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Gold Nanoparticle-Based Vaccines: A New Frontier In Immunotherapy

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Abstract: The advancement of immunotherapy has significantly transformed modern medical practices, with gold nanoparticles (AuNPs) emerging as a groundbreaking platform for vaccine innovation. Characterized by their exceptional physicochemical properties- such as biocompatibility, adjustable size, and surface functionalization- AuNPs offer remarkable potential in optimizing antigen delivery, preserving vaccine stability, and amplifying immune responses. This article provides a comprehensive analysis of the role of gold nanoparticles in vaccine technology, delving into their underlying mechanisms, distinct advantages over traditional systems, and cutting-edge progress in both preclinical and clinical research. Additionally, it examines the challenges and prospective pathways for AuNP-based vaccines as a pivotal evolution in the field of immunotherapy.

Keywords- Gold nanoparticles, Vaccines, Immunotherapy, Nanotechnology, Antigen delivery, Cancer immunotherapy, Infectious diseases.

1. INTRODUCTION

Vaccination has been a cornerstone of public health, serving as a fundamental strategy to combat and eradicate infectious diseases globally (Hajj Hussein et al., 2015; Okesanya et al., 2024). Over the years, vaccines have saved millions of lives; however, traditional vaccine formulations face persistent challenges, including diminished immunogenicity, susceptibility to degradation, and inefficient delivery mechanisms. These limitations not only reduce the effectiveness of vaccines but also hinder their accessibility in resource-limited settings (Dumpa et al., 2019; Jetha et al., 2024; Wallis et al., 2019). To address these issues, nanotechnology has emerged as a revolutionary tool, enabling the design of more efficient, robust, and adaptable vaccine platforms. Among the wide range of nanomaterials available, gold nanoparticles (AuNPs) stand out for their exceptional and versatile properties. These include ease of synthesis with precise control over size and shape, a large surface area-to-volume ratio conducive to multiple functionalizations, and a remarkable capacity to conjugate with a variety of biomolecules such as antigens, adjuvants, and targeting ligands (Damani et al., 2024; Duman et al., 2024; N. Li et al., 2014; Ramalingam, 2019; Sarfraz & Khan, 2021; Zare et al., 2022). Consequently, AuNPs have opened new avenues in vaccine development by improving antigen stability, enhancing immune responses, and providing targeted delivery systems, making them an indispensable innovation in the ongoing evolution of immunotherapy (Barchi, 2022; Chauhan et al., 2021a; J. Liu et al., 2019; Peng et al., 2024; Theivendren et al., 2024).This article delves into the principles behind AuNP-based vaccines and their applications in immunotherapy, focusing on their ability to enhance antigen presentation, stimulate immune responses, and enable targeted delivery.

2. GOLD NANOPARTICLES IN VACCINE DEVELOPMENT

2.1. Physicochemical Properties of Gold Nanoparticles

Gold nanoparticles are spherical or anisotropic nanomaterials typically ranging from 1 to 100 nanometers in size (N. Li et al., 2014; Priecel et al., 2016). Their small size and unique optical properties, such as surface plasmon resonance, enable them to interact efficiently with biological systems, including immune cells (Dykman & Khlebtsov, 2017a; Zeng et al., 2014). The high surface-to-volume ratio of AuNPs not only facilitates the attachment of a diverse array of biomolecules- such as antigens, adjuvants, or targeting ligands-but also enhances their effectiveness in biomedical applications (Liyanage et al., 2019; Mateu Ferrando et al., 2020).

AuNPs can be synthesized using a variety of techniques, including chemical reduction methods like citrate reduction, which allow for precise control over their size, shape, and surface characteristics (Ortiz-Castillo et al., 2020; Patil et al., 2023). Shapes such as spheres, rods, and stars are commonly used, as their morphology can influence biological interactions and efficacy in vaccine delivery (Georgeous et al., 2024; Kumar Sarangi et al., 2023; Venditti, 2019).

The surface functionalization of AuNPs is another critical property that contributes to their versatility. Functionalization with peptides, proteins, nucleic acids, or synthetic polymers provides a tailored platform for specific vaccine formulations, allowing for the simultaneous delivery of multiple components. This adaptability is essential for designing next-generation vaccines capable of addressing diverse pathogens or cancer-specific targets (Arcos Rosero et al., 2024; Mateu Ferrando et al., 2020; Naghib et al., 2024). Gold nanoparticles are spherical nanomaterials typically ranging from 1 to 100 nanometers in size (Daniel & Astruc, 2004; Kumari et al., 2019; N. Li et al., 2014). Their small size allows them to interact efficiently with immune cells, while their high

surface-to-volume ratio facilitates the attachment of antigens, adjuvants, or targeting ligands (Arcos Rosero et al., 2024; Kumar Sarangi et al., 2023). AuNPs can be synthesized using techniques such as citrate reduction, which allows precise control over their size and shape (D. T. Nguyen et al., 2011; Piella et al., 2016). Additionally, the surface of AuNPs can be functionalized with a variety of molecules, including peptides, proteins, or DNA, making them versatile carriers for vaccine components (Rai & Ferreira, 2021; J. Zhang et al., 2020; Zong et al., 2017a).

