Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Review article

Nanotechnology against COVID-19: Immunization, diagnostic and therapeutic studies

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ABSTRACT

The emergence of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in early 2020 soon led to the global pandemic of Coronavirus Disease 2019 (COVID-19). Since then, the clinical and scientific communities have been closely collaborating to develop effective strategies for controlling the ongoing pandemic. The game-changing fields of recent years, nanotechnology and nanomedicine have the potential to not only design new approaches, but also to improve existing methods for the fight against COVID-19. Nanomaterials can be used in the development of highly efficient, reusable personal protective equipment, and antiviral nano-coatings in public settings could prevent the spread of SARS-CoV-2. Smart nanocarriers have accelerated the design of several therapeutic, prophylactic, or immune-mediated approaches against COVID-19. Some nanovaccines have even entered Phase II/III clinical trials. Several rapid and cost-effective COVID-19 diagnostic techniques have also been devised based on nanobiosensors, lab-on-a-chip systems, or nanopore technology. Here, we provide an overview of the emerging role of nanotechnology in the prevention, diagnosis, and treatment of COVID-19.

1. Introduction

In December 2019 the novel coronavirus (2019-nCoV), also known as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), was first reported in Wuhan, China. The virus belongs to the betacoronavirus family, and is the causative agent of Coronavirus Disease 2019 (COVID-19) [1,2]. Due to its possible asymptomatic transmission, long incubation period, and its highly age-dependent infection fatality rate, SARS-CoV-2 is a growing threat to public health, and it has also ravaged the economy worldwide [3–9]. On March 11, 2020, the World Health Organization (WHO) declared COVID-19 to be a global pandemic [10]. As of December 3, 2020, at least 64,897,870 COVID-19 cases and 1,500,271 related deaths had been reported globally, according to the WHO [11].

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There is a certain degree of sequence similarity and structural homology between SARS-CoV-2 and the previously identified coronaviruses, SARS-CoV in 2002 and the Middle East respiratory syndrome coronavirus (MERS-CoV) in 2012 [12]. However, the transmissibility of SARS-CoV-2 is significantly higher, compared to the other two viruses [13]. The most common symptoms of COVID-19 are fever, dry cough, dyspnea, fatigue, and myalgia [6,14,15]. The severity of the disease varies from a mild or moderate respiratory illness to an acute respiratory syndrome mainly affecting the lower respiratory tract [16]. COVID-19 infections can also affect other vital systems and organs of the human body, such as the cardiovascular system [17], central nervous system [18,19], kidneys [20], liver [21,22], and gastrointestinal tract [23]. A common cause of death is an uncontrolled cytokine storm, which leads to multi-organ failure, or heart attacks and strokes due to blood clots.

Since the emergence of COVID-19, many strategies have been introduced for controlling the spread of this infectious disease, including social distancing, more effective disinfection protocols, lockdowns and quarantine in cities and countries, and antiviral treatment methods. Nanotechnology can help unlock the full potential of medicines and drugs at the nanoscale to develop novel approaches against viral infections [24–27]. Hence, not only does this cutting-edge technology offer successful treatment strategies for COVID-19, but it has also helped improve a wide variety of conventional preventative, diagnostic, and therapeutic methods (Fig. 1) in order to combat the ongoing global health emergency [28]. Here, we review some recent advances in the use of nanotechnology to prevent, diagnose, and treat COVID-19 infections.

2. SARS-CoV-2 immunization using nanotechnology approaches

2.1. Nanotechnology-based vaccines

In the past two centuries, the protective function of vaccination has saved innumerable lives in the battle against infectious and contagious diseases [29]. Today, amid growing concerns over the global threat of COVID-19, scientists have already developed some effective vaccine candidates, to contain the ongoing pandemic [30]. In an effort to further improve effectiveness of immunization and to provide safe alternatives to more traditional approaches, some nanotechnology-based vaccines have shown early promise against SARS-CoV-2.

2.1.1. Immunization by delivery of viral biomolecules

An excellent vaccine candidate should have some key features, including safety, the ability to elicit both antibody (humoral)-mediated immunity (AMI) and cell-mediated immunity (CMI), long-lived immune responses, and immune memory, even in elderly and immunocompromised individuals [31]. Currently, typical vaccine candidates such as whole-cell live attenuated vaccines, killed vaccines, subunit vaccines, and gene-based vaccines are being tested on volunteers all over the globe to develop safe and cost-effective vaccines against COVID-19 [32]. The vaccine safety, efficacy, immunogenicity, and risk of infection, are among the challenges that must be addressed before widespread application in healthy individuals [33]. Whole-virus vaccines are one of the oldest family of vaccines based on inactivated and live attenuated viruses. Many pharmaceutical companies and research institutes have employed this strategy for developing COVID-19 vaccines which are currently under different phases of clinical trials: Codagenix/Serum

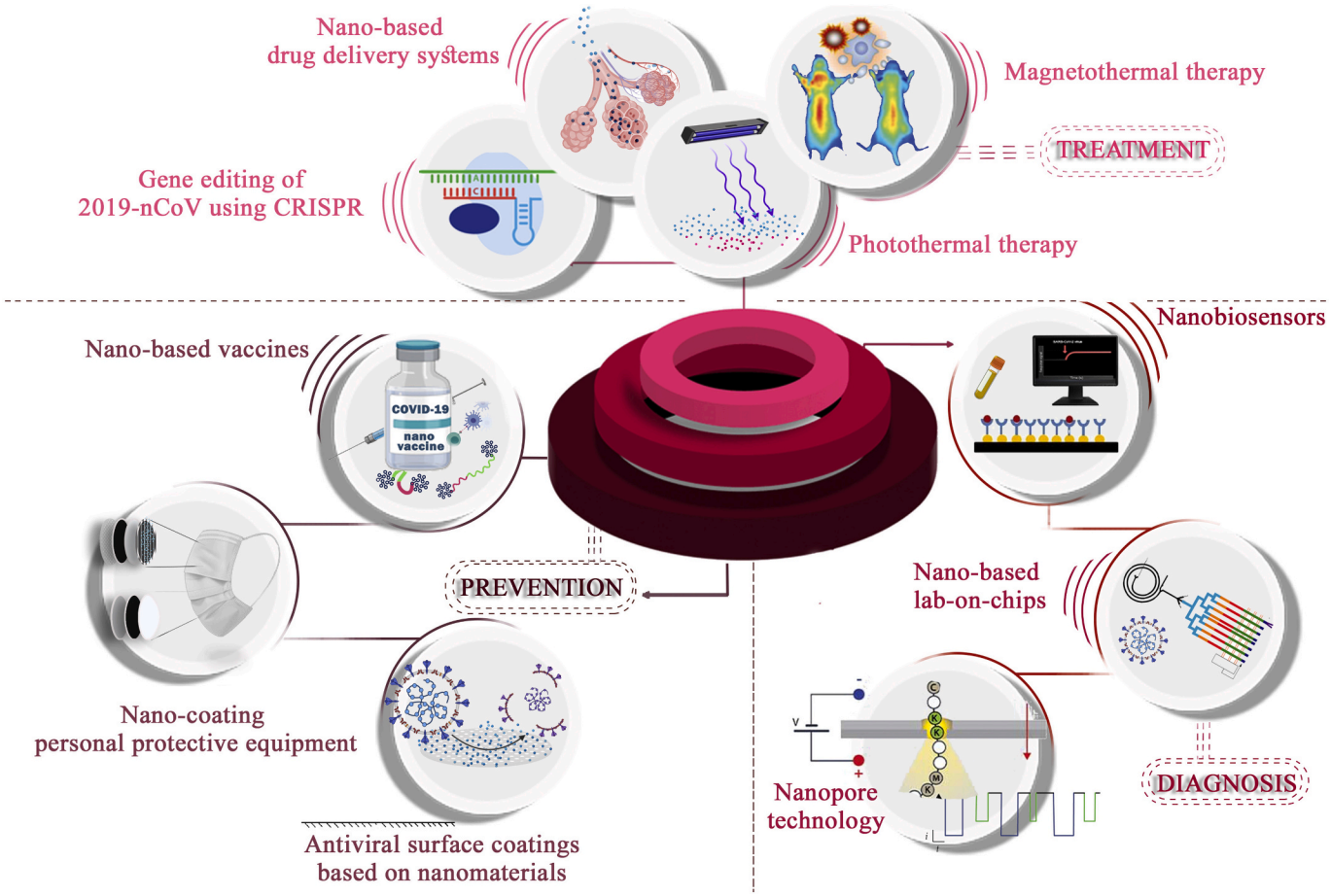

Fig. 1. Schematic representation of nanotechnology in the battle against COVID-19. Nanotechnology can enhance the efficacy of existing therapeutics, preventive methods, and diagnostic strategies, as well as providing novel approaches.

Institute (COVI-VAC) [34], Sinovac Biotech (CoronaVac), Wuhan Institute of Biological Products/Sinopharm (N.A.), Beijing Institute of Biological Products/Sinopharm (BBIBP-CorV), Bharat Biotech (Covaxin/BBV152), Institute of Medical Biology, Chinese Academy of Medical Sciences (N.A.), Research Institute for Biological Safety Problems (QazCovid-in), Beijing Minhai Biotechnology Co. (N.A.), Valneva, National Institute for Health Research (VLA2001), Erciyes University (ERUCOV-VAC), and Shifa Pharmed Industrial Co (N.A.) [35]. However, inactivated virus vaccines may revert to virulence, and live attenuated virus vaccines induce a minimal cell-mediated immune response and require multiple booster doses [36]. Another common vaccine type is subunit vaccines (e.g., synthetic antigens, polysaccharides, proteins, lipoproteins, and glycoproteins), but despite their high safety and reasonable cost, they mostly suffer from poor immunological memory and low immunogenicity, [37–40]. Anhui Zhifei Longcom Biopharmaceutical in collaboration with the Institute of Microbiology at the Chinese Academy of Sciences has developed ZF 2001 based on SARS-CoV-2 proteins. COVAXX, a subsidiary of United Biomedical Inc., has designed UB-612 relying on SARS-CoV-2 proteins, which is currently under Phase III clinical trial in Taiwan [35,41]. However, similar to inactivated vaccines, protein subunit vaccines induce a weak T-cell response and run the risk of antibody-dependent infection. Using adjuvants can address this issue and reduce the risk of antibody-dependent infection enhancement in this type of vaccine. As shown in two new studies, recombinant vaccines were successfully prepared using an adjuvant, cytotoxic T-lymphocyte (CTL), helper T-lymphocyte (HTL), and B-cell epitopes connected by linkers [42] and S1 domain conjugated with alum [43]. More recently, Clover Biopharmaceuticals Inc. (China), GSK (UK), and Dynavax (USA) developed a subunit vaccine based on an adjuvant, which passed Phase I and II clinical trials [35,44].

Nanovaccines have the potential to overcome some limitations of conventional immunization platforms [45,46]. Many nanosystems have been designed to prevent the premature degradation of subunit vaccines and enhance their targeted delivery. Mishra et al. employed HBsAg-functionalized solid lipid nanoparticles (SLNs) to deliver the surface antigen (HBsAg) to provide a subunit vaccine against hepatitis B virus. They showed that the HBsAg-functionalized SLNs had a higher cellular uptake, lower cellular toxicity, and greater induction of type 1 immune responses including CMI and AMI [47]. Nanocarriers such as poly(lactic-co-glycolic acid) (PLGA), approved by the United States Food and Drug Administration (FDA), along with polymeric NPs and calcium phosphate can be used for the delivery of immunogenic biomolecules [48–50]. Moreover, NPs loaded with antigens and immune-stimulating compounds (adjuvants) can act in a similar manner to whole-cell vaccines to ensure protective immunity, without any risk of active infection, and produce immunological memory, especially in immunocompromised individuals [51]. The administration of subunit vaccines together with adjuvants can provide broader, more rapid, longer-lived, and better tailored immune responses. This approach involves four separate mechanisms: enabling the slow release of antigens by acting as an antigen depot; creating a favorable microenvironment; facilitating the exposure of antigens to antigen-presenting cells (APCs); and enhancing antigen processing and presentation [52]. For example, Lin et al. encapsulated a recombinant MERS-CoV antigen RBD (receptor-binding domain) plus a canonical STING agonist, cyclic diguanylate monophosphate as an adjuvant, into a hollow polymeric nanocarrier that could successfully stimulate Th1 immunity [53].

