Journal of Vaccine Research 2024, Vol.14, No.5, 243-254
http://medscipublisher.com/index.php/jvr

Research Insight Open Access

# Nanoparticle Vaccines: Mechanisms of Action and Clinical Applications

Jianhui Li
Institute of Life Science, Jiyang College of Zhejiang AandF University, Zhuji, 311800, Zhejiang, China
Corresponding email: jianhui.li@jicat.org

Journal of Vaccine Research, 2024, Vol.14, No.5 doi: 10.5376/jvr.2024.14.0023
Received: 07 Aug., 2024
Accepted: 13 Sep., 2024
Published: 27 Sep., 2024



**Preferred citation for this article:**
Li J.H., 2024, Nanoparticle vaccines: Mechanisms of action and clinical applications, Journal of Vaccine Research, 14(5): 243-254 (doi: 10.5376/jvr.2024.14.0023)

**Abstract** In recent years, nanoparticle vaccines have gained widespread application in combating infectious diseases and cancer immunotherapy, particularly highlighted by the remarkable success of lipid nanoparticle-based mRNA vaccines during the COVID-19 pandemic. However, the development of nanoparticle vaccines still faces challenges related to manufacturing, stability, and safety. This study analyzes the types of nanoparticle vaccines, their mechanisms of action, and their broad clinical applications. It focuses on the use of lipid, polymer, and inorganic nanoparticles in vaccine development, explaining how they enhance immune responses through antigen presentation, targeted delivery, and adjuvant effects. The study also evaluates the application of nanoparticle vaccines in infectious diseases, cancer, and autoimmune diseases, and reviews the success of nanoparticle-based vaccines in COVID-19. Findings indicate that nanoparticle vaccines not only significantly improve immune responses but also offer controlled release properties and versatile formulation options, making them widely applicable in the fields of infectious diseases and cancer immunotherapy. A deeper understanding of the mechanisms and clinical applications of nanoparticle vaccines will not only aid in the development of more efficient and safer vaccines but also promote the advancement of personalized medicine and universal vaccines. The multifunctionality and design flexibility of nanoparticles provide innovative avenues for the development of new vaccines, addressing the limitations of traditional vaccines in immunogenicity and dosage constraints.

**Keywords** Nanoparticle vaccines; Immune activation; Targeted delivery; COVID-19; Vaccine development

## 1 Introduction

Nanoparticle vaccines represent a cutting-edge advancement in the field of immunization, leveraging the unique properties of nanoparticles to enhance vaccine efficacy. These vaccines utilize nanoparticles, which are structures with dimensions ranging from 1 to 1 000 nm, to deliver antigens in a manner that mimics the natural presentation of pathogens, thereby eliciting a robust immune response. The development of nanoparticle vaccines has been driven by the need to address the limitations of traditional vaccines, such as low immunogenicity and the risk of reversion to pathogenic forms in live-attenuated vaccines (Zhao et al., 2014; Pati et al., 2018; Kelly et al., 2019).

The concept of nanoparticle vaccines is not entirely new, with the first successful use of virus-like particles (VLPs) for vaccination against Hepatitis B reported nearly four decades ago (Gomes et al., 2017). Since then, the field has expanded significantly, with various types of nanoparticles, including liposomes, polymers, and inorganic particles, being explored for their potential to improve vaccine delivery and efficacy (Cappellano et al., 2021; Curley and Putnam, 2022). Recent advancements in nanotechnology have enabled the precise control of nanoparticle size, shape, and surface properties, which are critical for optimizing antigen presentation and immune activation (Lung et al., 2020; Bezbaruah et al., 2022). Despite these advancements, challenges remain, particularly in understanding the in vivo behavior of nanoparticles and their interactions with the immune system (Zhao et al., 2014).

Nanoparticle-based delivery systems offer several advantages over traditional vaccine formulations. These systems can protect antigens from premature degradation, facilitate targeted delivery to antigen-presenting cells, and provide controlled release of antigens, thereby enhancing both humoral and cell-mediated immune responses (Pati et al., 2018; Nguyen and Tolia, 2021; Tursi et al., 2023). Additionally, nanoparticles can be engineered to include adjuvants that further boost the immune response, making them highly versatile platforms for vaccine development (Kelly et al., 2019; Curley and Putnam, 2022). The ability to display antigens in a repetitive, ordered

array on the surface of nanoparticles mimics the natural presentation of pathogens, leading to stronger engagement with B cell receptors and enhanced T cell help in driving B cell activation (Kelly et al., 2019; Nguyen and Tolia, 2021).

This study provides a comprehensive overview of the mechanisms of action and clinical applications of nanoparticle vaccines. By synthesizing existing knowledge on the immunological basis, development process, and clinical potential of nanoparticle vaccines, it highlights the transformative impact of nanotechnology on vaccine design and efficacy. Understanding these mechanisms is crucial for the rational design of next-generation vaccines that can effectively address both existing and emerging infectious diseases. It also offers insights for future vaccine development strategies, contributing to improved global public health outcomes.

## 2 Types of Nanoparticles Used in Vaccines

### 2.1 Lipid-based nanoparticles

Lipid-based nanoparticles (LNPs) have emerged as a cornerstone in the development of modern vaccines, particularly highlighted by their pivotal role in the COVID-19 mRNA vaccines. These nanoparticles, which include liposomes, solid lipid nanoparticles, and nanostructured lipid carriers, offer several advantages such as enhanced stability, targeted delivery, and controlled release of antigens (Thi et al., 2021; Namiot et al., 2023). Liposomes, the earliest form of LNPs, have been extensively studied and utilized due to their biocompatibility and ability to encapsulate both hydrophilic and hydrophobic substances. Subsequent generations of LNPs, such as solid lipid nanoparticles and nanostructured lipid carriers, have been developed to improve physical stability and drug loading capacity (Tenchov et al., 2021).

The success of LNPs in the COVID-19 vaccines, such as those developed by Pfizer and Moderna, underscores their potential in vaccine delivery. These LNPs protect the encapsulated mRNA, enhancing its stability and facilitating its delivery to target cells (Sarangi et al., 2022). Moreover, the versatility of LNPs allows for the incorporation of various adjuvants and antigens, making them suitable for a wide range of vaccines, including those for infectious diseases and cancer (Chatzikleanthous et al., 2021). Despite their success, challenges remain in optimizing the physicochemical properties of LNPs for specific applications and understanding their in vivo behavior to further enhance their efficacy and safety (Thi et al., 2021; Namiot et al., 2023).

