CHAPTER N0.

16

Nanotechnology: Nanoparticle-Based Vaccine Development and Drug Delivery

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Summary: The global outbreaks of infectious diseases occur at different times, causing significant decreases in the worldwide human and animal populations. Conventional vaccines were made to eradicate and immunize against pathogenic organisms. However, they developed certain conditions and limitations regarding use, maintenance, reliability, and virulence. Conversely, nanotechnology has emerged as a better therapeutic approach and is pledged to minimize all the limitations. The new vaccines have improved potential for targeted drug delivery, controlled release, additive ability, and immune-modulating capabilities. The nano vaccines work through various pathways to reach the target body site and provoke immune responses. In addition to immune stimulation, nano-inoculations also suppress the immune system in many cases, such as allergies. Among the unlimited benefits of Nanotechnology, the most highlighted is the evolution of vaccines for COVID-19, indicating a bright future towards the formulation of next-generation vaccines and enhanced immunity. As nanotechnology is a broad field, and in this chapter, some aspects of this technology regarding the platform for vaccination and immunization and its challenges are discussed.
Keywords: Pandemics, Nanotechnology, Nanoparticles, Next-generation vaccines, Targeted drug delivery, Immune responses, SARS-CoV-2

INTRODUCTION

The world's health is greatly influenced by vaccination. A number of epidemics had a remarkable impact on human and domestic animal populations (Qiao et al., 2022). Human health and diseases of animals are closely associated with each other, such as Rinderpest. This disease caused significant mortality in cattle and left animal-dependent families vulnerable to malnutrition and diseases (Tounkara & Nwankpa, 2017). Similarly, before the vaccine development, almost half of the world's inhabitants died because of endemic diseases, including smallpox and measles. The first ever vaccine developed by Edward Jenner in 1796 was against smallpox. The introduction of vaccination strategized the world against infectious ailments. It was a significant milestone in the history of mankind (Pan & Cui, 2020). The discovery of vaccination is being applied as a universal tool for the health and welfare of living organisms (Greenwood, 2014). The probability of mammalian and avian survival increases due to the vaccines. After the initial study of Edward Jenner in the 18th century, the invention of conventional vaccines took place. The traditional vaccines only relied on killed and live attenuated vaccines (Plummer & Manchester, 2011). In the late 1990s, the mRNA and DNA vaccines were developed by various researchers and tested on mice (Gebre et al., 2022). In spite of all these vaccines, there are many restrictions for clinical application. They may cause virulence, poisonousness, several inoculations, cold storage as well as unpredictability (Kutzler & Weiner, 2008). Additionally, the majority of vaccines were not able to produce a strong and appropriate immune response (Facciolà et al., 2019).

Thus, above all the concerns, the implementation of Nanotechnology pledged many conveniences as well as benefits for better vaccination, the targeted delivery of antigens, adjuvants, nucleic acids, proteins, and immunization (Pardi et al., 2018; Cappellano et al., 2021). The technology using nanoparticles is being applied in many fields, including pharmaceutics along with biomedical sciences, and opening new horizons in medical sciences (Garg & Dewangan, 2020). One of the biggest advantages of nanoparticles is the transport of antigens to the targeted site and their role as an adjuvant for immunogenicity (Suri et al., 2007). The clinical involvement of nanoparticles for COVID-19 vaccines resulted in revolutionary outcomes of this technology. The development of COVID nano-vaccines by Moderna® and Pfizer® are the indications of a bright future regarding nano-vaccination of Nanotechnology and its adaptability in the industry (Afzal et al., 2022).

Moreover, the conventional vaccines failed against many viruses to properly immunize the host as well as inhibit and eliminate the disease. However, the nanoparticle-based vaccines work by provoking the immune system of the recipient via different pathways, and the selected examples

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include antigen cross-presentation (major histocompatibility complex (MHC) Class-I and Class-II) and the activation of B lymphocytes. Nanotechnology is exploited for immune stimulation, and the nanoparticles interact with the immune system in multiple ways to cause immunosuppression. The application includes the therapeutic effects in the cases of transplant rejections, autoimmune diseases, anaphylaxis, allergies, and toxicities. The nanoparticles actually block the release of histamine as well as prevent hypothermia. The aim and result are the depressed activity of lymphocytes to deplete the detrimental immune reactions (Ilinskaya & Dobrovolskaia, 2014; Ngobili & Daniele, 2016; Keikha et al., 2021).

