Nanomaterials for Viral Diseases Diagnosis, Prevention, and Treatment

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Nanomaterials can be tailored for specific uses by modulating physical and chemical properties, including size, morphology, surface charge, and solubility. Due to these controllable properties, nanomaterials have been used in biosensors to potentiate target-specific reactions that respond to biochemical environments, such as temperature, pH, and the presence of enzymes.

nanomaterials viral diseases vaccines diagnosis therapeutics

1. Introduction

Since 2009, numerous infectious diseases have been occurring periodically, including those caused due to infection by influenza A virus (IAV; H1N1), West African Ebola virus, Middle East respiratory syndrome coronavirus (MERS-CoV), and the recent severe acute respiratory syndrome coronavirus 2 [SARS-CoV-2; known as coronavirus disease (COVID-19)]. SARS-CoV-2 has infected numerous individuals, which has resulted in millions of deaths. Owing to the rapid global spread of SARS-CoV-2 infections and the consequent damage, the World Health Organization (WHO) declared a COVID pandemic [1].

Strict measures, such as quarantining infected individuals, and technology-based approaches have been employed to prevent the further spread of COVID. Various types of healthcare technologies, including on-site rapid testing kits, vaccines, and antiviral therapeutics for COVID, have been developed and applied in a short period of time via Emergency Use Authorization (EUA) approvals. Most governments have carried out extensive testing to identify potential infections and have rolled out mass vaccination programs to prevent infection and reduce economic loss and human damage [2]. FDA-approved antiviral agents, such as remdesivir, have been used to treat SAR-CoV-2-infected patients, to reduce the number of severe cases that pose a serious burden on public health systems. It is now being recognized that the peak of the pandemic has passed, although the morbidity and mortality rates require further reduction. However, infection rates are fluctuating due to sporadic, rapidly rising infections with viral variants. The current pandemic situation is a potent warning indicating that the emergence or re-emergence of viral diseases is unpredictable but inevitable. Therefore, it is imperative to develop technology-based countermeasures for diagnosis, prevention, and treatment to cope with potential viral diseases in the future.

The introduction of nanomaterials in the development of technological countermeasures has advantages in many respects, such as facile functionalization, control of surface chemistry, and availability as a delivery carrier [3]. Nanomaterials can be tailored for specific uses by modulating physical and chemical properties, including size,

morphology, surface charge, and solubility. Due to these controllable properties, nanomaterials have been used in biosensors to potentiate target-specific reactions that respond to biochemical environments, such as temperature, pH, and the presence of enzymes (**Table 1**) [4]. Furthermore, drug delivery carriers constructed with biocompatible nanomaterials have been actively researched to improve the efficacy of therapeutics, especially in cancer therapy. Nanomaterials can be applied in diagnosis, prophylaxis, and treatment systems to combat infectious diseases [5] (**Figure 1**).

Table 1. Nanomaterial-based diagnostics for emerging and re-emerging viral diseases.

Nanomaterials	Diagnostic Techniques	Target	LOD	Time	Ref.
Carbon nanotubes	RDT	DENV	8.4 × 102 TCID50/mL	>10 min	[6]
		SARS-CoV-2	0.55 fg/mL	>5 min	[7]
	Immunological	Influenza A Virus (H1N1)	1 PFU/ml	30 min	[8]
Graphene	Immunological	JEV/AIV	1 fM/10 fM	1 h	[9]
		AIV	1.6 pg/mL	30 min	[10]
		HIV-1	2.3×10^{-14} M	1 h	[11]
		Influenza A Virus (H5N1)	25 PFU/mL	15 min	[12]
		Zika Virus	450 pmol/L	5 min	[13]
AuNPs	Optical	SARS-CoV-2	0.18 ng/μL	>10 min	[14]
			50 RNA copies per reaction	30 min	[15]