### 2.2 Polymer-based nanoparticles

Polymer-based nanoparticles represent another significant class of nanocarriers used in vaccine development. These nanoparticles are composed of biodegradable and biocompatible polymers such as poly(lactic-co-glycolic acid) (PLGA), chitosan, and polyethylene glycol (PEG). Polymer-based nanoparticles offer several advantages, including controlled release of antigens, protection of antigens from degradation, and the ability to co-deliver multiple antigens and adjuvants (Zhao et al., 2014; Pati et al., 2018). The versatility in the design of polymer-based nanoparticles allows for the fine-tuning of their size, surface charge, and hydrophobicity, which are critical parameters for optimizing their interaction with the immune system.

One of the key benefits of polymer-based nanoparticles is their ability to enhance the immunogenicity of antigens. By providing a sustained release of antigens, these nanoparticles can prolong the exposure of the immune system to the antigen, thereby enhancing the immune response (Pati et al., 2018). Additionally, polymer-based nanoparticles can be engineered to target specific cells or tissues, further improving the efficacy of the vaccine. Despite these advantages, challenges such as potential toxicity, scalability of production, and regulatory hurdles need to be addressed to fully realize the potential of polymer-based nanoparticles in vaccine development (Zhao et al., 2014; Pati et al., 2018).

### 2.3 Inorganic nanoparticles

Inorganic nanoparticles, including gold nanoparticles, silica nanoparticles, and iron oxide nanoparticles, have also been explored for their potential in vaccine delivery. These nanoparticles offer unique properties such as ease of functionalization, stability, and the ability to induce strong immune responses (Zhao et al., 2014; Curley and Putnam, 2022). Gold nanoparticles, for example, can be easily synthesized and functionalized with various

biomolecules, making them suitable for delivering antigens and adjuvants. Their ability to enhance the presentation of antigens to immune cells and induce robust immune responses has been demonstrated in several studies (Curley and Putnam, 2022).

Silica nanoparticles are another promising class of inorganic nanoparticles used in vaccine development. Their porous structure allows for high loading capacity of antigens and adjuvants, and their surface can be easily modified to improve biocompatibility and targeting (Zhao et al., 2014). Iron oxide nanoparticles, on the other hand, offer the added advantage of being used as contrast agents in magnetic resonance imaging (MRI), providing a dual function of vaccine delivery and diagnostic imaging (Curley and Putnam, 2022). However, the use of inorganic nanoparticles in vaccines also presents challenges, including potential toxicity, long-term biocompatibility, and the need for extensive safety evaluations (Zhao et al., 2014; Curley and Putnam, 2022).

## 3 Mechanisms of Action of Nanoparticle Vaccines

### 3.1 Antigen presentation and immune activation

Nanoparticle vaccines enhance antigen presentation and immune activation through several mechanisms. One key mechanism is the efficient delivery of antigens to antigen-presenting cells (APCs) such as dendritic cells (DCs) and macrophages. For instance, guanidinylated cationic nanoparticles have been shown to encapsulate antigens and facilitate their uptake by DCs, leading to enhanced antigen presentation and subsequent immune activation. These nanoparticles stimulate the maturation of DCs and increase the production of cytokines, which are crucial for initiating and sustaining immune responses. Additionally, nanoparticles can promote antigen cross-presentation, a process where exogenous antigens are presented on MHC class I molecules, thereby activating CD8+ T cells and inducing robust cellular immune responses (Li et al., 2016).

Another example is the use of aminated β-glucan and CpG-oligodeoxynucleotides (CpG-OND) in nanoparticle formulations. These nanoparticles target and activate specific receptors on APCs, such as dectin-1 and Toll-like receptor 9 (TLR9), enhancing antigen uptake and processing. This dual targeting approach significantly boosts both humoral and cellular immune responses, comparable to traditional adjuvants like Freund's adjuvant but with reduced toxicity (Jin et al., 2018). The ability of nanoparticles to enhance antigen presentation and immune activation is a critical factor in their effectiveness as vaccine platforms.

### 3.2 Targeted delivery

Targeted delivery is another crucial mechanism by which nanoparticle vaccines enhance immune responses. Nanoparticles can be engineered to target specific tissues or cells, improving the localization and concentration of antigens at the desired site (Xuan, 2024). For example, ultra-small nanoparticles (25 nm) have been shown to efficiently enter lymphatic capillaries and target lymph node-residing dendritic cells via interstitial flow. This targeted delivery ensures that a significant proportion of the antigen reaches the lymph nodes, where immune responses are initiated (Reddy et al., 2007). In contrast, larger nanoparticles (100 nm) are less efficient in targeting lymph nodes, highlighting the importance of nanoparticle size in targeted delivery.

Moreover, nanoparticles can be designed to exploit natural transport mechanisms within the body. For instance, nanoparticles coated with polyethylenimine (PEI) can enhance the uptake of antigens by macrophages and promote their migration to draining lymph nodes. This targeted delivery not only improves antigen presentation but also prolongs the duration of antigen exposure, leading to more sustained immune responses (Gu et al., 2019). The ability to precisely target and deliver antigens to specific immune cells or tissues is a significant advantage of nanoparticle vaccines.

### 3.3 Adjuvant effects

Nanoparticles also exhibit adjuvant effects, which are essential for enhancing the immunogenicity of vaccines. These effects can be attributed to the inherent properties of the nanoparticles themselves or the incorporation of additional immunostimulatory molecules. For example, nanoparticles made of biodegradable materials such as poly(lactic-co-glycolic acid) (PLGA) can act as adjuvants by promoting the activation of dendritic cells and the production of pro-inflammatory cytokines (Silva et al., 2013). This activation is crucial for the initiation of adaptive immune responses.

Additionally, nanoparticles can be designed to include specific adjuvants that further enhance their immunostimulatory properties. For instance, cyclic dinucleotides (CDNs) encapsulated within PEGylated lipid nanoparticles have been shown to target lymph nodes and induce strong CD8+ T cell responses. This nanoparticulate delivery system enhances the efficacy of the adjuvant while minimizing systemic toxicity (Hanson et al., 2015). The combination of delivery and adjuvant effects in nanoparticle vaccines results in more potent and durable immune responses, making them a promising platform for vaccine development.