In another study, Tao et al. formulated a vaccine against influenza virus H1N1, H3N2, and H5N1 based on membrane matrix protein 2 (M2e) conjugated to AuNPs plus a TLR-9 agonist adjuvant (CpG) [54]. Recently, Novavax used an adjuvant (Matrix M) to create a recombinant SARS-CoV-2 glycoprotein NP-based vaccine called NVX-CoV2373, which passed Phase III clinical trial with 89.3% efficiency [55,56]. Not only can NPs serve as delivery vehicles for antigens and adjuvants at the same time, but they can also act as stimulators of immune response due to their inherent adjuvanticity, thereby synergistically promoting an antigen-specific cellular immune response. In this regard, Sekimukai et al. prepared a vaccine adjuvant using gold NPs combined with the NALP3 inflammasome against SARS-CoV, which was capable of activating dendritic cells (DCs) in a similar manner to alum (aluminum hydroxide) used as the most common adjuvant [57]. Other nanoparticle-based vaccine adjuvants, such as metallic NPs, magnetic NPs, polymeric NPs, dendrimers, and quantum dots may also have the potential to be used in both, prevention of infectious disease, and in cancer therapy [58].

The development of virus-like proteins (VLPs) has enabled the self-assembly of different genetically-engineered viral structural proteins with a diameter of 20-100 nm, which facilitates their uptake by DCs and macrophages. The use of VPLs can boost the weak immune response typical of subunit vaccines, while avoiding the risk of active infection caused by whole-virus vaccines due to their non-replicative property [59]. Using VLPs for inoculation allows for both robust AMI and CMI, and researchers formulated commercially available prophylactic VLP-based vaccines against both the hepatitis B virus (HBV) and human papillomavirus (HPV) [60]. Pushko et al. working at Novavax produced a trivalent seasonal influenza (H3N2, H1N1, and type B influenza) vaccine based on a VLP platform containing three hemagglutinin (HA) subtypes of H5N1, H7N2, and H2N3 influenza viruses [61]. Additionally, a large number of non-pathogenic VLP-based vaccines with strong AMI and CMI were designed to control MERS-CoVs and SARS-CoVs [62–66]. Currently, extensive research is underway to create a viable vaccine against the novel coronavirus relying on highly-ordered, stable, and monodisperse VLP-based vaccine formulations. For instance, *Nicotiana benthamiana* is being studied by some companies to develop genetically engineered VLP vaccines using the spike (S) protein of SARS-CoV-2. The vaccine candidates of Medicago and SpyBiotech (Serum Institute of India) have entered Phase I/II and II/III clinical trials [35,67], respectively.

2.1.2. nucleic acid-based nanovaccines

Genetic fragments that encode antigenic peptides or proteins can be delivered to indirectly induce an immune response against viral proteins [68]. These nucleic acid-based vaccines enjoy a range of benefits, including scalability, safety, and prolonged-expression of antigens [69], thereby eliciting antigen-specific B cells, $CD4^+$ T cells, and $CD8^+$ cytotoxic T cells [70,71]. However, there are some serious challenges regarding the delivery of gene-based vaccines, including low cellular uptake efficiency, several off-target effects, and low stability under physiological conditions [70,72,73], which have led many clinical trials to failure [74]. Thus far, Inovio Pharmaceuticals/International Vaccine Institute (USA) [75], Osaka University/AnGes/Takara Bio (Japan) [76,77], Cadila Healthcare Limited (India) [78], Genexine Consortium (South Korea) [79], Providence Health & Services (USA) [80], Entos Pharmaceuticals Inc. (Canada) [81], GeneOne Life Science, Inc. (South Korea) [82], University of Sydney, Bionet Co., Ltd. Technovalia (Australia) [83], and Takis/Rottapharm Biotech (Italy) [84] have developed DNA vaccine candidates for COVID-19, which are currently under different phases of clinical trials. All these DNA vaccines are administered using replacement delivery methods such as adjuvants, nanovehicles, etc. to avoid the low immunogenicity associated with the needle-injection of this vaccine type [35]. Nanocarriers hold great promise in the delivery of vaccines to target specific cells and subcellular locations. Xu et al. synthesized surface-engineered gold nanorods to transfer the human immunodeficiency virus (HIV)-1 Env plasmid DNA for the immunization against HIV-1. The nanosystem was reported to stimulate good cellular and humoral immunity, coupled with T cell proliferation via APCs, compared to naked HIV-1 Env plasmid DNA [85]. Shim et al. demonstrated the induction of AMI and CMI by plasmid DNA encoding the S protein of SARS-coronavirus coupled with polyethylenimine NPs [86]. Non-replicating and non-integrating mRNA-based vaccines can be superior to DNA-based vaccines, in that they have no risk of insertional mutagenesis [87]. For example, Zhao et al.

developed polyethyleneimine-stearic acid (PSA) cationic nanomicelles for the delivery of mRNA encoding HIV-1 gag to DCs for immunization [88]. In another study, Zhang et al. formulated a vaccine candidate (ARCoV) based on a lipid-nanoparticle-encapsulated mRNA (mRNA-LNP) encoding the receptor-binding domain (RBD) of SARS-CoV-2, leading to Th1-biased cellular responses and production of effective neutralizing antibodies against SARS-CoV-2 as shown in mice and non-human primates (Fig. 2) [89]. Overall, liposomes, polysaccharide particles, dendrimers, and cationic nanoemulsions have all shown the potential to enhance the stability and delivery of mRNA-based vaccines [70,90]. Providence Therapeutics (Canada) [91], Imperial College London (UK) [92], Arcturus (USA)/Duke-NUS (Singapore) [93], Curevac (Germany) [94], BioNTech (Germany)/Pfizer (USA) [95], and ModernaTX [96] have developed different types of LNP-formulated SARS-CoV-2 mRNA vaccines. The mRNA-based vaccines produced by BioNTech (Germany)/Pfizer (USA) and ModernaTX have been conditionally approved in some countries and the rest have entered different phases of clinical trials.

2.1.3. Vaccine administration and distribution

With the aim of overcoming an aversion to vaccination, especially among children, approaches are being made to replace invasive administration routes including intramuscular and subcutaneous injections, with painless, non-invasive vaccination methods such as oral administration, inhalation, and microneedle injection. Recently, a growing number of nanovaccines have been designed to be administered by non-invasive routes (e.g., oral, nasal, diffusion nanopatches, or microneedle arrays) (Fig. 3) [98–100]. Mucosal nanovaccines have shown improved immune responses, with advantages of encapsulating security payloads for protection against degradation, targeting the mucosal immune system, and integrating a mucosal adjuvant with the vaccine preparation [101]. Nanotechnology has also allowed the oral delivery of VLPs, and intranasal delivery of viral vectors or proteasomes in clinical trials [46]. For instance, gold NPs and alginate-coated chitosan NPs have been synthesized for the intranasal delivery of H1N1Me2 and HBsAg, respectively [102,103]. Plant virus-derived NPs with good oral bioavailability and stability in the gastrointestinal tract have also been found suitable for oral immunization [104,105]. Another drawback of conventional vaccines is the requirement for a booster dose, which may lessen patient compliance and acceptance even further. Thus, needle-free and pain-free nanopatches have been suggested to be a safe, effective, and self-administered vaccine delivery approach that could accelerate the dissemination of vaccines and ease the burden on healthcare systems [106,107]. Furthermore, there have been some single-dose slow-release systems, including nanotechnology-based implants [108], thin-film-based vaccines, needle-free nanovaccines, and intranasal nanotechnology-based vaccines, which have been developed to overcome the challenges mentioned above [109,110]. The worldwide distribution of conventional common vaccine formulations, such as solution-based vaccines, particularly in least-developed countries, is logistically difficult due to their need for constant refrigeration to preserve their efficacy. Hence, various types of long-term stable nanotechnology-based vaccines that do not require a cold-chain process have been created. For example, nanoscale building blocks derived from cowpea mosaic virus could act as stable nanocontainers with the ability to protect their cargo for over one hour at around 60°C, and indefinitely at ambient temperature [111]. Moreover, nanoemulsion vaccines with the potential to stimulate all arms of the immune system, were stable at the temperature of tropical countries, without any damage to their constituent proteins [112]. Recent nanotechnology advances have led to nanovaccines that can maintain their stability independent of temperature over long periods, and still produce a good immune response with a self-administrated single dose, and are expected to contribute to the fight against the ongoing COVID-19 pandemic, and could even prevent future pandemics.

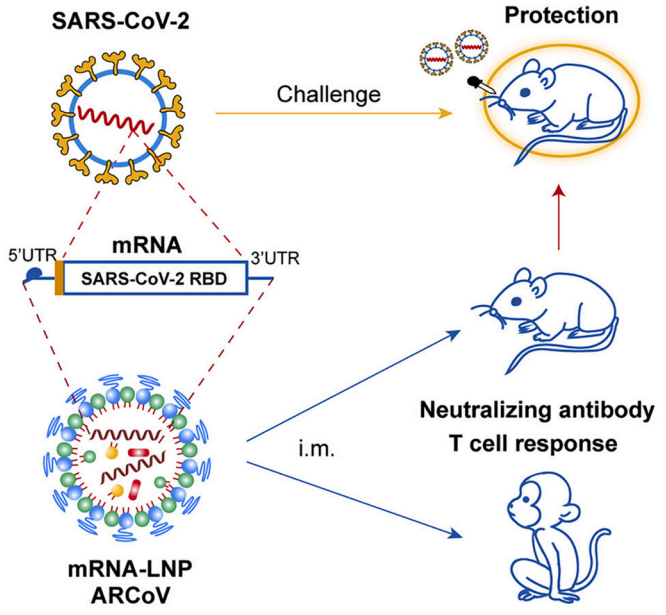

Fig. 2. Schematic representation of production of neutralizing antibodies and T cell responses after intramuscular immunization with ARCoV mRNA-LNPs. Reprinted with permission from ref. (89, 97), copyright 2020, Elsevier.

2.1.4. Administrated-COVID-19 candidate vaccines

Based on the latest research and news some COVID-19 candidate vaccines (e.g. Pfizer-BioNTech and Moderna COVID-19 vaccines) have being administrated to people in many of countries. Some of them with additional information will bring in the following table 1.

3. Antiviral nano-coatings for personal protective equipment (PPE)

The lack of an effective treatment method and (until recently) a viable vaccine against COVID-19 has compelled scientists worldwide to seek other approaches to contain the pandemic. Generally, if the possibility of contact with an infectious virus is lower, the lower the chance of catching that disease. The complete protection of health workers, patients, and the rest of the population may be improved if currently employed PPE (e.g., gloves, face masks, face shields, and gowns) can serve as a physical barrier against disease agents and viral pathogens. The shortage in the worldwide supply of PPE has compelled many individuals to reuse their equipment, which is highly likely to be unsafe. Nanotechnology offers a way around this issue by modifying the surface of PPE not only to capture and inactivate viruses, but also to be reusable and washable without compromising the efficiency and safety (Fig. 4). Some researchers at the University of Central Florida (UCF) developed washable and reusable nano-coatings composed of alternating layers of cationic and anionic nanoparticles, that could successfully trap and destroy viruses, and specifically SARS-CoV-2 [121]. In a recent study, zinc-oxide NPs were employed to create a face mask with good antimicrobial activity, and this new technology is expected to help the production of washable, reusable, and antimicrobial PPE by the end of 2020 [122]. Given the significant role of face-masks in controlling the COVID-19 pandemic, many nanotechnologists are scrambling to adapt their research to enhance the performance of this type of PPE. Rainy et al. fabricated a new type of highly-breathable mask based on cellulose nanofibers that was considered very comfortable and did not distress the wearer when used for long hours. The mask was also appropriate for persons with respiratory problems and for use in hot and humid conditions [123]. Other companies have also utilized nanotechnology to design additional options for face-masks. Table 2 lists nanotechnology-based face-masks that are currently available or will be soon launched