Nanomaterials	Diagnostic Techniques	Target	LOD	Time	Ref.
			4 copies/μL	40 min	[16]
		Hepatitis B virus	100 fg/mL	10–15 min	[17]
	Immunological	SARS-CoV-2	370 vp/mL	15 min	[18]
			0.08 ng/mL	30 min	[19]
		Influenza A Virus	7.8 HAU	30 min	[20]
		Zika Virus	0.82 pmol/L	50 min	[21]
Quantum dots	ELISA	Influenza A Virus	22 pfu/mL	>35 min	[22]
		Influenza A Virus (H5N1)	0.016 HAU	>15 min	[23]
		SARS-CoV-2	5 pg/mL	>15 min	[24]
	Immunological	HEV3	1.23 fM	20 min	[25]
		SARS-CoV	0.1 pg/mL	1 h	[26]
Synthetic polymer	Immunological	Influenza A Virus (H1N1)	5×10^3~10^4 TCID50	9 min	[27]

IV: avian influenza virus, HEV3: hepatitis E virus 3, AuNP: gold nanoparticle, HIV: human immunodeficiency virus, ELISA: enzyme-linked immunosorbent assay, LOD: limit of detection, SARS-CoV-2: severe acute respiratory syndrome coronavirus 2, TCID50: 50% tissue culture infectious dose, HAU: haemagglutinin unit.

Nanomaterials	Diagnostic Techniques	Target	LOD	Time	Ref.
Nanofibers	Immunological	SARS-CoV-2	0.8 pg/mL	20 min	[28]