## 4 Clinical Applications of Nanoparticle Vaccines

### 4.1 Infectious diseases: COVID-19 vaccines utilizing lipid nanoparticles

Lipid nanoparticles (LNPs) have played a crucial role in the rapid development and success of COVID-19 vaccines. These nanoparticles serve as delivery vehicles for mRNA, protecting the genetic material and facilitating its delivery into cells. The mRNA-1273 vaccine, developed by Moderna, is a prime example of this technology. It encodes the spike protein of SARS-CoV-2 and has demonstrated a 94.1% efficacy in preventing COVID-19 illness, including severe disease, in a phase 3 clinical trial (Baden et al., 2022). The Pfizer-BioNTech vaccine also utilizes LNPs to deliver mRNA, showcasing the versatility and effectiveness of this delivery system (Jung et al., 2022). The success of these vaccines underscores the potential of LNPs in addressing infectious diseases rapidly and effectively (Tenchov et al., 2021;Thi et al., 2021; Sarangi et al., 2022).

### 4.2 Cancer vaccines: nanoparticles used in therapeutic vaccines for tumor-specific antigens

Nanoparticle-based cancer vaccines have shown promise in the treatment of various cancers by targeting tumor-specific antigens. One notable example is the use of RNA-lipoplexes for melanoma treatment. These RNA-based vaccines can be personalized to target specific mutations in a patient's tumor, enhancing the immune response against cancer cells. The Lipo-MERIT vaccine, which consists of RNA lipoplexes encoding shared tumor antigens, has successfully transitioned from bench to bedside, demonstrating the feasibility of this approach in clinical settings (Grabbe et al., 2016). Additionally, lipid-mRNA nanoparticles are being explored for their potential in cancer immunotherapy and gene editing techniques, further expanding the therapeutic applications of nanoparticle vaccines in oncology (Wang et al., 2021; Li et al., 2022).

Li et al. (2022) discovered that RNA-LNP (lipid nanoparticle) vaccines show great potential in cancer immunotherapy, particularly against tumor-specific antigens. By encoding tumor antigens as mRNA and encapsulating them within lipid nanoparticles, the vaccine can effectively guide the host immune system to generate a strong response against tumors (Figure 1). The nanoparticles enhance the stability of mRNA and improve cellular uptake efficiency, thereby increasing antigen expression and immunogenicity. This approach not only helps in the specific elimination of tumor cells but also offers a personalized and low-side-effect solution for cancer treatment, with broad application prospects.

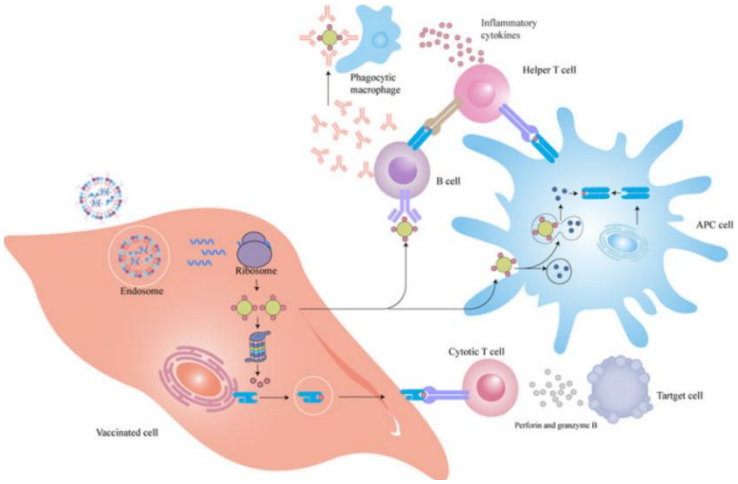


Figure 1 Mechanism of Action of mRNA-LNP (Lipid Nanoparticle) Vaccine in Cancer Immunotherapy (Adapted from Li et al., 2022)

### 4.3 Allergy and autoimmune disease vaccines: Potential for nanoparticle vaccines to induce immune tolerance

Nanoparticle vaccines hold significant potential in the treatment of allergies and autoimmune diseases by inducing immune tolerance. The ability of nanoparticles to deliver antigens in a controlled manner can help modulate the immune system, reducing hypersensitivity and autoimmune responses. While the clinical application of nanoparticle vaccines in this area is still in its early stages, the principles demonstrated in infectious disease and cancer vaccines provide a strong foundation for future developments. The precise delivery and controlled release capabilities of nanoparticles make them ideal candidates for developing vaccines that can induce long-lasting immune tolerance, potentially transforming the management of allergies and autoimmune diseases (Tenchov et al., 2021; Thi et al., 2021; Jung et al., 2022).

## 5 Advantages of Nanoparticle Vaccines

### 5.1 Improved immunogenicity

Nanoparticle vaccines have demonstrated a significant enhancement in immunogenicity compared to traditional vaccines. This is primarily due to their ability to mimic the size and structure of pathogens, which facilitates better recognition and uptake by immune cells. Nanoparticles can be engineered to display antigens in a repetitive, ordered array, similar to the surface of a pathogen, thereby enhancing the activation of both B cells and T cells (Kelly et al., 2019). Additionally, nanoparticles can be loaded with adjuvants, which further boost the immune response by stimulating innate immunity and promoting antigen presentation (Smith et al., 2015; Garg and Dewangan, 2020). The use of nanoparticles has been shown to improve the stability and presentation of antigens, leading to stronger and more durable immune responses (Zhao et al., 2014; Bezbaruah et al., 2022).

### 5.2 Controlled release properties

One of the key advantages of nanoparticle vaccines is their ability to provide controlled release of antigens. This controlled release can be achieved through various formulations, such as polymer-based nanoparticles, which allow for the sustained release of antigens over an extended period (Guo et al., 2019). This slow and sustained release ensures prolonged exposure of the immune system to the antigen, thereby enhancing the overall immune response. For instance, hybrid systems like the "PEG-g-PEI/DNA nanoparticle-in-PLGA microsphere" have been developed to integrate the benefits of both nanoparticles and microspheres, resulting in a controlled release that follows near zero-order kinetics (Lu et al., 2020). Such systems not only improve the immunogenicity but also ensure that the antigens are protected from premature degradation (Figure 2) (Pati et al., 2018).

