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Leveraging Nanotechnology for Addressing COVID-19: Revealing Antiviral Approaches and Hurdles

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Abstract

The emergence of COVID-19 has caused extensive harm and is recognized as a significant threat to human life worldwide. Currently, the application of nanomedicine techniques in pre-clinical studies related to various infections, such as respiratory viruses, herpes viruses, human papillomavirus, and HIV, has demonstrated success. Nanoparticles, due to their specific attributes, have garnered considerable attention in combating COVID-19. Strategies employing nanomaterials for COVID-19 prevention encompass the development of rapid, precise diagnostic tools, the creation of effective disinfectants, the delivery of mRNA vaccines to the biological system, and the administration of antiretroviral medications within the body. This article focuses on recent research regarding the effectiveness of nano platforms as antiviral measures against coronaviruses. It delves into the molecular characteristics of coronaviruses and the affected target systems, highlighting challenges and limitations in combating SARS-CoV-2. Additionally, it explores potential nanotechnology-based treatments to confront current and future variants of coronaviruses associated with COVID-19 infections.

Keywords

COVID-19, Coronavirus, Nanomaterials, Nano-Based Vaccine, SARS-CoV-2

1. Introduction

The COVID-19 pandemic continues to affect millions worldwide with no signs of abating. Nanotechnology presents potential strategies involving antigen distribution, adjuvants, and mimicking viral structures. Among these, an mRNA vaccine delivered via lipid nanoparticles marks the initial vaccine candidate in

clinical trials. A robust vaccination platform should expedite development, streamline production, and widespread distribution, aiming to quell current and future pandemics [1] [2] [3]. Nanomaterials, boasting unique physical and chemical properties like nano-scale dimensions, extensive surface area, and adaptable surface alterations, have been crafted to combat viral, bacterial, and fungal ailments. These attributes aid in optimizing drug delivery, enhancing drug solubility, modulating pharmacokinetics, facilitating cell membrane penetration, and elevating drug bioavailability against diverse viruses, fostering optimism for COVID-19 diagnostic and therapeutic tools [4] [5].

Nanoparticles, nano-based vaccines, and Smart Medicines offer multifaceted roles in preventing coronaviral infections. However, challenges and limitations in this technology prompt a comprehensive exploration. This review systematically outlines recent nanoparticle advancements in the realm of antiviral therapeutic options in light of the new coronavirus mutations [6] [7]. Presently, the US FDA has approved treatments for COVID-19, but no vaccines as of yet. Therefore, there's a pressing need to develop comprehensive therapies, and the utilization of nanotechnology appears promising [8].

Nanotechnology-based vaccines or monoclonal antibodies have been proposed as viable approaches for swift diagnosis and effective treatment. Enhancing treatment efficacy involves innovative nanotherapeutic components guided by specific techniques: designing polymeric nanoparticles with rapid mucosal penetration, crafting biodegradable and non-toxic lung-targeted nanoparticles to minimize pulmonary toxicity, and surface modifications to mitigate adverse effects while ensuring efficient treatment by coupling PEG with compounds.

1.1. Properties of NPs for COVID-19 Treatment

In recent times, the rapid advancement of nanomaterials has significantly transformed various scientific domains such as aeronautics, military applications, and medicine. This progress has led to improved drug availability, precise delivery at cellular and intracellular levels, and minimized adverse effects, thereby enhancing therapeutic effectiveness through nanotechnology. Nanomedicine can also address the advantageous medication resistance observed in viral therapy.

Nanoparticles (NPs) exhibit distinct physicochemical traits that demonstrate virucidal activity. Their small size, extensive surface area, targeted action, and responsive properties make them efficient antiviral agents. Studies have shown inactivity of viruses like H1N1, H5N1 influenza [9], poliovirus [10], NIPAH, respiratory syncytial virus, herpes simplex, human papillomavirus, Dengue, and lentivirus when exposed to NPs. Nanomaterials like AuNPs, through infrared light emissions, can bind to and disrupt the structure of coronaviruses, effectively killing the virus. Beyond their direct antiviral effects, NPs are seen as potential carriers for antiviral medications, especially since specific antiviral therapies for many viruses remain limited [11] [12].