2.2. Mechanisms of Action in Immunotherapy

Antigen Delivery: Gold nanoparticles (AuNPs) play a critical role as carriers for antigens, offering unparalleled stability by shielding antigens from enzymatic degradation, aggregation, and adverse environmental conditions. This protective mechanism ensures that antigens maintain their structural integrity and functionality throughout their journey in the body, even under physiological stress (Ghobashy et al., 2024; Kumar Sarangi et al., 2023; W. Zhou et al., 2015). Moreover, the nanoscale dimensions of AuNPs enable their preferential uptake by antigen-presenting cells (APCs) such as dendritic cells, macrophages, and B cells, due to their efficient size for endocytosis and trafficking (Chauhan et al., 2021a; Hocevar, 2020; F. Wang et al., 2021). Once internalized, the antigens conjugated to AuNPs are processed and presented on major histocompatibility complex (MHC) molecules, amplifying the immune system's recognition and response (Gamucci et al., 2014; Huang et al., 2023a). The multivalency of AuNPs further allows for the simultaneous delivery of multiple antigens or adjuvants, enhancing the overall immunogenic potential. This targeted and multifaceted delivery system not only improves the efficiency of antigen presentation but also fosters the development of long-lasting and robust immune responses, establishing a strong foundation for both preventive and therapeutic vaccine applications (Dykman & Khlebtsov, 2017a; Mateu Ferrando et al., 2020; C. Wang et al., 2017).

Immune Activation: Functionalized gold nanoparticles (AuNPs) have a remarkable capacity to modulate immune responses by directly interacting with pattern recognition receptors (PRRs) expressed on antigen-presenting cells (APCs), such as dendritic cells, macrophages, and monocytes (Koushki et al., 2021; Z. Li et al., 2023; W. Song et al., 2019). Upon binding to PRRs like toll-like receptors (TLRs) and C-type lectin receptors (CLRs), AuNPs activate intracellular signaling cascades, including the nuclear factor-kappa B (NF-κB) and mitogen-activated protein kinase (MAPK) pathways (Choudhury et al., 2024; Ghosh, 2022). These signaling events lead to the production of pro-inflammatory cytokines (e.g., interleukin-6 and tumor necrosis factor-alpha) and chemokines (e.g., CCL2 and CXCL10), creating a localized inflammatory milieu that recruits and activates additional immune cells (Antony et al., 2024).

Furthermore, AuNPs enhance the expression of co-stimulatory molecules, such as CD80 and CD86, on APCs. This upregulation is crucial for effective T-cell priming and activation, thereby bridging innate and adaptive immune responses (Orlowski et al., 2018; Yuan et al., 2023). AuNPs can also promote cross-presentation, allowing APCs to present exogenous antigens on MHC class I molecules, which is essential for activating cytotoxic T lymphocytes (CTLs) (Chauhan et al., 2021b; Est-Witte et al., 2021; C. G. Kim et al., 2019; Singha et al., 2018; F. Wang et al., 2021). This dual ability to stimulate innate immune pathways and potentiate adaptive immunity underscores the immense potential of AuNPs in vaccine design (D. Comber & Bamezai, 2015; Dings et al., 2018; Tao et al., 2015). By integrating these mechanisms, AuNP-based platforms can elicit robust, long-lasting, and pathogen-specific immune responses suitable for combating infectious diseases and cancers alike (Lim et al., 2021; Yadav & Bharti, 2024).

Adjuvant Effect: Gold nanoparticles (AuNPs) themselves exhibit inherent adjuvant properties, making them a valuable addition to vaccine formulations (Farfán-Castro, García-Soto, Aguilar-Aguilar, et al., 2024a; Mateu Ferrando et al., 2020). Their unique physicochemical attributes enhance the immunogenicity of conjugated antigens by providing a platform for multivalent antigen presentation, which is critical for robust immune activation (Dykman & Khlebtsov, 2017a; Kumar Sarangi et al., 2023). AuNPs achieve this by stimulating the secretion of pro-inflammatory cytokines and chemokines, pivotal signaling molecules that orchestrate the recruitment, activation, and differentiation of immune cells (Elsabahy & Wooley, 2013; Mahhengam et al., 2022; Michelini et al., 2021). This adjuvant effect is driven by the activation of innate immune pathways, particularly through the engagement with pattern recognition receptors (PRRs) such as toll-like receptors (TLRs) and C-type lectin receptors (CLRs) on immune cells (Bhardwaj et al., 2020; Z. Li et al., 2023; Misra et al., 2023). These interactions initiate downstream signaling cascades, including the nuclear factor-kappa B (NF-κB) and interferon regulatory factor (IRF) pathways, leading to enhanced antigen presentation and co-stimulatory molecule expression (Kashfi et al., 2021; Zhu et al., 2023). Furthermore, the nanoscale nature of AuNPs facilitates their uptake and interaction with immune cells, amplifying their ability to stimulate both humoral and cellular immune responses. This dual capability makes AuNPs an exceptional platform for vaccines targeting a wide range of pathogens and cancer antigens (Chattopadhyay et al., 2017; Koushki et al., 2021; Kumar Sarangi et al., 2023).

Targeted Delivery: Gold nanoparticles (AuNPs) can be precisely engineered through surface functionalization with specific ligands such as antibodies, peptides, or small molecules that selectively bind to receptors expressed on lymphoid tissues or specific immune cell populations. This targeting capability enhances the accumulation of vaccine components at desired sites, reducing systemic distribution and minimizing off-target effects, thus increasing the overall efficacy of the vaccine (Chanda et al., 2010; Mateu Ferrando et al., 2020; Sapsford et al., 2013). By concentrating on lymphoid tissues, particularly lymph nodes, which are central hubs for immune activation, AuNPs enable a direct and efficient interaction with antigen-presenting cells (APCs) such as dendritic cells and macrophages. This localized delivery ensures that vaccine antigens are efficiently internalized, processed, and presented to T and B lymphocytes, leading to the activation of both cellular and humoral immune responses (Guo et al., 2024; Luo et al., 2017; Patel et al., 2024; Shukla & Steinmetz, 2016).

