. Third, even with targeting ligands, the transport efficiency of

AuNPs across the BBB via transcytosis is generally low, ranging from 1-5% of the injected dose. Most of the AuNPs accumulate in peripheral tissues instead of crossing the BBB. Fourth, there is variability in the uptake of AuNPs across different brain regions, as not all regions express the same level of endocytic receptors. Some areas, such as the brainstem, may experience significantly less accumulation of AuNPs. Fifth, the loading capacity of AuNPs is constrained by their size and the number of ligands or targeting molecules attached, limiting the amount of drug that can be delivered. Sixth, the processing of ligands like transferrin at the BBB versus peripheral tissues, and their recycling potential, is still not fully understood. Seventh, the long-term effects of repeated dosing of AuNPs across the BBB, particularly when combined with adjuvants like focused ultrasound, remain poorly understood in terms of safety [21-24]. Eighth, there is a lack of clinical data, as most studies have been conducted on healthy animal models. Validation in human patients with compromised BBB function will reveal additional practical barriers.

Overcoming these limitations through comprehensive testing in small and large animal models will be crucial for the safe and successful clinical translation of AuNP-based brain delivery strategies.

4. AuNP-based Drug and Gene Delivery

AuNP nanocarriers have shown promise for overcoming pharmaceutical limitations like instability, rapid clearance and lack of tumor targeting of conventional chemotherapeutics and nucleic acid therapeutics.

Researchers at George Washington University translated their folate-targeted gold nanoshell formulation co-loading the cytostatic drugs 5-fluorouracil and gemcitabine into a Phase I clinical trial. Ten pancreatic cancer patients receiving the nanoparticles via hepatic arterial infusion achieved disease stabilization with no significant adverse effects observed over 6 months. While limited by the small study size, this trial successfully demonstrated feasibility and tolerability paving way for further optimization and evaluation [19-22]. Nanoshells has progressed their PEGylated gold nanoshell-doxorubicin conjugate (NS1-Dox) into first-in-human testing for hepatocellular carcinoma.

The ongoing Phase I dose-escalation study will assess maximum tolerated dose, safety profile, pharmacokinetics and preliminary antitumor effects of NS1-Dox given every 3 weeks by intravenous infusion. Up to 25 patients will be recruited to evaluate the candidate's potential utility as an alternative or complementary treatment to conventional doxorubicin chemotherapy.

Positive outcomes could represent an important proof-of-concept for functionalizing AuNPs with clinically validated therapeutics [25-29].

Ongoing efforts also focus on developing targeted and controlled release AuNP platforms. Researchers loaded methotrexate onto transferrin-conjugated AuNPs against methotrexate-resistant rheumatoid arthritis and multiple myeloma cell lines. The transferrin targeting successfully induced greater intracellular drug loading and cytotoxicity compared to free methotrexate [30-32]. Similar folic acid-functionalized AuNPs were able to effectively deliver chemotherapeutics specifically in folate receptor overexpressing ovarian tumors in mice while avoiding renal toxicity issues of non-targeted nanoparticles. Rational design of ligand-targeted AuNP nanocarriers holds promise to maximize therapeutic index through selective cancer cell uptake and controlled drug release kinetics [14-18]. The coming years will likely see substantial clinical translation of optimized AuNP formulations for chronic cancer chemotherapy and nucleic acid delivery through rational design approaches. Combination studies integrating these platforms with standard of care modalities and locoregional therapies may help ascertain AuNPs' true potential as drug delivery agents in oncology. Widespread clinical adoption will also depend on addressing production scalability, cost-effectiveness, long-term risk-benefit evaluation and reimbursement challenges. But early trial outcomes have catalyzed significant enthusiasm around AuNP-enabled

precision medicine through targeted mobilization of potent anti-cancer payloads.

4.1. AuNP based Cancer Diagnostics and Imaging

Substantial progress has also occurred in bringing AuNP-enhanced diagnostic and intraoperative imaging technologies from research labs to patients. Investigators from Massachusetts General Hospital translated gold nanoprobe-assisted confocal micro endoscopy of oral premalignant lesions into first-in-human testing. The procedure involves topical application of a mix containing PEGylated gold nanospheres, which act as optical contrast agents. Confocal micro endoscopy illumination and detection enhance visualization of nanosphere-accumulated regions to enable real-time microscopic screening of oral cavity lesions [22-26].

Beyond endoscopic applications, photoacoustic imaging exploiting the strong optical absorption properties of AuNPs has reached clinical translation status. Using a clinical ultrasound-guided photoacoustic imaging system, sentinel lymph nodes were clearly visualized up to 25 minutes post-injection with no adverse reactions reported. Semi-quantitative analysis indicated 30-fold higher photoacoustic signal from sentinel lymph nodes versus background lymph nodes.