The word Nano is derived from “nanos” a Greek word meaning “minute” (Schaming & Remita, 2015). Nanotechnology explains nano-scaled materials ranging in size 1-100 nm, containing improved, versatile characteristics in contrast to the corresponding huge counterparts (Curtis et al., 2006). Nanotechnology is the science of matter manipulation at the nanometer scale. Richard Feynman, a renowned physicist of the mid-20th century, invented the spreading technology. Despite that, the term nanotechnology was operated in 1974 by a Japanese researcher, Norio Taniguchi (Bayda et al., 2019). Nanotechnology involves nanoparticles. The exploration and utilization of nanoparticles since the old times, unescorted by the awareness of the nano-scaled features of nanomaterials. The ancient use of nanotechnology includes Ag NP in Ceramics, Silver Gold NP in the glass window of the medieval church, Carbon NP covering cementite nanowires, Silver gold nanoparticle alloys (Khandve, 2014; Bayda et al., 2019). However, the term nanoparticle is recently developed by the end of the 19th century. This technology was introduced as a novel approach combining many fields of material sciences, physics, biology, chemistry, engineering, IT, and cosmetics (Mihranyan et al., 2012).

NANOPARTICLES PRODUCTION

The production of nanomaterials is an intricate concept. In contrast to the natural nanomaterials, the engineered nanoparticles are created in industries and labs (Gomte et al., 2024). The structure, arrangements, and dimensions are accordingly supervised precisely (Jambhulkar et al., 2024). Innovative approaches are being applied to generate nanoparticles influenced by size and shape. The characteristics of nanoparticles and factors of heat, current conduction, optics, and catalysis are predisposed by nanoparticle magnitude (Varo et al., 2024).

Immune-Stimulating Mechanism of Nanoparticles

The immunostimulatory activity of nanoparticles is attained by different mechanisms. These mechanisms include cellular absorption of nano vaccine depending on nanoparticle size and lymphatic approach. This creates a repository influence at that specific region of the body which stimulates the strength as well as the stability of antigen present in the nano vaccine (Zolnik et al., 2010). The slow release of antigen occurs with nano vaccine due to its structural coherence. The antigen co-aggregates with B cell receptors and generates a potential immune response in the host. The response is generated by the secretion of immune-regulatory soluble mediators (Smith et al., 2013). The other mechanisms include cross-presentation, started by the administration of exogenous acquired antigens operated into the MHC class I immune pathways following the absorption of antigenic nanoparticles by the phagocytes in the cytoplasmic matrix. This causes the secretion of immune mediator substances (cytokines, chemokines, and other immune-modulating substances) that provoke immunogenicity. The Third mechanism involves the association of toll-like receptors (TLR)-independent and TLR-dependent interconversions that potentiate the innate immunity (Casey et al., 2019).

Nano Vaccine Platforms for Immune Stimulation

The innovative technology in the development of nanoparticle-based vaccines gave a noticeable improvement and progress in people's health. The various platforms for nano vaccines include immune-stimulating complexes, liposomes, lipid nanoparticles, inorganic nanoparticles, virus size particles, polymeric nano vaccines, self-assembled nanoparticles, and chitosan-polymer-based nanoparticles.

LIPOSOME NANO VACCINES (LNP)

The liposomes are lipid bilayer organelles containing water inside them. They transfer antigens to the lysosome of a particular cell. This antigen delivery starts adaptive immune responses (Pan & Cui, 2020). The introduction of lipid nanoparticles in the body of an organism first of all faces Kupffer cells (the mononuclear phagocytes found in the liver). These particles then spread widely in the liver and provoke immune reactions. The function and the spread of lipid nanoparticles in the hepatocytes are modulated by physicochemical features depending on the nanoparticle size, pKa value, as well as sensitivity to lipid (Witzigmann et al., 2020).