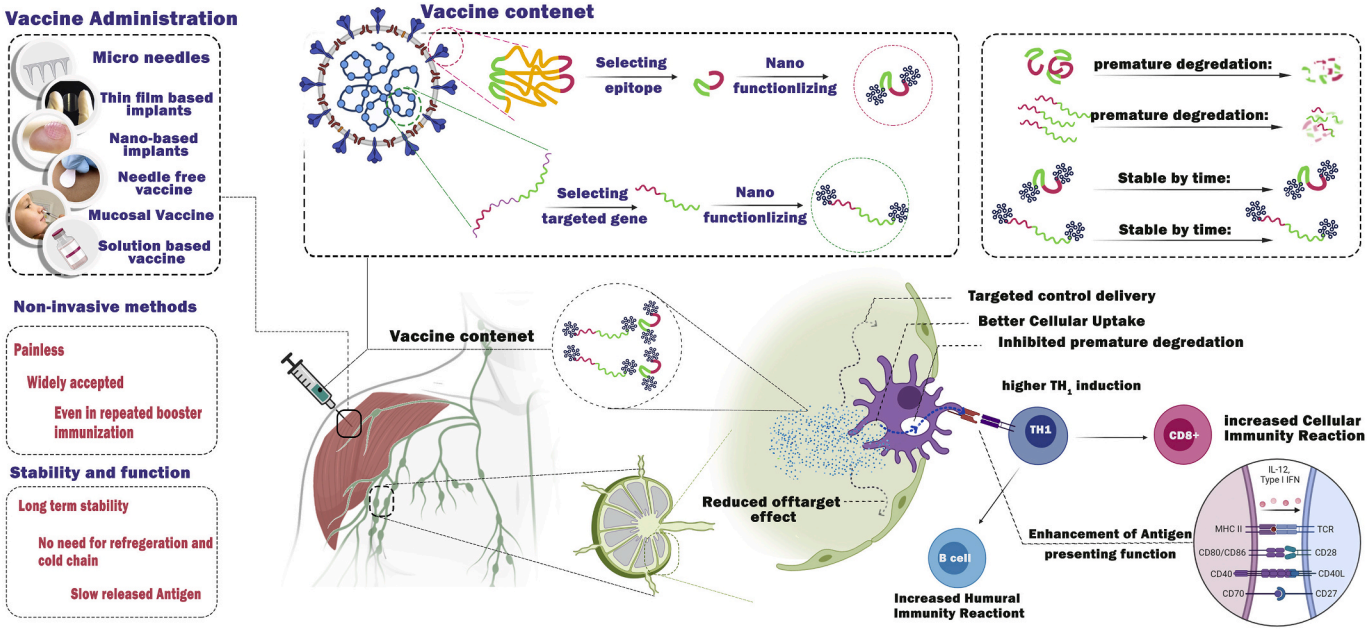

Fig. 3. Schematic illustration of non-invasive administration methods and the benefits of nanovaccines.

Table 1
Rolling out COVID-19 vaccine candidates

Developer	Vaccine	Side-effects	Advantages	Disadvantages	Vaccine efficiency
Pfizer-BioNTech	Lipid nanoparticle mRNA vaccines	Injection site pain, tiredness, headache, muscle pain, chills, joint pain, fever [113], allergic reactions, Bell's Palsy (partial facial paralysis) [114]	Does not interact with the genome; rapid production capacity; stimulates both cellular and humoral immunity	Needs to be kept at cold temperatures; two-dose vaccine	~ 95%
Moderna	Prefusion stabilized S protein mRNA vaccine	Injection site pain, fatigue, headache, muscle pain, chills, joint pain, fever	Does not interact with the genome; rapid production capacity; stimulates both cellular and humoral immunity	Needs to be kept at cold temperatures; two-dose vaccine	94.1%
Russian Gamaleya Institute's Sputnik V	Adenoviral vector-based vaccine	subjective heart palpitation [115], injection site pain, fatigue, headache, muscle pain, fever	Dry form; no need to be kept at cold temperatures; strong immune response; long-term gene expression	Two-dose vaccine; data on safety or efficacy have not been released; recombinant viruses may cause disease in immunocompromised hosts	91.4%
Wuhan Institute of Biological Products/ Sinopharm	Inactivated vaccine of SARS-CoV-2	Injection site pain, rash, headaches, muscle pain, fever, nausea, vomiting	Induces strong antibody response; no need to be kept at cold temperatures	Two-dose vaccine; data on safety or efficacy have not been released; recombinant viruses may cause disease in immunocompromised hosts	86%. [116]
University of Oxford/ AstraZeneca	Adenovirus vector-based vaccine	Neutropenia (temporary) [117], injection site pain, rash, headaches, muscle pain	Single-dose schedule; long-term gene expression	Recombinant viruses may cause disease in immunocompromised hosts; prior exposure to vector virus (e.g., adenovirus) may reduce immunogenicity [117]	62% [118]
Bharat Biotech	BBV152 Inactivated vaccine	Injection site pain, fever, headache, fatigue	Induces strong antibody response; no need to be kept at cold temperatures	Two-dose vaccine; requires large quantities of virus	N.A. [35]
Sinovac	CoronaVaca Inactivated vaccine	Injection site pain, fever, fatigue, nausea, vomiting, headache	Induces strong antibody response; no need to be kept at cold temperatures.	Two-dose vaccine; requires large quantities of virus	50.7% [119]
Johnson & Johnson	JNJ-78436735 Nonreplicating viral vector	Injection site pain, rash, headache, muscle soreness, mild to moderate febrile episode and myalgia	Fast manufacturing time; single-dose vaccine	Dependency of vaccine efficiency on hosts' immune responses	66% [120]
CanSino Biologics	Convidecia Nonreplicating viral vector	Injection site pain, rash, headaches, muscle soreness, fever	Single-dose vaccine; Rapid manufacturing	Dependency of vaccine efficiency on hosts' immune responses	65.3% [35,120]

onto the market. (See Fig. 5.)

4. Antiviral nanomaterials for inanimate surface coatings

Unlike many other viruses, SARS-CoV-2 can remain active even on inanimate surfaces, such as plastic, fabrics, wood, glass, and metal surfaces for up to several hours or even days [130], thereby encouraging its spread within different environments. Not only could nanotechnology facilitate the development of anti-coronavirus coatings with knowledge acquired in the battle against other contagious diseases, but it could also open new approaches to the design of antiviral coatings. A considerable number of virus-inactivating nanomaterials have so far

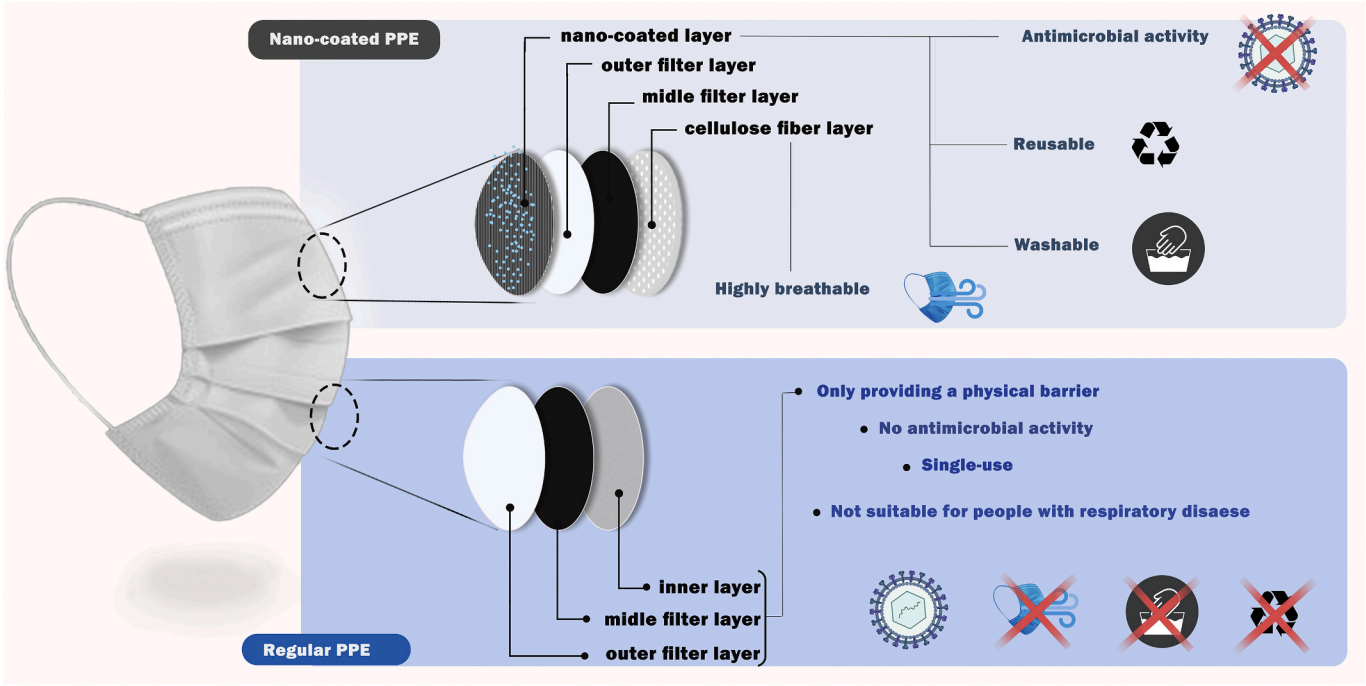

Fig. 4. Schematic depiction of a nanotechnology-enhanced face mask (top) and a regular surgical mask (bottom).

Table 2
Nanotechnology-based face masks designed for COVID-19

Developer	Related nanotechnology	Characteristics
Respilon	Nanofiber membranes	High virus removal [124]
Yamashin-filter Corp.	Polymer-based nanofiber membranes	High virus trapping, virus removal [125]
Verdex Technologies Inc.	Nanocomposite membranes	Virus removal, breathable [126]
ZEN Graphene Solution Ltd.	Nanocomposite membranes (silver-nanoparticle-modified graphene oxide nanocomposite)	Virus capture and killing, virucidal [126]
Promethean Particles Ltd.	Nanoparticle technology (copper NPs embedded into polymer fibers)	Antiviral and anti-microbial [127]
MVX Prime Ltd.	Nanoparticle technology	Self-cleaning, killed almost all contacting viruses [126]
Respilon	Nanoparticle technology (copper dioxide NPs within a nanofiber matrix)	99.9% filtration efficiency, natural skin-like color [126]
X.Tio2 Inc.	Nanoparticle technology	Humidity resistance, self-regenerating, non-allergic, 99.999% germ-killing ability under zero light [126]
LIGC Application Ltd.	Graphene-based technology	Reusable, self-sterilizing, antiviral activity [126]
Master Dynamic Limited	Nanoparticle technology (nanodiamond coating)	Breathable, water-proof, virus-killing ability [126]
Kim Il-Doo Research Institute	Nanofiber membranes	Water-proof, washable, high filtration efficiency [126]
Ghatak et al.	Nanoparticle technology (Nylon-polyester, cotton-polyester, PMMA-PVDF, nylon-PVDF, polypropylene-polyester)	Self-powered, smart, high filtration efficiency [128]
Balagna et al.	Nanoparticle technology (silver nanoclusters/silica composite sputtered coating)	Virucidal, increased lifetime of masks and filter media [129]

been suggested to be incorporated into anti-COVID-19 coatings, such as silver NPs [131–135], cuprous oxide NPs [136], gold NPs on silica NPs [137], silica NPs coated with a quaternary ammonium cationic surfactant didodecyldimethylammonium bromide (DDAB) [138], zinc oxide NPs [139–142], and quaternary ammonium cations called QUATs [143]. Behzadinasab et al. synthesized SARS-CoV-2-coated cuprous oxide (Cu_2O) particles bound onto polyurethane that could maintain their antiviral activity even after 13 days of immersion in water, or after multiple exposures to the virus [144]. Common disinfection solutions, i.e., diluted bleach and alcohol, have two major shortcomings: (a) the real-time sanitization of contaminated surfaces is practically impossible; (b) there is no guarantee that the sterilized surface will not be contaminated again. Nanomaterial-based coatings have the potential to address these issues using smart nanosystems. Some researchers at the Hong Kong University of Science and Technology (HKUST) developed a smart antimicrobial coating based on heat-sensitive polymers and a slow-release disinfectant. This safe nano-coating could not only inactivate viruses by disrupting their lipid envelope, but also prevented virus adhesion to the surface for up to 90 days [145]. Another research team from the Ben-Gurion University of Negev (BGU) designed a polymer-based coating using copper and other metal NPs, which allowed for controlled and slow release of the antiviral NPs, thus remaining effective for long periods [146]. Photoactive antimicrobial nanomaterials can kill germs when irradiated with light of appropriate wavelengths ranging from ultraviolet (UV) to near-infrared. The antimicrobial mechanism of these nanomaterials includes, photodynamic killing, photothermal lysis disinfection, and photocatalysis [147–150]. For example, Canadian scientists created a self-sterilizing nano-coating, called NanocleanSQ, which could kill 99.99% of viruses upon contact, and with a lifespan of several weeks or even years. The incorporation of a photocatalytic compound into this smart nanosystem improved its virus-killing activity even more when exposed to light [151]. The photocatalytic activity of TiO_2-based nano-coatings has also been shown to help reduce the spread of SARS infections [152]. Additionally, the modification of often-touched surfaces such as bed rails, bed surfaces, supply carts, and doorknobs with highly-repellent nanomaterials could keep germs and viruses away [153,154]. Table 3 summarizes some other nano-coatings with the potential to control the COVID-19 pandemic.

