



Advances in Nanomaterial-Based Platforms to Combat COVID-19: Diagnostics, Preventions, Therapeutics, and Vaccine Developments

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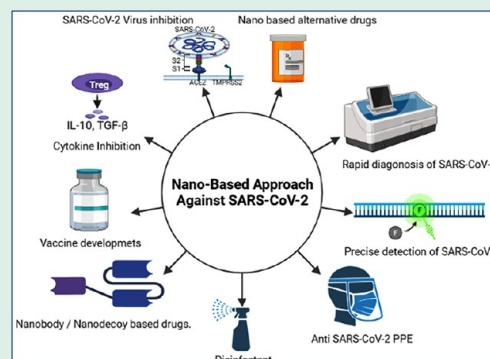
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ABSTRACT: The COVID-19 pandemic caused by the SARS-CoV-2, a ribonucleic acid (RNA) virus that emerged less than two years ago but has caused nearly 6.1 million deaths to date. Recently developed variants of the SARS-CoV-2 virus have been shown to be more potent and expanded at a faster rate. Until now, there is no specific and effective treatment for SARS-CoV-2 in terms of reliable and sustainable recovery. Precaution, prevention, and vaccinations are the only ways to keep the pandemic situation under control. Medical and scientific professionals are now focusing on the repurposing of previous technology and trying to develop more fruitful methodologies to detect the presence of viruses, treat the patients, precautionary items, and vaccine developments. Nanomedicine or nanobased platforms can play a crucial role in these fronts. Researchers are working on many effective approaches by nanosized particles to combat SARS-CoV-2. The role of a nanobased platform to combat SARS-CoV-2 is extremely diverse (i.e., mask to personal protective suit, rapid diagnostic tool to targeted treatment, and vaccine developments). Although there are many theoretical possibilities of a nanobased platform to combat SARS-CoV-2, until now there is an inadequate number of research targeting SARS-CoV-2 to explore such scenarios. This unique mini-review aims to compile and elaborate on the recent advances of nanobased approaches from prevention, diagnostics, treatment to vaccine developments against SARS-CoV-2, and associated challenges.

KEYWORDS: SARS-CoV-2, nanoparticles, preventions, diagnostics, antiviral therapeutics, vaccine developments



1. INTRODUCTION

SARS-CoV-2, a member of the human coronavirus family, has been infecting since late 2019 and has caused 6.1 million deaths to date.¹ Aside from the pathological aspect, the social situation was exacerbated by global and economic breakdown, social isolations, hampered general lifestyles, education, insufficient healthcare, emergency support, and mental strain. Aside from viral inhibitions, disease management, control, immune boosting, and preventive vaccinations, medical science has yet to discover a simple treatment for any viral disease including SARS-CoV-2.²

Over the last two decades, nanobiotechnology has grown in popularity as a treatment for emerging viral infectious diseases.³ The main reason for the interest is its precise and controlled delivery system, which allows for more precise diagnostics, therapeutics, and targeted destruction.³ Since the discovery of SARS-CoV-2 and its mechanism of action, many researchers have been attempting to develop novel nanoparticle-based approaches for the efficient management and prevention of this pandemic.⁴ Nanoparticles (NPs) refer to the application of particles with dimensions that fall into the nanometer range (10^{-9} nm or below) and are unique due to their smaller particle

size, larger surface area, variable shapes, bonding nature (i.e., gold–thiol interactions), conjugations characteristics (i.e., antimicrobial peptides, cell-penetrating peptides, or imaging contrast agents, etc.), encapsulation of unstable biomolecule (i.e., mRNA), surface plasmonic resonance, responsiveness to the external field (i.e., magnetic and optical), biocompatibility,^{5–7} and stabilizing agents, although toxicity, aggregation, and bioaccumulations also made their application challenging at the same time.^{8–16}

The kinetics of SARS-CoV-2 infection (Figure 1) comprises binding with the angiotensin-converting enzyme (ACE2) expressed in major organs (lungs, kidney, spleen, heart, pancreas, etc.).^{17–19} However, the morbidity due to SARS-CoV-2 is more likely to be due to severe cytokine storm against SARS-CoV-2, which ultimately causes severe organ damages or

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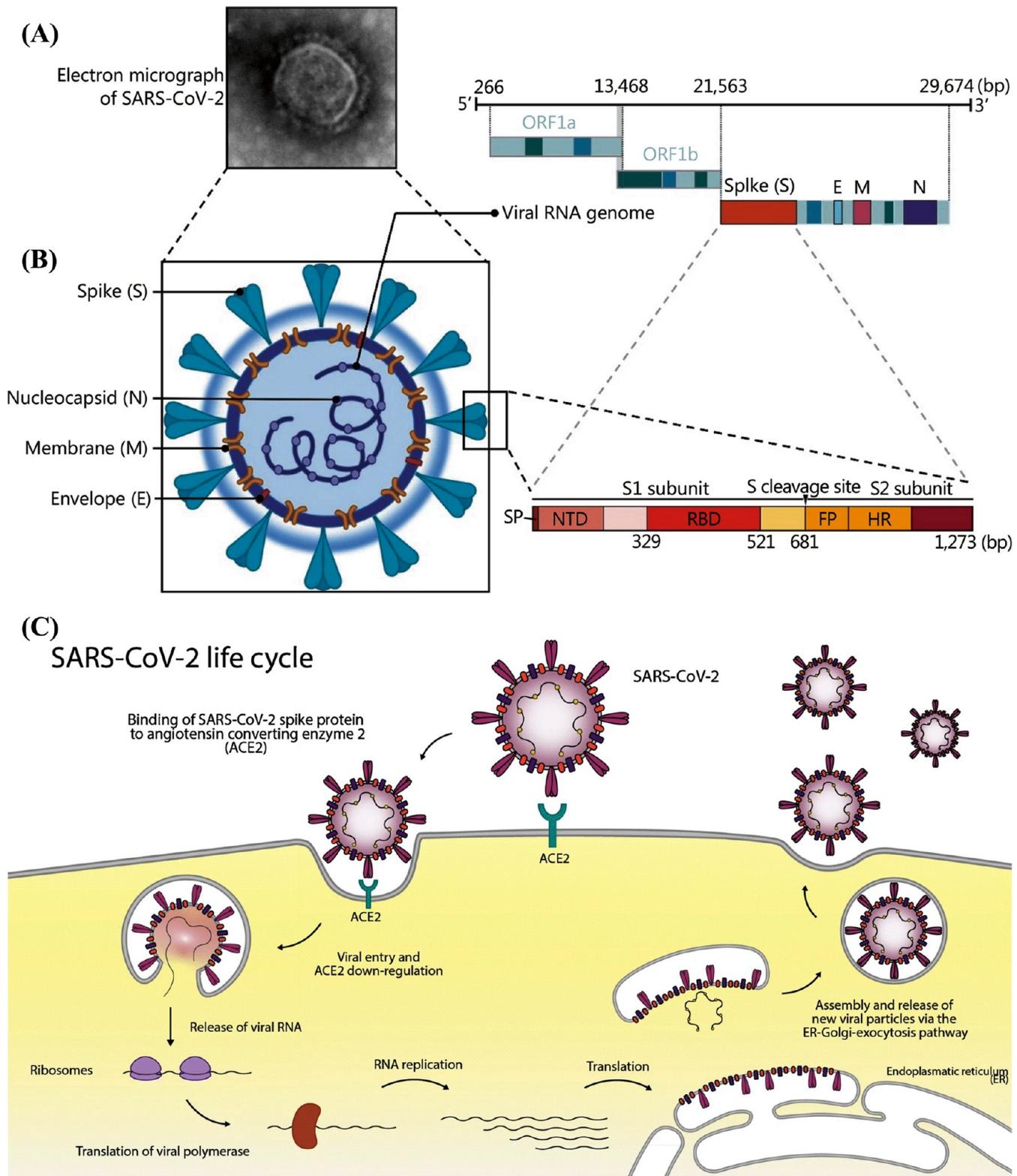


Figure 1. (A) Transmission electron microscope image of SARS-CoV-2 spherical viral particles in a cell and SARS-CoV-2 morphology. (B) Surface protein of SARS-CoV-2. Reproduced from ref 18. Copyright 2021 BMC. (C) Infection kinetics of SARS-CoV-2. Reproduced from ref 19. Copyright 2021 Springer.

failure and in extreme cases death.²⁰ NPs have been shown to inhibit the attachment of SARS-CoV-2 by directly destroying its spike protein, inhibiting the attachment by blocking ACE2, and also preventing the severe cytokine storm by targeted and controlled targeted drug delivery system^{21–23} in many studies

since the emergence of SARS-CoV-2.⁴ Apart from the therapeutics, due to the structure and properties, NPs have been thoroughly investigated to be effective for rapid detections, therapeutics, improvements, preventive ways (mask and personnel protective ways), and vaccine developments within the last

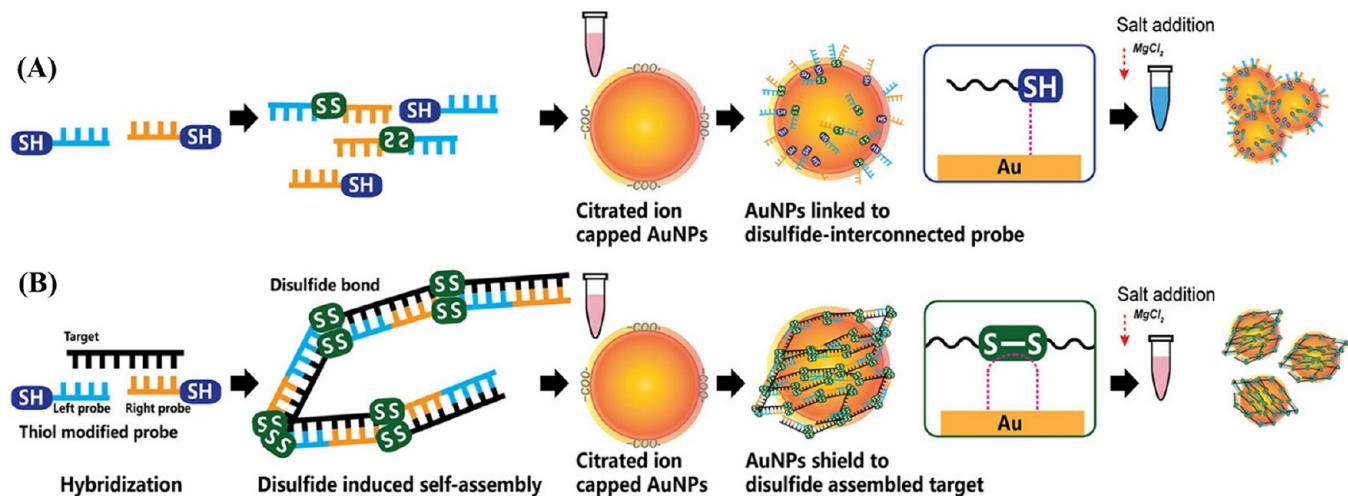


Figure 2. Colorimetric detection of DNA based on disulfide-induced self-assembly. (A) Salt-induced aggregation of AuNPs in the absence of targets, (B) procedures for preventing AuNPs from salt-induced aggregation by disulfide-induced self-assembly in the presence of targets. Reproduced from ref 29. Copyright 2019 American Chemical Society.

two years.⁴ Because of the growing interest in the development of a nanomolecule-based approach to combat SARS-CoV-2 from many researchers, we aimed to write a concise and focused review article that will elucidate the nano-based initiatives to combat SARS-CoV-2 until now.

2. NP-BASED BIOSENSORS FOR COVID-19 DIAGNOSTICS

Recent advancements in nanobiotechnology have bestowed upon us an effective tool to advance diagnostics and therapeutics applications. Unique properties of nanomaterials compared to their bulk counterpart, have been proven to be useful in various biomedical applications.^{24,25} The size and shape of the NPs can be tailored according to their usage in specific applications, and a surface modification with various ligands either covalently or noncovalently is possible to enhance detection limit and detection specificity. In terms of detecting biological materials such as DNA, RNA, and spike proteins, the major challenge is associated with the detection of a very low concentration of the materials, which results in a low detection signal (low signal-to-noise ratio). To overcome the low detection signal barrier, unique properties such as plasmonic properties of gold nanoparticles, magnetic properties of magnetic nanoparticles, and unique electrochemical properties of the carbon-based nanoparticles, fluorescence properties of quantum dots, and other polymeric nanomaterials provide a platform for rapid and low-cost detection. Another major challenge with biological materials detection is associated with specificity, which can be overcome by decorating the surface of the NPs with a specific ligand (antibody, protein, thiolated molecules). SARS-CoV-2 expressed protein on the surface (Figure 1), which is used to detect the virus with specific conjugation with the antispike antibody. Apart from the spike protein, nucleoprotein (N protein) and RNA can also be targeted as homing devices for the SARS-CoV-2 detection. In this section, various rapid, selective, and highly sensitive NPs-based detections of SARS-CoV-2 are discussed.

2.1. Gold NP-Based Biosensors. Owing to unique optical and plasmonic properties, gold nanoparticles (GNPs) have been used in various biosensors applications. Their tunable size, ease of synthesis, stability, and biocompatibility make them an

excellent choice as sensitive biosensors toward various pathogens and biomarkers.^{26–28} GNPs have additive interactions with sulfur (S) that have made the GNPs–S bond popular for colorimetric virus detections (Figure 2).²⁹ Generally, thiol modified nucleic acid surfaces interact with target RNA or DNA in the presence of a positively charged electrolyte that further interacts with GNPs and changes its color, the key philosophy of GNPs-based colorimetric assay.³⁰

Recently, Pramanik et al. reported a 4-aminothiophenol (4-ATP) functionalized GNPs system for rapid detection of coronavirus using UV-absorbance as well as surface-enhanced Raman scattering (SERS)-based detection mechanism.³¹ The 4-ATP functionalized GNPs are further functionalized with an antispike antibody, which then reacts with the antigen on the SARS-CoV-2 virus, causing aggregation within the GNPs colloidal system. This aggregation behavior is detected by naked eyes as the change in the absorbance is in the visible range of the light spectrum or can be quantified using a UV-absorbance. Apart from causing a change in the absorbance values, the aggregation state creates a certain “hot spot” for Raman measurement which can be quantified using the Raman instrument. Pramanik et al. reported a detection limit of 4 picogram/mL (pg/mL) at a concentration of 18 viruses per particle per mL where the result time was within a 5 min window.³¹ Similarly, Lew et al. have reported a colorimetric rapid detection assay using the aggregation behavior of GNPs. Short antigen epitope functionalized GNPs were used to detect SARS-CoV-2 IgGs in plasma, which resulted in aggregation of the functionalized GNPs.³² The degree of aggregation is dependent on the concentration of the SARS-CoV-2 IgGs analytes. With a higher concentration of SARS-CoV-2 IgGs, the change in aggregation state increases, resulting in a decrease in absorbance values in the visible light range. The dual peptide-functionalized epitopes S14P5/S20P2 and S14P5/S21P2 were reported to have a LOD of 4 nM and 3.2 nM, respectively. Moreover, Kim et al. have reported a label-free colorimetric assay for MERS-CoV using citrate capped GNPs, which undergoes salt-induced aggregation in the absence of the target MERS-CoV double-stranded DNA but does not aggregate in the presence of the target DNA.²⁹ The LOD of this label-free colorimetric platform was reported to be 1 pmol/μL. Gold nanoparticle-based thiol-modified antisense oligonucleotides