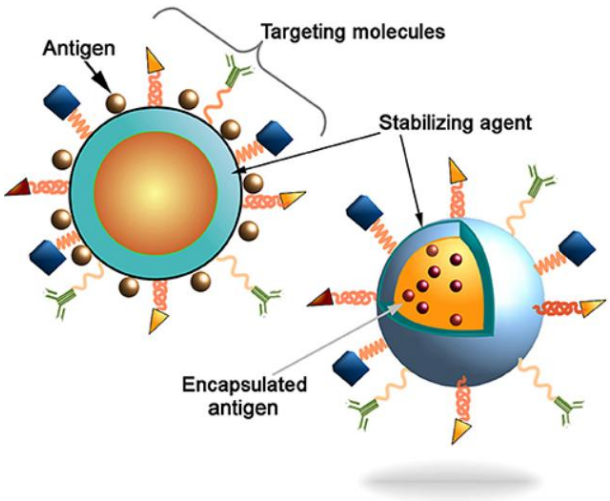


Figure 2 Schematic Diagram of Nanocarriers and Their Role in Immunotherapy (Adapted from Pati et al., 2018)

Image Caption: The figure illustrates the design of nanocarriers, where antigens can be attached to the surface of the nanoparticles or encapsulated within the core. The surface of the nanoparticles can be modified with targeting molecules (such as antibodies, Fab fragments, peptides, etc.) to enhance their delivery to antigen-presenting cells (APCs), thereby triggering innate and adaptive immune responses (Adapted from Pati et al., 2018)

Pati et al. (2018) found that by encapsulating or binding antigens to nanoparticles, this design allows for prolonged antigen delivery, effectively extending the duration of the immune response. Additionally, nanocarriers can control the release rate of antigens, preventing the release of a large quantity at once, which induces a stronger immune response. The modification of targeting molecules further enhances the efficiency of immune cells in recognizing the antigen. The controlled-release properties of nanovaccines make them an emerging technology for improving vaccine efficacy, particularly in the fields of cancer immunotherapy and infectious disease prevention.

### 5.3 Dose-sparing effects

Nanoparticle vaccines can achieve dose-sparing effects, meaning that lower doses of the antigen are required to elicit a strong immune response. This is particularly beneficial in scenarios where vaccine supply is limited or when dealing with expensive antigens. The enhanced delivery and presentation of antigens by nanoparticles ensure that even small amounts of the antigen are effectively recognized and processed by the immune system (Lung et al., 2020; Bezbaruah et al., 2022). This dose-sparing effect is attributed to the improved stability and targeted delivery of the antigens, which reduces the amount of antigen needed to achieve the desired immune response (Zhao et al., 2014; Pati et al., 2018).

### 5.4 Versatility in formulation

Nanoparticles offer remarkable versatility in vaccine formulation. They can be composed of various materials, including lipids, proteins, metals, and polymers, each providing unique advantages in terms of stability, biocompatibility, and functionality (Smith et al., 2015; Pati et al., 2018). This versatility allows for the design of vaccines that can be tailored to specific diseases and target populations. For example, polymer-based nanoparticles can be engineered to enhance the solubility and stability of antigens, while lipid-based nanoparticles can facilitate the delivery of hydrophobic antigens (Guo et al., 2019). Additionally, nanoparticles can be functionalized with targeting ligands to direct the vaccine to specific cells or tissues, further enhancing the efficacy and safety of the vaccine (Gupta et al., 2022). The ability to co-encapsulate adjuvants and antigens within the same nanoparticle also provides a platform for developing more effective and comprehensive vaccine formulations (Garg and Dewangan, 2020).

## 6 Safety and Biocompatibility of Nanoparticle Vaccines

### 6.1 Biodegradability of nanoparticles

Biodegradability is a crucial factor in the design of nanoparticle vaccines, as it ensures that the particles can be broken down and eliminated from the body without causing long-term adverse effects. Various natural and synthetic polymers, such as polylactic-co-glycolide (PLGA) and polyanhydrides, are commonly used due to their biodegradable properties. These materials can be engineered to degrade at controlled rates, which helps in the sustained release of antigens and adjuvants, enhancing the immune response while minimizing potential toxicity (Salem, 2015; Guo et al., 2019; Curley and Putnam, 2022). For instance, PLGA nanoparticles have been shown to be effective in delivering synthetic long peptides (SLPs) for cancer immunotherapy, demonstrating both high efficacy and safety profiles (Varypataki et al., 2016). Additionally, biologically derived nanoparticles, which can self-assemble and contain native pathogen-associated molecular patterns (PAMPs), offer an advantage in terms of biodegradability and biocompatibility, reducing the need for artificial adjuvants (Curley and Putnam, 2022).

### 6.2 Potential for immunotoxicity

While nanoparticle vaccines offer numerous benefits, their potential for immunotoxicity remains a concern. Immunotoxicity can arise from the materials used in the nanoparticles, their size, shape, and surface properties, as well as the immune system's response to these foreign particles. Studies have shown that nanoparticles can enhance antigen uptake and processing by dendritic cells (DCs), but this can also lead to unintended immune activation or suppression (Silva et al., 2013; Zhao et al., 2014; Pati et al., 2018). For example, cationic liposomes and PLGA nanoparticles have been found to induce strong immune responses, but their safety profiles need to be carefully evaluated to avoid adverse effects such as inflammation or autoimmunity (Salem, 2015; Varypataki et al., 2016). Moreover, the use of certain adjuvants, like aluminum hydroxide, in combination with nanoparticles can further complicate the immunotoxicity profile, necessitating thorough preclinical and clinical testing (Silva et al., 2019; Curley and Putnam, 2022).

### 6.3 Long-term safety considerations

Long-term safety is a critical aspect of nanoparticle vaccine development. It involves understanding the in vivo behavior of nanoparticles, including their biodistribution, degradation, and potential accumulation in tissues. Long-term studies are essential to assess the chronic effects of nanoparticle exposure and to ensure that they do not cause delayed toxicity or immune-related issues (Zhao et al., 2014; Salem, 2015; Kelly et al., 2019). For instance, the use of biodegradable polymers like PLGA and PCL in cancer vaccines has shown promise, but long-term studies are needed to confirm their safety and efficacy over extended periods (Silva et al., 2013). Additionally, the potential for nanoparticles to induce immunological memory and their impact on subsequent immune responses must be carefully evaluated to avoid any long-term adverse effects (Bezbaruah et al., 2022). Overall, a comprehensive understanding of the long-term safety of nanoparticle vaccines will facilitate their rational design and safe application in clinical settings.