Specifically targeting viral genes like SiRNA, microRNA, and shRNA as novel therapeutic agents against viruses like COVID-19 is being explored [13] [14]

[15]. The proposed drugs such as Remdesivir and hydroxychloroquine might be co-encapsulated in mice using Nanocarriers to treat COVID-19. Additionally, the development of self-assembly protein nanoparticles (SANPs), a new nanostructure generated by the oligomerization of monomeric protectins via recombination technologies, shows promise in medicinal applications. SANPs ranging from 20 - 100 nm have potential in creating respiratory virus nanovaccines [16]. Researchers have developed nucleoprotein-based SANPs from the respiratory syncytial virus (RSV) and studied their potential as an antigenic vaccine in the RSV model [16].

1.2. Nano Based Gene for Treatment of Coronaviruses

The utilization of SiRNA therapy offers several advantages compared to conventional medications and vaccines. Employing smaller amounts of siRNA to diminish viral RNA proves to be an effective strategy in preventing RNA viral replication. Insights gained from SARS-CoV studies can be extrapolated to SARS CoV-2, exhibiting high nucleic acid homology. Researchers have identified the efficacy of RNAi against the SARS-CoV virus, utilizing siRNAs from a plasmid to target specific regions of the viral genome. This discovery holds promise for a new era of antiviral medications to combat SARS [17] [18].

Recent investigations have pinpointed the S generation in the SARS-CoV virus, associated with severe respiratory disease, as a viable target. Scientists have demonstrated that the S-section effectively inhibits viral infection and replication, suggesting its potential as a treatment option [19] [20]. In the context of COVID-19, a distinct strain of the MERS-CoV coronavirus, RNAi may play a transformative role. Researchers have identified specific siRNAs, Smad7-1 and Smad7-2, that exhibit potential in gene therapy utilizing RNAi to eliminate MERS-CoV in human lung and kidney cell lines, effectively suppressing viral replication and infection [19] [20].

SiRNA antivirals may be applied selectively to cells lacking adequate endosomal release. Various nanocarriers composed of polymers, lipids, hybrid (polymer/lipid) NP, Nanochrome, silica, dendrimers, iron oxide NPs, and AuNPs are potential candidates for delivering targeted siRNA. FDA-approved materials like poly (lactic acid), polycaprolactone, poly[glycolic acid], and their copolymers have been authorized for tailored in vivo siRNA delivery. Additionally, NP configurations such as solid-lipid NPs, nanocarriers, nanostructured lipids, and liposomes are suitable for advancing SiRNA delivery systems. Cationic lipids or polymers maintain low endosomal pH, enhancing proton and water influx, leading to endosomal rupture and subsequent release of bound siRNA into the cytoplasm. Nanotechnology-based structures can facilitate SiRNA loading for inhalation and pulmonary delivery via aerolite-based systems. The incorporation of antibodies targeting alveoli-specific surface markers-I and II shows promise for nanocarrier functionality and targeted delivery to lung cells and other tissues expressing these therapeutic siRNA indicators [21] [22].

1.3. Nucleic Acid-Based Vaccines

DNA and mRNA vaccines are currently under investigation in the context of the COVID-19 pandemic. The CD8+ cytotoxic T cell responses triggered by DNA vaccines play a crucial role in eliminating the virus. In vitro transcription mutation vaccines offer a potential solution to cell requirements and associated regulatory hurdles. Notably, DNA vaccines demonstrate greater longevity compared to mRNA vaccines; while mRNA is non-integrating and doesn't pose a risk of insertion mutations, DNA vaccines provide more enduring protection. Modifications can be made to mRNA, altering its half-life, stability, and immunogenicity. For instance, research at the Imperial College of London and by Arcturus Therapeutics involves incorporating self-amplifying RNA to prolong the otherwise short half-life of RNA and boost S protein production [23] [24] [25].

The Moderna mRNA vaccine employs nanoparticles with a lipid platform, although several other nucleic acid delivery nanotechnologies are in development. Nanotechnology platforms such as cationic nanoemulsions, liposomes, dendrimers, or polysaccharides have been utilized to enhance the stability and distribution of mRNA-based vaccines. These platforms hold promise for improving the nuclear translocation of plasmid DNA [26].