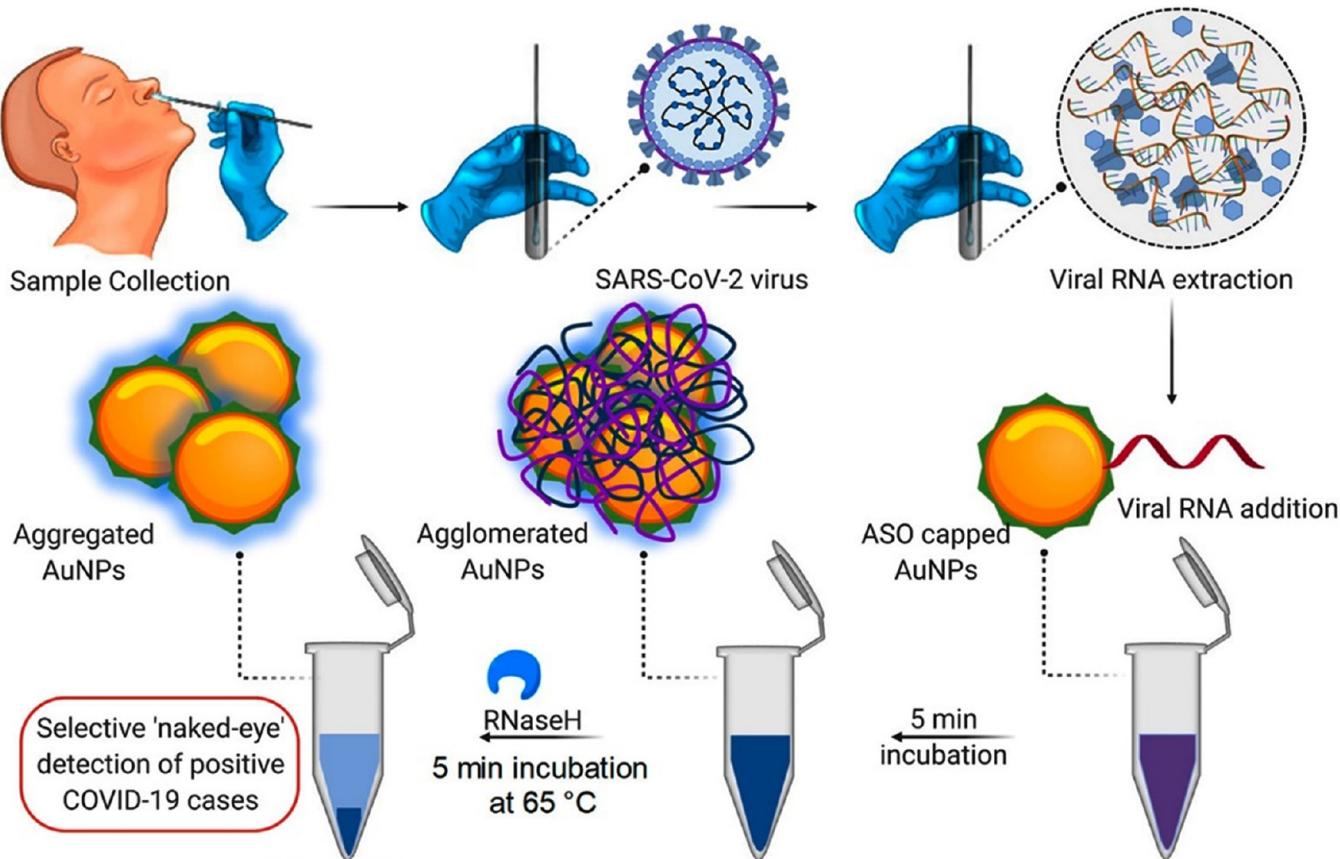


Figure 3. Schematic representation for the selective naked-eye detection of SARS-CoV-2 RNA mediated by the suitably designed ASO-capped GPs. Reproduced from ref 33. Copyright 2020 American Chemical Society.

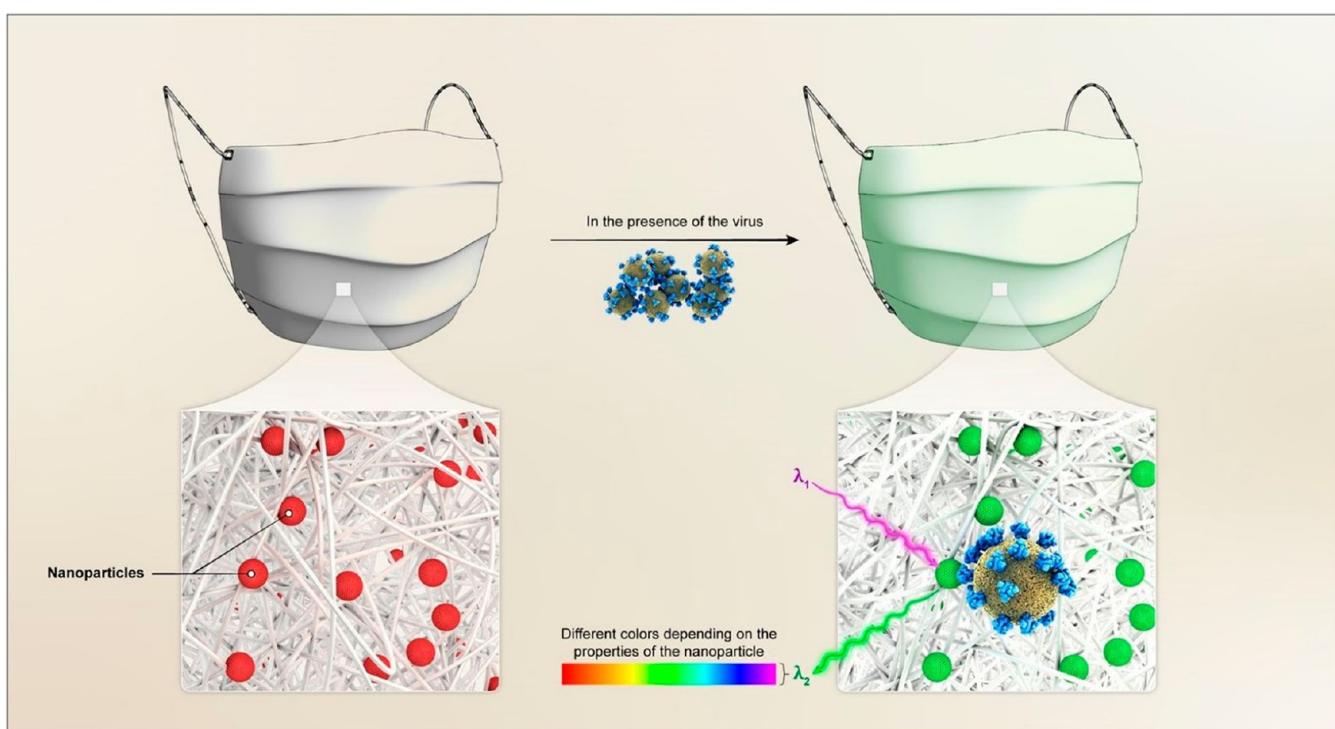


Figure 4. SERS intensity and color changes of mask-embedded nanoparticles (GNPs) in the presence of SARS-CoV-2. Reproduced from ref 34. Copyright 2020 MDPI.

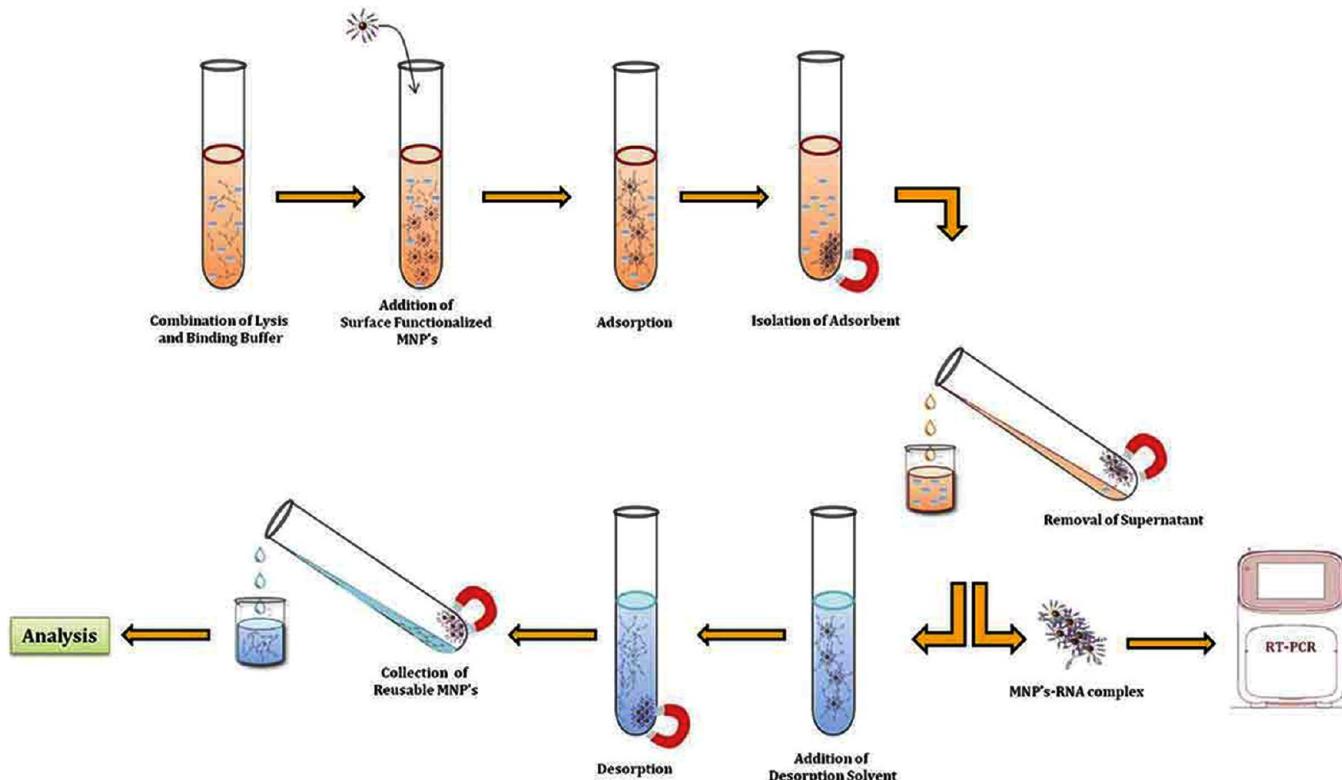


Figure 5. Surface functionalized magnetic nanoparticles (MNP's) assisted RNA-extraction protocol for potential detection of viral RNA. Reproduced with permission from ref 42. Copyright 2021 Taylor and Francis.

(ASOs) specific for N-gene (nucleocapsid phosphoprotein) of SARS-CoV-2 virus have been shown promising toward detecting 0.18 ng/uL viral RNA (Figure 3).³³ The functionalized nanoparticles aggregate selectively in the presence of viral RNA, which is detectable visually.

The GNPs–sulfur bond and SERS pave the way for detection at the point of care (POC). GNPs and organic framework in a paper-like strip can interact with viral membrane protein, causing bonds between metal and an organic framework to be broken. The protein–GPN interaction can essentially be considered as an electron–hole effect, in which the SERS intensity and color of the GNPs would appear to change. Thus, GNP's-based point of care and rapid detection (Figure 4) can be possible.³⁴

2.2. Magnetic NP-Based Biosensors. Magnetic nanoparticles (MNPs) are widely used in biomedical applications due to their unique properties including but not limited to magnetism, low cytotoxicity, high surface area, and rapid response toward the external magnetic field.^{28,35–38} Recently, Zhong et al. reported a rapid and sensitive detection platform using magnetic particles as a detection substrate.³⁹ The detection mechanism depends on the response of the SARS-CoV-2 spike protein antibody functionalized MNPs in the presence of an alternating magnetic field (AMF), where in the absence of any viral antigen, the particles respond quickly to the AMF as a result of Brownian and Néel relaxation. In the presence of the viral antigen, the functionalized MNPs have a different response to the AMF, which is detected by magnetic particle spectroscopy. The cross-linking of the surface antibody of the MNPs with the viral antigens increases the hydrodynamic diameter of the particles, resulting in a significant change in two important parameters: (i) Brownian relaxation time and (ii)

dynamic magnetization. The LOD of this MNPs-based platform was reported to range from 0.1 to 0.37 nM.³⁹ Since viral genetic materials are very small (29 891 nucleotides in size), it is imperative to extract and purify the genetic materials as efficiently as possible.⁴⁰ To address this challenge, Chacón-Torres et al. reported a negatively charged MNPs-based RNA extraction platform (Figure 5), which is utilized to purify viral RNA in a shorter time with higher purity.^{41,42} The MNPs are functionalized with AETPS to form amino magnetic nanoparticles compound, which is later functionalized with diacrylate amine polymerization to form a strongly negative MNPs-based nanoplatform for viral RNA extraction. In addition, Somvanshi et al. reported a Zn ferrite nanoparticles system where the MNPs are functionalized with silica and carboxyl modified poly(vinyl alcohol), which induces an overall negative charge on the particles.⁴² These negatively charged particles are used to extract viral RNA for the potential detection of COVID-19.

2.3. Carbon Nanotube-Based Biosensors. Carbon nanotubes (CNTs) have been proven a successful tool as biosensors and imaging modalities due to their unique characteristics such as high electron conductivity, high aspect ratio, higher mechanical strength and flexibility, response to fluorescence, and Raman analysis (Figure 6).^{43–45} According to a recent study, CoV-2 can be selectively identified by application of CNT field effect transistor (FET), where LOD of 10 fM can be obtained.⁴⁶ A flexible Kapton substrate was used to immobilize the reverse sequence of the RNA-dependent RNA polymerase gene of SARS-CoV-2 on the CNT field-effect transistor-based substrate. Furthermore, it is well established that SARS-CoV-2 utilizes the ACE2 receptor expressed on the outer membrane of the host cells to enter the cell's cytoplasm. To prevent ACE2 and SARS-CoV-2 interaction, Badhe et al. reported a CNT-based

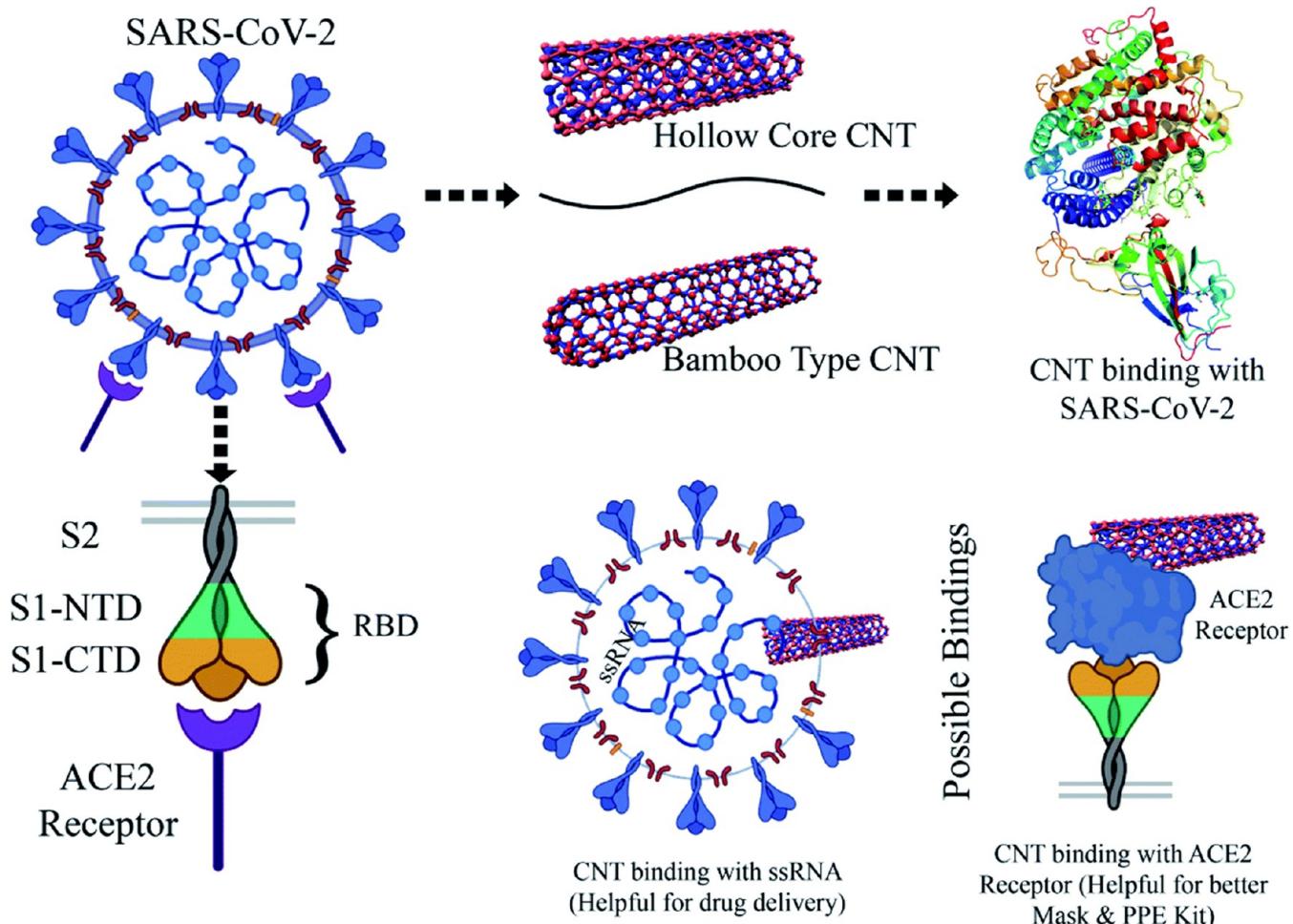


Figure 6. CNT biosensor for SARS-CoV-2 detection. Reproduced with permission from ref 43. Copyright 2021 Royal Society of Chemistry.