Moreover, functionalized AuNPs can incorporate multiple targeting moieties, allowing them to interact with diverse immune cell types simultaneously, further amplifying the immunological response. This ability to "fine-tune" targeting specificity extends to delivering antigens or adjuvants to rare immune cell subsets or tumor microenvironments in cancer immunotherapy (Amina & Guo, 2020; Graczyk et al., 2020; A. Kumar et al., 2024; X. Liu, Xie, et al., 2021; Rahmat et al., 2024; C. Wang et al., 2018). The nanoscale dimensions of AuNPs also improve their penetration and retention in target tissues, enhancing their overall immunostimulatory effects (Chauhan et al., 2021b; Dykman & Khlebtsov, 2017a; J. He et al., 2021). Furthermore, targeted delivery via AuNPs is pivotal in the development of precision medicine approaches, enabling the design of personalized vaccines that address individual patient profiles, such as unique biomarker expression patterns in infectious diseases or cancers (R.

Deshmukh et al., 2024; Dey et al., 2024; Kumar Sarangi et al., 2023). These advances highlight the transformative potential of AuNP-based delivery systems in modern vaccine technology.

3. Advantages of Gold Nanoparticle-Based Vaccines

3.1. Enhanced Stability

Gold nanoparticles (AuNPs) play a pivotal role in preserving the structural integrity and functionality of antigens by acting as a protective shield against enzymatic degradation, aggregation, and adverse environmental conditions such as temperature fluctuations, humidity, or exposure to light. This encapsulation capability ensures that antigens remain intact and active throughout manufacturing, storage, and administration processes, ultimately prolonging the vaccine's shelf life. By significantly reducing the susceptibility of vaccines to degradation, AuNPs alleviate the dependency on stringent cold chain storage requirements, making these vaccines not only cost-effective but also practical for deployment in remote and resource-limited regions where refrigeration infrastructure is scarce or unreliable (Alshangiti et al., 2023; Ghobashy et al., 2024; Khan et al., 2020). Additionally, the unique physicochemical properties of AuNPs, such as their chemical inertness and high thermal stability, provide an extra layer of protection, enabling vaccines to withstand transportation and storage under suboptimal conditions without compromising their immunogenicity. This ensures that vaccines maintain consistent performance across diverse environments, enhancing their applicability in global immunization campaigns (Bai et al., 2020; Duman et al., 2024; Hu et al., 2020). Furthermore, by preventing antigen aggregation, AuNPs facilitate optimal antigen presentation and bioavailability, which is crucial for eliciting robust and targeted immune responses (S. Ahmad et al., 2017; Chauhan et al., 2021c; Huang et al., 2023a). Through these multifaceted contributions, AuNPs address critical challenges in vaccine stability and distribution, marking a significant advancement in the field of immunotherapy (Arcos Rosero et al., 2024; Dastgheib et al., 2024; Wu et al., 2024).

3.2. Improved Immunogenicity

AuNPs boost antigen presentation and T-cell activation. Gold nanoparticles amplify the immune response by serving as highly efficient platforms for antigen presentation (Chauhan et al., 2021c; Lee et al., 2012; Q. Zhou et al., 2016). Their nanoscale size provides an exceptionally high surface area-to-volume ratio, enabling the conjugation of multiple antigen molecules to a single nanoparticle. This feature ensures enhanced interaction with antigen-presenting cells (APCs), improving the efficiency of antigen delivery (S. Ahmad et al., 2017; Dreaden, Austin, et al., 2012; Georgeous et al., 2024; Huang et al., 2023a; Kumar Sarangi et al., 2023). Furthermore, the surface of AuNPs can be modified with a variety of functional groups, allowing for precise attachment of antigens, adjuvants, or targeting ligands. This customizability enhances the specificity of immune targeting, reducing off-target effects and increasing cellular uptake by APCs (Carabineiro, 2017; Chauhan et al., 2021c).

The particulate nature of AuNPs also mimics pathogen-associated molecular patterns (PAMPs), a characteristic that activates innate immune sensors such as toll-like receptors (TLRs). This activation results in the recruitment of immune cells, the release of cytokines, and a robust priming of adaptive immune responses (Farrera & Fadeel, 2015; W. Song et al., 2019). Moreover, the stability of antigens attached to AuNPs prevents premature degradation, ensuring their integrity until they reach the target cells. Together, these features enable AuNPs to elicit stronger, more durable immune responses, making them promising candidates for vaccines against both infectious diseases and cancers. Their ability to stimulate both humoral and cell-mediated immunity further underscores their transformative potential in immunotherapy (Arcos Rosero et al., 2024; Dykman & Khlebtsov, 2014; Tan et al., 2023; W. Zhou et al., 2015).

3.3. Customizable Design

The surface functionalization of AuNPs allows for tailored vaccine formulations. Gold nanoparticles (AuNPs) offer unparalleled flexibility in their design, enabling precise customization to suit diverse biomedical applications. Their unique physical and chemical properties can be tailored by controlling key parameters such as size, shape, surface chemistry, and functionalization (Alex & Tiwari, 2015; Ielo et al., 2021; J. Zhang et al., 2020). The size of AuNPs can be adjusted to influence their interaction with biological systems. For example, smaller nanoparticles can penetrate tissues more easily, while larger ones may be better suited for surface-based applications like imaging. The shape, ranging from spheres and rods to stars and cages, impacts their optical properties, enhancing functions like photothermal therapy or bioimaging (Hang et al., 2024; Khlebtsov et al., 2022; Moreira et al., 2018; Venditti, 2019).