## 7 Case Study: Nanoparticle Vaccines in COVID-19

### 7.1 mRNA vaccines using lipid nanoparticles: Pfizer-BioNTech and Moderna vaccines

The Pfizer-BioNTech (BNT162b2) and Moderna (mRNA-1273) vaccines are both mRNA-based vaccines that utilize lipid nanoparticles (LNPs) to deliver the mRNA encoding the spike protein of SARS-CoV-2. These LNPs protect the mRNA from degradation and facilitate its delivery into host cells, where it is translated into the spike protein, eliciting an immune response (Baden et al., 2020; Polack et al., 2020; Pilkington et al., 2021). The rapid development and deployment of these vaccines have been pivotal in the global response to the COVID-19 pandemic, showcasing the potential of mRNA-LNP technology in vaccine development (Pilkington et al., 2021; Tenchov et al., 2021).

### 7.2 Clinical efficacy and safety data

Clinical trials and real-world data have demonstrated the high efficacy and safety profiles of both the Pfizer-BioNTech and Moderna vaccines. The Pfizer-BioNTech vaccine showed 95% efficacy in preventing COVID-19 in persons aged 16 years and older, with a favorable safety profile characterized by mild-to-moderate side effects such as pain at the injection site, fatigue, and headache (Polack et al., 2020; Thomas et al., 2021). Similarly, the Moderna vaccine demonstrated 94.1% efficacy in preventing COVID-19 illness, including severe disease, with transient local and systemic reactions being the most common side effects (Baden et al., 2020).

Real-world studies have further confirmed the effectiveness of these vaccines. For instance, the Pfizer-BioNTech vaccine was found to be 90% effective in preventing COVID-19-associated emergency department and urgent care encounters among adolescents aged 12-17 years (Klein et al., 2022). Additionally, a comparative study indicated that the Moderna vaccine had a slightly higher efficacy (93%) in preventing COVID-19 hospitalizations compared to the Pfizer-BioNTech vaccine (88%). Both vaccines have shown substantial protection against severe outcomes, including hospitalization and death, across various age groups and populations (Bernal et al., 2021; Klein et al., 2022).

### 7.3 Challenges and future improvements

Despite the success of mRNA-LNP vaccines, several challenges remain. One significant issue is the gradual decline in vaccine efficacy over time, necessitating booster doses to maintain high levels of protection (Thomas et al., 2021; Klein et al., 2022). Additionally, the emergence of new variants, such as Omicron, has posed challenges to vaccine effectiveness, particularly in preventing mild to moderate disease (Klein et al., 2022).

Future improvements could focus on enhancing the stability and delivery efficiency of LNPs, as well as developing multivalent vaccines that can provide broader protection against multiple variants (Pilkington et al., 2021; Tenchov et al., 2021). Continued research and development in nanotechnology and mRNA vaccine platforms are essential to address these challenges and improve the overall efficacy and durability of nanoparticle vaccines (Pilkington et al., 2021; Tenchov et al., 2021; Sarangi et al., 2022; Shou and Cai, 2024).

## 8 Challenges in the Development of Nanoparticle Vaccines

### 8.1 Manufacturing complexities

The manufacturing of nanoparticle vaccines presents several complexities due to the intricate nature of nanoparticle synthesis and formulation. The production process must ensure uniformity in size, shape, and surface properties of nanoparticles, which is crucial for their efficacy and safety. The scalability of manufacturing processes from laboratory to industrial scale is another significant challenge. For instance, biologically derived nanoparticles, while advantageous for their biocompatibility and self-assembly properties, still require sophisticated techniques for large-scale production (Curley and Putnam, 2022). Additionally, the precise control over the physicochemical properties of nanoparticles, such as those used in lipid-based formulations, is essential to maintain their stability and functionality during production (Thi et al., 2021).

### 8.2 Stability and storage issues

Nanoparticle vaccines often face stability and storage challenges, which can affect their efficacy. The stability of nanoparticles can be influenced by various factors, including temperature, pH, and the presence of other biological molecules. For example, lipid nanoparticles, which are widely used in mRNA vaccines, require stringent storage conditions to maintain their integrity and prevent degradation (Tenchov et al., 2021). The need for cold chain logistics, as seen with COVID-19 mRNA vaccines, poses significant logistical challenges, especially in resource-limited settings (Thi et al., 2021). Moreover, ensuring the long-term stability of nanoparticle formulations without compromising their immunogenic properties remains a critical area of research (Zhao et al., 2014; Lozano et al., 2023).

### 8.3 Regulatory hurdles

The regulatory landscape for nanoparticle vaccines is complex and evolving. Regulatory agencies require comprehensive data on the safety, efficacy, and quality of nanoparticle-based formulations. The lack of standardized guidelines for the evaluation of nanoparticle vaccines adds to the complexity. For instance, the unique properties of nanoparticles, such as their ability to enhance antigen presentation and immune response, necessitate novel assessment criteria that differ from traditional vaccines (Lung et al., 2020). Additionally, the potential for unforeseen immunological reactions due to the novel nature of nanoparticle adjuvants and delivery systems requires thorough preclinical and clinical evaluation (Kelly et al., 2019). The approval process can be lengthy and resource-intensive, posing a significant barrier to the rapid deployment of nanoparticle vaccines (Hussein et al., 2023).

## 9 Future Directions in Nanoparticle Vaccine Research

### 9.1 Nanoparticles for universal vaccines

The development of universal vaccines, which can provide broad protection against multiple strains or types of pathogens, is a significant goal in vaccinology. Nanoparticles offer a promising platform for such vaccines due to their ability to enhance antigen stability, immunogenicity, and targeted delivery. Recent advances in nanotechnology have enabled the design of nanoparticles that can present multiple antigens simultaneously, potentially leading to broader immune responses. For instance, lipid-based nanoparticles have been pivotal in the rapid development of COVID-19 vaccines, demonstrating their potential for universal vaccine applications (Wen et al., 2019; Anselmo and Mitragotri, 2021). However, challenges remain in understanding the in vivo behavior of nanoparticles and optimizing their design for maximal efficacy and safety (Zhao et al., 2014).

### 9.2 Personalized cancer vaccines

Personalized cancer vaccines represent a frontier in cancer immunotherapy, aiming to tailor treatments based on individual tumor profiles. Nanoparticles are particularly suited for this purpose due to their modularity and ability to co-deliver antigens and adjuvants. For example, polyethyleneimine (PEI)-based nanoparticles have been developed for the rapid and facile production of personalized cancer vaccines, showing potent antitumor efficacy in preclinical models (Nam et al., 2021). Additionally, RNA-lipoplexes have been successfully translated into clinical applications for melanoma treatment, highlighting the potential of nanoparticle-based personalized vaccines (Grabbe et al., 2016). These advancements underscore the importance of continued research into

nanoparticle design and manufacturing processes to overcome technical and regulatory challenges (Silva et al., 2013; Wen et al., 2019).