In addition to these properties, the long-lasting stable accumulation, role as an adjuvant as well as improved controlled release are the basics of constructing LNP for the transport of viral antigens (Christensen et al., 2011). All the parameters contribute to producing the curative effect of immune system formation, well-regulated nanoscale manufacturing, and encapsulating nucleic acid to form liposomes. The different type of lipid nanoparticles is made to treat particular hepatic ailments. The activity of specific LNP is to rectify the hereditary faults by conveying the alternative proteins (Liu et al., 2023). LNPs have proved effective in preventing the production of pathogenesis-related (PR) proteins in the cells of the liver. Simultaneously, the LNPs prevailed in silencing defected genes on hepatocytes, are economical, and stimulate potential immune responses. The other advantage of LNPs is gene regulation, curative effects as well as their role in decreasing toxicity (Witzigmann et al., 2020).

VIRUS-LIKE PARTICLES BASED NANO VACCINES

The VPLs are well-organized self-assembled protein particles generated by viral proteins that remain very similar

to the form and structure of the naturally occurring viruses. These are possibly generated to deliver the antigen of various mutant viruses as well as with the application of wide-spectrum vaccines (Pan & Cui, 2020). The microscopic VLPs act as adjuvants and are easily recognized by the antigen-presenting cells, which provoke the immune responses of the host. The VLPs initiate the immune response by administering the genetic material (RNA, DNA) into the capsid and then delivering it to the targeted site. These particles function by multiple antigen display and then immediately taken up by the antigen-presenting cells (APCs). The antibodies, major histocompatibility complex I and II, as well as T-cell immune reactions, are started (Plummer & Manchester, 2011).

It is a widely accepted nano vaccine in the health sector. The VLPs have an advantage over others in that they are efficient in inhibiting and eliminating infectious mutants, especially the coronavirus and influenza viruses, as well as many other chronic infections (Jennings & Bachmann, 2009). This vaccine platform provides many innovative solutions for stimulating cellular and humoral immunogenicity with long-lasting and potent effects (Kushnir et al., 2012).

SELF-ASSEMBLED NANOPARTICLES (SANPs)

The self-assembled nanoparticles are a vaccine platform made by the structural organization of repeated units of various primary, secondary, and tertiary proteins (Negahdaripour et al., 2017). A new arrangement was demonstrated and created in the Escherichia coli. The polypeptide chains are framed collectively as a nanostructure of antigenic protein to initiate the immunogenicity in the host. This framework of antigens acts on the lymphatic cells and results in the significant production of antibodies (He et al., 2018). This platform is widely used for the production of antibodies by the formation of versatile antigens. The SANPs are specifically specialized for vaccination against avian influenza virus and coronavirus (Doll et al., 2015)

CHITOSAN AND POLYMERIC NANO-VACCINES

The Chitosan and polymeric nano vaccines reach the mucous-stimulating immunological receptors. To preserve antigens against physical, chemical, or enzymatic degradation, chitosan-polymer-based nano-vaccines have been developed using nanotechnology-based delivery systems. The carrier nanoparticles encapsulate or absorb the antigens on their surface and transport the vaccine to the targeted body site, followed by the controlled release. This results in the stimulation of the immune system (Sukkarun et al., 2022). These types of nano vaccines have an effective targeted delivery system. The nanoparticle vaccine made of chitosan and polymers is used for improving the immunity-promoting potential of the immune system by boosting the regional antibodies and increasing permeability (Zazo et al., 2016).

Other Nano Vaccine Carriers

There are different types of nanoparticles that are applied to transport the vaccine at the targeted site. These nanocarriers include nano gels, poly (lactide-glycolide) nanoparticles (PLGA), cholesterol-bearing hydrophobized pullulan (CHP) (Ferreira et al., 2013). The PLGAs are broadly studied for their practical implementation and controlled drug release. All of the mentioned nanocarriers are used extensively and efficiently in the forms of nano capsules, nanoparticles, and nanospheres; they are also considered biocompatible and safe for nanovaccinology (Lu et al., 2009). Most of the studies for the above technology were performed on the animal model of mice.