Surface functionalization is another critical aspect of customization. By attaching specific molecules, such as peptides, antibodies, or polymers, AuNPs can target particular cells, improve biocompatibility, or carry therapeutic agents. This versatility makes them highly effective for applications like drug delivery, where targeted therapy minimizes side effects. Additionally, the ease of integrating various functionalities enables AuNPs to perform multiple roles in a single system, such as simultaneous imaging and therapy (theranostics). This customizable nature ensures that AuNPs can be precisely engineered to address specific medical challenges, enhancing their potential for personalized medicine and innovative healthcare solutions (Arcos Rosero et al., 2024; Fratoddi et al., 2014; Goddard et al., 2020; Siddique & Chow, 2020b; Singh et al., 2018).

3.4. Biocompatibility

Biocompatibility is a fundamental aspect of gold nanoparticle (AuNP)-based applications in medicine, determining their safety and effectiveness in biological systems. AuNPs are generally considered biocompatible due to gold's inert nature, minimizing the risk of adverse immune responses or toxicity. This property makes them highly appealing for use in vaccines, drug delivery, imaging, and cancer therapies (Anik et al., 2022; Kadhim et al., 2021; Kus-Liśkiewicz et al., 2021; Versiani et al., 2016).

However, achieving optimal biocompatibility requires careful consideration of several factors. The size, shape, surface charge, and functionalization of AuNPs can significantly influence their interaction with cells and tissues. For instance, improperly designed nanoparticles might induce oxidative stress, inflammation, or toxicity (Bhamidipati & Fabris, 2017; Bodelón et al., 2017; Fernandes et al., 2015). To mitigate such risks, AuNPs are often coated with biocompatible molecules, such as polyethylene glycol (PEG) or specific proteins, which enhance their stability and compatibility within the body (Anik et al., 2022; Arcos Rosero et al., 2024; Kus-Liśkiewicz et al., 2021).

Ensuring biocompatibility is especially important for applications involving repeated or prolonged exposure, such as in vaccine boosters or chronic treatments (Bhardwaj et al., 2020; Dastgheib et al., 2024). Rigorous testing during preclinical and clinical trials is essential to confirm that AuNPs do not elicit harmful effects while maintaining their functional properties. As research advances, the development of standardized guidelines for AuNP synthesis and testing will further enhance their safety and reliability in medical applications, supporting their integration into mainstream healthcare.

3.5. Versatility

AuNPs are effective for both infectious disease vaccines and cancer immunotherapy. Gold nanoparticle (AuNP)-based vaccines have demonstrated exceptional potential in addressing infectious diseases, including influenza, HIV, and COVID-19 (Naghib et al., 2024; Sengupta et al., 2022; Zakharova et al., 2023). The unique properties of AuNPs, such as their ability to stabilize antigens and enhance targeted delivery, ensure robust and durable immune responses. By conjugating antigens from pathogens to AuNPs, these vaccines protect the antigen's structural integrity and promote efficient uptake by antigen-presenting cells (APCs), such as dendritic cells and macrophages. This interaction facilitates antigen processing and presentation, leading to the activation of both humoral and cellular immunity (Achmad et al., 2022; Priyanka et al., 2023; Shen et al., 2018). AuNPs enable multivalent antigen presentation, allowing vaccines to target multiple strains or epitopes simultaneously (Carabineiro, 2017; Farfán-Castro, García-Soto, Aguilar-Aguilar, et al., 2024a; Mateu Ferrando et al., 2020; Sanchez-Villamil et al., 2022). This capability is particularly valuable for rapidly mutating pathogens like influenza or HIV (Draz & Shafiee, 2018; J. Kim et al., 2020). Moreover, the use of AuNPs can reduce antigen dosages while maintaining high immunogenicity, lowering production costs and minimizing adverse effects. As a scalable and adaptable platform, AuNP-based vaccines represent a transformative approach to combating infectious diseases (Arcos Rosero et al., 2024; Huang et al., 2023a).

Gold nanoparticles (AuNPs) have emerged as a powerful tool in cancer immunotherapy, offering unique advantages in the design of effective cancer vaccines (Aikins et al., 2020; J. He et al., 2021; Huang et al., 2023a). These nanoparticles serve as carriers for tumor-associated antigens (TAAs), delivering them directly to antigen-presenting cells (APCs) such as dendritic cells (Aikins et al., 2020; Est-Witte et al., 2021; J. He et al., 2021; Hou et al., 2022). This targeted delivery enhances antigen uptake, processing, and presentation on major histocompatibility complex (MHC) molecules, leading to the activation of cytotoxic T lymphocytes (CTLs) that can selectively destroy cancer cells (S. Ahmad et al., 2017; Chauhan et al., 2021c; Conniot et al., 2014; Huang et al., 2023b). AuNP-based vaccines are particularly effective at overcoming the immunosuppressive tumor microenvironment. Functionalized AuNPs can co-deliver adjuvants, stimulating innate immune responses and amplifying the adaptive immune response. They can also be engineered to target immune checkpoints, reducing tumor-induced immune evasion (Chauhan et al., 2021c; Dings et al., 2018; Gorbet & Ranjan, 2020; J. He et al., 2021; Huang et al., 2023c; Saeed et al., 2019). Preclinical studies have shown that AuNP-based cancer vaccines improve tumor infiltration by effector T cells, inhibit tumor growth, and even achieve complete tumor regression. Their versatility and efficacy make AuNPs a promising platform for advancing personalized cancer immunotherapy (X. He et al., 2018; P. P. P. Kumar et al., 2024; W.-H. Li & Li, 2020; A. Nguyen et al., 2022).

