Applications of nanotechnology in vaccine development for coronavirus (SARS-CoV-2) disease (Covid-19)

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Abstract: **This review paper highlights the use of nanotechnology as a new opportunities for the development of novel strategies in terms of prevention, detection, diagnosis and treatment of severe acute respiratory syndrome coronavirus (SARS-CoV-2). Coronavirus (SARS-CoV-2) disease (covid-19) infection is characterized by severe respiratory diseases, including bronchiolitis, pneumonia, high fever, throat infections, and common cold. SARS-CoV-2 infection is not limited to any particular class, and people of all age groups are vulnerable. The coronavirus is airborne mainly transmitted through droplets from the infected person or symptomatic patients or from asymptomatic people. The transmission of SARS-CoV-2 from one human to another human is much faster, which has already resulted in its spread around the world and led the WHO to declare the covid-19 outbreak as a global pandemic. These outbreaks have tested the limits of healthcare systems and have posed serious questions about anagement using conventional therapies and diagnostic tools. Therefore, new controlling measures to overcome this covid-19 pandemic is the development of a suitable and cost effective vaccines and therapeutics. Hence nanotechnology platforms in the development of vaccines and therapeutic drugs have been developed based on nanomedicine, and have the potential to become innovative alternatives for overcoming COVID-19. A nano-based (mRNA-lipid nanoparticle) formulation for SARS-CoV-2 vaccine and therapeutics is being developed as a delivery vehicle and found successful**.

Keywords: **Antigen, coronavirus, delivary vehicle, SARS-CoV-2, nanotechnology, nanoparticles, viral disease.**

I. INTRODUCTION

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a novel coronavirus responsible for an ongoing human pandemic (COVID-19) (Yang, 2021; Shin et al., 2020). WHO officially identified coronavirus (SARS-CoV-2) as a pandemic, due to its quick global spread (Zhou et al., 2020a, 2020b; Wu et al., 2020a, 2020b; Wu et al., 2004; Shi et al., 2020; V'kovski et al., 2020; Shin et al., 2020). The coronavirus can infect cells of the lungs, kidneys, heart and intestine, resulting in organ damage leading to the multiple organ dysfunction syndrome (Zhou et al., 2020a, 2020b; Shin et al., 2020). The cause of the respiratory illness is a coronavirus of the betacoronavirus class now termed coronavirus infectious disease-19 (COVID-19). The virus was named as SARS-CoV-2 due to its genetic and structural similarity with SARS-CoV, and is the causative agent of the COVID-19 disease outbreak (Zhou et al., 2020a, 2020b; Wu et al., 2020a, 2020b; Wu et al., 2004; Shi et al., 2020; V'kovski et al., 2020; Kammila et al., 2008). Airborne transmission is highly virulent and represents the dominant route for the spread of SARS-CoV-2 (covid-19) (Zhang et al., 2020; Shin et al., 2020). The worldwide impact of this pandemic is frightening, and threat to human population (Yang, 2021; Chauhan et al., 2020; Campos et al., 2020). The human race is also facing a crisis situation due to mandatory quarantines and lockdowns (Yang, 2021; Chauhan et al., 2020). The world economy is already facing a long lasting dent, and the situation will surely worsen if the viral spread is not controlled (Yang, 2021; Chauhan et al., 2020; Campos et al., 2020; Chauhan et al., 2020; Corum et al., 2020). Therefore, immediate control measures in terms of vaccine are very much essential for the eradication of this deadly coronavirus-2 (SARS-CoV-2). The COVID-19 crisis also demands an urgent analysis of all the available nanotechnology tools (Shin et al., 2020;Vijayan et al., 2019; Mufamadi, 2020; Yang, 2021). Nanomedicine strategies are in use for the design of the vaccine carriers, there are not enough other nanotechnology approaches being explored to tackle the current coronavirus outbreak (Shin et al., 2020; Chung et al., 2020; Yang, 2021; Das and Suresh, 2006). Nanocarrier-based therapeutics offers several opportunities to address the limitations of current antiviral therapy (Yang, 2021; Rangayasami et al., 2021; Shin et al., 2020; Mufamadi, 2020; Campos et al., 2020; Chauhan et al., 2020; Chung et al., 2020; Kaczmarek et al., 2016; Lung et al., 2020; Reichmuth et al., 2016; Pardi et al., 2015, 2018). Nanotechnology benefits the modern vaccine design since nanomaterials are ideal for antigen delivery, as adjuvants, and mimics the structural features of viruses (Chung et al., 2020; Shin et al., 2020).