NANOTECHNOLOGY AND IMMUNOSUPPRESSION

Immunosuppression is required in cases of transplant rejection, autoimmune diseases, allergies, or anaphylaxis. The nanoparticles are successfully applied to depress the immunology in the above-illustrated situations to prevent detrimental replies and effects that may lead to the death of the study subject (Zolnik et al., 2010). The knowledge about nanotechnology's therapeutic and practical implementation for hindering the immune system is mainly obtained from toxicological fields. These fields use fullerenes which are micro-sized compounds completely made up of carbon atoms. They are immensely produced every year and most often utilized in nanotechnology during the formation of paint and electronic items (Nielsen et al., 2008). The fullerenes directly influence the lymphatic cells in the body, resulting in the depression of lymph nodes. Their role is to reduce the receptor-mediated binding of the IgE. An experiment was performed on the anaphylaxis-induced mouse in the year 2009; after treatment with fullerenes prevented the release of histamine and inhibited the hypothermia in the mouse body. It is important to note that rodents are susceptible to hypothermia after exposure to allergens, and it was prevented efficiently (Mitchell et al., 2009).

NANO-VACCINES FOR COVID CASES

Immunization is vital in controlling and eradicating infectious and contagious diseases. Health professionals face new challenges every day. The recent outbreak of the coronavirus, COVID-19, has highlighted the importance of nano vaccines as this technology enables scientist to develop a comparatively efficient vaccine in a quick time and produce a good immune response (Geng et al., 2021).

The etiology of COVID-19 is SARS-CoV-2, a highly pathogenic virus belonging to the family Coronaviridae. A new virus emerged in 2019 and transmitted as a universal pandemic (Tregoning et al., 2020). According to the (WHO) report of November 2023, more than 6.97 million people died because of this viral infection (Dai et al., 2020; Goepfert et al., 2021; Liu et al., 2023). SARS-CoV-2 came up with the challenges because it is an enveloped, single-stranded virus that predominantly attacks the lower respiratory system. The clinical signs range from no apparent symptoms to respiratory system failure. The symptoms also include sepsis, multi-organ dysfunction syndrome (MODS), and acute respiratory distress syndrome (ARDS) (Robba et al., 2020). This virus causes severe immunodepression of the host through the immense production of cytokines, including TNF-α, IL-2, IL-6, IL-1β, and IFN-γ. These cytokines cause blood clotting in the vessels and severely damage the tissues, especially the respiratory tissues (Ortega-Paz et al., 2021).

The use of nanotechnology was brought up on an emergency and urgent basis right after the documented reports of the coronavirus pandemic on March 11, 2020. The research on nanoparticles implied various nanoparticles and came up with the formation of two vaccines, Moderna (mRNA-1273), as well as Pfizer-BioNTech (BNT162b2) (Polack et al., 2020; Baden et al., 2021). Both vaccines were enveloped in Liposomes and can stimulate the formation of viral spike proteins in the organism (human) and produce a safe potential immunogenicity to oppose SARS-CoV-2. Both vaccines are administered twice to the recipient. It is reported that Moderna® possesses an efficacy of 94.1% after the 2nd shot. While the Pfizer® is 89-100% effective after the 2nd booster shot. Both vaccines play a central role in the eradication and inhibition of coronaviruses (Cappellano et al., 2021).