### 9.3 Advances in nanoparticle design

The design of nanoparticles is critical to their function as vaccine delivery systems. Recent research has focused on optimizing the physicochemical properties of nanoparticles, such as size, shape, surface charge, and functionalization, to enhance their interaction with the immune system and improve their biodistribution and cellular uptake (Toy and Roy, 2016; Liu et al., 2019). For instance, biomimetic nanoparticles, which incorporate natural materials to mimic biological functions, have shown promise in targeting dendritic cells and stimulating robust immune responses (Meng et al., 2023). Furthermore, understanding the relationship between nanoparticle characteristics and their in vivo behavior is essential for the rational design of effective vaccines (Zhao et al., 2014). Continued innovation in nanoparticle engineering will likely lead to more effective and versatile vaccine platforms, capable of addressing a wide range of infectious diseases and cancers (Anselmo and Mitragotri, 2021; Thi et al., 2021).

## 10 Concluding Remarks

The report of nanoparticle vaccines has highlighted several critical advancements and applications in the field. Nanoparticles have been shown to significantly enhance antigen stability and immunogenicity, providing targeted delivery and controlled release of vaccines. The unique properties of nanoparticles, such as their size, shape, and surface characteristics, mimic the natural structure of pathogens, thereby enhancing immune responses. Notably, the success of lipid nanoparticles in mRNA vaccines against COVID-19 has underscored the potential of nanoparticle-based vaccines in addressing global health challenges. Despite these advancements, there remains a need for a deeper understanding of the in vivo behavior of nanoparticles to optimize their design and application.

For the future development of nanoparticle vaccines, several best practices should be considered. Firstly, a multidisciplinary approach that integrates immunology, materials science, and nanotechnology is essential to design vaccines with high efficacy and safety. The rational design of nanoparticles should focus on enhancing antigen presentation and immune activation while ensuring biocompatibility and minimal toxicity. Additionally, leveraging the virus-like properties of nanoparticles can further potentiate immune responses, making them more effective than traditional vaccines. It is also crucial to standardize the characterization of nanoparticles to ensure consistent quality and performance across different formulations.

Future research should aim to address the current gaps in understanding the mechanisms of action and in vivo behavior of nanoparticle vaccines. Studies should focus on elucidating the precise immunological pathways activated by nanoparticle vaccines to facilitate the rational design of more effective formulations. Investigating the long-term safety and efficacy of nanoparticle vaccines in diverse populations and under various clinical conditions is also imperative. Furthermore, exploring the potential of personalized nanoparticle vaccines, particularly in the context of cancer immunotherapy, could open new avenues for targeted and individualized treatment strategies. Finally, continued innovation in nanoparticle design, including the development of multifunctional nanoparticles that can deliver multiple antigens or adjuvants, will be crucial in enhancing vaccine efficacy and addressing emerging infectious diseases.

### Acknowledgments

Thank you for the constructive feedback provided by the peer reviewers on the manuscript of this study.

### Conflict of Interest Disclosure

The author affirms that this research was conducted without any commercial or financial relationships that could be construed as a potential conflict of interest.

### References

Anselmo A., and Mitragotri S., 2021, Nanoparticles in the clinic: an update post COVID-19 vaccines, Bioengineering and Translational Medicine, 6(1): e10246.
https://doi.org/10.1002/btm2.10246

Baden L., El Sahly H., Essink B., Kotloff K., Frey S., Novak R., Diemert D., Spector S., Rouphael N., Creech C., McGettigan J., Kehtan S., Segall N., Solis J., Brosz A., Fierro C., Schwartz H., Neuzil K., Corey L., Gilbert P., Janes H., Follmann D., Marovich M., Mascola J., Polakowski L., Ledgerwood J., Graham B., Bennett H., Pajon R., Knightly C., Leav B., Deng W., Zhou H., Han S., Ivarsson M., Miller J., and Zaks T., 2020, Efficacy and safety of the mRNA-1273 SARS-CoV-2 vaccine, The New England Journal of Medicine, 384(5): 403-416.
https://doi.org/10.1056/NEJMoa2035389

Bernal J., Andrews N., Gower C., Robertson C., Stowe J., Tessier E., Simmons R., Cottrell S., Roberts R., O' Doherty M., Brown K., Cameron C., Stockton D., McMenamin J., and Ramsay M., 2021, Effectiveness of the Pfizer-BioNTech and Oxford-AstraZeneca vaccines on COVID-19 related symptoms, admissions, and mortality in older adults in England: test negative case-control study, The BMJ, 373: n1088.
https://doi.org/10.1136/bmj.n1088

Bezbaruah R., Chavda V., Nongrang L., Alom S., Deka K., Kalita T., Ali F., Bhattacharjee B., and Vora L., 2022, Nanoparticle-based delivery systems for vaccines, Vaccines, 10(11): 1946.
https://doi.org/10.3390/vaccines10111946

Cappellano G., Abreu H., Casale C., Dianzani U., and Chiocchetti A., 2021, Nano-microparticle platforms in developing next-generation vaccines, Vaccines, 9(6): 606
https://doi.org/10.3390/vaccines9060606

Chatzikleanthous D., O'Hagan D., and Adamo R., 2021, Lipid-based nanoparticles for delivery of vaccine adjuvants and antigens: toward multicomponent vaccines, Molecular Pharmaceutics, 10(6): 447/
https://doi.org/10.1021/acs.molpharmaceut.1c00447

Curley S., and Putnam D., 2022, Biological nanoparticles in vaccine development, Frontiers in Bioengineering and Biotechnology, 10: 867119.
https://doi.org/10.3389/fbioe.2022.867119

Garg A., and Dewangan H., 2020, Nanoparticles as adjuvants in vaccine delivery, Critical Reviews in Therapeutic Drug Carrier Systems, 37(2): 183-204.
https://doi.org/10.1615/critrevtherdrugcarriersyst.2020033273

Gomes A., Mohsen M., and Bachmann M., 2017, Harnessing nanoparticles for immunomodulation and vaccines, Vaccines, 5(1): 6.
https://doi.org/10.3390/vaccines5010006