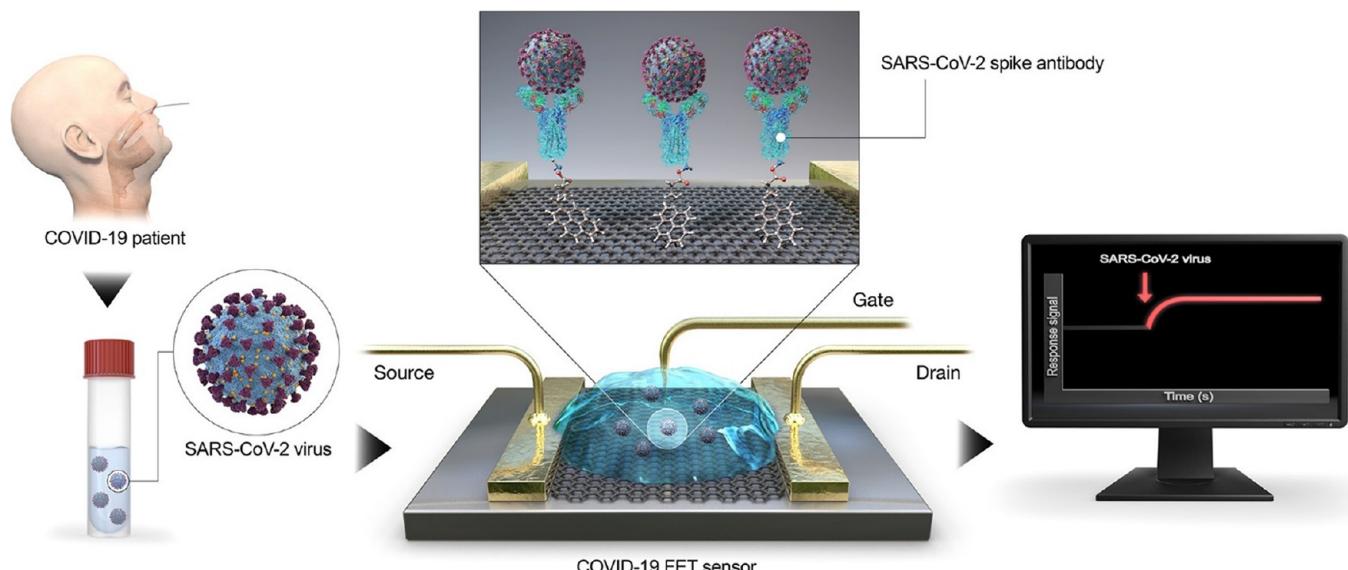


Figure 7. COVID-19 FET sensor operation by graphene where SARS-CoV-2 spike antibody is conjugated onto the graphene sheet probe linker (1-pyrene butyric acid N-hydroxy-succinimide). Reproduced from ref 54. Copyright 2020 American Chemical Society..

platform stabilized with a short peptide chain (EQEERIQQQDKRKNENEDKRYQRYGRGKGHQ) to bind to the S-protein of the virus to inhibit the ACE2 mediated uptake of the virus particles.⁴⁷ However, these simulated findings need to be further

verified by in vitro and in vivo experiments to study the feasibility and LOD of these nanoplatforms for SARS-CoV-2 sensing. In addition to expressing spike protein antigen (SAg), the SARS-CoV-2 virus also contains nucleocapsid protein

Table 1. Nanoparticle-Based Platforms to Detect SARS-CoV-2

nanoplatform	functionalization	detection mechanism	LOD	ref
SWCNTs	ACE2	fluorescence (ACE2 binds to the RBD of S protein, resulting in turn on fluorescence signal)	12.6 nM	49
TiO ₂ nanotubes	cobalt	fluorescence (ACE2 binds to the RBD of S protein through S-RBD protein electrochemical sensor through S-RBD protein)	14 nM	64
SWCNTs	ssDNA	purification of the viral genomic RNA extraction followed by RT-qPCR	6.4 copies/ μ L in PBS buffer and 9.2 copies/ μ L in 50% human saliva (LOQ)	50
GNPs	4-aminothiophenol (4-ATP) and antispike antibody	S-RBD protein and antispike protein result in aggregation of GNPs which can be detected by UV-vis absorbance and SERS measurement	4 pg/mL at 18 viruses per particles per mL	31
CNT	N/A	electrochemical	10 fM	46
graphene	complementary PMO	electrochemical (FET)	0.37 fM in PBS	55
graphene	SERS-CoV-2 spike RBD antibody	the interaction of spike protein and antibody leads to p-doping of p-type graphene, resulting from a blue shift in SERS measurement	2.29 fM in nasal swab	56
GNPs	N-protein antibody	SERS-CoV N protein binds to antibody resulting in higher fluorescence signal due to LSPR of GNPs	3.99 fM in serum	56
gold nano stars	Rhodamine 6G dye conjugated DNA aptamer	dye fluorescence quench due to distance-dependent nanoparticle surface energy transfer (NEST) process in the presence of SERS-CoV-2 virus	3.75 fg/mL in artificial saliva and 1 fg/mL in phosphate buffered saline	65
selenium nanoparticles	SARS-CoV-2 nucleoprotein	upon interaction with the anti-SARS-CoV-2 IgM and IgG, the selenium nanoparticles develop an orange color that is detectable visually	1 pg/mL in buffer solution	66
GNPs	thiol-modified antisense oligonucleotides (ASOs) specific for N-gene (nucleocapsid phosphoprotein) of SARS-CoV-2	the thiol-modified ASO-capped AuNPs aggregate in the presence of the target RNA sequence of SARS-CoV-2 and cause a colorimetric change due to surface plasmon resonance	0.18 ng/uL of RNA of SARS-CoV-2 virus	33

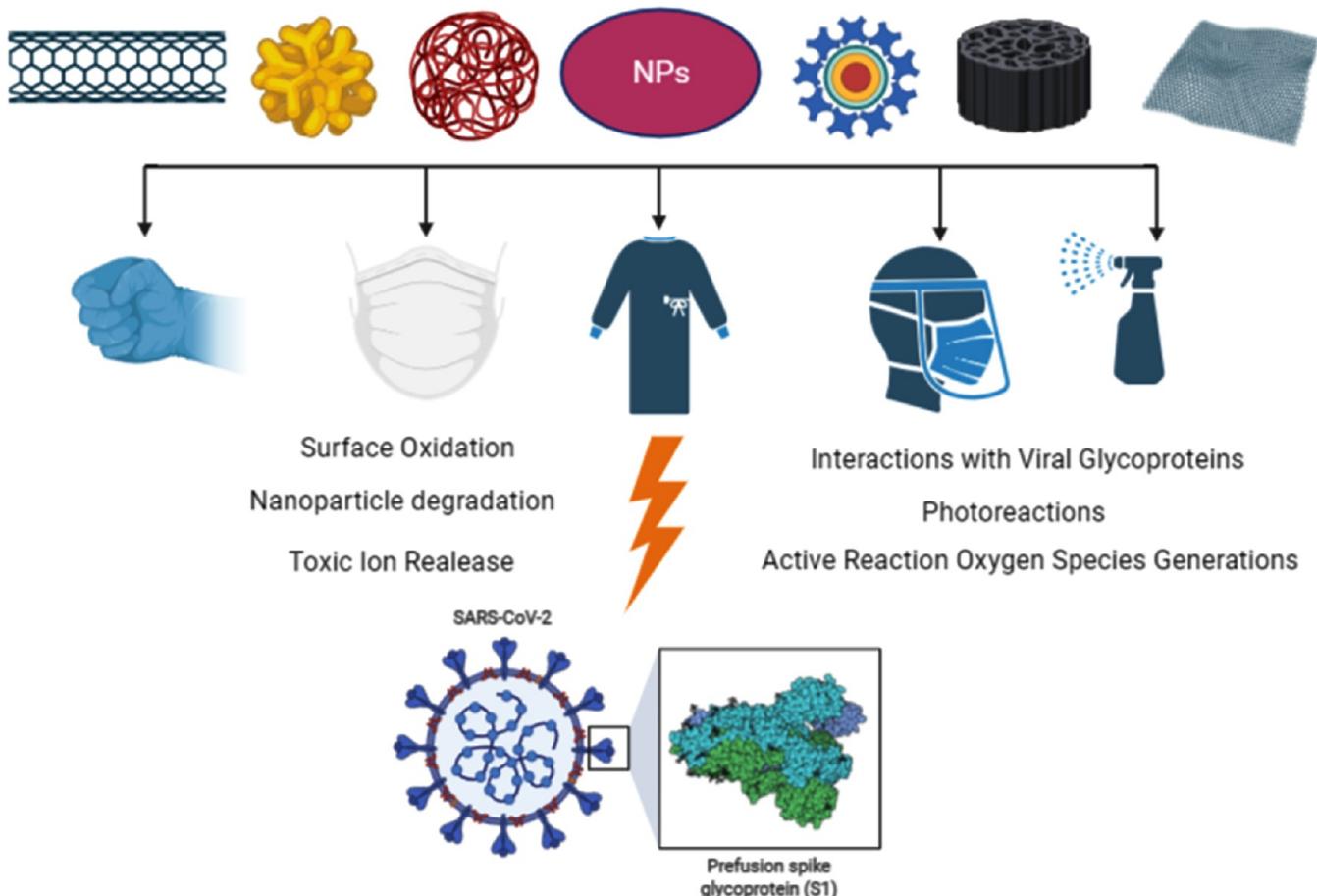


Figure 8. NP-based viral disinfectants against SARS-CoV-2 by preventing viral dissemination on-air, surfaces, and protective equipment.

(NAg), which can be utilized for viral biosensing. Single-walled carbon nanotubes (SWCNTs) decorated with SERS-CoV-2 spike protein antibody and antinucleocapsid protein antibody detected the S antigen and N antigen through field-effect transistor mechanism (FET) with a reported LOD of 0.55 fg/mL for SAg and 0.016 fg/mL for NAG .⁴⁸ Apart from electrical sensors, fluorescence-based biosensors showed promising results in viral COVID-19 detection.⁴⁹ Briefly, SWCNTs were functionalized covalently with ACE2 receptor, which resulted in a 2-fold nano sensor fluorescence increase within 90 min exposure to SARS-CoV-2 spike protein. The nano sensor system reported a LOD of 12.6 nM of SARS-CoV-2.⁴⁹ Although this LOD is on the lower side compared to electrochemical biosensing, this detection mechanism could be a pioneer toward developing optical biosensors for COVID-19 detection. Another implementation of CNT-based nanoplateforms can be an increase in the detection sensitivity of reverse transcription-polymerase chain reaction (RT-qPCR) detection. SWCNTs coupled with ssDNA have shown an extraction yield of 40% higher compared to the commercial silica-column kit.⁵⁰ This high yield will facilitate increased copies of viral genomes in the RT-qPCR eventually increasing the sensitivity of the viral detection technique.

2.4. Graphene-Based Biosensors. The discovery of graphene in 2004 unlocked a novel electrochemical biosensor utilizing unique electron transport, thermal, and mechanical properties along with low cytotoxicity. Proper bioconjugation between biological molecules and graphene sheets is important to develop a reliable and effective detection probe. The

graphene-based platform also showed promising antimicrobial and antiviral properties due to the abundance of electron cloud on their structure and their fast transferability toward the pathogenic structure, which eventually produced reactive oxygen species (ROS), oxidized the lipids on the membrane, and caused cellular death.^{51–53} Graphene-based FET biosensing device functionalized with SARS-CoV-2 antibody (Figure 7) was proven successful in detecting antigen protein, cultured virus, and nasal swab specimen from COVID-19 positive patients.⁵⁴ The novel COVID-19 biosensor reported a LOD of 1 fg/mL in phosphate buffer saline and 100 fg/mL in a clinical transport medium. The reported graphene-based electrochemical sensor is a sensitive immunological diagnostics method that could be potentially used for accurate sophisticated detection of the COVID-19 virus.⁵⁴ Another sensor is fabricated by immobilizing a graphene FET sensor decorated with a complementary phosphorodiamide morpholino oligos (PMO) probe on a gold surface.⁵⁵ The reported LOD of this biosensor in PBS is 0.37 fM , in throat swab of COVID-19 positive patient is 2.29 fM , and in serum is 3.99 fM within a very rapid experimental time of 2 min. In addition, Nguyen et al. reported a graphene-based photonics sensor armed with SERS-CoV-2 spike antibody, which in the presence of the antigen initiated a p-doing of the p-type graphene resulting in a blue shift in SERS detection.⁵⁶ The LOD of the sensor was reported as 3.75 fg/mL in artificial saliva and 1 fg/mL in phosphate buffer saline. At the early stage of infection with COVID-19, most of the patients remain asymptomatic whereas some patients develop fever, cough, and fatigue, whereas a subgroup of the

patients suffered from cytokine storm syndrome (CSS). The CSS is an overshoot immune response that results in excessive release of cytokines interferon (IFN), interleukin (IL), and tumor necrosis factor (TNF). This excessive release of cytokines could result in severe complexity within the patient, which could even lead to death.⁵⁷ Thus, the abnormal elevation of these biomarkers could be potentially used as an early diagnostic of COVID-19. Moreover, Hao et al. reported a dual-channel graphene-TWEEN 80 FET biosensing device for rapid (7 min) onsite detection of IFN-gamma, TNF-alpha, and IL-6 with a LOD of 476 fM, 608 fM, and 611 fM, respectively, in biofluid.⁵⁸

2.5. Other NP-Based Biosensors. Recent studies have strengthened the viewpoint that IgM and IgG antibodies are important biomarkers that indicate acute infection period. Developing a device for rapid and low-cost detection nanoparticle-based lateral flow assay has been shown promising.^{59–61} Recently, Wang et al. reported a selenium nanoparticle-based lateral flow immunoassay kit where the nanoparticles are modified with SARS-CoV-2 nucleoprotein, which detects anti-SARS-CoV-2 IgM and anti-SARS-CoV-2 IgG in human serum in a 10 min where the detection mechanism does not require any expensive equipment and can be detected visual color change.⁶⁰ The LOD of this flow system was reported as 5 ng/mL for IgG and 20 ng/mL for IgM. Although the development of the color is weak in the lower concentration region, this device can be a quick screening device similar to the pregnancy test lateral flow assay. A similar assay based on lanthanide doped polystyrene particles for anti-SARS-CoV-2 IgG in human serum was reported by Zu et al., which could be useful to determine the patient's response to COVID-19 therapeutics.⁶² Takemura et al. reported a nanosensor platform compiled with quantum dots, gold nanoparticles, magnetic nanoparticles, and carbon nanotubes (QD-GNP-MNP-CNT), which was used for magnetic separation and signal enhancement of the virus genomics.⁶³ CdSeTeS quantum dots (QDs) were used as an electrochemical signal-generating material. In the presence of the virus, the QD exhibits a viral concentration-dependent fluorescence. The fluorescence signal is further enhanced by the presence of GNPs due to localized surface plasmon resonance. The signal enhancement is due to the increase in Cd²⁺ concentration, which increased because of conjugation of antibodies with the increased influenza viral materials (IFV/A). The MNPs were incorporated into the nanoplateform to separate the detected virus, whereas CNT was used as a backbone matrix to provide a platform that can incorporate all the nanomaterials. Investigating the ability of a similar platform in detecting the SARS-CoV-2 virus could result in successful and rapid detection of COVID-19 as well as rapid separation. Table 1 lists a few nanoparticles, their functional agents, detection mechanism, and LOD to detect the SARS-CoV-2 virus.