4. Recent Advances

4.1. Infectious Diseases

Gold nanoparticle (AuNP)-based vaccines have emerged as a powerful tool in combating various infectious diseases, including influenza, HIV, and COVID-19 (Naghib et al., 2024; Sengupta et al., 2022; Zakharova et al., 2023). By leveraging the unique physicochemical properties of AuNPs, such as their ability to enhance antigen stability and facilitate targeted delivery, these vaccines have demonstrated the capacity to elicit robust and sustained immune responses. For example, in the context of the COVID-19 pandemic, conjugating the spike proteins of SARS-CoV-2 to AuNPs has shown remarkable efficacy in preclinical studies, enhancing both humoral and cellular immune responses (Farfán-Castro, García-Soto, Betancourt-Mendiola, et al., 2024; U. S. Kumar et al., 2021; Medhi et al., 2020; Rauf et al., 2022).

Furthermore, AuNPs enable precise functionalization with pathogen-specific antigens and adjuvants, allowing for the creation of multivalent vaccines that target multiple strains or epitopes simultaneously. This adaptability is particularly valuable in addressing the rapid mutation rates observed in viruses like influenza and HIV, where traditional vaccines often struggle to keep pace. Studies have also indicated that AuNP-based platforms can reduce the required antigen dose while maintaining or even amplifying immunogenicity, thereby lowering production costs and minimizing potential side effects. These promising findings underscore the potential of AuNP-based vaccines to revolutionize the prevention and control of infectious diseases by providing a scalable, adaptable, and highly effective immunization strategy (Bhardwaj et al., 2020; Mateu Ferrando et al., 2020; Panigrahi et al., 2022; Shetty et al., 2024; Yenkoidiok-Douti & Jewell, 2020).

4.2. Cancer Immunotherapy

Gold nanoparticles (AuNPs) have emerged as a transformative tool in cancer immunotherapy, primarily by enhancing the efficacy and specificity of cancer vaccines. These nanoparticles serve as carriers for tumor-associated antigens (TAAs), facilitating their delivery to dendritic cells and other antigen-presenting cells (APCs) (Aikins et al., 2020; N. L. Dhas et al., 2018; Est-Witte et al., 2021; J. He et al., 2021; Hou et al., 2022; Huang et al., 2023c). This targeted delivery ensures the efficient internalization, processing, and presentation of TAAs on major histocompatibility complex (MHC) molecules, a crucial step in activating cytotoxic T lymphocytes (CTLs) that can identify and destroy cancer cells (X. Chen & Zhang, 2020; Conniot et al., 2014; Huang et al., 2023c; A. Nguyen et al., 2022).

One of the remarkable advantages of AuNP-based cancer vaccines is their ability to generate robust and sustained immune responses. Studies have demonstrated that AuNPs, functionalized with TAAs and adjuvants, can significantly enhance both cellular and humoral immune responses. This results in improved tumor infiltration by effector T cells, inhibition of tumor growth, and, in some cases, complete tumor regression in preclinical models (Farfán-Castro, García-Soto, Betancourt-Mendiola, et al., 2024; U. S. Kumar et al., 2021; Medhi et al., 2020; Rauf et al., 2022). Furthermore, the nanoscale size of AuNPs allows them to penetrate the tumor microenvironment effectively, overcoming barriers such as high interstitial pressure and dense extracellular matrices that often limit the efficacy of conventional therapies (Huo et al., 2020; Mahhengam et al., 2022; Omidi & Barar, 2014).

In addition to their role in antigen delivery, AuNPs can be engineered to co-deliver adjuvants that amplify the immune response. By engaging pattern recognition receptors (PRRs) on APCs, these adjuvants trigger innate immune pathways that enhance the

immunostimulatory properties of cancer vaccines. AuNPs can also be functionalized with ligands or molecules that target specific immune checkpoints, providing a dual function as both a vaccine platform and an immunomodulatory agent (Chauhan et al., 2021c; J. He et al., 2021; Z. Li et al., 2023; Peng et al., 2024; Ren et al., 2023; C. Wang et al., 2017; Yi et al., 2023a).
Emerging research has highlighted the potential of AuNP-based cancer vaccines in combination therapies. When used alongside immune checkpoint inhibitors or other immunotherapeutic agents, AuNPs can synergistically enhance anti-tumor immune responses by targeting multiple pathways simultaneously. This approach has shown promise in overcoming immune resistance mechanisms, which are a major challenge in cancer immunotherapy (J. He et al., 2021; Huang et al., 2023c; Qin et al., 2023; L. Zhou et al., 2021).
Overall, AuNP-based platforms represent a versatile and potent strategy in cancer immunotherapy, offering improved targeting, enhanced immunogenicity, and the ability to integrate with other therapeutic modalities. These advancements underscore the growing importance of AuNPs in developing next-generation cancer vaccines aimed at achieving durable and personalized cancer treatment outcomes. In cancer vaccines, AuNPs are used to deliver tumor-associated antigens (TAAs) to dendritic cells, eliciting robust cytotoxic T-cell responses (Dong et al., 2023; Huang et al., 2023c; X. Liu, Su, et al., 2021). Studies have shown that AuNP-based cancer vaccines can inhibit tumor growth and improve survival rates in animal models (Dings et al., 2018; Hosseini et al., 2023; Huang et al., 2023c).