II. VACCINE

A biological material (expressed protein or antigen or pathogen) that stimulates a person's immune system to produce immunity to a specific disease, protecting the person from that disease is called as vaccine. Vaccines are the most promising solution to mitigate the new viral strains (Shin et al., 2020). Vaccination is defined as a process of introducing foreign antigenic material (s) (pathogen) in order to activate a host immune system, has been a key deliver strategy to control diseases (Malabadi, 2008; Malabadi et al., 2010; Malabadi et al., 2011; Malabadi et al., 2016; Malabadi et al., 2017; Khan et al., 2011, 2012; Yun and Cho, 2020). Plants were also used as expression platforms for the vaccine production. In addition to this, antiviral compounds could also be isolated from many medicinal plants since plants contains many active bio-molecules (Malabadi et al., 2021; Malabadi and Chalannavar, 2020). Vaccine provides active and protective immunity against a target disease, contains an agent (antigen) that originated from and/or resembles a disease-causing microorganism (Malabadi et al., 2017; Khan et al., 2011, 2012; Yun and Cho, 2020). In general, vaccines are catagarized as

1) Live-attenuated vaccine: A weakened form of pathogens (antigen) capable of replication, but not causing illness (Shin et al., 2020).

2) Inactivated vaccine: killed form of pathogens (antigen) incapable of replication or infection.

3) Subunit vaccine: minimal antigenic element of a pathogen, a protein, protein subunit or polysaccharides or virus-like-particles (VLPs) self-assembled from these components (Shin et al., 2020). These antigens in a purified forms are administered in combination with molecular adjuvants or expressed *in vivo* using RNA, DNA or viral vectors (Shin et al., 2020).

4) Peptide-based vaccines: Peptides are fundamental elements of a protein subunit recognized by the immune system; all antigens described above contain peptide epitopes (Shin et al., 2020). Further an adjuvant is defined as a stimulatory agent designed to boost the immune response towards a co-delivered antigen. The adjuvant occurs as 'independent entities' in a mixture with antigens (Shin et al., 2020). Adjuvant also occurs as 'conjugate-entities' *via* chemical fusion directly to antigens (Shin et al., 2020). Vaccine is often made from a weakened or inactivated pathogen, expressed protein or one of its nucleotides, peptides or proteins (Chung et al., 2020; Malabadi et al., 2017; Khan et al., 2011, 2012; Yun and Cho, 2020). The DNA and mRNA-based vaccines deliver the genetic sequence of a specific viral proteins to the host cells using nanotechnology platforms (Nanomedicine and the COVID-19 vaccines, 2020; Shin et al., 2020; Chung et al., 2020). Traditional vaccines instead trigger the immune responses upon injection of the entire viruses, either as attenuated live viruses, inactivated viruses or engineered viruses, into the host body. Both types of vaccines are being tested against COVID-19 in clinical trials (Corum et al., 2020 Shin et al., 2020; Chung et al., 2020).

Following is the list of available vaccines for SARS-CoV-2 and approved for the immunization programme to combat the viral disease covid-19.

1) The *ChAdOx1 nCoV-19* vaccine (AZD1222) was developed at Oxford University (UK) -Astra Zeneca, and consists of a replication-deficient chimpanzee *adenoviral* vector ChAdOx1, containing the SARS-CoV-2 structural surface glycoprotein antigen (spike protein; nCoV-19) gene. Oxford University. London, *UK* has entered into a partnership with *AstraZeneca* for further development of ChAdOx1 nCoV-19.

2) *COVISHIELD:* SII's Recombinant Chimpanzee Adenovirus vector vaccine, Covishield, encodes the SARS-CoV-2 Spike (S) glycoprotein with technology transfer from AstraZeneca-Oxford University for the first made-in-India vaccine, COVISHIELD, *Serum Institute of India,* Pune, Maharashtra, *India*.

3) *Covaxin* (inactivated whole virus vaccine), *Bharath Biotech*, Hyderabad, Telangana, *India.*

4) *COVAXIN*^{TM}, India's indigenous COVID-19 vaccine by Bharat Biotech is developed in collaboration with the Indian Council of Medical Research (ICMR) - National Institute of Virology (NIV), Pune, Maharashtra, India. The indigenous, inactivated vaccine is developed and manufactured in Bharat Biotech's BSL-3 (Bio-Safety Level 3) high containment facility.