3. COMBAT OF SARS-COV-2

3.1. NP-Based Antiviral Disinfectant and PPE to Combat SARS-CoV-2. Many disinfectants (chlorines, peroxides, quaternary amines, alcohols, etc.) have already been proven against various broad-spectrum bacteria and viruses (including SARS-CoV-2).^{67,68} The existing limitations of regular disinfectants are volatility, high concentration requirement for 100% viral inhibition, lack of efficacy on nonlipid viruses, potential risk of exposure, health hazards, nonreusability, and economics.⁶⁹ After the Covid-19 outbreaks, many attempts have been taken to eliminate the existing drawbacks of disinfectant and protective masks.^{70,71} Nanotechnology also plays an

important role in the development of potentially cost-effective, reusable, user-friendly, and more effective disinfectants and surface modifications for the protective mask (Figure 8).⁷² Metallic NPs (silver, copper, titanium dioxide nanoparticles) have broad-spectrum antiviral potentials that can be utilized as a coating for public surface and protective mask coatings.⁷³ Metallic NPs can have intrinsic photocatalytic and photodynamic functionalities to inhibit viral protein.^{72,74}

ZnO nanospray as a potential disinfectant has shown to be promising in deactivating SARS-CoV-2.^{75,76} ZnO-induced ROS generations make up one of the potential pathways for cellular death. Notably, the study found a slight cytotoxic effect on the cell host, which requires further optimization before mass usage of ZnO-based disinfectant. ZnO is among the most studied NPs for its broad-spectrum antimicrobial potentialities. Viral RNA polymerase can also be significantly disturbed by zinc ions.⁷⁷ ZnO NPs undergo UV photocatalysis pathways in the presence of sunlight, which promotes ROS generations such as superoxide, hydroxyl radicals, and hydrogen peroxide.⁷⁸

TiO₂-NPs (nanotubes) have also been proposed as a potential disinfectant to prevent SARS-CoV-2. Even at low concentrations, TiO₂-NPs can demonstrate antiviral activity, as depicted by recent *in vitro* studies.^{79,80} TiO₂-NPs under ultraviolet (UV) light produce a strong oxidative effect and utilizing the property can be used as a photocatalytic disinfectant.⁸¹ TiO₂-NPs activate during the photocatalytic reaction and generate hydrogen peroxide and hydroxyl radicals, thus reducing glycosylation of the main protease of the virus.

In a recent preprinted article published by *bioRxiv*, it has been claimed that copper surface can also be an effective tool for the prevention of SARS-CoV-2. It was shown that Hu-CoV-229E has been deactivated within 10 min of application due to the involvement of the Cu surface.⁸² The use of copper NPs as a potential disinfectant has also been observed for SARS-CoV, influenza, HIV, and other respiratory viruses by inhibiting the replication and propagation abilities from many previous studies.⁸³ The U.S. Environmental Protection Agency (EPA) has already suggested specific long-term effectiveness against CoV-2, but it does not replace standard infection control practices.⁸⁴

Silver NPs (AgNPs) have been assumed to be potential nanobiocides and fighters against SARS-CoV-2.⁸⁵ One of the important reasons why AgNPs have interested researchers is that they are not likely to be noncytotoxic in oral and dermal exposure at a dose of 2000 mg/kg in the rat model. AgNP's main functionality is preventing the binding between host cell and main protease, probably by destroying the active sites of viruses.⁸⁶ Jeremiah et al. found that AgNPs with a diameter of 2–15 nm can inhibit extracellular SARS-CoV-2 within 1 and 10 ppm concentrations.⁸⁷

Surgical and common masks, impregnated with antiviral NPs, can be an effective approach in the prevention of SARS-CoV-2. When NPs are embedded in the mask fibers, NPs can interact directly with viruses that come in contact with the mask.⁷³ Silver (Ag), a potential NP, was found in the literature to be effective in mask modifications for its antimicrobial potentialities. It is shown in a recently published article that rather than the formation of a thick NPs coating (which negatively impacts the comfort of breathing like N95), highly dispersed spherical 5–13 nm AgNPs impregnated to textile fiber mask provide significant improvement against SARS-CoV-2 and other secondary infection-causing agents.⁸⁸ The study has already been patented by the Mexican (part of the patent application No.

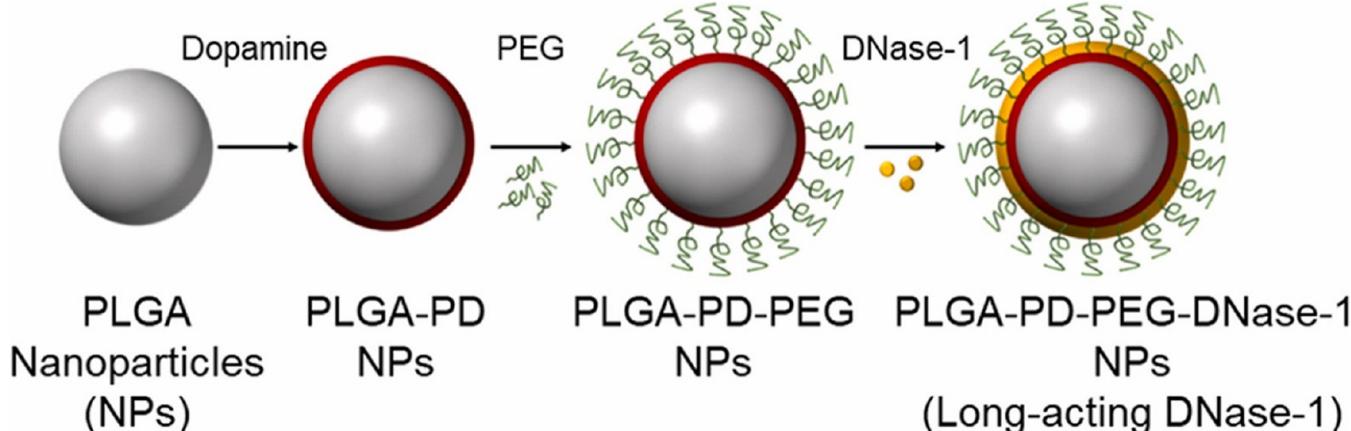


Figure 9. Preparation of long-acting nanoparticulate DNase-1. Reproduced with permission from ref 97. Copyright 2021 Elsevier.

10202002135U) patent office, although the application of NPs-impregnated masks needs further evaluations by several agencies before commercial manufacturing.⁸⁹

Graphene (G) and graphene-oxide (GO) have potentialities to interact and bind with microorganisms (including RNA and DNA) providing an opportunity to develop antimicrobial surfaces as well as personal protective items (PPE) during SARS-CoV-2.⁷³ Maio et al. showed that G/GO-functionalized polyurethane or cotton can reduce the viral load of SARS-CoV-2 by nearly 97 to 99%.⁹⁰ These NPs-based virus trapping methods can also apply to water filtration, air purification technology, etc.

Many NPs show photothermal or photoactive potentials that can be utilized for self-cleaning and reusable PPEs. NPs-embedded masks can be reusable and self-sterilizable without harming the fabric quality. Hybrid nanocoating of shellac/Cu NPs can be activated by solar or external lights that rise in temperature up to 70 °C.⁷⁴ Poly (methyl methacrylate) (PMMA) nanofibers decorated with ZnO nanorods and Ag nanoparticles (with average diameter 450 nm) in PPE have photosensitizing potentiality that provides the PPE self-cleanability and reusability by denaturing viruses and other pathogens.⁹¹ The graphene-coated mask can quickly rise to a temperature over 80 °C under sunlight illumination, which ensures reuse or is recycled for PPE during the pandemic times.⁹²

Apart from metallic NPs, organic NPs are effective in many pathogenic inhibitions including SARS-CoV-2. Quaternary benzophenone-based ester and quaternary benzophenone-based amide cross-link on other surfaces upon UV irradiation. Such coating is effective against variations of influenza virus, probably due to hydrolytic degradation with 100% killing efficacy.⁹³ Although the study did not include anything about SARS-CoV-2, this study can be used to control fomites in hospital settings and PPE to impart self-sterilizing properties.

3.2. NP-Based Therapeutics Development Approach to Combat SARS-CoV-2. Nanoparticle-based antiviral therapy has been assessed by many researchers and also has few clinical applications. The viral infection process propagates simply by four steps: cellular attachment, cell penetration, viral replication, and budding. Nanoparticle serves both the purpose of antiviral and inhibitory effect by blocking or suppressing any of these pathways.^{94–96} Lu Chen et al. mentioned a list of 13 nanoparticles and their typical viral inhibitory pathways.³ Inhibiting attachment at early stages, inactivating virus, inhibiting attachment, shield attachment and penetration,

reducing the amount of progeny of viral load, blocking viral RNA synthesis, oxidation of viral protein, degradation of the viral genome, and promoting the expression of cytokines are the antiviral events of NPs mentioned by Lu Chen et al.

SARS-CoV-2 arises just more than 18 months and it is quite unexpected that NPs-based therapy has gone a long way. As per NCBI PubMed search, we have found 130 articles regarding nanoparticle-based antiviral applications against SARS-CoV-2. Until now, there is no FDA-approved NPs-based drug that could be used confidently in the case of SARS-CoV-2.

Intravenous administration of deoxyribonuclease (DNase-1) coated polydopamine-poly (ethylene glycol) nanoparticulate can be a weapon for severely infected patients (Figure 9).⁹⁷ One of the major reasons for SARS-CoV-2 (also at sepsis disease) induced death is severe cytokine storm and uncontrolled inflammatory innate immune responses. Neutrophil extracellular traps (NETs) exhibit antimicrobial activity by capturing pathogenic microbes (i.e., virus, bacteria, fungi, etc.) and preventing their growth and spread by blocking/inactivating pathways. The NETs formation process by NETOSIS may cause local or systematic tissue damage. It has been almost well established that the NETOSIS factor (cell-free DNA, myeloperoxidase, and neutrophil elastase) might increase among the patient infected with SARS-CoV-2 and this hyperinflammatory event is responsible for organ damage and multiple organ failure.⁹⁷ Because of a shorter half-life, polymer-coated DNase-1 has been developed for NETOSIS factor inhibition. DNase-1 inhibited NF-κB activation and cytokine levels, which prevented organ damage or complexity of the patients.⁹⁷

TiO₂ supported single-atom enzyme (SAN) where Ag atoms are atomically dispersed (Ag-TiO₂ SAN) has been proven to be important with regard to direct interaction with the main protease of CoV-2. The receptor-binding domain (RBD), spike 1 protein of SARS-CoV-2 interacts with Ag-TiO₂ SAN. NPs-mediated peroxidase-like activity produces ROS, and SAN/virus complex is typically phagocytosed by macrophages and colocalized with lysosomes. From in vitro assessment, it was found that the ability of SARS-CoV-2 spike protein-1-RBD binds to hACE2 is significantly inhibited by Ag-TiO₂ SAN. Additionally, from in vivo experiment, it was found that serum proteins were negligibly impacted by the antiviral activities of Ag-TiO₂ SAN. It was hypothesized that Ag-TiO₂ SAN adsorbed in SARS-CoV-2 spike protein-1-RBD inhibited cell attachment via hACE2 and protected host cell from SARS-CoV-2 infections.⁹⁸ Although the study has many limitations in terms

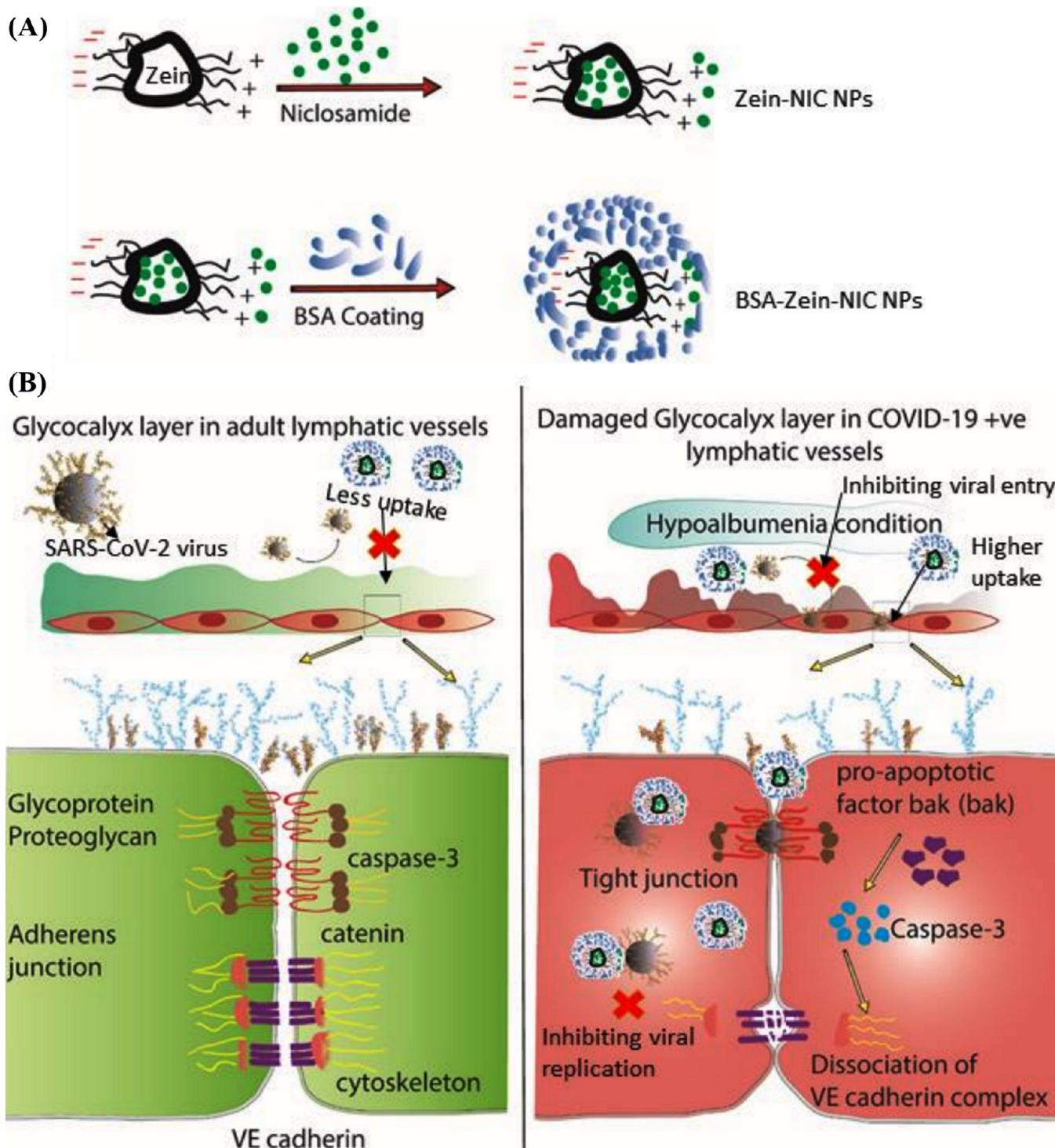


Figure 10. (A) Synthetic strategy of injectable NIC formulation with Zein and BSA; (B) proposal for how the injectable NIC formulation could be useful for treating COVID-19 patients with a damaged glycocalyx followed by a cytokine storm. Reproduced from ref 115. Copyright 2021 MDPI.

of the biological impact of Ag-TiO₂ SAN over mammalian cells, physiological parameters, biochemical and metabolic assay, etc. still it can be a hope for the best.