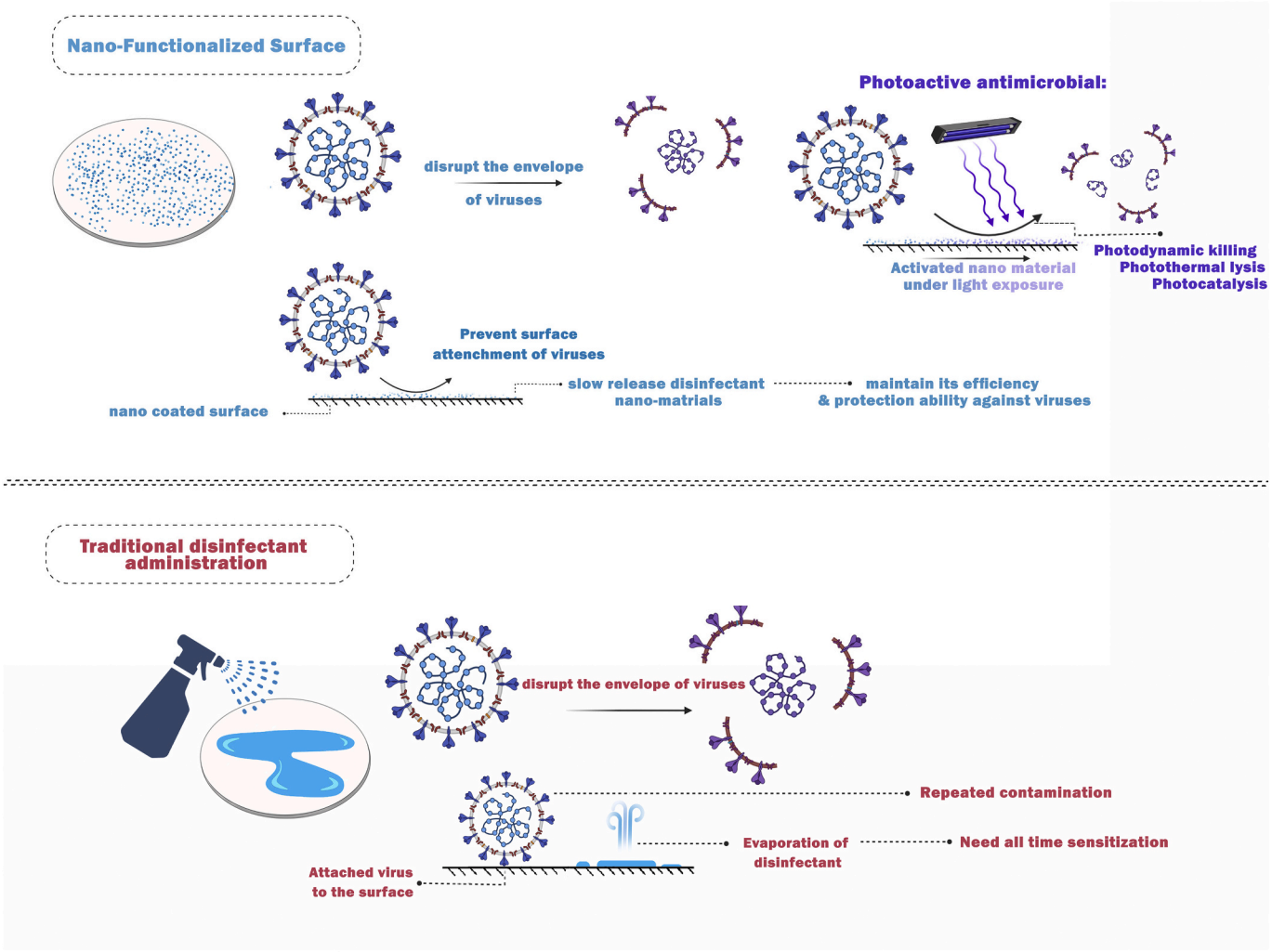

Fig. 5. Schematic illustration of a surface modified with nanomaterial-based antiviral coating compared to unmodified surface.

5. SARS-CoV-2 diagnosis by nanotechnology-based strategies

Viruses have been a serious threat to human health throughout the ages, but since the discovery of their biological structure it has been possible to make a more accurate diagnosis [165,166]. Since the emergence of COVID-19, many scientists have been seeking reliable, sensitive, and selective diagnostic tests that can be used on a large scale. The standard method for the diagnosis of COVID-19 is the reverse transcription-polymerase chain reaction (RT-PCR). However, some false-negative and false-positive results have been reported for this test, suggesting its low sensitivity [167]. Nanobiosensors have shown some potential for the rapid-response and real-time detection of SARS-CoV-2 [168]. Thus far, many such tools have been developed using different read-out methods, including optical, electrochemical, electrochemiluminescence (ECL), quartz crystal microbalance (QCM), and surface plasmon resonance (SPR) techniques [168].

5.1. Nanobiosensors

An optical biosensor is an analytical system relying on a bio-recognition sensing element integrated with an optical transducer system. The advantages of these devices include, small size, high specificity, high sensitivity, and cost-effectiveness [169]. Many optical sensors have been based on plasmonics, among which localized surface plasmon resonance (LSPR) has been widely used to detect specific viral strains in laboratory studies [170].

5.1.1. Optical biosensors for RNA samples

Optical sensors can play a key role in the high-resolution imaging of viruses during pandemics. For instance, Wei et al. introduced an optical sensor for imaging viruses based on laser diode excitation [171]. These systems can be easily integrated into the camera module of a smartphone, and can achieve an imaging resolution of less than 50 nm [172]. Recently, a new sensor was designed based on gold NPs and laboratory-designed DNA receptors for the detection of SARS-CoV-2. An optical agent coupled to a thermal agent was incorporated into the sensor to ensure its reliability. The optical system comprised an LSPR sensor, in which the optical response occurred in metal NPs, and the local refractive index changed when molecules were attached to its surface via nucleic acid base pairing. Since the coronavirus genome consists of a single-strand RNA, it can bind to stabilized complementary DNA receptors. Hence, the device can be used to determine whether a sample contains a specific target RNA strand. Any non-complementary strands could be removed if the temperature increased to near the melting point, where only fully complementary base-hybridization could remain [173].

In another study, Okamoto et al. described a highly-sensitive system based on an enzyme-linked immunosorbent assay using chemiluminescence (CLEIA) for detecting the SARS-CoV nucleocapsid (N) protein. They incorporated gold NPs with particular optical properties such as LSPR to improve the detection limits of the biosensor, and incorporated two monoclonal antibodies against the SARS-CoV N protein that were tagged with glutathione S-transferase (GST). The study

Table 3
Nanotechnology-based coatings for inactivating SARS-CoV-2

Developer	Nanotechnology	Main advantages
Turn-Key Environmental Consultants	A compact air purifier with a dense network of nanofibers	Captures 95.5% of particles – even viruses [155]
University of South Florida	An air purification device with nanoparticle-covered filter, producing free radicals	Oxidizes and destroys viral particles based on photoelectrochemical oxidation (PECO) [156]
Design.123	A PreLynx Portal device equipped with a colorless nano-polymer-based disinfectant vapor	Inactivates whole lipophilic and hydrophilic viruses on clothing [157]
Nanoveu	Antiviral coating for mobile phones and tablets using copper oxide nanoparticles	Kills 99.99% of viruses within 1 minute [158]
Nanotouch Materials, LLC	Light-activated nano-coating based on mineral nanocrystals	Destroys organic contaminants by powerful oxidation reactions [159]
Nano4lifeEurope L. P	A surface sanitizer using a positively-charged layer of "swords"	Kills viruses via a physical effect [160]
Shepros SDN BHD	A nanosilver-based multipurpose sanitizer (NSMS)	Powerful antiviral effect, non-skin irritating, non-foaming, environmentally friendly [161]
FN Nano Inc.	Intelligent multifunctional photocatalytic coating based on titanium oxide nanoparticles	Decomposes and eliminates viruses, molds, and bacteria [162]
A.T Marmo Service SRL	Transparent disinfectant solution based on titanium dioxide and silver nanoparticles for surfaces	Self-sterilizing surface for up to 2 years [163]
MVX Prime Ltd.	An antimicrobial spray relying on nanotechnology	Preserves the efficiency of nano-coating for five years [164]
Balagna et al.	Nano-coating based on a silver nanocluster/silica composite for filters in air conditioning systems and medical respiratory devices	Virucidal effect [129]

relied on an interaction between the anti-GST-N antibodies and GST-N protein. This biosensor had a detection sensitivity of 1 pg/mL for GST-N protein in human serum, with promise for the clinical diagnosis of SARS patients in the early phase of infection [174].

5.1.2. Dual-functional plasmonic photothermal biosensors

Recently, Guangyu et al. developed a dual-functional plasmonic photothermal (PPT) biosensor for clinical COVID-19 diagnosis by functionalizing gold NPs with complementary DNA receptors. The diagnostic system was based on the specific hybridization of complementary bases and operated by measuring the local refractive index change after virus binding to the LSPR-based sensor [175].

5.1.3. Point-of-care biosensors

Since conventional diagnostic techniques (e.g., quantitative real-time PCR) are time-consuming and labor-intensive, there is an urgent need for point-of-care (POC) COVID-19 diagnostics that can be used in the community. POC biosensors, including chip-based and paper-based biosensors, are some examples under investigation. Thus far, two types of rapid POC biosensors have been designed using polydimethylsiloxane (PDMS), carbon nanosheets, and paper for COVID-19 screening. In these novel biosensors, nucleic acids and antibodies were used to detect the virus in the early and late stages of infection, respectively [176]. Colorimetric biosensors can also be designed to detect analytes due to apparent color changes visible to the naked eye. One of the most reliable colorimetric methods for virus detection is the loop-mediated isothermal amplification (LAMP). The advantages of this method include low cost, high efficiency, good reliability, and highly reproducible assay results. Furthermore, nanoparticle-based colorimetric biosensors are particularly suitable for lab-on-a-chip (LOC) devices. Coupled with the LAMP technique, LOC devices can detect viruses with much higher sensitivity. For example, one such device was fabricated for SARS-CoV screening [177,178].

5.1.4. Smartphone-based nanobiosensors

Miniaturization approaches allow the integration of nanomaterial-based sensors into smartphones, thereby transforming them into an effective tool to detect a wide variety of harmful agents such as viruses, bacteria, and toxins. Natesan et al. developed a high-performance digital nanosensor equipped with a flow cell for capturing specific antibodies via recombinant antigens displayed in a microarray. This device was incorporated into a smartphone-enabled fluorescence reader for the rapid POC detection of Ebola virus [179]. Furthermore, Mulpur et al. introduced a rapid, cost-effective POC tool for detecting low numbers of *Mycobacterium tuberculosis* bacteria using a cellulose-based substrate coated with silver and fullerene NPs as a biosensor incorporated into a smartphone [180]. The combination of nanobiosensors with mobile devices may facilitate COVID-19 population screening, as well as the collection of data, and tracking infected cases.

5.1.5. Electronic and electrochemical biosensors

Field-effect-transistors (FETs), three-electrode potentiometric sensors, and amperometric systems are among the major types of electronic biosensors with advantages including, low cost, miniaturization, and possibility of mass production [181,182]. In one recent study, Seo et al. devised a FET biosensor for the detection of SARS-CoV-2 in clinical samples. The biosensor was constructed from antibody-modified graphene sheets, and could detect SARS-CoV-2 S protein at low concentrations in biological fluids, as well as capturing the virus in real-time [97]. In another study, a carbon-based three electrode biosensor was developed to detect SARS-CoV-2 in non-clinical samples [183].

Electrochemical techniques such as electrochemical impedance, cyclic voltammetry, and amperometry can provide label-free detection, and do not require any additional signaling molecules or a sandwich assay. In 2020, Tripathy and Singh showed that an electrochemical biosensing approach based on surface-modified gold NPs could be used for COVID-19 detection. They designed a sensing electrode that was highly stable even under harsh chemical conditions, together with a complementary thiolated nucleic acid probe that matched the target sequence. The sequence attached to the sensing electrode through gold-thiol self-assembly. The viral RNA or the cDNA of SARS-CoV-2 could be detected after hybridization to the complementary thiolated probe using the electrochemical biosensor. The device was also equipped with a smartphone-based read-out for smart POC healthcare [184].