4.3. Combination Therapies
Gold nanoparticles (AuNPs) are increasingly being integrated into combination therapies to enhance the efficacy of cancer immunotherapy. By acting as a delivery platform for tumor-associated antigens (TAAs), AuNPs facilitate the activation of immune responses that can be further amplified when used alongside other therapeutic agents. For example, combining AuNP-based vaccines with immune checkpoint inhibitors, such as anti-PD-1 or anti-CTLA-4 antibodies, can synergistically promote T-cell activation and reduce immune evasion by tumors (Gowsalya et al., 2024; A. Nguyen et al., 2022; Tang et al., 2022; Z. Wang et al., 2018).
Additionally, AuNPs can be functionalized to co-deliver multiple therapeutic agents, such as adjuvants and small molecule drugs, directly to the tumor microenvironment (Kemp et al., 2016; Peng et al., 2024). This targeted approach not only reduces systemic toxicity but also maximizes the therapeutic impact by addressing multiple pathways of tumor progression and immune suppression simultaneously (Gupta & Malviya, 2021; Huang et al., 2023c; Mendes et al., 2017). Research has also shown that AuNPs can improve the efficacy of radiation therapy by serving as radiosensitizers, thereby complementing immunotherapy to achieve a more comprehensive anti-tumor effect (H. Li et al., 2023; N. Sun et al., 2024; Varzandeh et al., 2023; Yu et al., 2022).
The versatility of AuNPs in combination therapies underscores their potential to overcome resistance mechanisms that often limit the success of standalone treatments. By integrating AuNP-based platforms into multimodal therapeutic regimens, researchers aim to develop more effective and durable strategies for cancer management, paving the way for personalized and precision medicine approaches are also being explored in combination with immune checkpoint inhibitors, amplifying the therapeutic effects of cancer immunotherapy by simultaneously targeting multiple pathways (Farhana, 2023; Gorbet & Ranjan, 2020; Y. Li et al., 2024; Sandbhor et al., 2024).

5. CHALLENGES

5.1. Toxicity Concerns
Although AuNPs are generally biocompatible, their accumulation in tissues may pose long-term risks, including potential cytotoxic effects and chronic inflammation. Prolonged retention of AuNPs in specific organs, such as the liver, spleen, and kidneys, could lead to disruptions in normal cellular processes or trigger immune responses (Hashim et al., 2022; Haute & Berlin, 2017; Niżnik et al., 2024; Y. Zhang et al., 2014). Additionally, the surface coatings or functionalization of AuNPs, while enhancing their efficacy, might influence their toxicity profiles, necessitating extensive evaluation. Addressing these concerns requires rigorous preclinical and clinical studies to optimize nanoparticle design for minimal toxicity and maximum safety in long-term applications (T. Ahmad et al., 2021; Fratoddi et al., 2014; Hornos Carneiro & Barbosa, 2016; Kus-Liśkiewicz et al., 2021; Niżnik et al., 2024).

5.2. Regulatory Hurdles
The approval process for nanotechnology-based vaccines involves rigorous evaluation of safety and efficacy, necessitating adherence to both established vaccine development guidelines and emerging regulatory frameworks for nanomaterials. Regulatory agencies, such as the FDA and EMA, require detailed characterization of the nanoparticles, including their physicochemical properties, biodistribution, and potential toxicological effects (Abdel-Mageed et al., 2021; Desai, 2012; Hirulkar et al., 2024). These evaluations must also account for the novel interactions of AuNPs with biological systems, which may not align with conventional vaccine assessment protocols. As a result, developers face challenges in designing comprehensive preclinical and clinical studies that satisfy regulatory standards while addressing the unique attributes of nanotechnology-based platforms. Bridging these gaps requires ongoing collaboration between researchers, industry, and regulatory bodies to establish clear and efficient approval pathways (Aikins et al., 2020; Desai, 2012; Souto et al., 2024).

5.3. Cost
Cost is a critical consideration in the development and deployment of gold nanoparticle (AuNP)-based technologies in medicine. While AuNPs offer numerous advantages in vaccine development, diagnostics, and therapeutics, their economic feasibility must be carefully evaluated to ensure scalability and accessibility. The synthesis of AuNPs, although increasingly streamlined, involves precise control over size, shape, and surface functionalization, which can increase production costs. The incorporation of specialized biomolecules, such as antigens, antibodies, or adjuvants, further adds to the expense. Additionally, high-quality purification processes are required to ensure the biocompatibility and safety of the nanoparticles for medical applications (Ghobashy et al., 2024; Hemdan et al., 2024; Koushki et al., 2021; Ramachandran et al., 2024).
Despite these costs, AuNP-based solutions may offer long-term economic benefits. Their high stability and efficiency mean smaller doses of active materials can be used, potentially reducing manufacturing costs for vaccines and therapies. Furthermore, their ability to enable early diagnosis and personalized treatment can lead to significant healthcare savings by improving outcomes

and reducing the need for prolonged treatment. Efforts are underway to optimize AuNP production techniques and explore alternative materials that balance efficacy with affordability. As these advancements continue, AuNP-based technologies may become increasingly cost-effective, enabling broader adoption in both developed and developing healthcare systems (Draz & Shafiee, 2018; Hernández-Neuta et al., 2019; Huang et al., 2023a; Karnwal et al., 2024; Naghib et al., 2024).