5) *Pfizer-BioNTech* COVID-19 (mRNA vaccine) (Tozinameran or BNT162b2) is used to prevent COVID-19. The Pfizer-BioNTech COVID-19 vaccine is manufactured by Pfizer Inc, USA and BioNTech Inc., Manufacturing GmbH, *Germany.*

6) *Moderna COVID-19 vaccine* (mRNA-1273) is used to prevent coronavirus-2 (SARS-CoV-2) (COVID-19). The Moderna COVID-19 mRNA vaccine is manufactured by Moderna Therapeutics Inc, Cambridge, Massachusetts, *USA*. Moderna COVID-Vaccine (mRNA-1273) (mRNA-based vaccin), Moderna, BARDA, NIAID, USA

7) *Sputnik V* (Non-replicating viral vector), Gamaleya Research Institute, Acellena Contract Drug Research and Development, *Russia*

8) *EpiVacCorona* (Peptide vaccine), Federal Budgetary Research Institution, State Research Center of Virology and Biotechnology, *Russia*.

9) *BBIBP-CorV* (Inactivated vaccine), Beijing Institute of Biological Products; China National Pharmaceutical Group (Sinopharm), *China*

10) *Comirnaty (BNT162b2)* (mRNA-based vaccine), Pfizer, BioNTech; Fosun Pharma, Multinational.

11) *Novavax candidate vaccine, (NVX-CoV2373)* Novavax, Inc. (Nasdaq: NVAX) is a biotechnology company, Gaithersburg, Maryland, USA (Tian et al., 2021)

NVX-CoV2373 is a vaccine candidate engineered from the genetic sequence of SARS-CoV-2, the virus that causes COVID-19 disease. NVX-CoV2373 was created using Novavax' recombinant nanoparticle technology to generate antigen derived from the coronavirus spike (S) protein and contains Novavax' patented *saponin-based Matrix-M*™ adjuvant to enhance the immune response and stimulate the high levels of neutralizing antibodies. NVX-CoV2373 contains purified protein antigen and cannot replicate, nor can it cause COVID-19 (Tian et al., 2021)

12) *Covovax*- (It's a protein subunit vaccine, and uses nanoparticles): The Serum Institute of India (SII), Pune, Maharashtra, India hopes to launch Covovax — developed in partnership with American vaccine developer Novavax, Gaithersburg, Maryland, USA.

13) *Johnson & Johnson covid-19 vaccine* (Ad26.COV2.S) (Janssen Biotech, Inc) Johnson & Johnson has developed a coronavirus (SARS-CoV-2) vaccine that works differently than the Pfizer and Moderna vaccines and is highly effective for preventing moderate to severe COVID-19 (Livingston et al., 2021; Bos et al., 2020; Sadoff et al., 2021; Solforosi et al., 2020)

The COVID-19 vaccine from Johnson & Johnson uses existing technology that involves a virus called *adenovirus*, a common cause of respiratory infections (Livingston et al., 2021). The DNA in the adenovirus is modified so that it produces a key part of the SARS-CoV-2 virus particle to which the body then develops an immune response (Livingston et al., 2021; Bos et al., 2020; Sadoff et al., 2021; Solforosi et al., 2020). The adenovirus that delivers the SARS-CoV-2 DNA particle cannot multiply, so it does not cause infection (Livingston et al., 2021). Because this system is based on stable DNA molecules, it does not require ultra cold storage, making it easier to distribute (Livingston et al., 2021; Bos et al., 2020; Sadoff et al., 2021; Solforosi et al., 2020).

Johnson & Johnson covid-19 vaccine, known as Ad26.COV2. S, is a replication-incompetent *adenovirus type* 26 (Ad26) vectored vaccine encoding a stabilized variant of the SARS-CoV-2 S protein (Livingston et al., 2021; Bos et al., 2020; Sadoff et al., 2021; Solforosi et al., 2020). The proposed use under an Emergency Use Authorization (EUA) to FDA is for active immunization to prevent COVID-19 caused by SARS-CoV-2 in individuals 18 years of age and older. The proposed dosing regimen is a single intramuscular injection at the dose level of 5×1010 viral particles (vp).