5.2. Nanotechnology-based lab-on-a-chip systems

One promising approach to control the pandemic is the manipulation of microscale fluids, or microfluidics [185]. Many microfluidic biosensors have been suggested to detect bacteria, foodborne pathogens, or viral infections [186]. These biosensors could be far superior to culture-based methods, and also to molecular techniques in terms of portability, precision, response time, sample consumption, and costs. A novel extension of microfluidics, called lab-on-a-chip (LOC) technology can contribute to the development of rapid and accurate diagnostic tests. Takahashi et al. created a Nanochip 400 system for the multiplexed detection of influenza type A and B viruses, respiratory syncytial virus types A and B, and human parainfluenza virus types 1, 2, and 3 using PCR chemistry and an electronic microarray. They showed that this innovative detection device could carry out direct fluorescent-antibody

staining (DFA) as well as real-time PCR [187]. Moreover, Li et al. employed an isothermal nucleic acid amplification method to prepare a rapid and sensitive micro/nanofluidic chip (MNC) for screening influenza type A and B viruses [188]. Recently, some researchers at Rochester Institute of Technology (RIT) designed a next-generation LOC based on magnetic nano-beads for the isolation and detection of SARS-CoV-2 and also the Ebola virus [189].

5.3. Nanopore technology

Due to the frequent mutations that occur in viruses called genetic plasticity, the sequence analysis of RNA viral genomes remains a challenge. Nanopore sequencing is a robust technology that enables the real-time reading of the base sequences in long DNA or RNA segments. In this technology, a change in the electrical current is monitored as the nucleic acids pass through a protein nanopore. Viral RNA can be detected in coronavirus-infected cells using nanopore-based direct RNA sequencing (DRS) approaches [190]. LamPORE has developed the first-ever nanopore sequencing machine for the detection of SARS-CoV-2 in samples, that may also contain influenza or other respiratory viruses. In this assay, nanopore sequencing was incorporated with the loop-mediated isothermal amplification procedure, creating a scalable, controllable, rapid, and highly-sensitive assay [191].

5.4. Other nanotechnology-based strategies for SARS-CoV-2 detection

Researchers at the University of Maryland devised an accurate test for the detection of viruses in nasal swabs or saliva samples within 10 minutes. When the virus is present the RNA genetic sequence attaches to the plasmonic gold NPs and produces a color change of the suspension from purple to blue [192].

Upon acute infection, humans generate a specific IgM antibody against SARS-CoV-2, which can act as a reliable indicator. In one recent study, a colloidal gold-NP-based lateral-flow (AuNP-LF) test was designed for COVID-19 screening based on an analytical membrane coated with the SARS-CoV-2 nucleoprotein to detect the anti-nucleoprotein IgM antibody present in the sample. The efficiency of the AuNP-LF test was assessed in serum samples from healthy humans and COVID-19 patients, and its sensitivity and specificity were reported to be 100% and 93.3%, respectively. The advantages of this test included high specificity and stability, easy operation, low cost, and rapid response. It provided results within 15 min using only 10–20 μL of serum for each test [193].

Porous nanomaterials can be employed to recognize a wide range of pathogens. An interaction between the surface of metal-organic frameworks (MOFs), which have been functionalized with optical active molecules as quenchers or activators, and the pathogen could be detected [194–196]. For instance, a highly accurate nanosystem was developed based on MOF-5@Au-nanorods to detect SARS-CoV-2. The nanosystem allowed surface-enhanced Raman scattering (SERS) as a powerful spectroscopic technique to measure a sub-attomolar concentration on MOF-5@Au-nanorods [197,198].

The discovery of clustered, regularly interspaced short palindromic repeats (CRISPR) was a major step forward in gene editing and other biological applications. CRISPR is a type of adaptive immunity used by bacteria to protect themselves against infection with bacteriophages Recently, a CRISPR-Cas enzymology platform, called specific high sensitivity enzymatic reporter unlocking (SHERLOCK), was created, which could distinguish sequences that varied only in a single nucleotide at very low concentrations [199]. Liu et al. described an all-in-one dual CRISPR-Cas12 system for the simultaneous detection of SARS-CoV-2 as well as the human immunodeficiency virus (HIV) [200]. Broughton et al. described a DNA endonuclease-targeted CRISPR trans-reporter (DETECTR) platform, which could detect SARS-CoV-2 in < 30 min [201]. A new study showed that a CRISPR-Cas13-based strategy could be used to destroy SARS-CoV-2 sequences in human lung epithelial cells, killing up to 90% of all coronavirus particles [202]. Two different diagnostic tools based on CRISPR-Cas12 and CRISPR-Cas13 have also been shown to be capable of detecting SARS-CoV-2 RNA sequences [203,204].

6. Perspective on COVID-19 treatment using nanotechnology-based strategies

In addition to vaccine-based approaches, nanotechnology is also being investigated for new therapeutic approaches to fight the COVID-19 pandemic [205–208]. Up to now, nanotechnology has been employed in several successful treatment methods for infections caused by the AIDS virus, respiratory viruses, and herpes simplex viruses [209–212]. As for COVID-19, some nanotechnology-based therapeutic techniques are currently under investigation, including magnetic-based hyperthermia therapy, photothermal therapy, antiviral drug delivery, and gene editing of SARS-CoV-2 via CRISPR type systems.

6.1. Magnetothermal therapy

Magnetic NPs with good biocompatibility and low toxicity are often used in hyperthermia therapy [213,214]. The underlying mechanism of magnetic hyperthermia is that doses of injected magnetic NPs can be accumulated in specific locations within the body by application of a static external magnetic field. Next the application of a powerful alternating external magnetic field produces heat within the NPs thus causing thermal damage to pathogenic organisms [215,216]. This treatment technique has been employed in clinical practice to treat inoperable cancers such as glioblastoma multiforme or prostate tumors. Some benefits of this technique include, minimal invasiveness (i.e., needing only a single-dose injection of NPs), accessibility in all areas of the world, low costs, and possibility of complete elimination of target cells [217]. Magnetic hyperthermia therapy has been explored to treat influenza. Magnetic NPs were encapsulated into erythrocyte membranes that could bind to influenza viruses in a similar manner to erythrocytes. The membranes were functionalized with sialic acid to bind to the virus hemagglutinin. After exposure to a magnetic field, the viruses could be isolated and inactivated by the generated heat [218].

Magnetic field hyperthermia (MFH) was also suggested as an effective method to target latent HIV reservoirs (e.g., T cells). A preparation of superparamagnetic iron oxide NPs (SPIONs) called Feraspin R (10 mg/mL) showed low toxicity to cytotoxic T lymphocytes (CTLs) under normal conditions. However, applying a magnetic field created a temperature of 44.5°C for 20 min which killed half of the Feraspin R-loaded HIV-infected CTLs [219]. More recently, Chin et al. showed that SARS-CoV-2 could be inactivated by incubation at elevated temperatures. Accordingly, incubating the virus at 56 °C for 30 min resulted in a 3-log unit decrease in the virus titer, and no virus at all remained after incubation at 70 °C for 5 min. Hence, hyperthermia-based therapeutic strategies have the potential to treat COVID-19 [220]. Zhao et al. found that the SARS-CoV-2 RNA could attach to the carboxyl groups of poly (amino ester) coated magnetic NPs (pcMNPs), which were used for the extraction of viral particles [221]. The successful results of Phase I/II clinical trials of magnetothermal therapy based on the intratumoral delivery of magnetic NPs, followed by application of an alternating magnetic field (AMF) with variable field strength (0-18 kA/m) for patients with glioblastoma and prostate cancer suggests the potential of this technique for the treatment of cancers in general [222,223]. Magnetothermal therapy could also be employed for the treatment of viral infections, and COVID-19 in particular, provided that the following four conditions are met: [1] use of biodegradable and biocompatible magnetic NPs; [2] successful delivery of the NPs into viral-infected sites; [3] producing large amounts of heat from a small amount of NPs; and [4] using a safe and non-invasive source to deliver the magnetic field.

6.2. Photothermal therapy (PTT)

Photothermal therapy (PTT) is a minimally-invasive technique that leverages NPs to convert near-infrared (NIR) light into heat in order to destroy target cells [224]. Photodynamic therapy (PDT), on the other hand, takes advantage of photosensitizers, which produce reactive oxygen species (ROS) using photochemistry to kill viral infected cells. The application of PDT has some limitations due to the short lifespan of the ROS, while PTT allows for localized light-induced hyperthermia, which is not limited by the microenvironment because of using tissue-penetrating NIR light [225,226]. NIR irradiation (650–900 nm) is generally preferred for clinical applications since it can penetrate tissues and is less harmful than shorter wavelengths of light [227]. Photothermal agents can rapidly generate intense heat under NIR laser irradiation, thereby inactivating viruses and killing pathogens by denaturing their enzymes, or damaging their cell membrane proteins, nucleic acids, or lipids [220,228]. PTT is commonly used for cancer therapy and sometimes for killing bacteria, but the studies are still in very early stages for treatment of viral infections,

The PTT method generally combines a pulsed laser with light-absorbing nanomaterials [229]. Although organic NPs are biocompatible and low-cost, metal NPs (e.g., gold NPs) have much higher absorption coefficients and are therefore required in much lower amounts [230,231]. Another group of photothermal sensitizers are carbon-based nanomaterials, such as graphene oxide (GO) [232], or carbon nanotubes (CNTs) due to their good ability to convert NIR into heat [233]. PTT methods based on CNTs have demonstrated several advantages over magnetothermal therapy using magnetic NPs. Using magnetic fields to excite magnetic NPs to produce heat involves a slower heating rate with a higher depth of energy penetration than NIR, which increases the risk of off-target damage to healthy tissues [234]. In 2008, poly (ethylene glycol) (PEG)-carbon nanohorns (CNH) were tagged with an anti-T7 antibody at one end, and di-stearoyl phosphatidylethanolamine (PL) at the other end. PEG and PL were used for to improve the stability and solubility, and the bacteriophage T7 (phage T7) was employed as the viral target. The CNH complex bound to the virus through antigen-antibody recognition, and the T7 phage was destroyed by the photothermal effect produced under NIR laser irradiation (1064 nm). These functionalized nanomaterials were also found to be effective for the photothermal elimination of other viruses, including influenza, HIV, and SARS-CoV [235].

Graphene has high thermal conductivity, large surface area (~2,700 m^2 per 53 g), high light-to-heat conversion ability, and better antibacterial effects compared to CNTs [236]. Gedanken et al. reported that sulfonated magnetic NPs functionalized with reduced graphene oxide (SMRGO) could capture and inactivate herpes simplex virus type 1 (HSV-1). The HSV particles have a diameter of 170-200 nm, and the nucleic acids are wrapped within four layers for protection. The first layer is a protein called the capsid, next a layer called the capsid tegument, and then two more lipid layers called the envelope. The envelope glycoproteins (gB, gC, gD, gH, gL) play a significant role in the binding and entry of the virus into host cells. Virion glycoproteins can attach to the heparin sulfate (HS) present on the surface of host cells, and thus the virus gains entry into the cells. The SMRGO nanostructure mimicked the HS molecules on the cells and trapped the viruses. Under NIR irradiation (808 nm, 1.6 W/cm^2), the photothermal efficiency of the SMRGO (100 ppm) produced a temperature rise up to 55 °C, leading to the inactivation of ~99.99% of the HSV-1 virions within 10 min. The surface modification of GO with target molecules enhanced its affinity for viruses, and the SMRGO was an efficient, rapid antiviral therapeutic agent with potential to fight coronaviruses [237,238].

More recently, scientists have shown that metal NPs, such as gold NPs, have high absorption coefficients for NIR light and can generate intense heat [229,239]. These NPs can be attached to a wide variety of receptors and antibodies, allowing them to be used as photothermal sensitizers. For example, anti-epithelial growth factor receptor (EGFR) antibody-conjugated gold NPs could destroy EGFR expressing cells under NIR irradiation [240]. In clinical studies, gold and silver NPs have displayed the surface plasmon resonance (SPR) effect, producing a strong photothermal effect, as well as showing better biocompatibility compared to other metal NPs. Gold NPs have some benefits over CNTs, including more uniform particle sizes [241,242]. In 2017, gold nanorods were employed for the photonic inactivation of murine leukemia virus (MLV) using an 805-nm NIR laser. It was found that NIR irradiation produced a plasmonic shock in the nanorods, which altered the virus membrane, thereby reducing its ability to bind to host cells [243].