5.4. Scalability

Manufacturing processes for gold nanoparticle-based vaccines must be optimized to meet the demands of large-scale production. This involves developing cost-effective and reproducible synthesis techniques that ensure uniform size, shape, and surface properties of AuNPs. Consistency in nanoparticle quality is critical for maintaining vaccine efficacy and safety. Scaling up also requires advancements in conjugation strategies to efficiently attach antigens and adjuvants to nanoparticles without compromising their stability or bioactivity. Furthermore, integrating these processes into existing industrial frameworks is essential to minimize production costs and facilitate widespread adoption. Regulatory compliance presents another layer of complexity, as large-scale production must adhere to stringent standards for quality control and validation. Addressing these challenges will require interdisciplinary collaboration among nanotechnologists, immunologists, and manufacturing experts to develop robust, scalable production pipelines. Successfully overcoming these hurdles will pave the way for making gold nanoparticle-based vaccines accessible to global populations, particularly in resource-limited settings where scalable and cost-effective solutions are most needed (Hosseini et al., 2023; D. Liu et al., 2024; Mostafavi et al., 2022; Paliwal et al., 2014; Souto et al., 2024).

6. Future Directions

6.1. Personalized Vaccines

Gold nanoparticles (AuNPs) are emerging as a key platform for the development of personalized vaccines tailored to an individual's unique genetic and immunological profile. Unlike traditional "one-size-fits-all" vaccines, personalized vaccines are designed to target specific antigens derived from an individual's own cells, such as tumor-specific antigens in cancer or unique pathogen variants in infectious diseases (Bhardwaj et al., 2020; Chauhan et al., 2021c; Dykman & Khlebtsov, 2017b; Trabbic et al., 2021). AuNPs enhance the efficacy of personalized vaccines by acting as carriers that protect the antigens from degradation and deliver them efficiently to immune cells. Their high surface area allows for the attachment of multiple antigens and adjuvants, enabling a robust and tailored immune response. Additionally, the size, shape, and surface chemistry of AuNPs can be engineered to optimize cellular uptake and antigen presentation (Aikins et al., 2020; Brinãs et al., 2012; D. Comber & Bamezai, 2015; Dykman & Khlebtsov, 2014).

In cancer immunotherapy, for example, AuNPs can deliver neoantigens- proteins arising from tumor-specific mutations to dendritic cells, activating T-cells to specifically target and destroy cancer cells (Aikins et al., 2020; Barchi, 2022; Gurunathan et al., 2024; Hou et al., 2022; Zou et al., 2024). Similarly, in infectious diseases, AuNP-based vaccines can be customized to address emerging strains or drug-resistant pathogens. AuNPs also enable real-time monitoring of vaccine efficacy through imaging and diagnostic techniques, providing immediate feedback to refine treatment strategies. This personalized approach not only improves efficacy but also minimizes adverse reactions, making AuNP-based vaccines a promising tool for precision medicine (J. Kang et al., 2021; Mukherjee et al., 2024; Sherilraj et al., 2024; Yadav & Bharti, 2024).

6.2. Clinical Translation

More clinical trials are needed to validate the efficacy and safety of AuNP-based vaccines. Conducting large-scale clinical trials to validate the efficacy and safety of gold nanoparticle-based vaccines is a critical step in translating this innovative technology from the laboratory to widespread clinical use. Such trials must involve diverse populations to ensure broad applicability and identify any variations in response due to genetic, environmental, or lifestyle factors. These studies will evaluate not only the immunogenicity and protective effects of AuNP-based vaccines but also their long-term safety, including potential accumulation and clearance of nanoparticles in the body. Comprehensive phase I, II, and III trials will be necessary to assess dose optimization, immune response durability, and effectiveness across different disease contexts, such as infectious diseases and cancers. Moreover, these trials should incorporate advanced biomarker analysis and imaging technologies to monitor the biodistribution and interaction of AuNPs with biological systems in real-time. This data will provide valuable insights into the mechanisms of action and any potential off-target effects. Collaboration between academic institutions, pharmaceutical companies, and regulatory agencies will be essential to streamline the design and execution of these trials, ensuring compliance with ethical and safety standards. Successfully completing these clinical trials will not only establish the credibility of AuNP-based vaccines but also pave the way for their approval and integration into public health programs globally (J. Chen & Cong, 2023; Kumbhar et al., 2023; Mateu Ferrando et al., 2020; Mundekkad & Cho, 2022; Shan et al., 2022; Wahab et al., 2023; Younis et al., 2022).

6.3. Multifunctional Platforms: Developing multifunctional AuNPs that combine antigen delivery, adjuvancy, and imaging capabilities could further enhance their utility.

Antigen delivery: Gold nanoparticles (AuNPs) excel as antigen carriers in vaccine development due to their ability to enhance stability, ensure targeted delivery, and promote efficient antigen presentation. AuNPs protect antigens from degradation by enzymes and environmental factors, preserving their structural integrity and immunogenicity. This shielding effect is particularly valuable for vaccines requiring storage or transport in suboptimal conditions (Arcos Rosero et al., 2024; Jiang, 2021; Kader, 2024; Reddy, 2022; Sekimukai et al., 2020). The nanoscale size of AuNPs facilitates their uptake by antigen-presenting cells (APCs), such as dendritic cells and macrophages, through endocytosis. Once internalized, antigens conjugated to AuNPs are processed and presented on major histocompatibility complex (MHC) molecules, a critical step for activating T cells and initiating a robust adaptive immune response (Chauhan et al., 2021c; Dykman & Khlebtsov, 2017b; Michelini et al., 2021; F. Wang et al., 2021). AuNPs also allow for multivalent antigen delivery, enabling the simultaneous presentation of multiple antigens or a combination of antigens and adjuvants. This multivalency enhances the breadth and potency of the immune response, making AuNP-based delivery systems highly effective for combating infectious diseases and cancers (Bhardwaj et al., 2020; Dykman, 2020; Farfán-Castro, García-Soto, Aguilar-Aguilar, et al., 2024b; Mateu Ferrando et al., 2020).