III. APPLICATIONS OF NANOTECHNOLOGY

Nanotechnology has paved new pathways and provided a new avenue in vaccine development for infectious diseases, such as COVID-19 (Shin et al., 2020;Vijayan et al., 2019; Mufamadi, 2020; Yang, 2021; Chung et al., 2020). Nanotechnology has a potentiality in COVID-19 treatment and vaccine development. Nanoparticles triggered the antigen-specific immune responses and helping in the smooth delivery of the antigen into the host cell (Vijayan et al., 2019; Malabadi et al., 2017; Khan et al., 2011, 2012; Yun and Cho, 2020). Nanoparticle-based antigen delivery has many advantages than traditional vaccine delivery system such as safe delivery vehicles, vaccine adjuvant, improved antigen stability, targeted delivery, long-time controlled release and evasion of immune responses (Yang, 2021; Vijayan et al., 2019; Malabadi et al., 2017; Khan et al., 2011, 2012; Yun and Cho, 2020; Chung et al., 2020; Corum et al., 2020; Jackson et al., 2020; Lung et al., 2020; Maruggi et al., 2020; Reichmuth et al., 2016). Antigens can either be encapsulated inside the nanocarriers or bound (conjugated) to the surface of the nanoparticle and administered together with the adjuvant to the target (Yang, 2021; Campos et al., 2020; Rangayasami et al., 2021). Nanotechnology based vaccines are easy to design, synthesize, or scale up in a larger volume compared to the traditional vaccine approaches (e.g., inactivated and live-attenuated strains (Shin et al., 2020;Vijayan et al., 2019; Mufamadi, 2020; Yang, 2021; Chung et al., 2020). Nanocarriers to potentiate the success of COVID-19 vaccine in terms of efficacy and safety (Rangayasami et al., 2021; Campos et al., 2020). Some of these opportunities include nanocarrier-based effective/targeted delivery, better antigen presentation, and the induction of complimenting immunomodulatory effect (Chauhan et al., 2020; Kaczmarek et al., 2016; Lung et al., 2020; Reichmuth et al., 2016; Pardi et al., 2015; Campos et al., 2020). Nanocarrier delivery technology to make these repurposed therapeutics safer and more effective.

Nanoparticles are classified into liposomes, and lipid-based nanoparticles, polymeric nanoparticles, gold nanoparticles, silver nanoparticles, inorganic nanoparticles, virus-like particles, self-assembled proteins, and carbon-based nanoparticles (carbon nanotubes and graphenes) (Vijayan et al., 2019; Malabadi et al., 2017; Malabadi et al., 2012a, 2012b, 2012c, 2012d; Khan et al., 2011, 2012; Yun and Cho, 2020). Nanotechnology thus has a great potential to be a vital tool for tackling the COVID-19 outbreak and may be a crucial technology to prevent the future infectious disease outbreaks (Shin et al., 2020;Vijayan et al., 2019; Mufamadi, 2020; Yang, 2021). The scope of nanotechnology for COVID-19 therapeutics and vaccine research is not limited to conventional therapeutic and vaccine designs (Yang, 2021; Rangayasami et al., 2021; Campos et al., 2020; Chauhan et

al., 2020; Kaczmarek et al., 2016; Lung et al., 2020; Reichmuth et al., 2016; Pardi et al., 2015).

Rational designing of nanocarrier-based vaccine is equally important for its clinical success, hence strategies related to the nanocarrier selection for antigen loading and effective delivery (Chauhan et al., 2020; Kaczmarek et al., 2016; Lung et al., 2020; Reichmuth et al., 2016; Pardi et al., 2015). Nanocarrier-based therapeutics offers several opportunities to address the limitations of the current antiviral therapy (Rangayasami et al., 2021; Chauhan et al., 2020; Kaczmarek et al., 2016; Lung et al., 2020; Reichmuth et al., 2016; Pardi et al., 2015. 2018). Nanomedicine strategies are in use for the design of the vaccine carriers. Targeted nanoparticles provide an improved rate of endocytosis which is better to ensures the delivery of a therapeutic nanoparticle dose to the target cell. To improve the efficacy and safety of the vaccine approach, a big advantage presented by nanoparticles is their ability to deliver molecular adjuvants, and, in some cases, nanomaterials themselves possess an intrinsic adjuvant property for the loaded antigens (Chauhan et al., 2020; Kaczmarek et al., 2016; Lung et al., 2020; Reichmuth et al., 2016; Pardi et al., 2015; Chung et al., 2020).