1.4. Protein-Based Nanoparticles

Vaccines derived from SARS and MERS proved to be more prone to infection-related antibody enhancement (ADE) compared to other vaccinations. This susceptibility stems from the full-length S protein's wide array of potent epitopes, triggering diverse antimicrobial and cellular responses. However, this broad reaction spectrum might pose an increased risk of adverse effects on the immune system's ability to combat the disease [27] [28] [29]. As antibodies that don't neutralize SARS-CoV-2 infections and potentially life-threatening allergic inflammations are on the rise, the La Jolla Institute of Immunology (LJI), funded by the National Health Institutes (NIH), has initiated efforts in this domain. In silico analysis has unveiled various protein B- and T-cell epitopes, and LJI is pioneering a peptide epitope vaccination that holds promise for more efficacious antigens in second-generation SARS vaccines [30] [31] [32] [33] [34].

Peptide-based vaccines represent the simplest, swiftly validated, and rapidly producible vaccine format. These can be formulated as peptides or blends, delivered with suitable nanocarriers, or encoded within nucleic acid vaccine formulations. Industry and academic institutions are leveraging predicted B- and T-cell epitopes in their SARS-CoV-2 subunit vaccines, such as OncoGen and the University of Cambridge/DIOSypVax, utilizing immunoinformatic sequences from the S-protein [35] [36] [37].

Nanoparticles offer potential in targeting lymph nodes (LNs) or subcellular subsets and locations. The "albumin hitchhiking" strategy exploits LNs' natural transportation capability via albumin. Nanoparticles have been instrumental in designing dual-targeted hepatitis B virus (HBV) vaccines, directing them to-

wards specific lentil-resident dendritic cell and macrophage subsets. This targeting led to enhanced viral clearance in chronic HBV mice models [38]. Nanotechnologies are also employed for various vaccination and therapeutic purposes, generating VLPs from mammalian viruses, insect viruses, plant viruses, and bacteriophages (**Figure 1(a)** and **Figure 1(b)**). VLPs mimic infection-associated molecular patterns, triggering robust antigen-specific immune responses. Their visualization and administration systems serve as potent adjuvant systems, activating and amplifying immune responses [39].

The design features of vaccines, such as encapsulated antigens versus surface-displayed antigens, dictate antigen processing and presentation, influencing the ensuing immunological response. Nano-barriers like polymeric micelles (PEG-PE) alter antigenic peptides' structure, enabling cytosolic transport for LN targeting, APC absorption, and antigene cross-presentation (**Figure 1(c)**). A