Organic molecules and conjugated polymer NPs are considered a safe group of nanomaterials, which can absorb photons in the NIR range and generate heat using non-radiative energy transfer [244,245]. Conjugated polymers are electrically conductive owing to multiple double bonds along the polymer backbone, leading to electron delocalization [246]. Polymeric NPs are commonly used as coatings for metal NPs to boost their biocompatibility and photothermal properties, especially for *in vivo* applications. According to one study, polyurethane-Au-polyethylene glycol (PU-Au-PEG) composite NPs demonstrated good anti-fouling properties after 10 min of exposure to 808-nm NIR laser irradiation. The anti-fouling effect of the nanocomposite stemmed partly from the PEG creating a hydrophobic layer on the gold nanorods and preventing the adhesion of pathogens to the surface; and partly from the surface temperature of the PU-Au rising to 55°C due to the gold nanorod LSPR photothermal effect. The *in vitro* results confirmed the effective antibacterial properties of the nanocomposite against different types of bacteria, and drug-resistant bacteria in particular. Furthermore, the antimicrobial activity of the PU-Au-PEG nanoplatform was studied using a subcutaneous implantation animal model, showing its biocompatibility, low cytotoxicity, and low hemolysis ratio (less than 5%) [247].

As discussed above, PPT holds real promise in the treatment of COVID-19, especially in the acute stage of the disease. To this end, light-sensitive plasmonic nanoplatforms could be designed with specific cell surface receptors such as heparan sulfate (HS) or complementary DNA receptors to capture the viruses and inactivate them under NIR irradiation.

6.3. Nanotechnology-based drug delivery systems

The use of nanotechnology for antiviral drug delivery has enabled the development of smart and targeted nanocarriers that minimize the side effects of antiviral drugs. Many of these drugs can also damage healthy non-infected cells, and cause other harmful side effects when used at high doses. This strategy also addresses an issue arising from the low water solubility of antiviral drugs posing difficulties for *in vivo* delivery [248,249]. The unique properties of nanomaterials, including small size, biocompatibility, good solubility, easy surface functionalization, extended circulation time, and their ability to deliver required doses of a drug, make them outstanding candidates for drug delivery [250]. Given the success of nanotechnology-based drug delivery systems in the treatment of viral infections, summarized in Table 4, it is anticipated that they will also be able to help treat COVID-19.

Metal NPs can deliver therapeutic antiviral agents and drugs to target cells, as well as having intrinsic antiviral activity. Their size is generally smaller than organic NPs (1-100 nm), with a higher drug loading capacity [242,251]. Some studies have focused on selenium NPs (SeNPs) for the delivery of therapeutic agents. It has been reported that these NPs could affect the function of the immune system cells, and reduce the generation of free radicals inside host cells by preventing mitochondrial depolarization [252,253]. SeNPs have also shown the potential to inhibit the proliferation of hepatitis virus in human hepatoma cell lines [254]. Additionally, these NPs have been employed for the delivery of various antiviral drugs, such as zanamivir, oseltamivir (OTV), or ribavirin (RBV). A SeNP-OTV combination was found to prevent apoptosis induced by the H1N1 influenza virus [255]. OTV-loaded SeNPs could also inhibit the activity of enterovirus 71 (EV71) by decreasing the

Table 4
Nanotechnology-based drug delivery systems for the treatment of viral infections

Nanoplatform	Size	Drugs	Virus	Results
Inorganic Nanomaterials				
Selenium (Se)	100 nm	OTV	Influenza H1N1	High effectivity and low cytotoxicity of Se@OTV in kidney cells infected with virus; higher viability of Se@OTV (93%) compared to free OTV (53%) [200]
Silver (Ag NPs)	2 nm	AM	Influenza H1N1	Low cytotoxicity (~90%) of Ag NPs loaded with AM [289]
Gold NPs	29.25 nm	Interferon α (IFNα)	HCV	High stability of the nanoplatform in human serum; sustained delivery of HA-AuNP/IFNα for 7 days [290]
PMA-coated MNPs	35.2 ± 2.2 nm	ENF	HIV	Increased drug translocation across the BBB; nontoxic *in vivo* and *in vitro* ENF-NPs [291]
ox-MWCNT	-	CHI360 / CHI415	HIV	High antiviral activity; low cytotoxicity [263]
Lipid-coated mesoporous silica nanoparticles (LC-MSNs)	75 nm	ML336 Antiviral immunostimulant	Venezuelan equine encephalitis virus (VEEV)	Decreased brain viral titer in infected mice compared to controls; absence of bioaccumulation in tissues; non-toxicity of LC-MSNs [279]
PEG-PLGA	178 nm - 197 nm	Diphyllin/ bafilomycin	Influenza H1N1	Antiviral activity and biocompatibility; high safety of carrier; CC_{50} value of 12.5 μM and 21.89 μM for free diphyllin and encapsulated diphyllin [273]
PLGA	~185 Nm	EFV	HIV	Increased bioavailability of NFV PLGA-NPs by 4.94 fold compared to free NFV [292]
PLGA	116 -143 nm	GCV	HSV-1	Non-cytotoxic PLGA NPs after 24-48 h contact with HCEC cells [293]
PLGA/PLA/MMA-SPM/ PMMA	58-224 nm (PLGA), 91-823 nm (MMA-SPM NPs)	LAM/AZT	HIV	Non-toxicity of NPs in mouse model [294]
Squalene-based NPs	-	Adenosine/ α-tocopherol	SARS-CoV-2	High efficacy; potential to control inflammation [288]

Lamivudine: LAM; Zidovudine: AZT; Efavirenz: EFV; Oseltamivir: OTV; Amantadine: AM; Enfuvirtide: ENF; Ganciclovir: GCV; Amphiphilic polymer: PMA; Poly (methyl methacrylate): PMMA; Methyl methacrylate: MMA

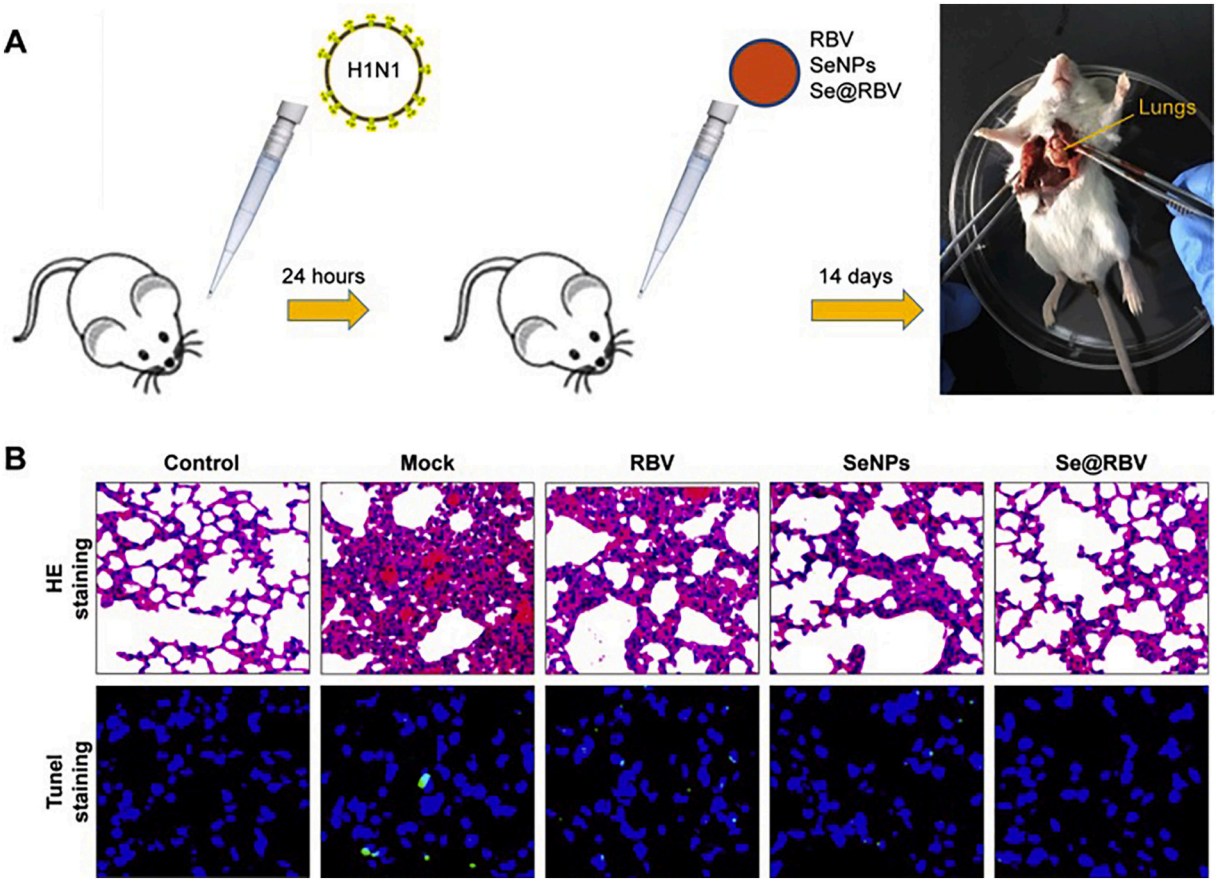

Fig. 6. Schematic representation of the *in vivo* antiviral efficacy of Se@RBV. (A) Viral infection of mice, followed by their treatment using Mock (saline), SeNPs, and Se@RBV; (B) hematoxylin and eosin and TUNEL staining show that the mice treated with Se@RBV had low levels of lung injury, DNA damage, peribronchiolar, and perivascular edema. Reprinted with permission from ref (259), copyright 2018, Elsevier.

generation of ROS in an EV71-infected U251 cell line [256].

RBV has proved successful in the treatment of SARS-CoV, MERS-CoV, and most influenza virus strains [257,258]. In a recent study, RBV-modified SeNPs (Se@RBV) with a diameter of 65-100 nm could prevent apoptosis induced by H1N1 influenza virus through resisting of the caspase-3 pathway, resulting in a reduced virus titer. After the nasal administration of Se@RBV, H1N1 influenza infected BALB/c mice aged 4–6 weeks displayed lower levels of lung injury. Levels of DNA damage, peribronchiolar, and perivascular edema were lower compared to control groups (Fig. 6). The *in vitro* antiviral activity of the system was assessed using assay for viral titer and cell viability (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide, MTT). The MTT assay showed a viability of 80.6% in Madin-Darby canine kidney (MDCK) cells exposed to Se@RBV, compared to controls. Hence, Se@RBV could provide a powerful antiviral therapeutic effect that reduced oxidative stress in cells, and may be able to treat viral infections before they turn into pandemics [259]. Because chronic inflammation and oxidative stress have been reported in COVID-19 patients, SeNPs may be effective in controlling the inflammation, and boost an effective immune response against COVID-19.

Gold NPs can enter different types of cells and tissues, such as the central nervous system and can persist for some time These NPs have good biocompatibility coupled with the SPR effect and can be functionalized with various agents (e.g., polymers with antiviral properties) [211,260]. In 2018, gold NPs were employed to deliver RBV to the African green monkey kidney cell line (Vero cells) to destroy the measles virus. It was found that the gold NPs-RBV at a dose of 99.5 μg/mL had a stronger antiviral effect compared to 500 μg/mL of free RBV [261]. Nevertheless, other metal NPs can suffer from poor biodegradability, low biological distribution, high accumulation within the body, and in some cases, high toxicity as a consequence of surface modification.

Due to their high surface area to volume ratio, and ability to penetrate through cell membranes, CNTs can serve as suitable nanocarriers for the delivery of antiviral drugs [262]. Studies showed that the toxicity of oxidized CNTs and polymer-coated CNTs was within the accepted range for clinical application [263,264]. For instance, isoprinosine is an antiviral immunostimulant composed of inosine and dimepranol acedoben, which was attached to the surface of oxidized single-walled CNTs (ox-SWCNTs) to transport the therapeutic agent across biological membranes for the treatment of viral nervous necrosis (VNN) disease. This preparation showed a greater antiviral effect at a lower concentration in comparison to the free drug [265]. Cyclodextrin-functionalized (CD)-oxidized-multi-walled CNTs (MWCNTs), called CD-ox-MWCNTs were successfully tested for the sustained release of acyclovir to treat HSV-1 infection [266].