The live-attenuated and inactivated viral vaccines can be regarded as nanoparticles. Nanoparticle (viral or non-viral) can be employed as nanocarrier to encapsulate or present the antigen to the host cell (Shin et al., 2020). Nanocarriers synchronize the delivery of both, antigen and adjuvant, to target an immune cells (Shin et al., 2020;Vijayan et al., 2019; Malabadi et al., 2017; Khan et al., 2011, 2012; Yun and Cho, 2020). Viruses are nanoscale objects and therefore, can be regarded as a naturally occurring nanomaterials. The key advantages of vaccine nanocarriers are their nanosize, since many biological systems such as viruses (including SARS-CoV-2) and proteins are also nanosized (Chauhan et al., 2020; Kaczmarek et al., 2016; Lung et al., 2020; Reichmuth et al., 2016; Pardi et al., 2015). Active targeted nanocarriers offer the opportunity to cross the biological barriers and attain the therapeutic concentrations in sheltered viral reservoirs. Nanoparticles and viruses operate at the same length scale (Shin et al., 2020). Therefore, nanomedicine strategy is a powerful tool to transform the antivirals repurposing and improving the COVID-19 therapeutic management. In addition to this, nanoparticles also improved the delivery and presentation of antigens to the antigen-presenting cells (APCs) (Chauhan et al., 2020; Kaczmarek et al., 2016; Lung et al., 2020; Reichmuth et al., 2016; Pardi et al., 2015). One of the biggest challenges in the COVID-19 vaccine research is to identify the approaches that stimulate both the T cell and B cell immunity against coronavirus-2 (SARS-CoV-2) (Chauhan et al., 2020; Kaczmarek et al., 2016; Lung et al., 2020; Reichmuth et al., 2016; Pardi et al., 2015). Both humoral and cell mediated immunity performs a protective role in the SARS-CoV-2 infection. Nanoparticles have shown their ability to target both adaptive (T cells, B cells) and innate immune systems (macrophages, monocytes, neutrophils) at the cellular level (Chauhan et al., 2020; Kaczmarek et al., 2016; Lung et al., 2020; Reichmuth et al., 2016; Pardi et al., 2015). Modulating the antigen-presenting cells (APCs) using nanoparticles could be very important, particularly for COVID-19 (SARS-CoV-2) vaccine strategies (Chauhan et al., 2020; Kaczmarek et al., 2016; Lung et al., 2020; Reichmuth et al., 2016; Pardi et al., 2015). Hence nanotechnology approaches in vaccine development and immunoengineering become very powerful platforms (Vijayan et al., 2019; Malabadi et al., 2017; Khan et al., 2011, 2012; Yun and Cho, 2020). Nanoparticles can be loaded with a wide range of antigenic moieties (by physical entrapment or chemical conjugation), and a correct antigenic display makes it a highly relevant alternate in vaccinology when compared to the conventional approaches. The development of more potent and versatile vaccine platforms is therefore, urgently needed. The ability of nanoparticles to deliver antigen to dendritic cells (DCs) by enhancing the antigen presentation and several other mechanisms can promote T cell immunity (Chauhan et al., 2020; Kaczmarek et al., 2016; Lung et al., 2020; Reichmuth et al., 2016; Pardi et al., 2015).

Nanoparticles enables the development of next-generation designer vaccine technologies (Shin et al., 2020; Rangayasami et al., 2021). The development of SARS-CoV-2 vaccine utilized the modern nanotechnology design since nano-formulations are ideal for the antigen delivery which mimics the adjuvants and structural features of viruses (Shin et al., 2020; Chauhan et al., 2020; Kaczmarek et al., 2016; Lung et al., 2020; Reichmuth et al., 2016; Pardi et al., 2015). During the recent covid-19 outbreak, the first vaccine candidate launched into clinical trials is an mRNA vaccine delivered via lipid nanoparticles (Shin et al., 2020). This new vaccine delivery platforms and devices to break the cold chain limitations (Shin et al., 2020; Yang, 2021). Nanotechnology platforms offers a great utility in the modern vaccine design and have helped to catalyse the novel candidate vaccines towards a clinical testing at unprecedented speed (Shin et al., 2020; Rangayasami et al., 2021). Moderna's mRNA vaccine is based on a lipid nanoparticle platform (Shin et al., 2020). Other nanotechnology platforms such as cationic nanoemulsions, liposomes, dendrimers or polysaccharide particles have also been employed for improving the stability and delivery of mRNA based vaccines (Shin et al., 2020). Subunit vaccines can also take the form of protein nanoparticles or virus-like particles (VLPs). Virus-like particles (VLP) vaccines can be produced by recombinant expression and allows for the genetic engineering to incorporate ligands, immunomodulators and targeting moieties (Shin et al., 2020; Yang, 2021). Peptide based vaccines are dependent on adjuvants and delivery systems for efficacy, and nanoparticles can serve both these roles (Shin et al., 2020; Chauhan et al., 2020; Kaczmarek et al., 2016; Lung et al., 2020; Reichmuth et al., 2016; Pardi et al., 2015).

COVID-19 is known to be very contagious and has many routes of transmission. Therefore, the use of appropriate

personnel protection equipment (PPE), such as masks and gloves, is also important to combat the spread of the coronavirus (Yang, 2021;Campos et al., 2020; Rangayasami et al., 2021). Nanotechnology is offering new materials that are more comfortable, resistant, and safer means for protection against biological and chemical risks (Yang, 2021; Campos et al., 2020; Rangayasami et al., 2021). Facemasks, lab or medical aprons and others have also been nanoengineered to provide a new functions, for instance, hydrophobicity and antimicrobial activity without affecting the material's texture or breathability of personnel protection equipment (PPE) products, which can provide an effective barrier on its own against airborne droplets emitted during the coughing or sneezing (Campos et al., 2020; Rangayasami et al., 2021). Similarly, the use of nanomaterials can build antimicrobial properties in textiles used in the personnel protection equipment (PPE). This strategy has been used to prevent the growth of microorganisms in clothes (Campos et al., 2020; Rangayasami et al., 2021).The surfaces modified by nanoscale biocides, such as quaternary ammonium or quaternary phosphonium salts, polymers or peptides, can control microorganisms through oxidation of the microbial (Campos et al., 2020; Rangayasami et al., 2021; Yang, 2021).