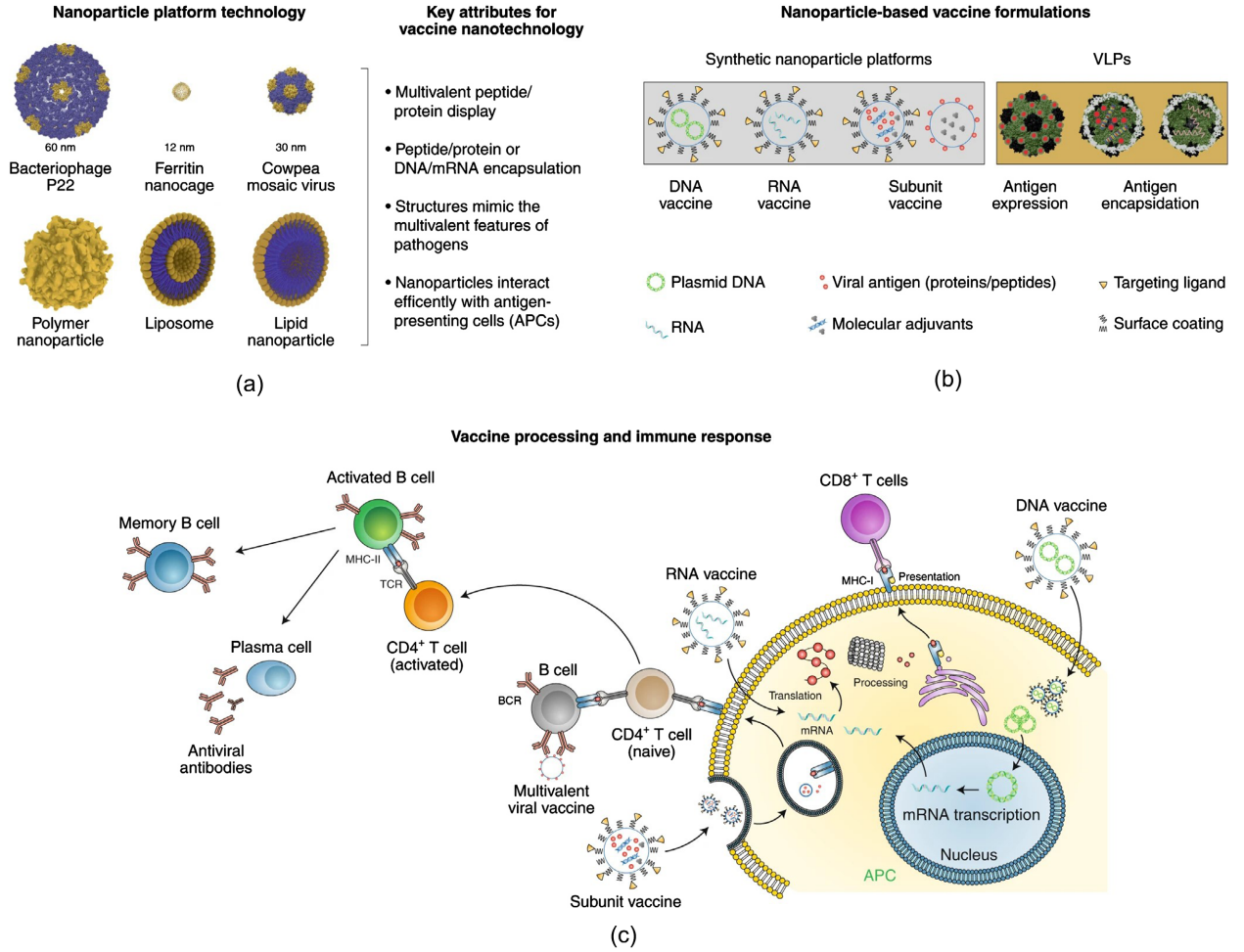

Figure 1. (a) Nanoparticle vaccine technologies utilize proteins and nanoparticles ranging in diameter from 10 to 1000 nm. Protein nanoparticles have been produced using PDB data through Chimera software (P22, ferritin, and CPMV represented by 3IYI, 1FHA, and 1NY7, respectively). (b) Components integral to nanoparticle-based vaccinations include protein nanoparticles. (c) Important processes involved in antigen-presenting cell (APC) vaccine production using nanoparticles imply the presentation of MHC-I and MHC-II epitopes. This presentation leads to the generation of CD8+ cytotoxic T cells and CD4+ T helper cells necessary for synthesizing antiviral agents.

well-developed delivery framework is crucial for combatting future waves of SARS-CoV-2 and other emerging viruses effectively and efficiently [40].

1.5. Nano Based Immunotherapy against Coronaviruses

Immunotherapy utilizing Nanoparticles (NPs) has proven highly effective in managing infectious diseases. Nonetheless, improving treatment efficacy while minimizing adverse effects remains challenging. Understanding the immune system's response to infections and exploring potential methods for immune modulation are crucial steps in developing successful immunological treatments. Recent studies have revealed that pathogen-associated molecular patterns (PAMPs) on the virus's surface alert innate immune cells upon encountering the first line of immune defense (such as mucus and ciliated cells). This triggers the release of type I interferons (IFN-α/β), heightening the risk of complications [41] [42] [43]. Subsequently, other immune cells like natural killer cells, alveolar macrophages, monocytes, and neutrophils become activated during acute infections, leading to the production of pro-inflammatory cytokines that affect respiratory epithelial cells. IFN-I halts viral reproduction via various pathways, contributing to cell cytotoxicity. While anti-PAMP injections may cause pulmonary complications in some individuals, this remains unclear in humans. SARS-CoV-2 infection has been associated with prolonged antibody production and decreased CD4+/CD8+ T cells. Macrophages and dendritic cells play pivotal roles in initiating specialized immune responses, retracting virus particles via phagocytosis, initiating IFN-I production, and triggering the adaptive immune response [45] [46].

Studies suggest that pretreatment with IFN-α may induce the development of IFN genes and signaling pathways pre-SARS-CoV infection. Early data suggest that IFN-1 exhibits antiviral activity against SARS-CoV-2, but further clinical studies are required to confirm these findings. Antibodies mediate the death of infected cells through various pathways like phagocytosis, neutralization, complement system activation, and antibody-related cell cytotoxicity. Regulating the virus's pathogenicity and the host's immune response is crucial to effectively combat viral infections [47] [48].