Morita et al. conducted an experiment about the antiviral tendency of AgNPs over SARS-CoV-2. However, the study merely did not claim about antiviral therapy but rather focused on AgNPs-based antiviral applications like protecting masks, sand sanitizer, disinfectant spray, etc. The study was focused on nanosized silver (2 to 15 nm at 2 ppm concentration)-treated

SARS-CoV-2 and cytotoxic assessment on the cell lines VeroE6/TMPRSS2 (nonhuman origin) and Calu-3 (human lung epithelial cell). All the studies (virus pretreatment by AgNPs, cell pretreatment by AgNPs, and cell post-treatment by AgNPs) were found to be positive compared to control studies. The authors hypothesized from previous studies that AgNPs exhibit an antiviral effect on SARS-CoV-2 by disrupting the disulfide bonds on the spike protein and ACE2 receptors.⁸⁷ However, the cytotoxic impact of AgNPs over mammalian cells is a challenge

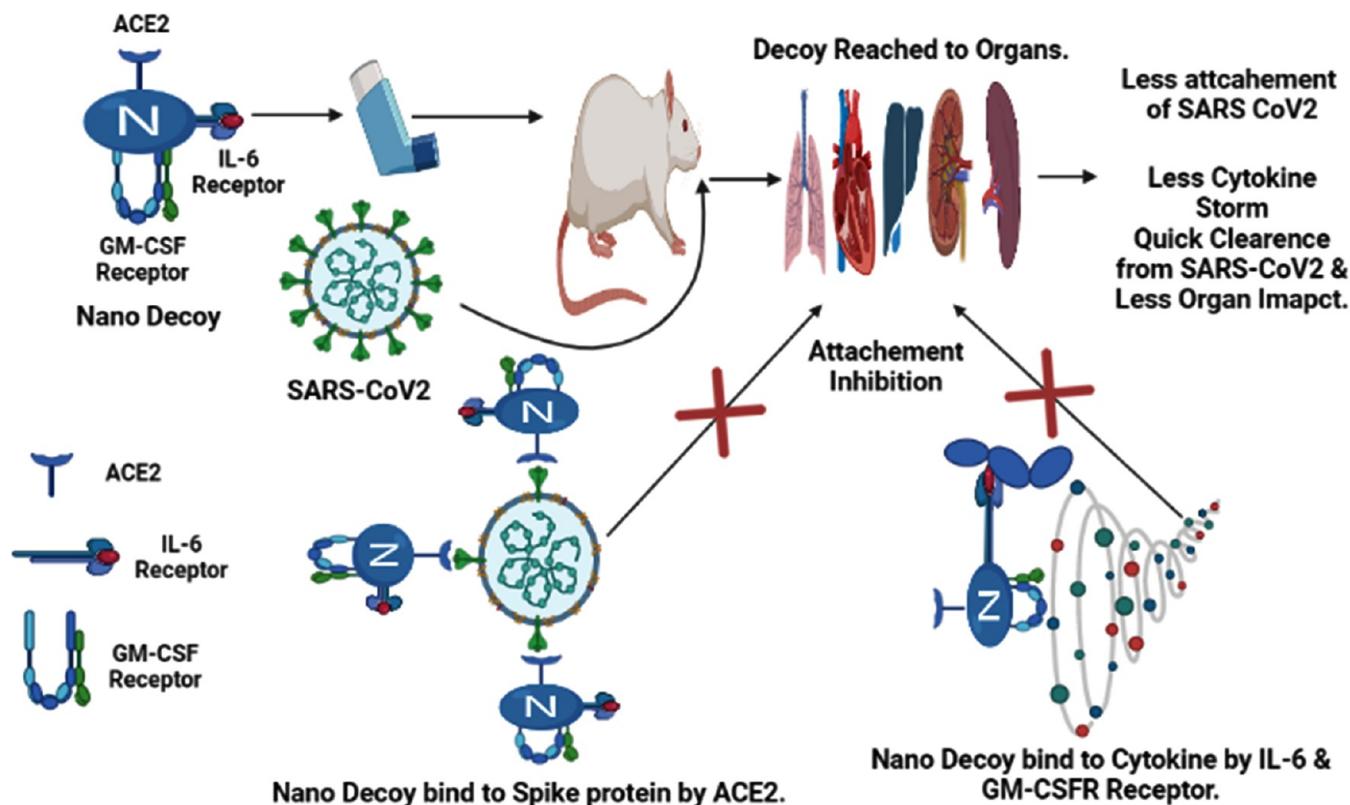


Figure 11. Schematic illustration of nano decoys against COVID-19. Image idea from refs 116 and 117.

for clinical setup, so careful investigation is required before potential applications.⁸⁷

ZnO-based NPs have been researched for antiviral effectiveness against SARS-CoV-2. Zn is an essential element of the physiological system and involves different cellular processes which include but are not limited to enzyme folding and transcription.⁹⁹ However, the concentration of Zn ion in blood serum and the intracellular system is controlled by Metallothionein's, a group of small cysteine-rich proteins that play an important role in metal homeostasis and protection against heavy metal toxicity, oxidative stress, and DNA damage.¹⁰⁰ Excessive levels of Zn²⁺ ion in the metabolic system may trigger apoptosis or a decrease in protein synthesis.^{101,102}

In some previous in vitro studies, it has been observed that Zn²⁺ concentrations higher than usual and compounds that stimulate cellular import of Zn²⁺ (hinokitol, pyrrolidine dithiocarbamate, and pyrithione) inhibit the replication of various RNA viruses (corona virus, influenza virus, respiratory syncytial virus, picornaviruses, arterivirus) by blocking RNA polymerase enzymes.^{100,103}

One study indicates that Hesperidin (found in many fruit peels) could be a potential antiviral to target the interaction site between SARS-CoV-2 Spike and ACE2 receptors, preventing infection of lung cells.^{104,105} Another study indicates that Hesperidin-mediated ZnO NPs (25 nm) exhibit antiviral activity against SARS-CoV-2 like RNA virus (Hepatitis A) more than hesperidin alone at maximum noncytotoxic concentration.¹⁰⁵ Merkl p. et al. experimented antiviral effectiveness of silver, copper oxide, and zinc oxide nanoparticle coatings in surface modifications to control the spreading of SARS-CoV-2. Nano silver and copper oxide performed well than ZnO nanocoatings.¹⁰⁵ Until now, we do not find any direct studies that ZnO can be a promising therapeutic antiviral against

Sars-CoV-2, but it has some promising possibilities in disinfectant and surface modification to prevent the spread of SARS-CoV-2.

Niclosamide (NIC), an older anthelmintic drug, has been shown to affect antiviral effects on acute respiratory syndrome coronavirus (SARS-CoV), Middle East respiratory syndrome coronavirus (MERS-CoV), Zika virus (ZIKV), Japanese encephalitis virus (JEV), hepatitis C virus (HCV), Ebola virus (EBOV), human rhinoviruses (HRVs), Chikungunya virus (CHIKV), human adenovirus (HAdV), and Epstein–Barr virus (EBV).¹⁰⁶ NIC can exert an antiviral mechanism through extracellular pathways by interfering with the human angiotensin-converting enzyme-2 (h-ACE2) by which the SARS-CoV-2 virus enters the cells. In the case of intracellular pathways, NIC can function in different ways: (i) blocking endocytosis, which leads to autophagy alteration, and (ii) blocking syncytia, leading to 16F protein suppression.¹⁰⁷

One of the major challenges to using these potential antiviral drugs is poor oral bioavailability due to its poor aqueous solubility.¹⁰⁸ Various physical and chemical modifications have been proposed to increase the oral bioavailability mostly by inorganic montmorillonite, dehydrated talc, and chitosan.^{108–110} The markers of SARS-CoV-2 infection are multifarious such as C-reactive protein, increased plasma concentrations of IL-6 and IL1- β , and increased lipid peroxidation and glycocalyx, D-dimer, neutrophilia, ferritin, lymphopenia, pulmonary intravascular coagulopathy, and microthrombi of alveolar capillaries.^{111,112} It has been assumed that extreme cytokine production and ROS generation associated with COVID-19 lead to endothelial glycocalyx degradation.^{113,114} Anti SARS-CoV-2, parenteral formulation of NIC for fast delivery to blood, has been proposed by Sanjo et al. (Figure 10).¹¹⁵ The formulations are developed by conjugations of Zein (a group of alcohol-soluble maize

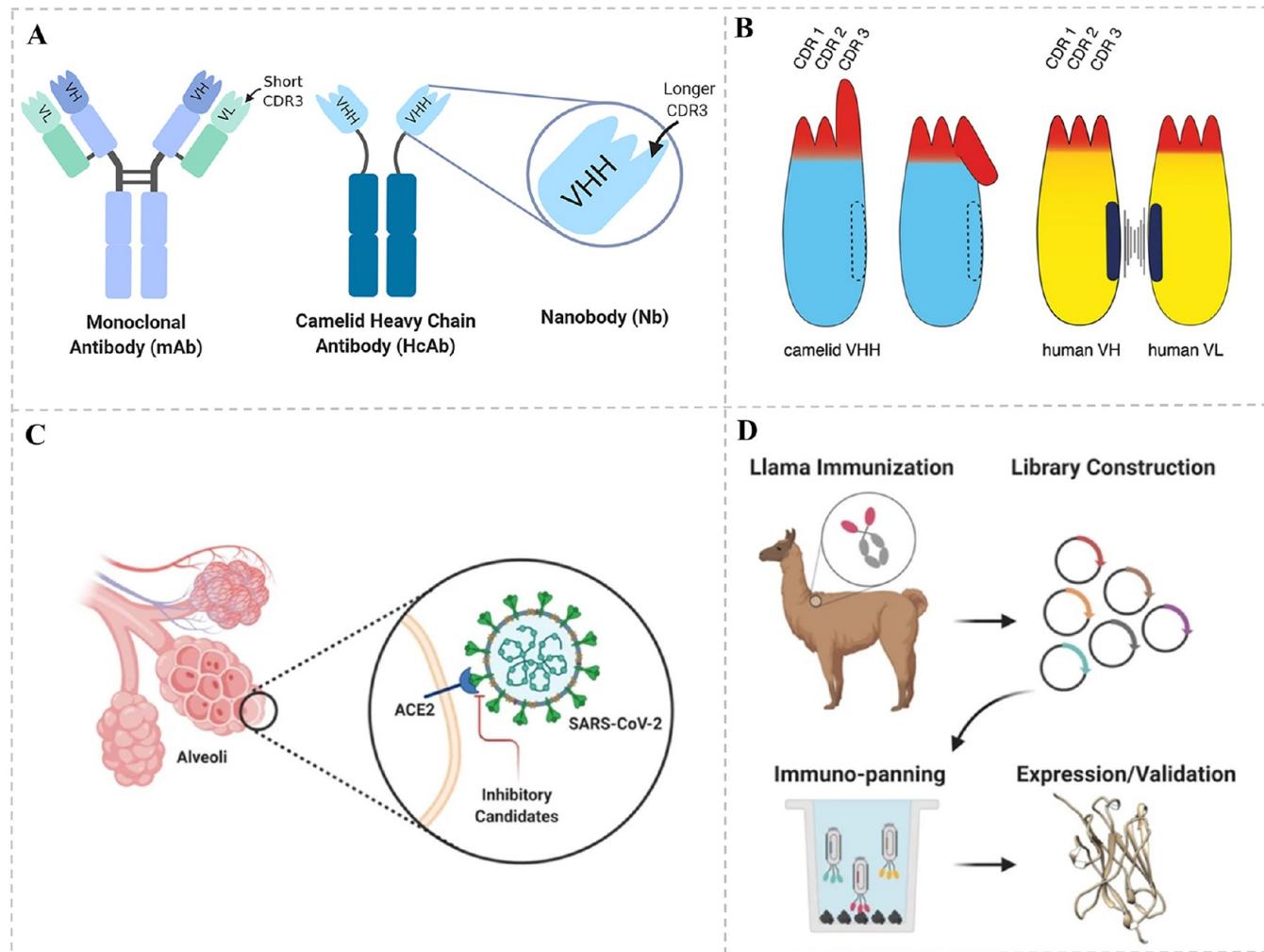


Figure 12. (A) Structure of nanobodies. Reproduced from ref 119. Copyright 2020 Frontiers. (B) Complementary determining regions of mABs and NBs. Reproduced from ref 120. Copyright 2020 Frontiers. (C) Illustration of the structure of SARS-CoV-2 spike protein, with RBD in contact with the human ACE2 receptor on the surface of a lung epithelial cell. (D) Isolation of nanobodies binding SARS-CoV-2 spike protein. Reproduced from ref 121. Copyright 2020 Nature.

proteins) and bovine serum albumin (BSA). Zein shell undergoes swelling and BSA molecules became negatively charged in an aqueous solution, nanohybrid matrix of Zein-BSA can make NIC much more suitable for intracellular drug delivery in parenteral form for a longer time at a sustained control rate. As per the reports, the conjugated NPs size: Zein-NIC hybrid was optimized with 173 ± 4.5 nm, and BSA-Zein-NIC was determined to be 207 ± 3.6 nm, and both are spherical in morphology. Here, the Zein-NIC colloids were stabilized by BSA coatings and satisfactory water solubility was found before and after the freeze-drying process. The polydispersity index (PDI) indicates (PDI values <0.05 , monodispersed, while values >0.7 , polydisperse) that injectable formulations should be more suitable for BSA-Zein-NIC NPs (PDI values: 0.032 ± 0.005) compared to Zein-NIC (PDI values: 0.314 ± 0.013) and NIC NPs (PDI values: 0.385 ± 0.026). BSA-Zein-NIC NPs showed a comparatively high NIC release in serum media than NIC alone or Zein-NIC conjugates.¹¹⁵ However, this study requires many more to go (i.e., *in vivo* and clinical trials), as these nanoformulations can be hoped as a future antiviral drug in the upcoming days.¹¹⁵