Nanotechnology through its numerous applications is an efficient and cost-effective tool to be used to improve the detection tests for SARS-CoV-2 (Yang, 2021; Campos et al., 2020; Rangayasami et al., 2021). Nano biosensors have the advantage of selectively detecting all types of pathogen (antigen) by combining the excellent electrical and optical properties of nanomaterials with biological or synthetic molecules used as receptors (Yang, 2021). In the case of applying Graphene, the detection of SARS- CoV-2 in clinical samples was attempted with a sensor produced by coating the graphene sheet of the field-effect transistor with a specific antibody against the SARS-CoV-2 spike protein (Yang, 2021). As a result of the study, it was possible to detect SARS-CoV-2 spike protein at a concentration of 1 fg/ mL in phosphate-buffered saline and 100 fg/mL clinical transport medium (Yang, 2021).

In another method, the SARS-CoV-2 biosensor using thiol-modified antisense oligonucleotides-Gold nanoparticles (GNs) can diagnose positive COVID-19 cases with the naked eye through color change within 10 minutes from total RNA isolated from infected biosamples (Campos et al., 2020; Rangayasami et al., 2021; Yang, 2021). The ability of gold nanoparticles (GNs) to induce an immune response by antigen-presenting cells easily is attractive for use in vaccine development. Gold nanoparticles (GNs) have the advantage of being easily transformed for the delivery through the nasal cavity. It has also the advantage of activating the immune response associated with CD8+ (cytotoxic) T cells by spreading to the lymph nodes (Campos et al., 2020; Rangayasami et al., 2021; Yang, 2021). Moreover, the technology that deactivates SARS-CoV-2 in the external environment using nanomaterials, and diagnostic technology that can quickly detect SARS-CoV-2 without the use of expensive equipment by applying gold nanoparticles are also contributing towards the prevention and control of COVID-19 (Yang, 2021).

Intranasal drug delivery has been proven to be an effective method of administration for treating the viral lung diseases (Campos et al., 2020; Rangayasami et al., 2021; Yang, 2021). In recent years, nanotechnology-based drug delivery systems have been applied to a intranasal drug delivery to overcome the various limitations that occur during the mucosal administration, and advances have been made to the stage where effective drug delivery is possible (Yang, 2021). Silver nanoparticles (Ag-NPs) have already been proven to display antiviral, antifungal and antibacterial effects against various pathogens (Yang, 2021; Vijayan et al., 2019; Malabadi et al., 2017; Malabadi et al., 2012a, 2012b, 2012c, 2012d; Khan et al., 2011, 2012; Yun and Cho, 2020). Therefore, nanotechnology and nanomedicine can be suitable alternatives and played an important role in controlling the SARS-CoV-2 viral disease (Yang, 2021).

Raghuwanshi et al., (2012) reported a promising strategy for enhancing immunogenicity of low-dose DNA vaccine through targeted delivery to nasal resident dendritic cells Raghuwanshi et al., 2012). The vaccine strategy demonstrated in this study could provide a better understanding of non invasive means of targeting vaccine antigens to the dendritic cells Raghuwanshi et al., 2012). The antigen formulations developed in this study warranted further evaluation in SARS-CoV virus challenge experiments. This study has important implications for designing vaccines against SARS or infections with similar mechanisms (Raghuwanshi et al., 2012).

IV. mRNA COATED LIPID NANOPARTICLES

The mRNA vaccines represents a promising alternatives to conventional vaccine approaches because of their high potency, capacity for rapid development and potential for low-cost manufacture and safe administration (Pardi et al., 2018; Jackson et al., 2020; Maruggi et al., 2019). The mRNA to become a promising therapeutic tool in the fields of vaccine development and protein replacement therapy (Jackson et al., 2020; Maruggi et al., 2019; Pardi et al., 2018). The use of mRNA has several beneficial features over subunit, killed and live attenuated virus, as well as DNA-based vaccines (Pardi et al., 2018; Jackson et al., 2020; Maruggi et al., 2019). The mRNA-based COVID-19 vaccine utilizes lipid nanoparticles as a carrier (Jackson et al., 2020; Maruggi et al., 2019). Naked mRNAs are sensitive to the degradation by extracellular RNases, thus formulating its delivery vehicle is essential (Pardi et al., 2018; Chauhan et al., 2020; Kaczmarek et al., 2016; Lung et al., 2020; Reichmuth et al., 2016; Pardi et al., 2015; Jackson et al., 2020; Maruggi et al., 2019). The mRNA-based vaccines are easily eliminated by nucleases through the reticuloendothelial system (RES), which makes it difficult to deliver them into host cells in the targeted tissues (Shin et al., 2020; Mufamadi, 2020; Yang, 2021). The use of