Grabbe S., Haas H., Diken M., Kranz L., Langguth P., and Şahin U., 2016, Translating nanoparticulate-personalized cancer vaccines into clinical applications: case study with RNA-lipoplexes for the treatment of melanoma, Nanomedicine, 11(20): 2723-2734.
https://doi.org/10.2217/NNM-2016-0275

Gupta J., Safdari H., and Hoque M., 2021, Nanoparticle-mediated cancer immunotherapy, Seminars in Cancer Biology, 69: 307-324.
https://doi.org/10.1016/j.semcancer.2020.03.015

Guo S., Fu D., Utupova A., Sun D., Zhou M., Jin Z., and Zhao K., 2019, Applications of polymer-based nanoparticles in the vaccine field, Nanotechnology Reviews, 8: 143-155.
https://doi.org/10.1515/ntrev-2019-0014

Gu P., Wusiman A., Wang S., Zhang Y., Liu Z., Hu Y., Liu J., and Wang D., 2019, Polyethylenimine-coated PLGA nanoparticles-encapsulated angelica sinensis polysaccharide as an adjuvant to enhance immune responses, Carbohydrate Polymers, 223: 115128.
https://doi.org/10.1016/j.carbpol.2019.115128

Hanson M., Crespo M., Abraham W., Moynihan K., Szeto G., Chen S., Melo M., Mueller S., and Irvine D., 2015, Nanoparticulate STING agonists are potent lymph node-targeted vaccine adjuvants, The Journal of Clinical Investigation, 125(6): 2532-2546.
https://doi.org/10.1172/JCI79915

Hussein M., Mumtaz M., Nasir I., and Abdullahi A., 2023, Nanotechnology-based vaccines, Biology, Medicine, and Natural Product Chemistry, 12(1): 343-361.
https://doi.org/10.14421/biomedich.2023.121.343-361

Jin J., Tang S., Rong M., and Zhang M., 2018, Synergistic effect of dual targeting vaccine adjuvant with aminated β-glucan and CpG-oligodeoxynucleotides for both humoral and cellular immune responses, Acta Biomaterialia, 78: 211-223.
https://doi.org/10.1016/j.actbio.2018.08.002

Jung H., Lee S., Lee S., Youn H., and Im H., 2022, Lipid nanoparticles for delivery of RNA therapeutics: current status and the role of in vivo imaging, Theranostics, 12: 7509-7531.
https://doi.org/10.7150/thno.77259

Kelly H., Kent S., and Wheatley A., 2019, Immunological basis for enhanced immunity of nanoparticle vaccines, Expert Review of Vaccines, 18: 269-280.
https://doi.org/10.1080/14760584.2019.1578216

Klein N., Stockwell M., DeMarco M., Gaglani M., Kharbanda A., Irving S., Rao S., Grannis S., Dascomb K., Murthy K., Rowley E., Dalton A., DeSilva M., Dixon B., Natarajan K., Stenehjem E., Naleway A., Lewis N., Ong T., Patel P., Konatham D., Embí P., Reese S., Han J., Grisel N., Goddard K., Barron M., Dickerson M., Liao I., Fadel W., Yang D., Arndorfer J., Fireman B., Griggs E., Valvi N., Hallowell C., Zerbo O., Reynolds S., Ferdinands J., Wondimu M., Williams J., Bozio C., Link-Gelles R., Azziz-Baumgartner E., Schrag S., Thompson M., and Verani J., 2022, Effectiveness of COVID-19 Pfizer-BioNTech BNT162b2 mRNA vaccination in preventing COVID-19-associated emergency department and urgent care encounters and hospitalizations among nonimmunocompromised children and adolescents aged 5-17 years—VISION Network, 10 States, April 2021-January 2022, Morbidity and Mortality Weekly Report, 71: 352-358.
https://doi.org/10.15585/mmwr.mm7109e3

Li P., Shi G., Zhang X., Song H., Zhang C., Wang W., Li C., Song B., Wang C., and Kong D., 2016, Guanidinylated cationic nanoparticles as robust protein antigen delivery systems and adjuvants for promoting antigen-specific immune responses in vivo, Journal of Materials Chemistry B, 4(33): 5608-5620.

Liu J., Miao L., Sui J., Hao Y., and Huang G., 2019, Nanoparticle cancer vaccines: design considerations and recent advances, Asian Journal of Pharmaceutical Sciences, 15: 576-590.
https://doi.org/10.1016/j.ajps.2019.10.006

Li Y., Fang H., Tao Z., Wang Y., Qi T., Li B., and Jiao H., 2022, Lipid-mRNA nanoparticles landscape for cancer therapy, Frontiers in Bioengineering and Biotechnology, 10: 1053197.
https://doi.org/10.3389/fbioe.2022.1053197

Lozano D., Larraga V., Vallet‐Regí M., and Manzano M., 2023, An overview of the use of nanoparticles in vaccine development, Nanomaterials, 13(12): 1828
https://doi.org/10.3390/nano13121828

Lung P., Yang J., and Li Q., 2020, Nanoparticle formulated vaccines: opportunities and challenges, Nanoscale, 12(10): 5315-5332.
https://doi.org/10.1039/c9nr08958f

Lu Y., Wu F., Duan W., Mu X., Fang S., Lu N., Zhou X., and Kong W., 2020, Engineering a "PEG-g-PEI/DNA nanoparticle-in-PLGA microsphere" hybrid controlled release system to enhance immunogenicity of DNA vaccine, Materials Science and Engineering: C, 106: 110294.
https://doi.org/10.1016/j.msec.2019.110294

Meng L., Teng Z., Yang S., Wang N., Guan Y., Chen X., and Liu Y., 2023, Biomimetic nanoparticles for DC vaccination: a versatile approach to boost cancer immunotherapy, Nanoscale, 15(2): 467-479.
https://doi.org/10.1039/d2nr07071e

Nam J., Son S., Park K., and Moon J., 2021, Modularly programmable nanoparticle vaccine based on polyethyleneimine for personalized cancer immunotherapy, Advanced Science, 8(6): 2002577.
https://doi.org/10.1002/advs.202002577

Namiot E., Sokolov A., Chubarev V., Tarasov V., and Schiöth H., 2023, Nanoparticles in clinical trials: analysis of clinical trials, FDA approvals and use for COVID-19 vaccines, International Journal of Molecular Sciences, 24(1): 787.
https://doi.org/10.3390/ijms24010787