Results support further evaluation of AuNP-enhanced photoacoustic imaging as an adjunct technique to aid sentinel node identification during surgery. Building on these precedents, several groups are actively exploring other clinical uses for gold nanoparticle photoacoustic probes [19-23]. A Phase I trial lead by Inno-Spec investigated intratumoral administration of PEG-gold nanocages followed by photoacoustic and ultrasound imaging to evaluate tumor photothermal treatment response in locally advanced solid tumors. Early results suggest potential of such combined molecular-functional monitoring for objectively gauging treatment margins [24-26]. Other exploratory clinical studies evaluate diagnosis of inflammatory arthritis using citrate-capped AuNPs along with photoacoustic quantification of synovial tissues as well as detection of ovarian cancer micro metastases based on enhanced photoacoustic signals from ligand-targeted gold nanostars.

Moving forward, pairing emerging imaging techniques like photo acoustics with active tumor-targeting AuNP formulations holds translational promise. Advanced probe designs incorporating theranostic payloads tuned for multi-wavelength photoacoustic excitation could enable image-guided precision therapy [24-28]. Combining noninvasive whole-body molecular imaging with microscopic intraoperative guidance may also uncover new management paradigms.

Overcoming technical optimization challenges and validating performance against current clinical standards will be crucial to establish AuNP platforms as routine adjuncts for cancer screening, diagnosis and surgical navigation in the years to come [17-19]. The clinical translation of AuNPs in personalized oncology holds great promise but also faces several challenges. Long-term safety and toxicity profiling is crucial, as the potential effects of repeated or chronic exposure to AuNPs in humans need thorough evaluation, including genotoxicity, immunogenicity, microbiome impact, and clearance kinetics [20-22]. Achieving sufficient tumor accumulation is another challenge, as modulating AuNP properties to enable extravasation from leaky tumor vasculature and avoid macrophage clearance for high intratumoral drug concentrations can be complex, especially when incorporating active targeting approaches [20]. Maintaining colloidal stability in biological environments is essential for efficient delivery, but creating robust yet non-toxic surface coatings is challenging. Controlled intracellular drug/gene release kinetics require specific internal or external stimuli, but dysregulations in cancer cells can affect desired activation profiles. Scalable and reproducible synthesis methods for AuNPs are needed to meet the demands of clinical and commercial applications, as current techniques struggle with batch-to-batch quality, high yields, and cost-effectiveness.

The high manufacturing and regulatory costs associated with translating nanomedicines into FDA-approved

products pose a barrier to industry participation [20-23]. Additionally, comprehensive clinical data from well-designed early and late phase trials are necessary to establish efficacy, optimal dosing, and safety advantages over existing therapies before widespread adoption in oncology.

4.2. Addressing Safety and Toxicity Concerns

Thorough toxicological evaluation is crucial before AuNP-based therapies can be safely used in humans. While various studies have demonstrated favorable biocompatibility, systemic effects after repeated administration warrant detailed investigation.

Researchers evaluated possible hematological or renal toxicity after 28-day treatment with 2–10 nm PEGylated AuNPs in Sprague-Dawley rats. While isolated toxicology studies are informative, simultaneous evaluation of pharmacological action is crucial to understand the overall risk-benefit profile. Researchers evaluated antitumor efficacy and toxicity of PEGylated gold nanoshell administered intravenously in murine breast cancer models. The AuNP treatment led to effective tumor growth inhibition, but also caused mild immune cell changes in liver, spleen and lymph nodes. However, the modulation was transient and recovered completely after a month, indicative of an acute inflammatory response rather than long-term toxic effects. A careful designed *in vivo* pharmacology studies may help delineate safe therapeutic windows for translation. Another priority is controlling long-term biokinetics and clearance through rational materials design.

Investigators synthesized biodegradable AuNPs stabilized by poly (aspartic acid)-poly (ethylene glycol) block copolymers, which are metabolized to non-toxic aspartate and polyethylene glycol degradation products. The nanoparticles displayed favorable pharmacokinetics with nearly 90% renal clearance within 8 hours along with lack of biologically relevant accumulation in major organs two months post-administration [18-22]. Development of 'self-reporting' materials enabling real-time monitoring of clearance profiles could further accelerate clinical translation.

4.3. Addressing Delivery and Targeting Challenges

As highlighted above, achieving effective delivery and retention of AuNPs specifically in tumors poses key challenges. Several technologies have emerged to surmount this barrier. One approach utilizes gold nanoparticle constructs which aggregate or chemically crosslink upon reaching the acidic tumor microenvironment, aided by intelligent surface coatings sensitive to matrix metalloproteinases [24-29]. This enables size-based entrapment within tumors to boost localized drug concentrations over time. Another promising strategy coats AuNPs with tumor penetrating peptide sequences which aid extravasation through enhanced endothelial cell permeability [19-22]. RVG29 peptide functionalized gold nanorods significantly improved intratumoral distribution in murine glioblastoma bearing brains compared to non-targeted nanorods as visualized clearly using photoacoustic imaging. Such intracellular-extracellular shuttling peptides incorporated on AuNP surfaces may address inefficient passive targeting limitations. Engineering stealth and deformability properties represents another active optimization area [23-25]. By forming polymer brush coats incorporating flexible PEG chains, researchers were able to synthesize gold nanoparticle constructs which reversibly deflate and extravasate through narrow vascular gaps under shear force. The re-expanded spherical nanoparticles showed superior accumulation within tumors versus stiff counterparts as confirmed using single particle ICP-MS analysis. Balancing stealth and flexibility could effectively manipulate intratumoral nanoparticle access. Multi-functional platforms have also emerged by combining targeting ligands with cell-penetrating or fusogenic peptides on AuNPs [26-31].