Monoclonal antibodies' use stands out among other techniques due to their specificity, minimal risk of bloodborne pathogens, and safety. They can be more effectively used in recovered patients than in new cases [49] [50] [51] [52]. IFNs combat infections by inducing antiviral protein production and cytokine-stimulated interferon genes, exerting antiviral effects by halting replication or aiding the immune system's adaptability. IL-6 is considered crucial in treating SARS-CoV-2 due to its association with heightened inflammatory cytokine levels [53] [54] [55] [56] [57]. Implementing these outlined immunotherapy techniques, independently or in combination with other medications, has been suggested for SARS-CoV-2-infected patients. However, the manufacturing of monoclonal antibodies remains challenging, expensive, and time-consuming, requiring sophis-

ticated infrastructure and components for cost-effective and timely immunotherapy [58] [59] [60].

Nanoparticles can influence the immune system's performance through various means such as enhancing multivalent receptor linkages, controlling intracellular processes, facilitating cytosolic transport, targeting the innate immune system, and reducing immune modulator toxicity. They can also integrate multiple antigens on their surface to more effectively activate the immune system [61] [62] [63] (**Figure 2**).

Development of vaccines

The immunization system, owing to its innate capability to induce a durable protective immune response, stands as one of the most efficient public health measures in preventing or curbing the spread of infectious diseases. Vaccines consist of two critical elements: the antigen, eliciting the immune response, and the adjuvant, which modulates or enhances the immune response to the antigen [64]. Various vaccine formulations have elicited immune responses against infectious diseases. Live Attenuated or Inactivated Entire Pathogen Vaccines have been extensively utilized to control human and animal diseases. However, safety