3.3. Nanobioformulated Drugs to Combat SARS-CoV-2.

Nano decoys derived from human lung spheroid cells (LSCs)

or fusing cell nanovesicles derived from genetically engineered cells expressed ACE2 and human monocytes are effective in SARS-CoV-2 management.¹¹⁶ The application of LSCs has been already known for other diseases and is already entered phase 1 clinical trials. Inhaled nano decoys from LSCs contain ACE2 receptor (2.1×10^6 receptors per LSC and 112 receptors per LSC-nano decoy), which neutralize SARS-CoV-2 and prevent the bind of SARS-CoV-2 with the cellular entry in the mouse model and cynomolgus macaques' models.¹¹⁶ Nano decoys had good biodistribution in lungs, heart, liver, spleen, kidney, etc. organs, and biodistribution of nano decoys in various tissues in a mouse model and nonhuman primate has been well established already by inhalation routes.¹¹⁶ LSCs application was not shown to elevate proinflammatory cytokines, but another study by Lang et al. showed that apart from virus capturing, engineered-nano decoys efficiently bind and neutralize inflammatory cytokines including interleukin-6 (IL-6) and granulocyte-macrophage colony-stimulating factor (GM-CSF) that potentially suppress immune disorder and lung injury in an acute pneumonia mouse model.^{116,117} In Figure 11, a schematic representation has been given that how nano decoys are distributed to major organs via inhalations and capture virus via

Table 2. Selective Nanobodies (NbS)-Based Approach to Combat Covid-19

nanobodies	sources of NbS	affinity for RDB (K_d)	target sites	impact	ref
NH-covnb-101 to NIH-covnb-113	llama, B-cell nanobody camelid HcAbs	1 to 5 nm	SARS-CoV-2 RBD	SARS-CoV-2 spike protein neutralization at pseudo typed lentivirus	121
VHH72	camelf HcAbs	39 nm	SARS-CoV-2 RBD	SARS-CoV-2 spike protein neutralization at Human Beta coronavirus	138
Ty1	alpaca-camelfids	50 nm	SARS-CoV-2 RBD	SARS-CoV-2 spike protein neutralization	139
Sysbodies14	synthetic nanobodies	30.7 nm	SARS-CoV-2 RBD	SARS-CoV-2 spike protein neutralization	140
Sb23	synthetic nanobodies	10 nm	SARS-CoV-2 RBD	SARS-CoV-2 spike protein neutralization	141
VHH-Ec fused nanobody	humanized llama antibody VHHS	12.2 to 36.7 nm	SARS-CoV-2 RBD	SARS-CoV-2 spike protein neutralization	142
Nb91-hfc	bactrian camel	54.07 nm	SARS-CoV-2 RBD	SARS-CoV-2 spike protein neutralization at pseudo typed lentivirus in vitro	143
Nb3-hfc	bactrian camel	32.36 nm	SARS-CoV-2 RBD	SARS-CoV-2 spike protein neutralization at pseudo typed lentivirus in vitro	143
H11–H4	llama single-domain	6 nm	SARS-CoV-2 RBD	SARS-CoV-2 spike protein neutralization.	144
H11–D4	llama single-domain	18 nm	SARS-CoV-2 RBD	SARS-CoV-2 spike protein neutralization	144
W25uach	camelid HcAbs	0.3 nm	SARS-CoV-2 RBD	SARS-CoV-2 wildtype and the D614G variant neutralization	145
Nb16–68 and Nb11–59	camelid HcAbs	21.6 to 106 nm	SARS-CoV-2 RBD	SARS-CoV-2 spike protein neutralization with Inhalation potentials	146
mNb6	camelid HcAbs	0.45 nM	SARS-CoV-2 RBD	SARS-CoV-2 spike protein neutralization with inhalation potentials	147
Nb12 and Nb30	nanomouse	below 30 nM	neutralization potency showed at SARS-CoV-2 variants that carry E484 K or N501Y substitutions		136
KAl.ep1	nonimmune library	3.50 nM	SARS-CoV-2 RBD	SARS-CoV-2 spike protein neutralization at pseudo typed lentivirus in vitro	148
K7.19	nonimmune library	3.79 nM	SARS-CoV-2 RBD	SARS-CoV-2 spike protein neutralization at pseudo typed lentivirus in vitro	148
K7.13	nonimmune library	3.97 nM	SARS-CoV-2 RBD	SARS-CoV-2 spike protein neutralization at pseudo typed lentivirus in vitro	148
aRBD-2, aRBD-3, aRBD-5, aRBD-7, aRBD-41, aRBD-42, aRBD-54	hetero-bivalent alpaca nanobodies	2.6 to 113 nM	SARS-CoV-2 RBD	SARS-CoV-2 spike protein neutralization	149
SR31	synthetic nanobodies	5.6 nM	SARS-CoV-2 RBD	SR31 fused to ultrapotent nanobodies to increase their size for longer in vivo half-lives and potently neutralizes SARS-CoV-2	150

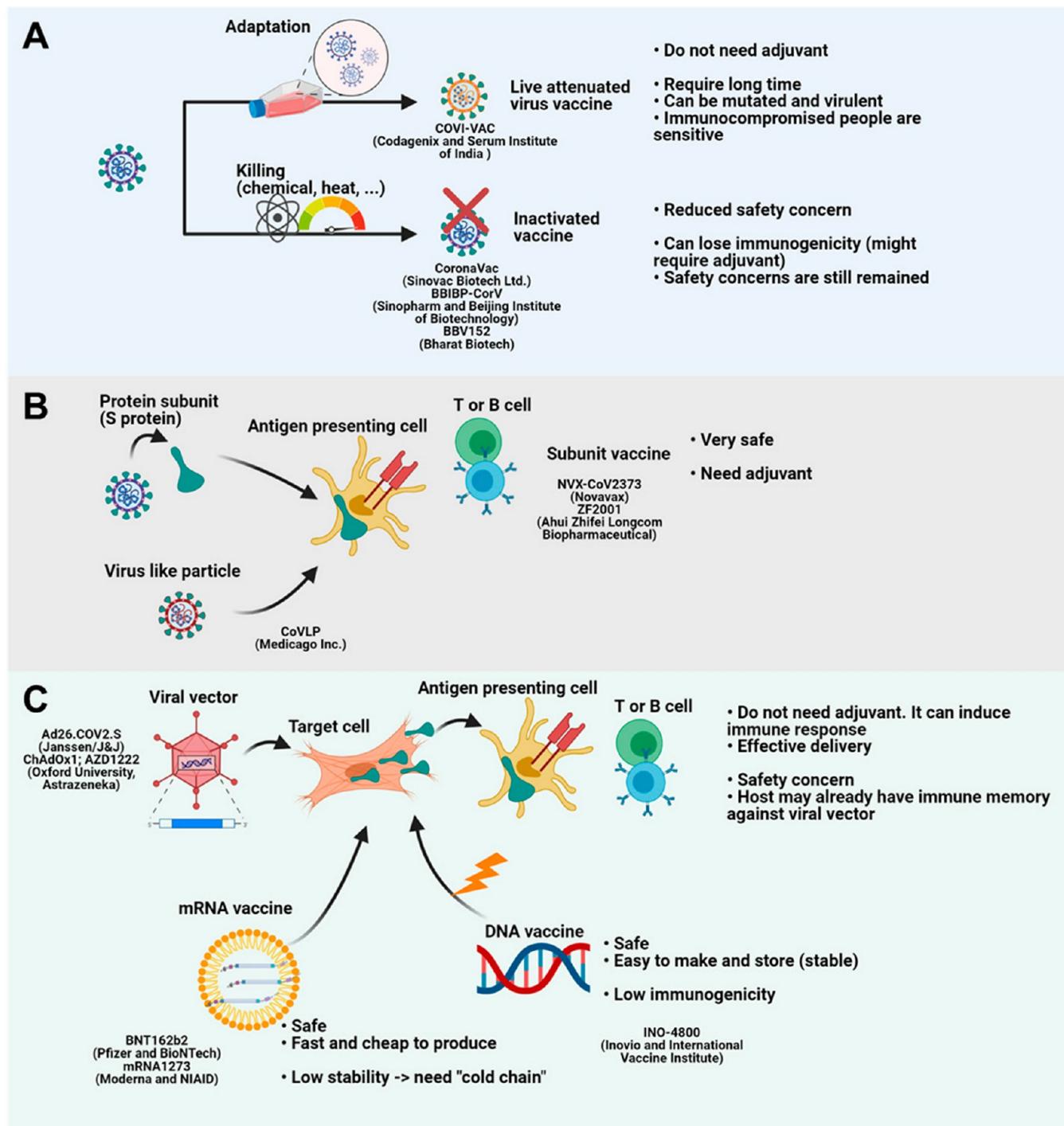


Figure 13. Major COVID-19 vaccines developments strategy: (A) live attenuated vaccination, (B) immune responsive vaccination, and (C) viral vectoral vaccination. Reproduced from ref 158. Copyright 2021 MDPI.

ACE2 receptor and neutralize inflammatory cytokines by relevant receptors present on the surface of decay.^{116,117}

Nanobodies (Nbs) are heavy-chain variable domains of camelids (llamas, alpacas, dromedaries, and camels) and sharks, which have been assessed for SARS-CoV-2 defense. Nbs are considered to be the smallest molecules in nature having intact antigen-binding domains. Nbs are extremely small (12–15 kDa, approximately one-tenth of antibody), low molecular weight, highly stable and soluble, readily penetrable in tissue, easy to produce by biotech, aerosolizable, anti-inflammatory, and antiviricidal in nature.¹¹⁸ In monoclonal antibodies (mAbs),

there are two variable antigen receptor domains: (i) variable heavy chains (VH) and (ii) variable short chains (VL) (Figure 12).^{119–121} In camelids, there is only a single domain variable heavy chain antibody (VHH) completely devoid of light chains and a larger antigen recognition region (CDR3) compared to CDR1 and CDR2 (in human monoclonal antibodies CDR1, CDR2, CDR3 are almost equal).^{122,123} This extended CDR3 loop of VHH provides antibody specificity, high-affinity binding to inaccessible cavity-like epitopes.¹²⁰ Nbs are unique from antibody-based therapy for antiviral applications in many ways.^{118,124} However, human blood plasma-derived monoclonal

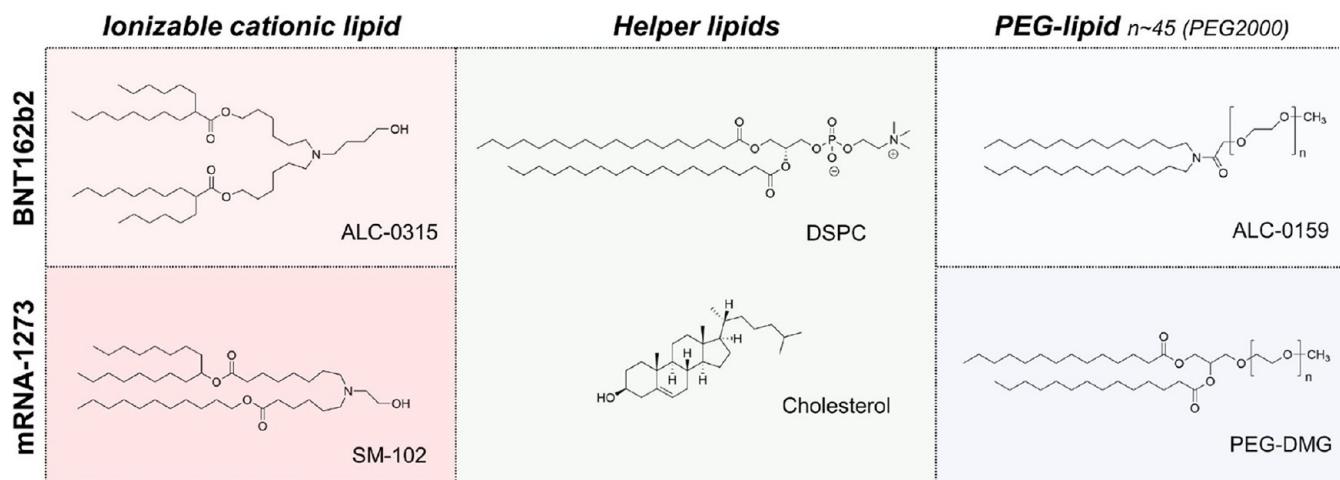


Figure 14. Lipid NPs used in the mRNA-LNP COVID-19 vaccines BNT162b2 and Moderna (mRNA-1273) [ALC-0315, (4-hydroxybutyl) azanediyl) bis(hexane-6,1-diyl) bis(2-hexyldecanoate); DSPC, 1,2-distearoyl-sn-glycero-3-phosphocholine; ALC-0159, 2-[{(polyethylene glycol)-2000}-N,N-ditetradecylacetamide; SM 102, heptadecan-9-yl 8-((2-hydroxyethyl)(6-oxo-6-(undecyloxy)hexyl)amino) octonate; PEG-DMG, 1,2-dimyristoyl-rac-glycero-3-methoxypolyethylene glycol-2000]. Reproduced from ref 155. Copyright 2021 Elsevier.

neutralizing antibodies are effective in terminal staged severely SARS-CoV-2 patients but have severe limitations.¹²⁵ Because of the limited supply of appropriate donors and blood-borne infection risk, Nbs treatment can be a much more convenient option than conventional antibody-based therapy. Moreover, Nbs can be commercially producible on large scale by recombinant bacterial (i.e., *E. coli*) bioprocess technique.¹²⁶ Nbs have been investigated for many viral diseases by targeting active sites of pathogens (mentioned in bracket beside the viruses) like MARS-CoV 9 (RBD), influenza (Hemagglutinin, Neucleoprotein), H1N1 (Hemagglutinin), respiratory syncytial virus (Fusion F protein), Hepatitis B (Capsid protein), HIV (gp120 and gp140), H5N1 (Hemagglutinin, Nuraaminidase), poliovirus (Capsid protein), norovirus (VLps), rotavirus (Vp6 inner capsid protein), chikungunya (VLps), ebola (EBOV GP and EBOV VLps), etc. In relevance, recently approved drug Caplacizumab (developed by Ablynx, a Sanofi company) was the first Nbs-based medicine for adults in November 2018 and in February 2019 for the treatment of thrombotic thrombocytopenic purpura and thrombosis. Two neutralizing antibodies, Lilly's (LY-Cov555) and Regeneron's (REGN-CoV2), have received FDA emergency use authorization for the treatment of COVID-19.

During the SARS-CoV-2 pandemic, Nbs is a promising therapy in many investigations.^{127–131} SARS-CoV-2 spike protein binds the cellular receptor ACE2 and penetrates inside the cellular system by membrane fusion. NAb bind generally to the RBD of the spike protein and made it less favorable for ACE2 binding. Nbs can work in two ways: (i) direct binding with RBD (class I) or (ii) modification of RBD structure conformation (class II). Apart from the direct viral entry inhibition, Nbs can also play an important role in SARS-CoV-2. The major cause of SARS-CoV-2 induced death is acute respiratory distress syndrome (ARDS). ARDS progression is initiated by the release of large amounts of pro-inflammatory cytokines (such as interferons; interleukins; tumor necrosis factor, TNF- α ; transforming growth factor β , TGF β ; etc.; and chemokines) by immune effector cells as a natural defense mechanism. Nbs can also block specific regions on T cells and macrophages, thus preventing ion channel-induced inflammations.