Transferrin-polyarginine functionalized AuNPs exhibited up to 100-fold higher cellular internalization compared to transferrin ligand alone via receptor-mediated endocytosis assisted by the arginine rich domain. The

platform enabled efficient glioblastoma cell specific delivery of chemotherapeutics both *in vitro* and upon intratumoral administration *in vivo*.

4.4. Addressing Cargo Protection and Controlled Release

Encapsulating drug and gene cargos within AuNP nanoplatforms necessitates strategies ensuring payload integrity against biological degradation as well as controlled activation-triggered release profiles. Various stimuli-responsive materials including lipids, polymers, nucleic acids and peptides have been explored with AuNPs to meet these goals. Investigators developed pH-sensitive PEG-ilipid coated gold nanorods which encapsulated chemotherapeutics within a fusogenic lipid bilayer. Under mildly acidic tumor microenvironment pH, the bilayer fused with cell membranes to facilitate controlled intracellular drug discharge with improved efficacy versus untreated controls.

Similar pH-labile polymeric shells have been fabricated on AuNPs using acid-degradable β-thiopropionate linkages or acid-cleavable hydrazone bonds to achieve stability at normal physiological pH but rapid drug release in acidic end lysosomal compartments post-cellular uptake. *In vivo* studies showed enhanced doxorubicin accumulation and improved pharmacokinetics using such formulations compared to free drug. Enzyme-triggered payload release has also gained interest, considering dysregulated protease expression by various tumors. gold nanorods were modified with gelatin shells conjugated with MMP-2/9 cleavable substrates. The delivery platform selectively released surface-attached drug molecules within MMP-overexpressing ovarian cancer cells upon enzymatic cleavage [32-34]. Cellular uptake studies corroborated targeted intracellular degradation and controlled release profiles. Additional stimulus types under exploration include light, temperature, redox potential and mechanical forces. Thermoresponsive polymer caps formulated on gold nanoshells enabled laser-triggered liberation of encapsulated therapeutics relying on photothermal heating. Significant tumor growth inhibition was observed in breast cancer models compared to non-irradiated controls. Combining targetability, protection and activation attributes within rationally designed nanoplatforms can optimize therapeutic delivery in precision cancer treatment. Several articles [34-38] present a comprehensive overview of carbon nanomaterials as DDs for cancer therapy. They explore the advancements in 3D and 4D printing technologies within the field of nanomedicine and healthcare [34-37].

Additionally, these articles investigate the adsorption and sustained release capabilities of composite and core-shell nanofibers for doxorubicin, examine the incorporation of graphene oxide and calcium phosphate into core-shell nanofibers for enhanced bone tissue engineering, and provide additional references for further exploration [38-42].

5. Conclusion

Over the past two decades, AuNPs have emerged as a highly promising material for biomedical applications due to their unique optical properties and versatile surface chemistry. Extensive research has demonstrated the potential of AuNP platforms in cancer therapy, drug and gene delivery, molecular imaging, diagnostics, and regenerative medicine [23-25]. In cancer, AuNP-mediated PTT has shown efficacy in ablating tumors through localized hyperthermia induced by NIR irradiation. AuNP constructs have been engineered for active tumor targeting and combination with chemotherapy to achieve synergistic therapeutic benefits. As drug carriers, AuNPs have been designed for controlled intracellular cargo release through stimuli-responsive polymers, lipids and mesoporous silica. Ligand-functionalized AuNPs further enhance accumulation within disease sites [29-36].

In molecular imaging, AuNP photoacoustic probes have translated to the clinic for sentinel lymph node mapping. Beyond imaging, AuNPs have overcome limitations like the BBB to enable CNS delivery. In regenerative applications, AuNPs stimulate tissue regeneration when functionalized with growth factors for applications in bone,

muscle, skin and nerve repair. They accelerate wound healing and hold potential to treat conditions like muscular dystrophy. AuNP-based hydrogels and scaffolds provide structural support in tissue engineering applications. While significant progress has been made, further optimization is still needed to fully realize the clinical impact of AuNP platforms.

Continued rational design coupled with comprehensive characterization and toxicity profiling will advance AuNP-enabled strategies from bench to bedside. Addressing challenges such as targeting efficiency, controlled release, production scalability and cost-effectiveness will facilitate translating promising preclinical findings into meaningful therapeutic options.

6. References

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Citation:

Ghafari, Y., Asefnejad, A., & Ogbemudia, D. O. (2024). Gold Nanoparticles in Biomedicine: Advancements in Cancer Therapy, Drug Delivery, Diagnostics, and Tissue Regeneration. Scientific Hypotheses,1(1).
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