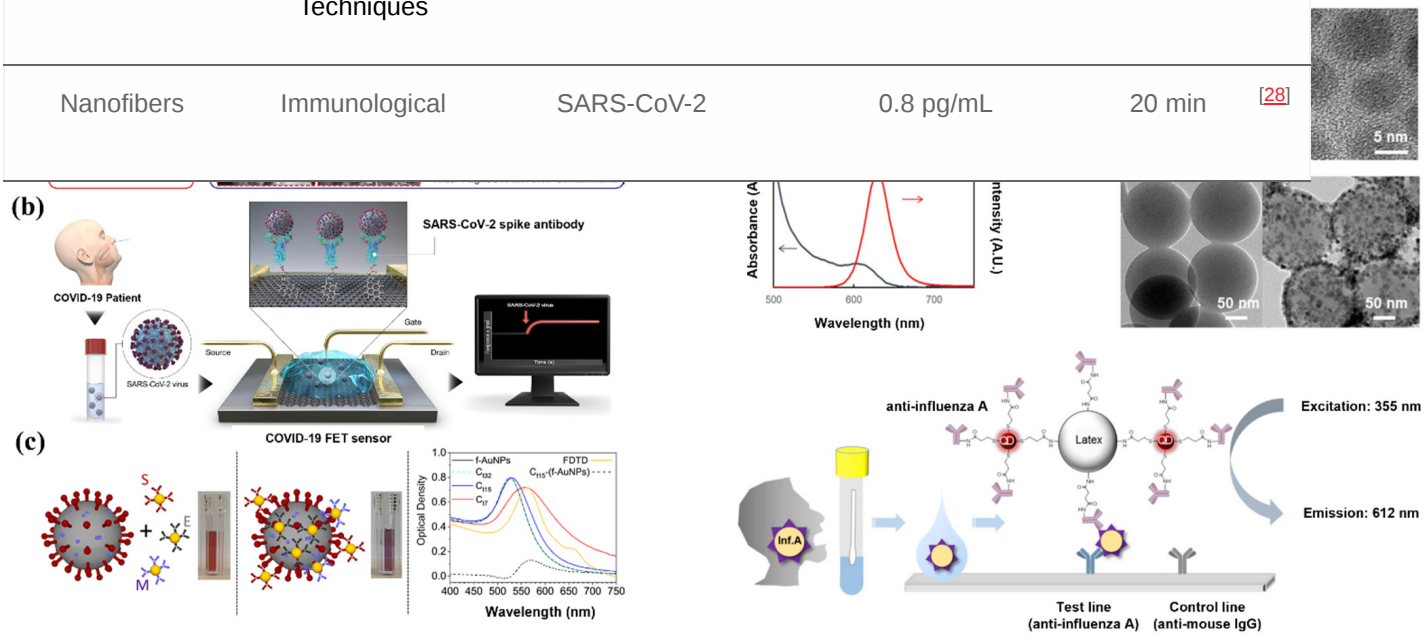

Figure 1. Application of nanomaterials for diagnosis with advanced sensitivity and selectivity. (**a**) Schematic of using carbon nanotubes for H5N2 isolation and concentration, directly from in situ samples. Transmission electron microscopy (TEM) and scanning electron microscopy (SEM) images of H5N2 separated by carbon nanotubes are shown. Reproduced with permission from [29]. Copyright (2016) American Association for Advancement of Science. (**b**) Schematic representation of graphene as a sensing material for detecting SARS-CoV-2. The SARS-CoV-2 spike antibody binds to graphene and the reaction with the target is converted into an electrochemical signal. Reproduced with permission from [30]. Copyright (2020) American Chemical Society. (**c**) AuNP-based colorimetric diagnosis of coronavirus disease (COVID-19). The surface-modified AuNPs with antibodies bind to the virus, which shifts the absorption wavelength of AuNPs. The shift in absorption wavelength changes the color of AuNPs from red to purple. Reproduced with permission from [31]. Copyright (2020) American Chemical Society. (**d**) Synthesis schematic of CdSe/CdS/ZnS quantum dots (QDs) and mechanism of application in rapid diagnostic strips. TEM images and fluorescence spectrum of synthesized QDs. Influenza A virus was detected using the fluorescence emission spectrum of the QDs on the rapid diagnostic strip. Reproduced with permission from [32]. Copyright (2020) Elsevier.

2. Diagnosis

Diagnostic tests are a key component of any successful strategy aimed at suppressing emerging and re-emerging viral diseases and play an important role at all stages from early detection to final resolution [33]. Diagnostic tests appropriate for epidemic prevention and suppression are technically difficult to develop, validate, and implement and in-volve complex and time-consuming processes.

The accuracy of nucleic acid amplification tests is highly dependent on the time of obtaining the sample, as well as the type, storage, and handling of the sample. These tests can only diagnose active infections. False-negative

results can occur if the sample is not obtained appropriately or if the subject is tested too soon or too late after exposure to the virus. In addition, the tests are complex and require specialized laboratory equipment and reagents, as well as specialists to perform the tests, which can be problematic due to the prolonged time required for obtaining the results.

Many researchers have attempted to overcome the limitations of reverse transcription polymerase chain reaction (RT-PCR) assays [34][35][36][37]. Antibody detection assays present several advantages over RT-PCR. Antibodies are more stable than RNA and are less degradable during transport and storage, thus reducing the risk of false-negative results. Although the research on antibody-based tests is ongoing, there are limitations to overcome. The main reason for this is the lack of specificity. Additionally, there is a lag phase from the initial virus exposure to the antibody response against infection. According to the accumulated immunological data, the antibody response peaks at approximately 11 days, indicating an insufficient time period for preventing the rapid spread of infectious diseases at early stages of infection. Therefore, antibody detection assays are less effective in diagnosing emerging and re-emerging viral diseases.

There is a need to develop new diagnostic platforms that are accurate, specific, fast, and easy to use, to facilitate rapid screening. Currently, research dynamics have shifted towards rapid diagnostics based on nanomaterials [38][39][40][41]. In this regard, nanotechnology-based applications can greatly improve the sensitivity of previously developed detection techniques, such as RT-PCR and immunoassays. Nanoparticles (NPs) have the characteristics of high adsorption capacity, the quantum size effect, and high reactivity. The large surface area of NPs can enhance detection effectiveness, as it allows efficient interaction with target analytes. Therefore, through physical or chemical bonding, nanomaterial-based diagnosis can be developed to increase selectivity and specificity and reduce detection time. Appropriately using advanced nanomaterials is the key to achieving improvements in nanotechnology. Nanomaterials are the basis for the design of a wide range of virus diagnostic tools. The unique characteristics of nanomaterials make them suitable for application in state-of-the-art virus detection technologies.