Adjuvancy: Gold nanoparticles (AuNPs) exhibit intrinsic adjuvant properties that amplify immune responses, making them a valuable component of advanced vaccine platforms. Their unique physicochemical characteristics enhance the immunogenicity of conjugated antigens by facilitating multivalent presentation, which is crucial for effective activation of immune cells. The high surface area-to-volume ratio of AuNPs allows for the simultaneous attachment of multiple antigens and adjuvants, creating a concentrated immunostimulatory platform (Akbar et al., 2022; Khatua et al., 2024; Negahdaripour et al., 2017; C. Song et al., 2020; Yi et al., 2023a). When introduced into the body, AuNPs interact with pattern recognition receptors (PRRs) on antigen-presenting cells (APCs), such as toll-like receptors (TLRs) and C-type lectin receptors (CLRs). This interaction triggers intracellular signaling pathways, including the nuclear factor-kappa B (NF-κB) and interferon regulatory factor (IRF) cascades, resulting in the secretion of pro-inflammatory cytokines and chemokines. These molecules recruit and activate additional immune cells, creating a robust localized inflammatory response (Z. Li et al., 2023; Misra et al., 2023; F. Wang et al., 2021; Yi et al., 2023b). Moreover, AuNPs upregulate co-stimulatory molecule expression on APCs, enhancing T-cell priming and activation. Their ability to induce cross-presentation, where exogenous antigens are displayed on MHC class I molecules, further strengthens cytotoxic T lymphocyte (CTL) responses. This dual enhancement of innate and adaptive immunity makes AuNP-based adjuvants highly versatile for vaccines targeting diverse pathogens and cancer antigens (Bhardwaj et al., 2020; Chauhan et al., 2021a; S. Kang et al., 2017; C. G. Kim et al., 2019).

Imaging: Gold nanoparticles (AuNPs) are revolutionizing biomedical imaging due to their exceptional optical, electronic, and surface properties. They serve as versatile contrast agents, enhancing the resolution and sensitivity of various imaging modalities (Hossain et al., 2024; Naghib et al., 2024; Yadav & Bharti, 2024). The ability of AuNPs to strongly absorb and scatter light, particularly in the visible and near-infrared (NIR) regions, makes them ideal for optical imaging techniques such as dark-field microscopy and surface-enhanced Raman scattering (SERS) (Dreaden, Alkilany, et al., 2012; Shanmugam et al., 2014; Sharifi et al., 2019; Yao et al., 2023; W. Zhou et al., 2015). In computed tomography (CT), AuNPs outperform conventional iodine-based agents due to their higher X-ray attenuation coefficient. This enables detailed visualization of structures and abnormalities with prolonged imaging windows, reducing the need for repeated injections (Anik et al., 2022; March, 2020; Owens et al., 2023). Similarly, AuNPs can be engineered for photoacoustic imaging, where they convert absorbed light into ultrasonic waves, providing high-contrast, high-resolution images of tissues and tumors (Copland et al., 2004; W. Li & Chen, 2015; Siddique & Chow, 2020a; I.-C. Sun et al., 2021). Moreover, AuNPs are easily functionalized with targeting ligands like antibodies, peptides, or small molecules. This specificity allows precise delivery to cellular or molecular targets, enabling real-time monitoring of biological processes or disease progression (Arcos Rosero et al., 2024; Carabineiro, 2017; Dykman & Khlebtsov, 2017a; Zong et al., 2017b). Additionally, their biocompatibility and tunable size make AuNPs suitable for applications in multimodal imaging, combining two or more imaging techniques for comprehensive diagnostics (Dastgheib et al., 2024; Van De Looij et al., 2022; C. Wang et al., 2019). By integrating AuNPs with cutting-edge imaging platforms, researchers and clinicians are advancing non-invasive diagnostics and enabling early detection of diseases such as cancer, cardiovascular disorders, and neurodegenerative conditions (Abid et al., 2024; Kader, 2024; F. Li et al., 2023; López-Espinosa et al., 2024).

7. Conclusion

Gold nanoparticle-based vaccines stand at the cutting edge of immunotherapy, presenting groundbreaking possibilities to revolutionize traditional vaccination strategies. These nanoparticles enhance antigen delivery and stability while offering robust immune activation mechanisms, effectively addressing limitations inherent in conventional vaccine platforms. By merging the precision of nanotechnology with the versatility required for combating infectious diseases and cancers, AuNPs promise to expand the horizons of medical science.

Despite challenges such as toxicity concerns, regulatory hurdles, and scalability issues, the continuous advancements in this field herald a transformative era in personalized medicine and multifunctional vaccine development. With sustained research and innovation, gold nanoparticles hold the potential to redefine global vaccination strategies, offering scalable and efficient solutions tailored to meet diverse medical needs in the 21st century.

Gold nanoparticle-based vaccines represent a promising frontier in immunotherapy, offering numerous advantages over traditional vaccine platforms. By enhancing antigen delivery, stability, and immune activation, AuNPs have the potential to transform the landscape of vaccination for both infectious diseases and cancer. Continued research and innovation are essential to address existing challenges and unlock the full potential of this transformative technology.

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Conflict of interest

The author declares no conflict of interest.

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