Nanocarriers can be functionalized with organic nanomaterials, including polymers and lipid NPs composed of biodegradable monomers, in order to encapsulate various therapeutic agents for targeted drug delivery [227,267]. The FDA has approved liposomal nanomaterials, such as DaunoXome, Abelcet, and Caelyxor, or polymer NPs such as Macugen [268] to treat various diseases. The enhanced permeability and retention effect allows for their accumulation in target tissues and organs. Some of these NPs (e.g., PLGA) have been approved by the FDA [269,270]. PLGA-based NPs have been widely used for antiviral drug delivery because of their high biocompatibility [271]. Moreover, the functionalization of antiviral drugs with PEG was reported to decrease opsonization, while increasing the biodistribution of drugs, through extending the blood circulation time [272]. In a recent study, dual block PEG-PLGA copolymers were employed for the sustained delivery of two vacuolar ATPase inhibitors, i.e. diphyllin and bafilomycin into influenza virus-permissive cell lines. As opposed to the free drugs, the encapsulated inhibitors exhibited lower toxicity and a stronger therapeutic effect with CC_{50} values of 21.89 μM and 12.5 μM for free diphyllin and encapsulated diphyllin, respectively. A mouse model demonstrated a reduced viral titer in the lungs after treatment with encapsulated diphyllin, and increased the mouse survival rate by 33% [273].

Biodegradable poly-d,l-lactic acid (PDLLA) NPs encapsulating RBV were used for the sustained release of the drug into hepatocytes. This nanoplatform may also be effective for the treatment of viral infections, namely COVID-19 and chronic hepatitis C virus (HCV). RBV monophosphate-loaded nanocarriers were synthesized using a blend of polylactic acid (PLA) and arabinogalactan (AG)–poly(l-lysine) conjugate, in which the phosphate groups of RBV bound to the carboxyl groups of PLAs through ionic interaction. These NPs enabled a longer half-life of RBV within the systemic circulation, and prevented the drug from accumulating in red blood cells. It was shown that RBV accumulated in the liver of mice after intravenous injection of the nanocarriers, but sustained release of the drug continued for seven days [274].

Lipid-based nanomaterials can deliver drugs across lipid cell membranes, and may be used for intravenous delivery of antiviral drugs to treat viral infections. The nasal cavity and nasopharynx are the major sites of infection with viral respiratory diseases such as COVID-19 [275–277]. The bioavailability of acyclovir administered by the intranasal route in an acyclovir mucoadhesive liposomal gel was increased by 60.72% compared to intravenous administration. The intranasal delivery of liposome-acyclovir formulations improved the ability of the drug to be absorbed in the nasal cavity [278]. Lipid-coated mesoporous silica NPs were prepared for the delivery of the benzamidine derivative ML336, used for treatment of Venezuelan equine encephalitis virus. The NPs showed better biocompatibility and a longer circulation time *in vivo* in comparison to the free drug [279]. Nonetheless, lipid-based NPs have some drawbacks, including a limited loading capacity for hydrophilic drugs, and the possibility of aggregation during storage [280]. Generally, NPs used for *in vivo* applications must be tested carefully to confirm the absence of hepatotoxicity, nephrotoxicity, neurotoxicity, or pulmonary toxicity [281–285].

Motivated by novel coronavirus pandemic, researchers have studied some combinations of nanotechnology with pharmacology for treating or relieving the symptoms of COVID-19. Chloroquine (CQ) and hydroxychloroquine (HCQ) were among the first therapeutic drugs suggested for the treatment of COVID-19 patients. However, the mechanism of action and the actual degree of efficacy are still unknown, and the incidence of side effects does not allow for long-term use, especially at high doses. For example, an increased risk of heart disease has been reported for HCQ [286]. Rezaee et al. used a computational approach to investigate the ability of HCQ to be adsorbed on a variety of metal NPs, such as Ag, Au, and Pt NPs. They performed density-functional calculations to estimate the affinity of the HCQ molecules for Au/Ag NPs. Subsequent computational calculations tested the effects of changing the size and composition of the NPs based on molecular dynamics simulations. They suggested that computational simulation of the adsorption of HCQ onto the NPs could help design safer and efficient nanocarriers for the delivery of HCQ with minimal side effects to treat COVID-19 [287].

In COVID-19 patients, the severity of the disease is often associated with the strength of the inflammatory responses. Dormont et al. developed multidrug loaded NPs that could lessen uncontrolled inflammation. The squalene NPs were prepared by encapsulating α-tocopherol as an antioxidant, and adenosine as an immunomodulator (Fig. 7). The nanoplatform could deliver the drugs to the target areas of inflammation to control excessive cytokine responses. Fig. 7 shows two mice models, one of local acute inflammation and the other of systemic inflammation that were used to study the targeted release of drugs from the NPs at the sites of inflammation. After the intravenous injection of fluorescent DiD-labeled NPs, the inflamed paw demonstrated a higher fluorescence emission than the control paw. When the mice received an injection of free DiD solution without any NPs, no significant fluorescence was observed in the inflamed paw. The simultaneous delivery of antioxidants and adenosine could not only relieve inflammation and reduce cytokine secretion caused by SARS-CoV-2, but could also decrease the side effects of the drugs [288].

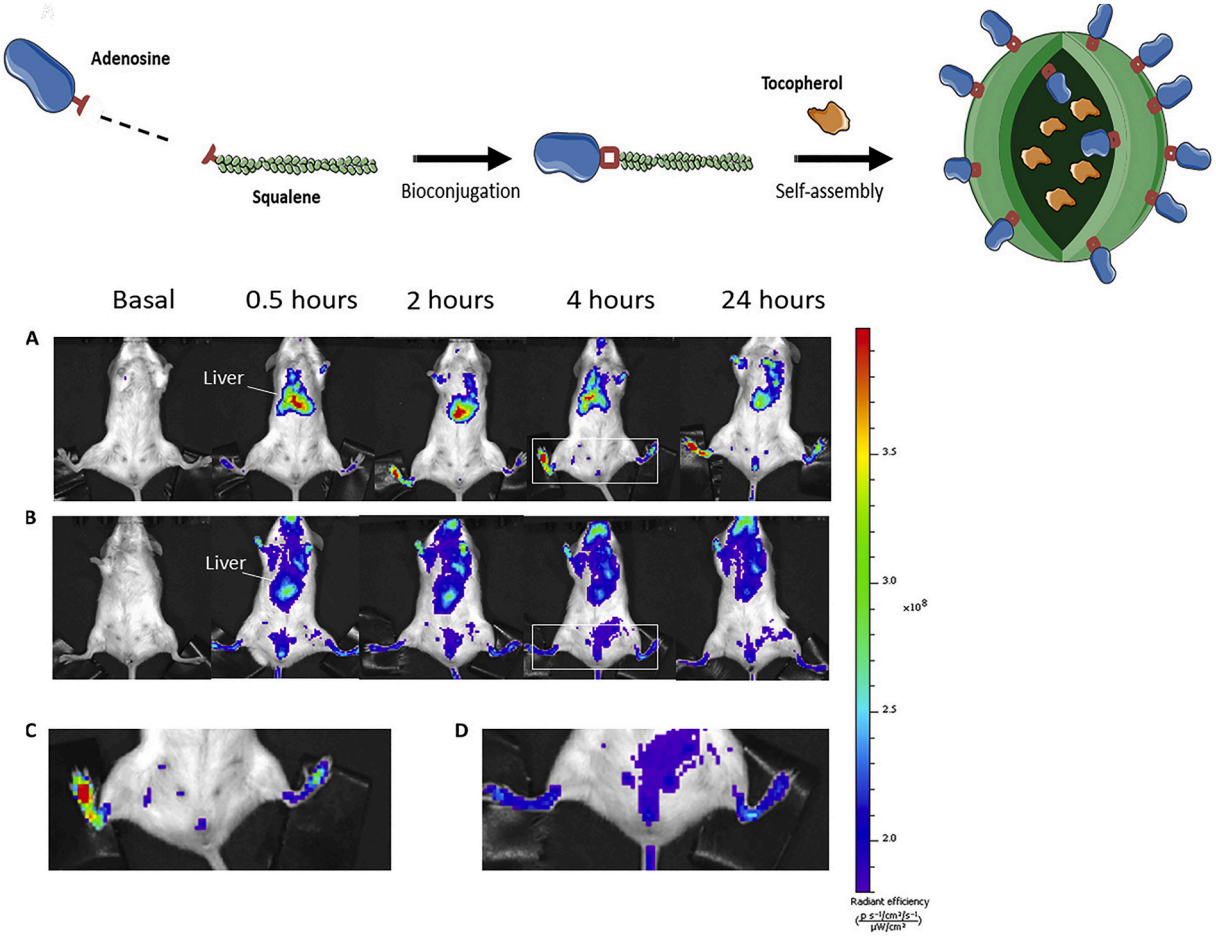

Fig. 7. Schematic illustration of the preparation of multidrug squalene-adenosine nanoparticles. (A) IVIS Lumina image of fluorescent-nanoparticles in mice with inflamed right paw and non-inflamed left paw; (B) Tracing the dye without nanoparticles in mice with inflamed right paw. Reprinted with permission from ref (288), copyright 2014, American Chemical Society.

6.4. Gene editing of SARS-CoV-2 using CRISPR/Cas systems

Viruses such as HIV, HCV, HBV, as well as respiratory viruses can cause persistent disease by integrating their genome into the human genome of the host cells [295]. The CRISPR/Cas9 technology was originally developed based on a bacterial defense mechanism against invading viruses, and can now be used to treat persistent viral infections [296,297]. The superiority of the CRISPR/Cas9 system over other treatment methods lies in its potential to target the viral RNA and DNA genomes directly, to eliminate the viruses and halt persistent infections [298]. Thus, this technology shows promise to control viral pandemics, e.g., SARS-CoV, SARS-CoV-2, or pandemic influenza in both the pre-integration and provirus stages [299,300]. However, the genetic alteration of viruses could lead to the emergence of new viral strains, which could be resistant to CRISPR/Cas9 or other therapeutic agents, thereby increasing the overall pathogenicity of the virus [301]. Hence, the simultaneous targeting of multiple genomic sites is of vital importance to permanently inactivate or remove viral genomes with little chance of escape. Although carrier-free CRISPR/Cas9 systems can be used for *in vivo* therapeutic applications, there are concerns regarding their instability toward serum nucleases, unwanted stimulation of the innate immune system, and excretion via the kidneys [302,303].

Designing CRISPR/Cas9 systems based on NPs could make them effective and safer for *in vivo* application. In 2018, the *Streptococcus pyogenes* Cas9 (SpCas9) mRNA and modified single-guide RNA (sgRNA) were co-loaded into lipid-based NPs (LNP-INT01), and tested in mouse models. In addition to being safe and well-tolerated *in vivo*, this stable and biodegradable nanosystem could edit the transthyretin (*Ttr*) gene in the mouse liver with a 97% decrease in the TTR serum protein levels for at least one year [304]. In another study, TT3 lipid-like nanomaterials (LLNs) were employed to deliver CRISPR/Cas9 to knock down the proprotein convertase subtilisin/kexin type 9 (*Pcsk9)* gene, and reduce the expression of HBV DNA in mice after intravenous injection. The injection of Cas9 mRNA-loaded TT3 LLNs and sgRNA-LLNs six hours apart resulted in the deletion of the targeted gene in the mouse liver tissue [305]. Overall, CRISPR/Cas9 systems incorporated into LLNs hold great potential for gene editing of viral infections in the lungs, liver, and kidneys. Many studies are now underway to create safer CRISPR/Cas9 systems for the diagnosis and treatment of COVID-19.

SARS-CoV-2 can undergo mutations in its genetic sequence resulting in alterations to membrane proteins that reduce the effectiveness of antiviral drugs and antibodies [306]. Instead of focusing on the membrane proteins of the virus, CRISPR/Cas9 systems can be used to target the genomic RNA of SARS-CoV-2, and prevent its replication by destroying its RNA [299,307]. *CRISPR/Cas* systems are classified into two *categories* according to the function and structure of their *Cas* protein. Class I is divided into *types* I, III, and IV, while class II is divided into *type* II, V, and VI. The type VI CRISPR/Cas system has a simple structure and requires one Cas13 protein and one crRNA molecule to carry out its function. There are several Cas13 proteins, including Cas13a, Cas13b, Cas13d, and Cas13e [308]. Cas13a from *Leptotrichia wadei* (LwaCas13a) can be used to target endogenous transcripts in human embryonic kidney HEK293 cells. Cas13b from *Prevotella sp.* (PspCas13b) is considered the most effective for use in mammalian cells. *Cas13d* belongs to class II

and is a type VI RNA-guided nuclease. CRISPR/*Cas13d* can cleave the RNA genome of viruses without damaging the human transcriptome. Since Cas13d has a smaller size (967 amino acids) and stronger catalytic activity compared to other Cas13 proteins, it is more efficient to target and destroy RNA viruses, and is likely to work with SARS-CoV-2 [309].