Nguyen B., and Tolia N., 2021, Protein-based antigen presentation platforms for nanoparticle vaccines, NPJ Vaccines, 6: 70.
https://doi.org/10.1038/s41541-021-00330-7

Pati R., Shevtsov M., and Sonawane A., 2018, Nanoparticle vaccines against infectious diseases, Frontiers in Immunology, 9: 2224.
https://doi.org/10.3389/fimmu.2018.02224

Pilkington E., Suys E., Trevaskis N., Wheatley A., Zukancic D., Algarni A., Al-Wassiti H., Davis T., Pouton C., Kent S., and Truong N., 2021, From influenza to COVID-19: Lipid nanoparticle mRNA vaccines at the frontiers of infectious diseases, Acta Biomaterialia, 131: 16-40.
https://doi.org/10.1016/j.actbio.2021.06.023

Polack F., Thomas S., Kitchin N., Absalon J., Gurtman A., Lockhart S., Perez J., Marc G., Moreira E., Zerbini C., Bailey R., Swanson K., Roychoudhury S., Koury K., Li P., Kalina W., Cooper D., Frenck R., Hammitt L., Türeci Ö., Nell H., Schaefer A., Ünal S., Tresnan D., Mather S., Dormitzer P., Şahin U., Jansen K., and Gruber W., 2020, Safety and efficacy of the BNT162b2 mRNA Covid-19 vaccine, The New England Journal of Medicine, 383(27): 2603-2615.
https://doi.org/10.1056/NEJMoa2034577

Reddy S., Vlies A., Simeoni E., Angeli V., Randolph G., O'Neil C., Lee L., Swartz M., and Hubbell J., 2007, Exploiting lymphatic transport and complement activation in nanoparticle vaccines, Nature Biotechnology, 25: 1159-1164.
https://doi.org/10.1038/nbt1332

Salem A., 2015, Nanoparticles in vaccine delivery, The AAPS Journal, 17(2): 289-291.
https://doi.org/10.1208/s12248-015-9720-1

Sarangi M., Padhi S., Rath G., Nanda S., and Yi D., 2022, Success of nano-vaccines against COVID-19: a transformation in nanomedicine, Expert Review of Vaccines, 21(12): 1739-1761.
https://doi.org/10.1080/14760584.2022.2148659

Silva C., Camps M., Li T., Chan A., Ossendorp F., and Cruz L., 2019, Co-delivery of immunomodulators in biodegradable nanoparticles improves therapeutic efficacy of cancer vaccines, Biomaterials, 220: 119417.
https://doi.org/10.1016/j.biomaterials.2019.119417

Silva J., Videira M., Gaspar R., Préat V., and Florindo H., 2013, Immune system targeting by biodegradable nanoparticles for cancer vaccines, Journal of Controlled Release, 168(2): 179-199.
https://doi.org/10.1016/j.jconrel.2013.03.010

Shou C.J., and Cai X.P., 2024, Analysis of animal vaccine classification and current status, Journal of Vaccine Research, 14(1): 10-16.
https://doi.org/10.5376/jvr.2024.14.0002

Smith J., Morton L., and Ulery B., 2015, Nanoparticles as synthetic vaccines, Current Opinion in Biotechnology, 34: 217-224.
https://doi.org/10.1016/j.copbio.2015.03.014

Tenchov R., Bird R., Curtze A., and Zhou Q., 2021, Lipid nanoparticles=from liposomes to mRNA vaccine delivery, a landscape of research diversity and advancement, ACS Nano, 15(11): 16982-17015.
https://doi.org/10.1021/acsnano.1c04996

Thi T., Suys E., Lee J., Nguyen D., Park K., and Truong N., 2021, Lipid-based nanoparticles in the clinic and clinical trials: from cancer nanomedicine to COVID-19 vaccines, Vaccines, 9(4): 359.
https://doi.org/10.3390/vaccines9040359

Thomas S., Moreira E., Kitchin N., Absalon J., Gurtman A., Lockhart S., Perez J., Marc G., Polack F., Zerbini C., Bailey R., Swanson K., Xu X., Roychoudhury S., Koury K., Bouguermouh S., Kalina W., Cooper D., Frenck R., Hammitt L., Türeci Ö., Nell H., Schaefer A., Ünal S., Yang Q., Liberator P., Tresnan D., Mather S., Dormitzer P., Şahin U., Gruber W., and Jansen K., 2021, Safety and efficacy of the BNT162b2 mRNA COVID-19 vaccine through 6 months, The New England Journal of Medicine, 385(19): 1761-1773.
https://doi.org/10.1056/NEJMoa2110345

Toy R., and Roy K., 2016, Engineering nanoparticles to overcome barriers to immunotherapy, Bioengineering and Translational Medicine, 1(1): 47-62.
https://doi.org/10.1002/btm2.10005

Tursi N., Xu Z., Kulp D., and Weiner D., 2023, Gene-encoded nanoparticle vaccine platforms for in vivo assembly of multimeric antigen to promote adaptive immunity, Wiley Interdisciplinary Reviews: Nanomedicine and Nanobiotechnology, e1880.
https://doi.org/10.1002/wnan.1880

Varypataki E., Silva A., Barnier-Quer C., Collin N., Ossendorp F., and Jiskoot W., 2016, Synthetic long peptide-based vaccine formulations for induction of cell-mediated immunity: a comparative study of cationic liposomes and PLGA nanoparticles, Journal of Controlled Release, 226: 98-106.
https://doi.org/10.1016/j.jconrel.2016.02.018

Wang C., Zhang Y., and Dong Y., 2021, Lipid nanoparticle-mRNA formulations for therapeutic applications, Accounts of Chemical Research, 54(23): 4283-4293.
https://doi.org/10.1021/acs.accounts.1c00550

Wen R., Umeano A., Kou Y., Xu J., and Farooqi A., 2019, Nanoparticle systems for cancer vaccine, Nanomedicine, 14(5): 627-648.
https://doi.org/10.2217/nnm-2018-0147

Xuan J., 2024, Innovative antiviral strategy targeting PLpro: Discovery of Jun12682 and analysis of its antipandemic effects, International Journal of Molecular Medical Science, 14(1): 56-60.
https://doi.org/10.5376/ijmms.2024.14.0008

Zhao L., Seth A., Wibowo N., Zhao C., Mitter N., Yu C., and Middelberg A., 2014, Nanoparticle vaccines, Vaccine, 32(3): 327-337.
https://doi.org/10.1016/j.vaccine.2013.11.069