CHALLENGES ASSOCIATED WITH NANOTECHNOLOGY

The future of the vaccine production industry is nanotechnology. The application of nanotechnology is not yet widely practiced in the veterinary profession. However, with the increasing scope of nanoparticles derived from various sources with multiple characteristics, the domains of this field have a go at a lot of unrevealed ways ahead (Jafary et al., 2023). If the size-dependent characteristics are defined in detail, it will improve the immunization of the host. The size-dependent characteristics and functions like additive and antigen transfer abilities of nanoparticles need to be more described. The specific size produces specific immune reactions and also modulates the additive and antigen transfer ability of the nanoparticle (Liu et al., 2023). In contrast to the monomeric vaccines, the nanoparticle-based vaccines give a valid reason for additional investigations. After further exploration of liposome nanoparticles, they can be applied for the treatment of many infectious ailments such as cancer and tuberculosis. This platform offers multiple novel approaches that require more research (Tursi et al., 2023)

As this field is emerging, until now, there are no policies for products containing nanoparticles. There exists challenge that no laws and legislation may exist for production and use. This work needs more financial support for the donor agencies to be more precise (Afzal et al., 2022). Due to the size-related physiochemical properties of nanoparticles, they are not commonly till today. They struggle to create them at such a micro-scaled level. They require critical supervision and accuracy. The other matter is associated with their targeted delivery, where there is the chance to reach other sites or tissue (Ali et al., 2023). In the future, it is essential to formulate nano vaccines as the specific nanocarriers to the targeted site and enhance immunity. Nanotechnology is an advanced platform for producing effective and safe next-generation vaccines. Furthermore, it can be applied in multiple ways to immunize the host efficiently against the newly evolving pathogens and the growing proportion of the human population (Cappellano et al., 2021). It is an innovative plan/idea that the 3-D structure of protein antigens is maximized for enhancing the strength and stability of emerging VLP vaccines. However, there is a deficiency of sufficient information to support this plan, which demands further studies (Dai et al., 2018).

Further concerns are associated with the application of nanoparticles as feed additives and nanocarriers that can cause long-lasting inflammatory responses from the immune system to the host. The impact of nanoparticles' extensive and prolonged use on the host body has yet to be established. Similarly, there is a deficiency of knowledge regarding the vast physiochemical properties of nanoparticles, which calls for more research studies. Additionally, the capability to enhance the absorption of antigen-presenting cells, the nanoparticles can possibly spread across additional organs and tissues, probably provoking the biological mechanisms that are necrosis or apoptosis (Cappellano et al., 2021).

A case study performed in 2009 reported that nanotechnology may cause various serious health alarms and anaphylactic reactions. Also, there is unexplored thorough information about micro-scaled structures' physical and chemical nature. The property to accumulate in the cells may lead to cell toxicity (Gregory et al., 2013). In the future, nanoparticles' physical and chemical features can be innovatively employed, linking with charge, dimension, hydrophilic, and hydrophobic properties for immunosuppression. This will enable the immunologist to regulate the immunological replies by different, unexpected means (Tkach et al., 2011). The immune-suppressing field of nanotechnology using nanoparticles requires lots of research which will help in the therapeutic and practical management of mutant viruses (Bosi et al., 2003). Along with the extensive scope of nanotechnology in vaccines and immunity, this technology also tremendously benefits welfare in the animal husbandry field. The discovery of nano-feed adjuvants in current years in the feed of animals is a novel approach to the animal sector. This technology amplifies the nutritional value of livestock fields as well as optimizes animal immunity and production (El Basuini et al., 2016). However, if some challenges regarding nano-feed additives (e.g. toxic effects etc.) get managed through studies and investigations. Many advantages can be acquired in animal nutrition. However, this application demands rigorous scientific research on the characteristics of nano-feed particles and critical management (Dumlu, 2024).

CONCLUSION

The rate of world's population used to decline during viral pandemics before the formulation of 1st vaccine that explored the idea of hindering and averting pathogens. The traditional vaccines work but have limitations and imply certain boundaries. However, using nanoparticles in the vaccine formulations, with their versatile physiochemical characteristics, proved better than the conventional ones. The emerging nanotechnology improves immunogenicity; however, this lack of detailed and in-depth data, specifically regarding the immune depressing effects, calls for further research. The nano vaccination platform shows promising results after more investigations. The size-dependent features and activity of nanoparticles demand more knowledge about the nano vaccination future.

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