A new study reported that CRISPR/Cas13d could precisely cleave the SARS-CoV-2 RNA genome. The system was developed based on gRNA-containing spacer sequences that were complementary to the S gene, ORF1ab, and Cas13d protein. An adeno-associated virus (AAV) was used for the delivery of the nucleic acids to the infected patients. One AAV was used to package Cas13d protein along with three gRNAs targeting different regions of the SARS-CoV-2 RNA genome to improve the efficacy of the treatment. Furthermore, some AAV serotypes display a highly-specific tropism for lung tissue, thereby enabling gRNAs to enter only lung cells without affecting the transcriptome of the lungs. Thus, this CRISPR/Cas13d system could potentially provide a successful strategy to fight RNA viruses and SARS-CoV-2 in particular [310].

Another novel method was devised based on the CRISPR/Cas13d system, as a prophylactic antiviral CRISPR active in human cells (PAC-MAN), which could efficiently degrade the RNA of SARS-CoV-2 sequences in the A549 human lung epithelial cell line. This strategy took advantage of a combination of 22 CRISPR RNAs (crRNAs) to target all the different RNA-dependent RNA polymerase (RdRP) genes as well as the nucleocapsid (N) gene sequence, to treat COVID-19. Fig. 8A illustrates the hypothetical life cycle of SARS-CoV-2, which is similar to that of SARS-CoV. When the virus enters a cell, it releases its genomic RNA into the cytoplasm and synthesizes negative-sense genomic RNAs from which a new copy of the positive-sense genome RNA and viral mRNAs are produced. As indicated in Fig. 8B, the PAC-MAN strategy relies on the destruction of the intracellular viral genome and the resulting viral mRNAs (Fig. 8B) [299].

In a recent study, a gene-editing system was developed based on Cas13e.1 (type VI) that could successfully cleave SARS-CoV-2 sequences as well as influenza A virus in cultured HEK293T and N2A cells. The Cas13e sequences were cloned into a pCX539 backbone via the Gibson Assembly method, and then transfected into cultured cells using lipofectamine 3000. The expressed Cas13e.1 could target more than 99% of the viral genome in a pool of 10 crRNAs with single nucleotide mismatches, which might also reduce the chance of the viruses escaping from antiviral destruction by mutation. [307].

CRISPR/Cas systems for COVID-19 gene editing can be delivered by either AAVs or by lipofectamine. Despite the high efficiency of AAV-based *in vivo* delivery systems, the possible long-term immunogenicity of viral carriers is a problem for the use of an antiviral gene-editing system [311]. On the other hand, the use of cationic lipofectamine for *in vivo* applications requires careful consideration because of its high toxicity and costs [312].

Although traditional delivery systems can transfer high concentrations of therapeutic agents, the instability of their cargo remains a major obstacle. The incorporation of CRISPR/Cas systems into NPs may lead to the introduction of safer and highly-efficient gene-editing platforms. Smart NPs, also known as stimuli-responsive NPs, have the ability to

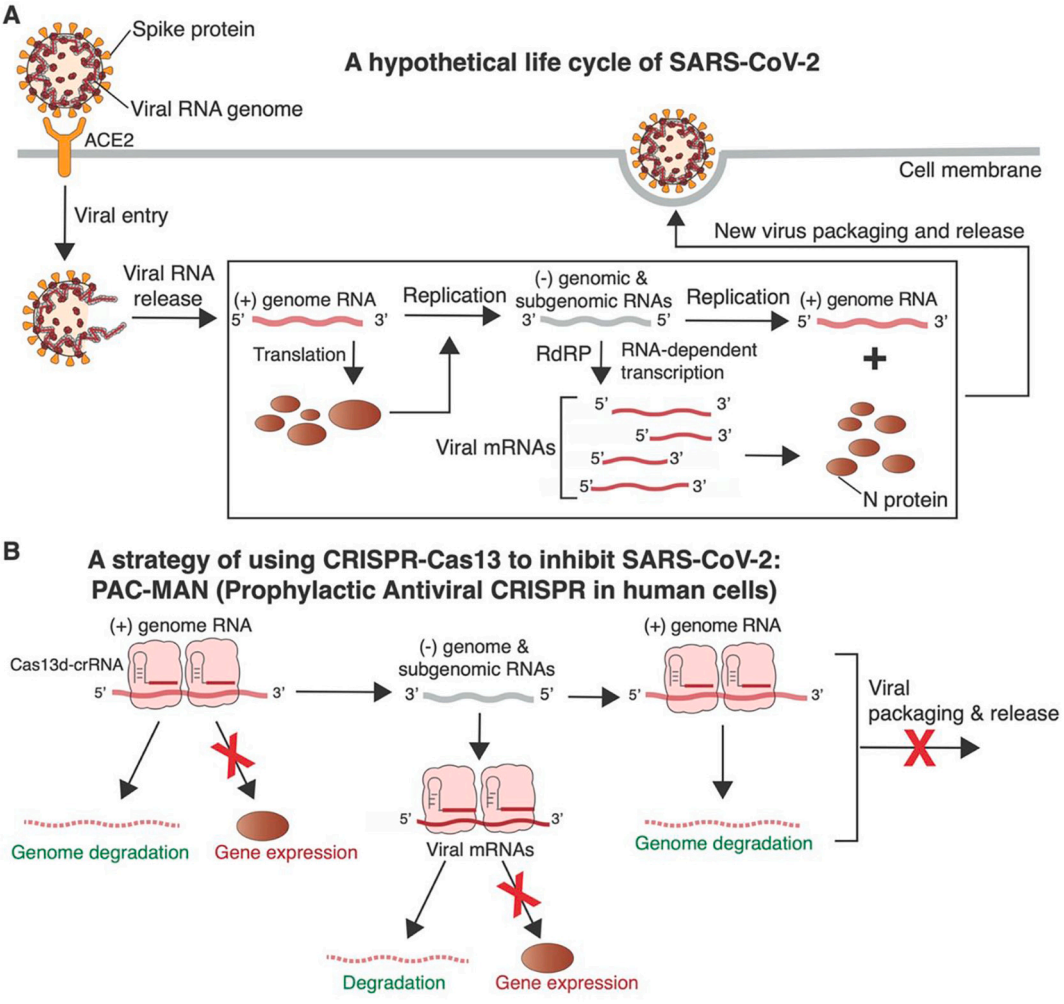

Fig. 8. Use of CRISPR/Cas13 for treating SARS-CoV-2. (A) Schematic representation of the life cycle of SARS-CoV-2; (B) PAC-MAN strategy against COVID-19 prevents viral function and replication by targeting and cleaving all viral positive-sense RNAs. Reprinted with permission from ref (299), copyright 2020, Elsevier.

control the spatio-temporal release of therapeutic agents in response to environmental stimuli, thereby reducing the side effects of antiviral drugs and protecting healthy tissues [313,314]. The triggering of these smart NPs by stimuli, can be categorized into two types: [1] internal stimuli, such as pH, redox potential, or enzyme activity; [2] external stimuli such as temperature gradient, light irradiation, magnetic field, or electrical field [315,316].

Since COVID-19 mainly affects specific types of cells, tissues, and organs, controlled drug delivery via smart NPs could improve patient compliance [317–319]. The differences in pH and glutathione (GSH) that exist between various cells and tissues of the body, allows scientists to design smart NPs that can precisely release drugs at predetermined sites. For example, the intracellular concentration of GSH in the blood and the extracellular matrix is 1-10 mM and 2-20 μM, respectively [320]. Additionally, there is a significant pH difference between different organs and tissues of the body; e.g., there is pH gradient within the gastrointestinal tract (from pH 2 - pH 7.4) which affects the absorption of drugs in different ways, and the pH of the cytosol (pH 7.4), lysosomes (pH 4.5-5), and endosomes (pH 5.5-6) are also different [321].

The targeted delivery of antiviral drugs such as abacavir (ABC) and lamivudine (3TC) in acidic environments (e.g., the vagina) was investigated by attaching pH-sensitive ester derivatives to gold glyconanoparticles as a new HIV treatment method [322]. The pH-sensitive NPs prepared for oral drug delivery also tackled the issue of precipitation upon administration as well as incomplete absorption of drugs from the GI tract. These nanocarriers can dissolve hydrophobic drugs and remain stable at acidic pH, thus increasing their oral absorption and reducing the drug release in the stomach. As the pH increases, these NPs become ionized and then release their cargo. These pH-responsive polymeric nanospheres have been shown to improve the oral absorption of human HIV-1 protease inhibitors in animal models [323,324].

There is a redox potential gradient between the intracellular and extracellular space, leading to redox-sensitive polymeric nanomaterials being investigated for controlled antiviral drug delivery [315,325]. These nanocarriers undergo the cleavage of disulfide bonds upon exposure to a reducing agent such as GSH [325]. Miao et al. studied the delivery of DrzBC and DrzBS (10-23 DNAzyme) as well as their endosomal escape in HBV-transfected human hepatoma cells by loading the drugs into redox-sensitive chitosan oligosaccharide-SS-octadecyl amine (CSSO) polymer micelles. The CSSO polymer self-aggregated in an aqueous medium to form micelles (123 nm), and the drugs were attached to them by electrostatic interactions. The intracellular GSH destroyed the redox-sensitive disulfide bonds of the CSSO polymer, leading to the release of the drugs. The complexes of CSSO/DrzBS and CSSO/DrzBC inhibited the secretion of HBsAg and HBeAg from the cell line, respectively [326].

Delivery systems based on external stimuli require external sources, such as light irradiation, temperature gradients, and magnetic fields, to release therapeutic agents. In recent years, smart drug-delivery systems have been attracting considerable attention, because of their non-invasive nature. Light-responsive and ultrasound-sensitive drug or gene delivery systems can release the agents exactly at the targeted site at the desired time upon exposure to an external source of energy [227,314]. Some nanoplatforms rely on magnetic fields for the delivery of antiviral drugs into the brain due to the remarkable ability of magnetic NPs to cross the blood-brain barrier (BBB) [327,328]. The stability and biocompatibility of magnetic NPs can be improved by coating with polymers or lipid-based nanomaterials [329,330]. For instance, an efficient delivery system was developed based on magnetic liposomes encapsulating azidothymidine-triphosphate (AZTTP) with an average diameter of 150 nm, for suppressing HIV-1 replication in peripheral blood mononuclear cells (PBMCs). The nanoplatform was transported across a BBB model using an external magnetic field, and provided sustained drug release for two weeks while maintaining the integrity of the BBB [331]. Hence, smart drug or gene delivery systems could be potentially used for the treatment of COVID-19 with minimal side effects, improved drug absorption, sustained drug release, and enhanced systemic circulation lifetime.

7. Conclusions

The fight against the SARS-CoV-2 pandemic has taken advantage of the knowledge and experience gained from the successful handling of previous coronavirus epidemics such as SARS and MERS. This knowledge may be combined with advances in nanotechnology, to create opportunities to better manage the latest COVID-19 pandemic by accelerating the development process of vaccines and drugs. Thus far, nanotechnology has shown great potential to prevent, diagnose, and even treat COVID-19 infections. Several immune-mediated, antigen-based, and gene-based nanovaccine candidates are currently undergoing clinical trials. Nanoplatforms have enabled the design of highly-stable, scalable, single-dose, and self-administrated vaccine preparations, that can not only facilitate vaccine dissemination, but also lift the heavy burden of COVID-19 from healthcare systems. Moreover, nanomaterials have considerably enhanced the efficacy of wearable PPE even after being washed and reused multiple times, simultaneously addressing the worldwide shortage of PPE, and reducing the need to dispose of massive amounts of used PPE. Antiviral and antibacterial nano-coatings have also helped to maintain surfaces in a sterile state for years, especially in high-risk locations for viral transmission. Furthermore, nanobiosensors (e.g., optical, electronic, electrochemical, or dual-function plasmonic and photothermal biosensors), lab-on-a-chip nanosystems, and nanopore technology have all contributed to the development of highly-accurate, real-time, and cost-effective COVID-19 diagnostic tests. Last but not least, the incorporation of nanoparticles into magnetothermal therapy, photothermal therapy, drug delivery systems, and gene-editing platforms (e.g., CRISPR/Cas9) has shown early promise for the treatment of COVID-19 infections with minimal side effects. However, as a lesson learned from the emergence of SARS-CoV-2, ongoing research efforts should continue not only to halt the COVID-19 pandemic, but also to increase the state of preparedness for tackling new viruses that may emerge in the future. This may help to prevent the outbreak of future pandemics.

Declaration of Competing Interest

There are no competing interests to declare.

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