With regard to high-affinity Nbs, Philip et al. identified such Nbs from alpacas immunized with SARS-CoV-2 spike protein and RBD that disrupted RBD engagement with the human ACE2 and neutralized both wild-types SARS-CoV-2 and the N501Y D614G variant at concentrations as low as 0.1 nM. The research team showed that this could potential prophylactic agent against SARS-CoV-2.¹³²

One of the potential applications of Nbs during Covid-19 can be oro-nasal drug delivery.¹³³ The potential route of SARS-CoV-2 transmission is an oro-nasal pathway and the most vulnerable sites are the upper respiratory (UR) and lower respiratory (LR) tracks. Nbs-based nasal formulations can block the pathogen entry by both classes I and class II mechanism in oropharyngeal and alveolar surface.¹³⁴ Moreover, Nbs can also inhibit inflammatory effects on lung surface by immunosuppressant nasal drug delivery. In a recent article, ultrapotent homotrimeric Pittsburgh inhalable Nanobody 21 (PiN-21), a novel aerosol cocktail, is effective in targeting the deep and local pulmonary structures from SARS-CoV-2 infections by blocking viral entry pathways.¹³⁵

Despite several advantages, Nbs cannot be widely used. The major sources of Nbs are camelids origin, which are large mammals, have difficult availability worldwide, and lack of reagents available to isolate antigen-specific memory B cells from immunized camelids.^{136,137} To eliminate this barrier, recently Xu et al. used CRISPR–Cas9 to insert the VHH cassette instead of the VH locus in mouse embryonic stem cells to produce engineered Nbs that neutralize SARS-CoV-2.¹³⁶ Table 2 lists a few more Nbs-based approaches to target SARS-CoV-2.

3.4. NP-Based Vaccine Developments to Combat SARS-CoV-2. As of GAVI–SARS-CoV-2 vaccine alliance (until July 24, 2021), there are 17 vaccines already in application to humans, 105 vaccines are ongoing in various clinical phases, and 184 exist in different preclinical phases.¹⁵¹

Traditional viral vaccines trigger immune responses upon injection of entire viruses, either as attenuated live, inactivated, or engineered viruses, into the body.¹⁵² In the current strategy, as per the New York Times Coronavirus tracker (until second July 2021), most of the leading SARS-CoV-2 defending vaccines are either in the form of mRNA, adenovirus vector, inactivated,

or protein-based.¹⁵³ Among them, mRNA (mRNA)-lipid nanoparticles (LNPs)-based vaccines (developed by Pfizer-BioNTech and Moderna) are becoming the first time hitting for clinical use.¹⁵⁴ However, mRNA vaccines have been studied previously for flu, Zika, rabies, cytomegalovirus, and mRNA-based immune-triggering to target specific cancer cells but not significantly widespread as Covid-19 preventive vaccines.^{155,156} mRNA-LNPs-based therapies have several advantages compared to traditional inactivated or recombinant adenovirus vector vaccines.¹⁵⁷ mRNA delivery is different from conventional DNA/direct organism delivery as mRNA itself is not infectious and has no chance to be integrated into the host genome, whereas DNA needs to be decoded at the nucleus. The major advantages of mRNA vaccines are that they are processed directly in the cytosol, have short half-life, and immunogenicity.¹⁵⁷ The mechanism of the mRNA-LNPs-based covid-19 vaccine is mRNA encodes a disease-specific (Figure 13) antigen by instructing cell for making spike protein of SARS-CoV-2.¹⁵⁸ When an animal is exposed to mRNA vaccines, few mRNAs penetrate inside the cytosol where the translation of the mRNA sequence into the spike protein occurs in the ribosomes. After translation, the antigen could be extracellularly transported where membrane-bound spike protein is recognized as an antigen-presenting cell (APC) by B cells (using antigen recognition pathways where T cells produce neutralizing antibodies).¹⁵⁹ The mRNA from vaccine delivery is highly unstable in physiological media and broken down after a very short time after exposure. These factors are also simultaneously challenging and require stabilization by molecular engineering techniques.^{157,160–163}

Pfizer-BioNTech (BNT162b2) and Moderna (mRNA 1273) both developed mRNA vaccines based on preclinical trials by modified mRNA nucleosides that encode spike glycoprotein of SARS-CoV-2 formulated in LNPs. Although both the companies followed the same philosophy, there are variations in ingredients and developments (Figure 14).¹⁵⁵ This lipid coating prevents premature degradation of mRNA-molecules made of ionizable lipids, which are positively charged at low pH and neutral at physiological pH (7–8). LNPs penetrate inside the cells via endocytosis. The ionizability of the lipids at low pH allows endosomal escape and release of the cargo molecules into the cytoplasm.¹⁶⁴ The function of helper lipids is to promote cell binding and fill the gaps between the lipids. Polyethylene glycol (PEG) at the surface of molecules prevents LNPs from aggregation, reduces opsonization by serum proteins, and reticuloendothelial clearance.¹⁵⁵

Major advantages of mRNA technologies are high scalability, rapid development, and fast manufacturing by appropriate nanoparticles coating.¹⁶⁵ Strong immune response against viral antigens has been observed in mice and Macaques model at the initials phase of studies (Elicit antigen-specific cytotoxic IFN γ CD8 $^{+}$ T cells, T_{FH}, and T_{H1}-type CD4 $^{+}$ T cell responses).¹⁶⁵

On May 10, 2021, the FDA expanded the emergency use authorization for the Pfizer-BioNTech COVID-19 vaccine and second most approved (111 countries) vaccine in the world.¹⁶⁶ On April 30, 2021, WHO listed the Moderna vaccine for emergency use and FDA also gave consent for emergency use only.^{167,168}

The major challenges associated with LNPs-mRNA-based vaccine are its instability and ultralow temperature preservations. As per the CDC, mRNA COVID-19 vaccines of mRNA 1273 and BNT 1262b have to be stored between -15 and -50 °C and between -60 and -80 °C, respectively.¹⁶⁹ The reason

behind the ultralow preservations can be explained by chemical and physical degradability, although the reason has not been fully understood. Adding excipients for stable chemical environments, stabilizing mRNA against hydrolysis, and lyophilizing can be the future to eliminate the existing limitations, proposed in different kinds of literature.^{155,170,171}

We have found that a significant amount of preclinical research is being conducted to develop SARS-CoV-2 LNPs-mRNA or LNPs formulated recombinant spike protein/virus-like particle-based vaccines. Translate Bio/Sanofi Pasteur, CanSino Biologics/Precision Nano Systems (China/Canada), Fudan University/Shanghai JiaoTong University/RNAcure Biopharma (China), University of Tokyo/Daiichi-Sankyo (Japan), BIOCAD (Russia) are trying to develop a LNPs-mRNA-based vaccine, whereas St. Petersburg Scientific Research Institute of Vaccines and Serums (Russia), Fudan University/Shanghai JiaoTong University/RNAcure Biopharma (China), and IMV, Inc. (Canada) are focusing on LNPs formulated with peptides epitopes from SARS-CoV-2 S protein.¹⁵⁹ Engineered virus-like nanoparticles (VLPs) can be used as a scaffold for heterologous antigen display because VLP has many similarities with natural viruses in terms of size and geometry (Figure 13).¹⁷² A biotinylated variant of the SARS-CoV-2 S protein conjugated by RNA bacteriophage MS2 (icosahedral sphere of 30 nm in diameter MS2 bacteriophage-streptavidin VLP) is a highly effective vaccine that protects Syrian hamsters against SARS-CoV-2 after a single immunization by producing neutralizing antibodies.¹⁷³ VLPs vaccine is mainly made by coated proteins that are self-assembled repetitive dense arrays of antigen, comparable to the size and geometry of natural viruses.¹⁷⁴ Chiba et al. explained how the experiment was done: VLPs have been coated with streptavidin for biotinylated antigens of SARS-CoV-2S protein (biotinylated protein shows strong affinity with streptavidin) display. To make a biotinylated variant of the SARS-CoV-2 S protein, a plasmid-encoded stabilized prefusion of S ectodomain with a C-terminal AviTag and a his-tag, (termed as S_{2Pro}) and more stable S_{6Pro} has been developed. Purified MS2-SA VLPs (30–50 nm diameter size measured by dynamic light scattering and NS-TEM) have been mixed with biotinylated S_{2Pro}/S_{6Pro} protein and converted to VLP-S_{2Pro} (~18 S_{2Pro} molecules/VLP and ~20 nm layer of a spike-containing protein shell) and VLP-S_{6Pro} (icosahedral sphere 30 nm in diameter). Enzyme linked immunosorbent assay (ELISA) experiments showed that both angiotensin-converting enzyme 2 fusion protein (ACE2-Fc) and RBD-binding monoclonal antibody CR3022 can bind to the S_{2Pro}/S_{6Pro} protein alone and VLP-S_{2Pro}/VLP-S_{6Pro}. Hamsters immunized with VLP-S_{2Pro} or VLP-S_{6Pro} have been infected with SARS-CoV-2 after 28 days and sacrificed after 3 days. Swab collection from Nasal turbinates shows that less virus presence with 150-fold lower (VLP-S_{2Pro}) and more than 700-fold lower (VLP-S_{6Pro}) relative to control group.¹⁷³ Novavax, an American biotechnology company, developed NVX-CoV2373S, a combined subunit and VLPs SARS-CoV-2S vaccine (27.2 nm thermostable nanoparticles with high-affinity toACE2) with saponin-based Matrix-M adjuvant has already been proven for eliciting B- and T-cell responses, ACE2-receptor-blocking antibodies, and SARS-CoV-2-neutralizing antibodies among nonhuman primates, also already in phase 3 clinical trials.^{175,176} Similar type vaccine development is ongoing by Ufovax, LLC (United States), with VLE with similar features of SARS-CoV-2 S protein protruding from a protein NP scaffold.¹⁵⁹

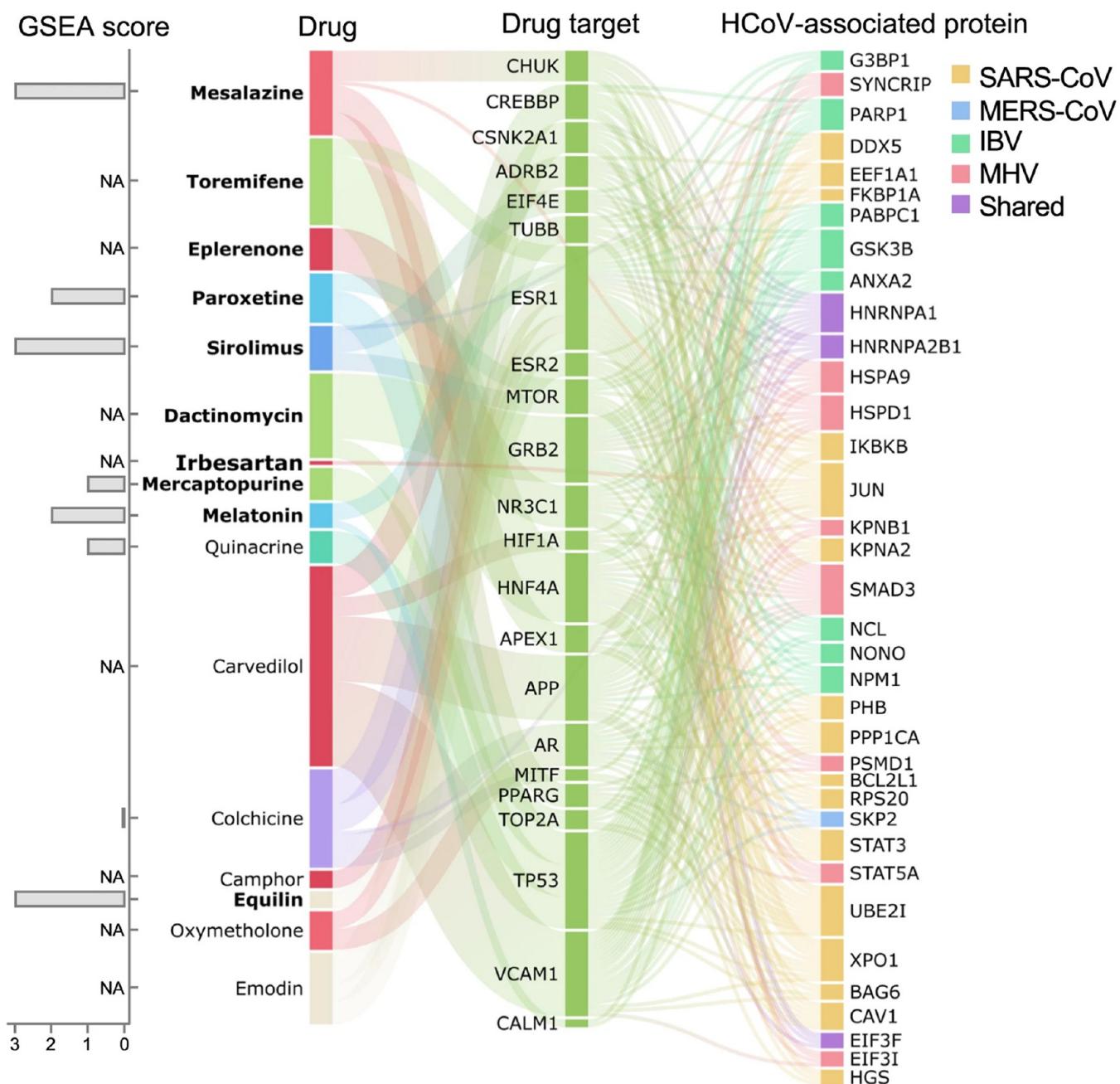


Figure 15. Scores from network-predicted evidence and gene set enrichment analysis (GSEA) for 16 potential SARS-CoV-2 repurposable drugs. Reproduced from ref 185. Copyright 2020 Nature.