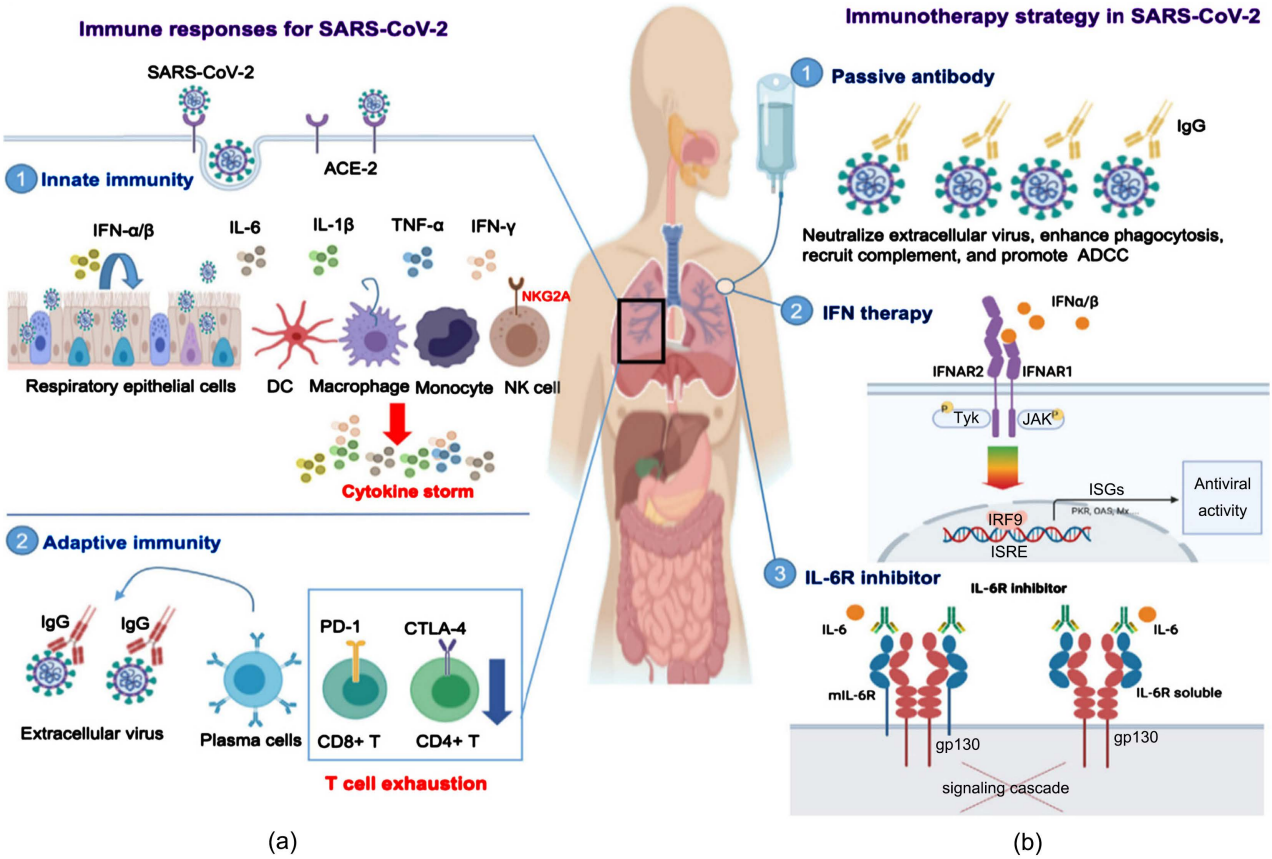

Figure 2. Strategies involving immune responses and therapies for combating SARS-CoV-2 infection: (a) Understanding the innate and adaptive immune responses triggered by SARS-CoV-2. (b) Immunotherapeutic approaches encompassing passive antibody treatment, interferon alpha/beta, and IL-6 receptor (IL-6R) inhibitors. Adapted from reference 45 with permission. Copyright 2020 Wiley.

concerns such as genetic reversion and potential tumorigenicity in immunocompromised hosts exist with attenuated vaccines. Not all pathogens can be employed as live vaccines due to their virulence or inherent immunity. DNA or RNA vaccines, the latest in vaccination, come with drawbacks like inadequate antigen immunogenicity, the need for adjuvants to bolster immune responses, and susceptibility to premature antigen breakdown in adverse conditions. Synthetic peptides, inactivated toxins, and recombinant subunit protein vaccines serve as alternatives to live-attenuated or inactivated vaccines, although evidence indicates their limited availability in the market [65] [66] [67].

Vaccines are preferred over chemotherapeutic drugs in combating infectious diseases due to their specificity and capacity to induce an immune response [68]. Many current vaccines utilize viral proteins to achieve CoV neutralization. Antibodies generated target CoV proteins like M, E, or S, hindering viral entry by binding to these proteins [69]. Nano-based therapies have emerged as potential options against various forms of CoVs due to the immunostimulatory effects of NPs.

2. Conclusions

Nanotechnology is swiftly emerging as a dynamic contender in combatting coronaviruses through antiviral treatment. Its primary objective is to enhance the delivery of biotherapeutics across physiological barriers, overcoming the traditional challenge of limited bioavailability. Nanomaterials present a multitude of physical and biological advantages, featuring smaller particle sizes that enable them to navigate natural barriers, ample surface areas for increased drug loads, adaptable surface properties aiding drug entry into cell membranes, ligand binding capabilities, and improved solubility and pharmacokinetic traits. Notably, these materials hold promise not only as antiviral agents but also in potential anticancer medications or various therapeutic approaches. While breaching the mucus barrier doesn't necessarily lead to reduced absorption or non-absorption by nanoparticles, it poses challenges such as molecular interactions causing macrophage opsonization and phagocytosis. An ideal nanocarrier for antiviral therapy must exhibit efficiency, accessibility, targeting capabilities, safety, and economic viability, minimizing intake, downtime, side effects, and therapeutic costs while being biodegradable, biocompatible, and non-toxic. Polymer-based nanoparticles, such as polyethylene glycol and poly(lactide co-glycolide), are anticipated to advance the development of single- and needle-free vaccines and drug carriers [70].

Metal nanoparticles (NPs) emerge as alternate options for delivering therapeutic agents against CoVs. Their nanometer size (<200 nm) significantly influences their distribution and consumption rates. Several nano-based vaccines have shown potential in generating a stronger immune response. However, further research is crucial to understand the interaction between viral particles and host cells [71] [72]. Emergency approvals for eight vaccines utilizing various

technologies have been granted since February 2021. The emergence of novel SARS-CoV variants with heightened transmissibility underscores the urgent need for highly efficient new vaccines. Currently, over 250 additional vaccines are in various stages of development for SARS. Remarkably, within just 40 days of the first candidate entering clinical development, sixteen vaccine candidates are in phase II, and one is in phase III. While the clinical reality for any vaccine remains months away, the rapid and concurrent efforts by academic and industrial laboratories offer hope for success. The lethal COVID-19 coronavirus has propelled the enhancement of platform technologies to prepare for future pandemics. Numerous nanomaterials provide scalable, stable, portable, distributable, and integrable platform technologies adaptable to address seasonal or novel coronavirus variants [73] [74] [75].

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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