3. NP Vaccines for Emerging Viruses

Vaccines are the most effective and cost-efficient means for preventing infectious diseases. Despite the significant successes of various vaccines, the ongoing development of new, safer, and more potent vaccines is required because of the emergence of new pathogens, recurrence of old pathogens, and mutations in existing pathogens. Typically, vaccines incorporate adjuvants, which are supplementary substances that compensate for the poor immunogenicity of antigens and enhance the cellular and humoral immunity. Several nanoplatforms that improve vaccine immunogenicity by enhancing the delivery of antigens to the immune system or via a depot effect have been developed. The WHO Emergency Use Listing for combating the COVID-19 pandemic includes vaccines that incorporate a delivery system based on NPs, such as lipid NPs (LNPs) (Moderna, MA, US and Pfizer-BioNTech, NY, US) and adenovirus viral vectors (Janssen, NJ, US and AstraZeneca, UK) (**Figure 2**).

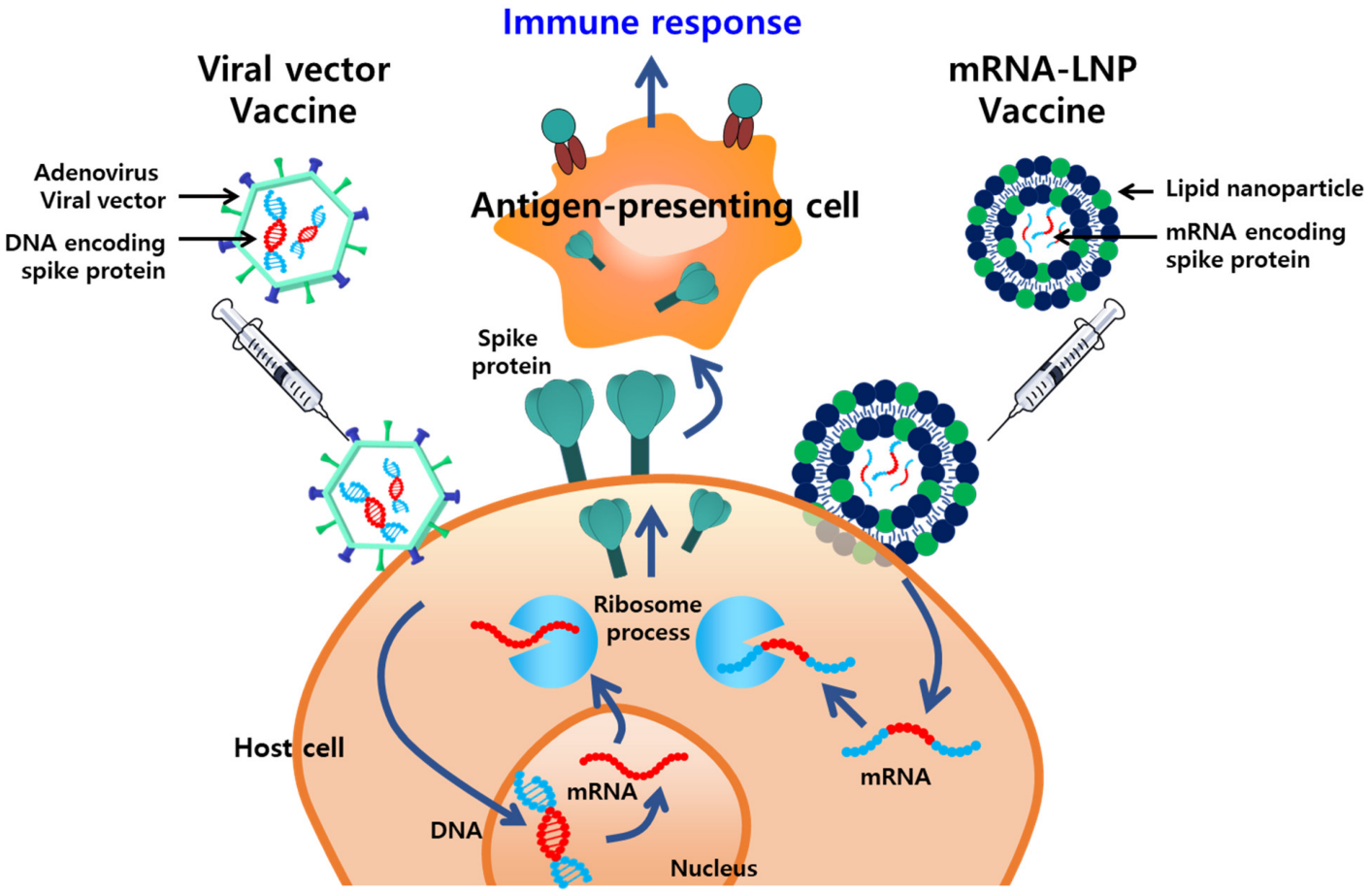

Figure 2. Overview of nanoplatform-based vaccines approved by the World Health Organization (WHO) for the prevention of emerging infectious diseases. Viral vectors and lipid NPs (LNPs) elicit potent immune responses by stably delivering DNA and mRNA encoding antigens, respectively, to antigen-presenting cells.

Delivery systems formulated with NPs are being used in next-generation vaccines for effectively delivering antigens and/or intrinsic immunostimulants [42][43][44][45][46]. These vaccines are being engineered not only for the prevention of emerging infectious diseases, but also for treating chronic diseases, such as diseases caused by hepatitis C infections [47][48], human immunodeficiency virus (HIV) infections [49][50], herpes [51], and cancer. Next-generation vaccines aim to induce both humoral and cellular immune responses, while being applied prophylactically and therapeutically [52][53]. Various nanoplatforms have been incorporated into delivery systems and immunogenicity-enhancing strategies, such as LNPs, polymeric NPs, nano-complexes, virus-like particles, and inorganic NPs. The main principle of delivery systems is to deliver the vaccine antigens or immunopotentiators to the antigen-presenting cells (APCs; including macrophages and