Four categories of S-domain ferritin nanoparticles, stabilized S-trimer-ferritin nanoparticles (SpFN), RBD-ferritin nanoparticles (RFN), S1-ferritin nanoparticles, and RBD-NTD-ferritin nanoparticles, have been assessed for elicit antibodies with potent S-binding activity, hACE2-blocking activity, and potent neutralization activity against the homologous virus.¹⁷⁷ The passive transfer of vaccine-elicited purified antibody prevented death and significant weight loss in a high-dose SARS-CoV-2 challenge in the K18-hACE2 mouse model.¹⁷⁷ Part of these studies has been where SpFN adjuvanted with AFLQS21 (Army liposome formulations) have entered phase one clinical trials.¹⁷⁸

4. PROSPECTS OF NANO-BIOMED TECHNOLOGY FOR MUTATING SARS-COV-2

COVID-19 induced pneumonia is likely to be associated with hyperinflammation due to severe cytokine storms.^{179–182} Elevated levels of IL-6, C-reactive protein (CRP), d-dimer, and ferritin are major indications of systemic inflammation and hypoxic respiratory failure among the COVID-19 patients.¹⁷⁹ As per NIH (National Institute of Health, USA), several immunomodulatory and anti-inflammatory agents like Baricitinib, Dexamethasone, Prednisone, Methylprednisolone, and Hydrocortisone have been recommended for the potential treatment approach.¹⁸³ Humanized monoclonal antibody-based, interferons or biosimilar therapies for inhibiting or blocking several cytokine/inflammatory pathways like GM-CSF blocker (Lenzilumab, Mavrilimumab, Otilimab), IL-1 receptor

Table 3. Nanoformulations Evidence and Current Role of Repurposable Drugs of Network Predicted Analysis¹⁸⁵

drug candidate	evidence of nanobased formulations for improving drug efficacy	reasons for using in SARS-CoV-2
Toremifene	PLGA–PEG nanoparticles encapsulating toremifene enhanced tumor necrosis greater than toremifene alone. ¹⁸⁶	Toremifene can treat COVID-19 by blocking the Spike glycoprotein and NSP14 of SARS-CoV-2. ¹⁸⁷ Toremifene, a first-generation nonsteroidal selective estrogen receptor modulator (SERMs), exhibits potential effects in blocking various viral infections, including MERS-CoV, SARS-CoV, and ebola virus in established cell lines. ^{188,189}
Paroxetine	Intranasal delivery of paroxetine suspension ($58.47 \pm 3.02) prepared by nanoemulsions.190$	Antidepressant Paroxetine may be associated with decreased plasma levels of inflammatory mediators, including IL-10, TNF- α , and CCL-2. ¹⁹¹
Sirolimus/Rapamycin/ Dactinomycin/ Actinomycin D	Rapamycin-loaded NPs (108 ± 2.3 nm) decrease in proliferating macrophage population by the reduction of key proinflammatory cytokines in mice model. ¹⁹²	Rapamycin can be a potential hope as (mTOR) inhibitor in the treatment of SARS-CoV-2 that can effectively block viral protein expression and virion release. ^{193,194}
Irbesartan	Dactinomycin nanosuspension, shown to inhibit transcription, has been researched for a long time as an effective chemo-therapeutics. ^{195–197}	Dactinomycin in association with rapamycin may inhibit DNA topoisomerase required for RNA synthesis as well as mammalian target of rapamycin (mTOR) signaling in human coronavirus infected cells. ¹⁹⁸
	Ultrasonic sonication of Irbesartan for improved dissolution rate found in the literature. ¹⁹⁹	Irbesartan targets SLC10A1, encoding the sodium/bile acid cotransporter (NTCP), thus inhibiting viral entry. ²⁰⁰
Mercaptopurine	Nanocrystalline suspension of Irbesartan by high shear homogenization. ²⁰⁰	Although this controversial angiotensin-receptor blocker (ARBs) was assessed for SARS-CoV-2 that can upregulate ACE2 expression found in animal studies. ^{203–205} Although in a recent study, it is safe and does not raise ACE2. ²⁰⁶
Melatonin	Solid lipid nanoparticles of Irbesartan by glyceryl monostearate and solvent emulsification. ²⁰¹	Mercaptopurine has been reported as a selective inhibitor of both SARS-CoV and MERS-CoV by targeting papain-like protease, which plays key roles in viral maturation and antagonism to interferon stimulation. ²⁰⁷
Quinacrine	6-Mercaptopurine-chitosan nanoparticles (6-MP-CNPs) in vitro anticancer activities on HT-1080 and MCF-7 cells and in vivo pharmacokinetics showed improved bioavailability.	As an anti-inflammatory, immunomodulatory, and protective antioxidant which protects against cellular oxidative damage. Melatonin has been proposed for early COVID-19 treatment. ^{210–213}
Carvedilol	Melatonin-loaded nanoparticles by nanoprecipitation (Eudragit S100 as a polymer) and Melatonin Loaded Chitosan-Tripolyphosphate NPs showed improvement in the bioavailability. ^{208,209}	Quinacrine is antiviral by inhibitions of RNA virus replication, has been assessed for SARS-CoV-2 treatment. ^{216,217}
Emodin	Nanoformulated Quinacrine can inhibit the process of endoand ectodomain NECTIN-4 activities during cancer progression and lowers the amount of doses. ^{214,215}	Carvedilol is an exceptional ACE inhibitor that decreases the expression of ACE. ²²¹ It has also IL-6 suppressing properties which can be a potential agent to defend SARS-CoV-2. ^{222,223}
	Carvedilol-loaded nanosuspension is effective for improved bioavailability and lowering drug doses. ^{218–220}	Emodin, an anthraquinone compound blocked the S protein and ACE2 interaction. ²²⁶
	The emodin nanoparticles were prepared by emodin and gelatin–cyclodextrin which was synthesized as a drug carrier, and the nanoparticles were 174 nm in size. ²²⁴ Aloë-emodin (AE) loaded solid lipid nanoparticles (SLNs) showed significantly higher in vitro cytotoxicity against human breast cancer MCF-7 cells and human hepatoma HepG2 cells. ²²⁵	

Table 4. NP-Based Platforms for Advanced Rapid Detection of SARS-CoV-2

detection method	materials and functions	impacts	ref
CRISPR/Cas12a-based	sequence-dependent aggregation of GNPs (200 nm) by colorimetric assay	visual detection of the N gene and E gene of SARS-CoV-2 within 45 min	235
nucleic acid-based	GNPs-based plasmonic photothermal biosensors	gold nano islands (GNIs) functionalized with complementary DNA receptors detect selected sequences of SARS-CoV-2 through nucleic acid hybridization	236
nucleic acid-based	graphene and gold nanoparticles conjugates citrate or antisense oligonucleotides	rapid, accurate, selective, and ultrasensitive detection of SARS-CoV-2 viral RNA within less than 5 min	237
nucleic acid-based	monodisperse silica microspheres	the electrochemical detection method enabled the detection of the viral N and S genes	238
PCR coupled spherical nucleic acid-based	linker-based single-component assembly of gold nanoparticle-core spherical nucleic acids. (AuNP-core SNAs)	the positive and negative viral COVID-19 samples are simply distinguished via different colors by naked eyes	239
CRISPR–Cas12a-based	nanoscale liposomes (100 nm)	detection of extracellular vesicles derived SARS-CoV-2 RNA in blood	240
nanophotonic biosensors	silicon nitride (Si_3N_4) waveguide covered with a silicon oxide (SiO_2) layer	identification of the SARS-CoV-2 virus in a few minutes and decentralized settings	241
CRISPR/Cas9 mediated lateral flow assay	GNPs	simultaneous dual gene analysis of SARS-CoV-2 for more accurate and rapid detections	242

antagonist (Anakinra), IL-6 inhibitors (Sarilumab, Tocilizumab, Siltuximab), kinase-inhibitors (Acalabrutinib, Ibrutinib, Zanubrutinib, Baricitinib, Ruxolitinib, Tofacitinib), TNF- α and IFN- γ blocker have also been shown to be effective among the hospitalized patient with COVID-19 pneumonia.¹⁸⁴ Nanoformulations or modifications of existing drugs (repurposing and modifications) for better bioavailability or targeted therapy to defend COVID-19 can be a potential utilization of existing resources.¹⁸⁵ In an earlier report on the advent of pandemics, Yadi et al. proposed 16 drugs as repurposable (Figure 15) drugs for targeting 2019-nCoV/SARS-CoV-2.¹⁸⁵ Most of the drugs have been assessed previously for nanobased formulations to improve efficacy and bioavailability for other diseases. In the following tables, a few selected previous nanoformulations examples and the current role of the following drugs to defend SARS-CoV-2 have been presented. These nanoformulations can be an example of how similar modifications can also play a significant role in SARS-CoV-2 treatment in upcoming days due to the emergence of several mutations. In Table 3, nanoformulations evidence and current role of repurposable drugs of network predicted analysis by Zhou et al. to combat COVID-19 in upcoming days have been expressed.

Clustered regularly interspaced short palindromic repeats (CRISPR) have offered a potential pathway for rapid detections and treatment of SARS-CoV-2.^{227–231} CRISPR is a part of the natural defense of prokaryotic organisms such as bacteria and archaea that play an antiviral role in the detection and destruction of viral bacteriophages; the functions of CRISPR are mostly like a pair of molecular scissors that can cut DNA strands and stop functioning. The CRISPR-directed detection system can identify viral presence at the shortest possible time with high precision, more effectively and economically. Apart from rt-PCR, q-PCR, rapid antigen, and antibody test, CRISPR-based detection can be a potential tool for SARS-CoV-2 diagnostics.²³² CRISPR-based diagnostics consists of two main elements: (1) Cas protein-guide (i.e., Cas 3, Cas9, Cas12a, Cas12b, Cas13a) RNA sequence and (2) modified nucleic acids used as reporter.^{233,234} Functionalized nucleic acid amplification products (amplicons) detection from the viral RNA is a potential way of SARS-CoV-2 rapid diagnostics but it requires fluorescence microscopy and lateral flow platforms. The NP-based approach can eliminate the existing barrier, which eliminates the requirement of light sources and sophisticated

instruments. Developing NPs induced CRISPR modifications, in on the pipelines, makes it possible for household and rapid detections of SARS-CoV-2. In Table 4, a few more NPs-based technological advancements in progress for the efficient and rapid detection of SARS-CoV-2 have been mentioned.

Apart from the mRNA-based vaccine design, many groups are attempting to develop NPs as adjuvants/nanocarrier in the COVID-19 vaccine.²⁴³ Adjuvants give the vaccine more bioavailability, effective innate immune response, immunomodulation, highly specific antibody productions, and long-lasting adaptive immune responses.²⁴⁴ Aluminum, emulsions, and silica will probably be the most used vaccine adjuvants in history.²⁴⁵ Amino-modified polymeric NPs, iron NPs, GNPs, chitosan, nanoemulsions, liposome, and peptide NPs are being investigated for utilizing SARS-CoV-2 vaccine developments.^{244–248} In a recent article, it was observed that manganese nanoadjuvant (MnARK) shows stronger humoral and cellular responses against SARS-CoV-2 than conventional Alum-adsorbed RBD vaccine.²⁴⁹ Using CRISPR engineering, recombinant bacteriophage T4 containing SARS-CoV-2 fragments (i.e., spike, envelop, nucleocapsid protein) has been shown to produce immunity against SARS-CoV-2 and ACE2 blocking antibodies without using any adjuvants.²⁵⁰ This nanovaccine technology can be a potential hope for rapid vaccine developments within a short possible time against upcoming newer variants of SARS-CoV-2.²⁵⁰

In terms of new variants (such as omicron), some perspective studies and original approaches suggest that there are several open-ended questions currently in the field that need immediate addressing such as the effectiveness of nanomedicines against newer variants, alteration and targeting via different sophisticated mechanisms such as by magnetic fields, and population-based confirmation of nanomedicine-based systems.²⁵¹ Bionanotechnology-assisted approaches, such as smart biocompatible nanomedicine, quick detective validated biomarkers to identify the selective SARS-CoV-2 variant, biomolecular assay system, dual functional photoplasmonic, identical gene sequencing principle, and efficient diagnostic tools could be useful in optimizing the mechanistic structures for the newer variant.²⁵² These newly developed systems have an immense prospect in terms of neutralizing mechanisms against several variations of SARS-CoV-2 such as delta and omicron in terms of trapping, targeting, creating a barrier to transmission to the human

system, and as high-efficiency drug transporters.^{253,254} Furthermore, optimized bioactive compounds, in very recent studies, have shown promising grounds in terms of addressing pre- and post-infection by SARS-CoV-2 from different fronts such as organ-specific and immune stimulatory actions. However, newer systems also should go through stringent approval criteria, as complete recovery from illness and long-term effectiveness of these agents still need multidisciplinary validation in terms of biocompatibility.²⁵⁵

Lastly, one very important aspect of development (along with a specific set of challenges) lies in the implementation of such nanomedicines in point of care testing and personalized medicines.^{256,257} It is important to develop schemes that enable patients' on-site treatment via electrochemical and biosensing, and personalized disease management,²⁵⁸ and in this regard, nanomaterial-based platforms can be a versatile repertoire, as a significant amount of biological samples for development purposes can be employed easily in most cases.²⁵⁹ The future of nanomedicine development to battle such diseases lies in smart technology development and manipulative medicine development for therapeutic purposes, which ensure controlled and confirmed drug release in specific sites and customizable electrochemical and biocompatibility criteria.^{260,261} In short, in this field, multidisciplinary expertise is required to develop smart and versatile technologies, such as smartphone-assisted detection, big data analysis, and bioinformatics, with the expertise and collaboration of structural biologists, nanomedicine experts, data scientists, machine learning algorithm developers, and clinicians.^{257,262}

5. CHALLENGES, CONCLUSION, AND FUTURE DIRECTIONS

NPs are promising for in vitro and small-scale studies in both diagnosis and therapy, but their clinical applications are not readily implementable in many cases. Major obstacles in this regard are economic parameters related to indirect-clinical (diagnostics) applications of NPs. Most NPs are expensive due to their precise synthesis methods and ubiquitous nature. Moreover, many NPs are rarely found in nature. Nanofabricated or nanocoated mask or PPE might be effective in some senses but low-cost production and affordability for mass populations can be a major challenge. The same concept can be equally applicable for detections and rapid identifications kits.

Biocompatibility and biodistribution assessment are among the crucial parameters for nanoformulated drugs to come into clinical applications. Many NPs may not excrete from the human body so quickly, pass through the brain–blood barrier, alter the biological reactions, induce inflammations, generate cellular ROS, and even in some cases cause regulated and unregulated cell death. To rule out the following dilemmas, the usage of NPs in biomedical applications requires close monitoring and vigorous assessment. NPs might be suitable for in vitro assessment in many cases but to validate biocompatibility, biodistribution, and possible side effects, it requires a longer time to come into clinical applications. That is why despite in vitro and in vivo promising studies, regulatory approval is one of the most challenging issues for nanoformulated drugs.

Therefore, we can summarize that while nanomaterial-based systems are of immense prospect on a small and large scale, there are several current and possible future challenges associated with them when the recently developed systems and their effectiveness are considered. The most significant concerns are (a) targeting specific organ and delivery site, (b) ensuring rapid

release and effectiveness in terms of both preventing SARS-CoV-2 transmission and spreading in the system, (c) complete recovery after an application, especially in case of newer variants, and (d) location and demographic-specific effectiveness of the newly developed drugs and vaccines, that is, versatility in terms of biocompatibility in a large spectrum of the population. While ensuring all these parameters and considerations requires a significant number of multidisciplinary studies, a future pathway considering biochemical, nanotechnology, and manufacturing parameters can be proposed as follows:

- (a) Setting an objective of SARS-CoV-2 related studies especially nanomedicine-associated studies with short- and long-term effectiveness.
- (b) Making an effective compromise between biocompatibility and physiochemical characteristics of the drugs.
- (c) Pinpointing nanoagents most significant for biofortification and showing least toxicity issues.
- (d) Establishing a versatile protocol for characterization and scaling up at industry level manufacturing of the nanomedicines.
- (e) Maintaining an interconnected database about variant-specific, demographic-focused effectiveness of newly developed systems.

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Notes

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ABBREVIATIONS

4-ATP, 4-aminothiophenol; ACE2, angiotensin-converting enzyme; Ag, silver; AgNP, silver NP; AMF, alternating magnetic field; ARDS, acute respiratory distress syndrome; ASO, antisense oligonucleotide; BSA, bovine serum albumin; CNT, carbon nanotube; CRISPR, clustered regularly interspaced short palindromic repeats; CSS, cytokine storm syndrome; DNase-1, deoxyribonuclease; EBOV, ebola virus; FET, field-effect transistor mechanism; GM-CSF, granulocyte-macrophage colony-stimulating factor; GNP, gold nanoparticle; GO, graphene-oxide; IFN, interferon; IL-6, interleukin 6; LNP, lipid nanoparticle; LSC, lung spheroid cell; mAbs, monoclonal antibodies; MERS-CoV, Middle East respiratory syndrome coronavirus; MNP, magnetic nanoparticle; N protein, nucleoprotein; Nbs, nanobodies; NET, neutrophil extracellular trap; NIC, niclosamide; PDI, polydispersity index; PEG, polyethylene glycol; PMO, phosphorodiamidate morpholino oligos; PPE, personal protective items; QD, quantum dot; RBD, receptor-binding domain; RNA, ribonucleic acid; ROS, reactive oxygen species; RT-qPCR, reverse transcription-polymerase chain reaction; SAg, spike protein antigen; SAN, single-atom enzyme; SARS-CoV, acute respiratory syndrome coronavirus; SERS, surface-enhanced Raman scattering; SpFN, stabilized S-trimer-ferritin nanoparticle; SWCNT, single-walled carbon nanotube; TNF, tumor necrosis factor; UV, ultraviolet; VHH, variable heavy chain antibody; VLP, virus-like nanoparticle

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