nanoparticles as the vehicle makes it easy to deliver the plasmid DNA into the nucleus for the production of encoded antigens or mRNA into the cytoplasm of the targeted host cell to tissues to build immunity against the coronavirus (Shin et al., 2020; Mufamadi, 2020; Yang, 2021; Pardi et al., 2018). Therefore, the use of nanoparticles or virus like particles (VLPs) can stimulate the body's adaptive immune system to produce neutralizing antibodies and T cells against coronaviruses (Mufamadi, 2020; Yang, 2021;Chung et al., 2020; Corum et al., 2020; Jackson et al., 2020; Lung et al., 2020; Maruggi et al., 2020; Reichmuth et al., 2016; Yun and Cho, 2020). Lipid nanoparticles (LNs) are biocompatible due to their lipid properties; hence, they can be selectively applied in fields such as biomedical science. Among the various lipid nanoparticles, liposomes in the form of spherical capsules, which are hydrophilic on the inside and consist of a phospholipid bilayer on the outside, are the most suitable for intranasal delivery (Shin et al., 2020; Yang, 2021; Mufamadi, 2020;Shin et al., 2020).

Further, these mRNAs entail their cell-specific receptor recognition and lipid membrane penetration (Pardi et al., 2018; Chauhan et al., 2020; Kaczmarek et al., 2016; Lung et al., 2020; Reichmuth et al., 2016; Pardi et al., 2015). Lipid nanoparticles are virus-sized (80−200 nm) particles synthesized by the self-assembly of an ionizable cationic lipid (Chauhan et al., 2020; Kaczmarek et al., 2016; Lung et al., 2020; Reichmuth et al., 2016; Pardi et al., 2015). They possess the ability to deliver mRNA efficiently into the cytoplasm, as demonstrated by several studies (Chauhan et al., 2020; Kaczmarek et al., 2016; Lung et al., 2020; Reichmuth et al., 2016; Pardi et al., 2015, 2018). The mRNA encoding a disease-specific antigen encapsulated lipid nanoparticles is used as a templete (Pardi et al., 2018; Jackson et al., 2020; Maruggi et al., 2019). Once the sequence of interest is inside the cells, it serves as a template to produce the antigen (protein) in situ. After translation, the antigen could be extracellularly transported and recognized by antibodies or could be intracellularly processed and presented to T-cells, resulting in the humoral and cellular immune response (Campos et al., 2020; Shin et al., 2020; Jackson et al., 2020; Maruggi et al., 2019). *Moderna Inc.,* biotechnology company in collaboration with Vaccine Research Center at the U.S. National Institutes of Health, has developed mRNA vaccines (mRNA-1273) encapsulated in lipid-based nanoparticles (Yang, 2021; Campos et al., 2020). Furthermore, mRNA vaccine (BNT162b2) developed by *Pfizer-BioNTech* can be considered as a great achievement of nanomedicine (Yang, 2021).

Nano-sized virus-like nanoparticles (VLPs), which have the characteristic function of the virus, have the advantage of being better delivered through the lymph and capillaries than other small vaccines (Pardi et al., 2015, 2018). Virus-like nanoparticles (VLPs) are capsids, comprising virus-derived structural proteins and adjuvants. Virus-like-particles (VLPs) can generate a potential immunogenic epitope, resulting in the higher immunogenicity (Yang, 2021; Shin et al., 2020). The journey of COVID-19 vaccine development is very impressive and involves high-tech platforms such as viral vectors, antigen carriers, and delivery technology. The mRNA-based vaccine employing lipid nanoparticles (LNPs) delivery is successful (Chauhan et al., 2020; Kaczmarek et al., 2016; Lung et al., 2020; Reichmuth et al., 2016; Pardi et al., 2015, 2018).

The main advantages of mRNA-coated lipid nanoparticles vaccine strategies are as follows.

1) mRNA delivery into the host cell is safer than whole virus or DNA delivery since mRNA is not infectious and cannot be integrated into the host genome. Therefore, there is no potential risk of infection or insertional mutagenesis. (Nanomedicine and the COVID-19 vaccines, 2020; Pardi et al., 2018; Jackson et al., 2020; Maruggi et al., 2019).