dendritic cells) responsible for the induction of innate immune responses. A delivery system that is similar in size to nano-sized pathogens is expected to be advantageous for APC phagocytosis and for presenting antigens to naïve T cells in lymphoid tissues. Further, nanoparticulate delivery agents can protect the payload, deliver it in an intact native conformation to a target site within the immune system, and create a sustained release of antigens over time. In the future, the usage of such next-generation nano-delivery systems in vaccine technology is expected continue with sufficient safety and stability. Herein, we discuss the use of several representative nanoplatforms (LNPs and polymer particles) in delivery systems that

enhance vaccine efficacy. We also review nanotechnology-based adjuvants that enhance the intensity and quality of cellular and humoral immune responses for the development of vaccines.

4. Treatment

The development of effective antiviral agents is essential for treating or alleviating severe symptoms and preventing death in infected patients. Timely antiviral therapy is an important measure to reduce the burden on the health care system. A variety of synthetic and natural antiviral agents have been developed, including chemical compounds, peptides, and essential oils. These agents exhibit antiviral activity against various types of viruses [54]. Other FDA-approved therapeutics, such as oseltamivir, zanamivir, and abacavir, are being utilized in antiviral therapy for influenza and HIV infection [55]. Remdesivir is now being used for the treatment of COVID-19, and its usage is associated with a significant reduction in the mortality of infected patients [56]. Despite the contributions of antiviral agents, there are several challenges associated with their usage, such as limited efficacy because of poor solubility, low biostability, and toxicity. Additionally, improvements can be made regarding the therapeutic effects of antiviral agents, which mostly block viral proteins and cellular receptors involved in viral infection pathways, such as site-specific delivery of antiviral agents to enhance efficacy and reduce off-target effects. Thus, there is a need for efficient delivery of antiviral agents [57].

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