2) mRNA is degraded by normal cellular processes, and its *in vivo* half-life can be regulated through the use of various modifications and delivery methods (Pardi et al., 2018). The inherent immunogenicity of the mRNA can be down-modulated to further increase the safety profile (Pardi et al., 2018; Jackson et al., 2020; Maruggi et al., 2019).

3) Various modifications can make mRNA more stable and highly translatable. Efficient *in vivo* delivery can be achieved by formulating mRNA into carrier molecules, allowing rapid uptake and expression in the cytoplasm (Pardi et al., 2018). The mRNA is the minimal genetic vector; therefore, anti-vector immunity is avoided, and mRNA vaccines can be administered repeatedly (Pardi et al., 2018; Jackson et al., 2020; Maruggi et al., 2019).

4) mRNA vaccines have the potential for rapid, inexpensive and scalable manufacturing, mainly owing to the high yields of *in vitro* transcription reactions (Pardi et al., 2018; Jackson et al., 2020; Maruggi et al., 2019),

5) DNA delivery needs to reach the nucleus to be decoded. mRNA is processed directly in the cytosol (Nanomedicine and the COVID-19 vaccines, 2020; Pardi et al., 2018; Jackson et al., 2020; Maruggi et al., 2019).

6) mRNA has a short half-life, which can be regulated by molecular design. mRNA is immunogenic, which might represent an advantage for vaccine design, yet its immunogenicity can be modulated with the molecular engineering techniques (Nanomedicine and the COVID-19 vaccines, 2020; Pardi et al., 2018).

7) mRNA needs a carrier for efficient transportations *in vivo* without being degraded in the circulation, and to

reach the cytosol across the cellular plasma membrane (Nanomedicine and the COVID-19 vaccines, 2020; Pardi et al., 2018).

8) For many mRNA-based therapeutics, the vehicles of choice are lipid nanoparticles (although other materials have also been used). Complexed with positively-charged lipid nanoparticles, mRNA is more stable and resistant to RNase-mediated degradation and forms self-assembled virus-sized particles that can be administered *via* different routes (Nanomedicine and the COVID-19 vaccines, 2020; Pardi et al., 2018)

9) mRNA coated lipid nanoparticles promote endosomal escape, and release their genetic cargo in the cytosol, where the mRNA is translated using host machinery into antigenic proteins, kick-starting the immune system machinery into producing neutralizing antibodies (Nanomedicine and the COVID-19 vaccines, 2020; Pardi et al., 2018).

10) Therefore, mRNA coated lipid nanoparticles encoding genetic variants of the SARS-CoV-2 spike protein that are more stable and immunogenic than the natural protein (Nanomedicine and the COVID-19 vaccines, 2020; Pardi et al., 2018).

11) mRNA is non-integrating and therefore, poses no risk of insertional mutagenesis. Additionally, the half-life, stability and immunogenicity of mRNA can be tuned through established modifications (Pardi et al., 2018; Jackson et al., 2020; Maruggi et al., 2019).

12) However, current drawback of these mRNA-coated lipid-nanoparticles formulations is that their long-term storage requires low temperatures, posing logistical hurdles to their potential distribution and administration. Therefore, nano-formulations (mRNA-coated lipid-nanoparticles) for the efficient packaging and safe delivery of genetic material is a major concern for the large scale immunization programmes particularly in the poor developing countries (Nanomedicine and the COVID-19 vaccines, 2020).

V. CONCLUSION

Nanotechnology platforms can play a significant role in the advancement of covid-19 (SARS-CoV-2) treatment and vaccine development. Nanotechnology innovative approaches has shown to enhance detection, diagnostics, protection and therapies in controlling covid-19 (SARS-CoV-2). The major technological innovation and research investment have enabled mRNA to become a promising therapeutic tool in the fields of vaccine development and protein replacement therapy. The future of mRNA vaccines is therefore, extremely bright and clinical studies promoted the basic research into mRNA-based therapeutics. Further, mRNA vaccines represent a promising alternative to the conventional vaccine approaches, because of their high potency, capacity for rapid development and potential for low-cost manufacture and safe administration. The development of more potent and versatile mRNA vaccine platforms is therefore, urgently needed to combat covid-19. Therefore, nanotechnology, is essential to end this covid-19 pandemic effectively in a short time. Various mRNA vaccine platforms have been developed in recent years and validated in studies of immunogenicity and efficacy. The significant advances in mRNA biology, delivery, and manufacturing, the biotechnology and vaccine industries are poised for further investment in the development of novel products. Currently, several biotechnology companies in many countries are moving away from traditional SARS-CoV-2 treatment and prevention strategies and using nanotechnology to develop various types of vaccines and therapeutics and conduct clinical evaluations. Therefore, nanotechnology and nanomedicine will be a new ray of hope for the effective production of future vaccine.

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