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Bionanomaterials for diagnosis and therapy of SARS-CoV-2

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1. Introduction
1.1 Overview

In December 2019, outbreak of a disease with severe respiratory syndrome and simultaneous death was seen in the Wuhan province of China. It was termed as n-CoV-2 or COVID-19 [1,2]. It is a highly contagious disease with a large basic reproducible value of \((R_0 = 3.77)\), which is much more contagious than Ebola, flu, and earlier found corona virus—related diseases [3]. This disease spreads dangerously breaking the barriers of province or country. It is transmitted worldwide within months. The World Health Organization (WHO) declared it as a Public Health Emergency of International Concern (PHEIC) on February 16, 2020, and alerted every country, but by then, it had spread worldwide and aroused a global pandemic [1,4]. Every country, rich or poor, small or large, tried to take drastic measures to prevent it, but the disease came as a massive blow to our global health and economy, killing 4.29 million lives to date.

Nations worldwide hurried to prevent the spread of this disease through severe lockdowns, thorough travel bans, and rigorous social distancing [5]. The WHO gave the guidelines to wear a mask, frequently wash hands with soap, use sanitizer, and maintain social distancing of at least 6 feet apart in public. Every nation engaged their scientists to urgently discover the genome sequences of the new virus, SARS-CoV-2 or COVID-19, and to elucidate proper medicine after diagnosis of the severe disease [6]. Nations worldwide have also laid key focus on rapid and precise detection of the pathogen in infected patients. Doctors and healthcare workers worldwide are engaged day and night to save the lives of infected patients and have tried to discover a proper line of action to provide a stable healthcare system for this pandemic. Finally, key resources worldwide have been focused on the discovery of a proper vaccine, the definite curative measure to wipe out the pandemic. The discovery of a vaccine for SARS-CoV-2 and its proper
implementation through rigorous human trials is a long-term phenomenon. All scientists, engineers, and doctors across the globe have been actively engaged on this target, and we have made immense progress. Along with the successful discovery of the vaccine, we also have to live our life taking preventive measures, and nanoscience can play a key role in both these aspects. This is because viruses are living nanomaterials.

1.2 Genome study and nature of n-CoV-2 virus

When an epidemic starts, the first task of scientists is to discover the genome structure of the pathogen. Wu et al. have been the first to point out the genome sequence of the new pathogen for this deadly COVID-19 pandemic [7]. Phylogenetic analysis of the viral genome depicts that the virus was closely related to a SARS-like coronavirus or Genus Betacoronavirus, subgenus sarbecoronavirus. These Betacoronaviruses were detected earlier and found in China. Wu. et al. have analyzed the new 29,903 nucleotides viral genome for genome sequences as well as its termini [7]. They have determined the sequence with the aid of the fundamental process of reverse transcription polymerase chain reaction (PCR) and have confirmed it by the 5'/3' rapid amplification of cDNA ends (RACE). The virus strain was named as WH-Human 1 coronavirus (WHCV) or as “2019-nCoV.” The whole-genome sequence (299,031) has been assigned as Gen Bank accession no. Mn908947. Remapping the RNA sequencing data to the complete genome coverage of the new pathogen read at 123,613 assemblies, exhibiting a protruding 99.99% genome coverage at a mean depth of 6.04 × (range: 0.01−78.84×). The viral load of bronchoalveolar lavage fluid cell (BALF) sample from the patient has been estimated by quantitative PCR (QPCR) to be 3.95 × 10^8 copies/mL.

The SARS-CoV-2 virus is spherical and approximately 62–140 nm in size [8–10]. It contains a single-stranded RNA genome of ~30,000 nucleotides encoding 27 proteins. Four structural proteins, the spike surface glycoprotein (S), a small envelope protein (E), matrix protein (M), nucleocapsid protein (N), and an RNA-dependent RNA polymerase make up the SARS-CoV-2 virion structure. Some sequence diversity of the virus has also been reported [11]. Fig. 14.1 shows a schematic and transmission electron microscope (TEM) image of SARS-CoV-2 [12]. SARS-CoV-2 are zonotopic pathogens and have infected humans via interspecies transmission. These viruses are believed to jump from their natural hosts (bats) to an intermediate adaptive animal before human transmission. The SARS-CoV-2 pathogen interacts with human angiotensin-converting enzyme 2 (ACE2) via their S protein [13–15]. Wrapp et al. have studied the structural conformations of the SARS-CoV-2 S protein via cryo-TEM and subsequent ab initio three-dimensional (3D) reconstructions of the micrographs [16]. They have shown that this virus exhibits a stochastic receptor-binding movement mediated through its spike proteins, similar to other Betacoronaviruses. The receptor-binding domain (RBD) of the S1 subunit of the spike protein undergoes hinge-like transformations that expose (i.e., up
conformation) or hide (i.e., down conformation) the determinants of receptor binding in the presence of a host cell membrane. Binding to the host cell receptor results in destabilizing the prefusion trimer, detachment of the S1 subunit, and a subsequent stable conformation of the spike protein through the S2 subunit. The SARS-CoV-2 S protein shows a high binding affinity to human ACE2 receptor. Wrapp et al. have explained from the structural evidences of the 2019-nCoV-S protein that it binds to ACE2 with higher affinity than SARS-CoV S ectodomain. ACE2 has bound to the n-CoV S ectodomain with $-15$ nM affinity, which is 10- to 20-fold greater than ACE2 binding to SARS-CoV S.

Figure 14.1
SARS-CoV-2 morphology. Transmission electron microscope image of SARS-CoV-2 spherical viral particles in a cell. The virus is colorized in blue (adapted from the US Centers for Disease Control). Representation of the viral structure is illustrated with its structural viral proteins. Reproduced with permission from B. Udugama, P. Kadhiresan, H. Kozlowski, A. Malekjahani, M. Osborne, V. Li, H. Chen, S. Mubareka, J. Gubbay, W. Chan, Diagnosing COVID-19: the disease and tools for detection. ACS Nano 14 (2020) 3822–3835.
This makes SARS-CoV-2 more transmissible and deadlier than other *Beta-coronaviruses*, inducing the global pandemic. The RBD of this virus is small (~21 kDa), making nanotechnology strategies more attractive in our fight against the virus. In his 2020 editorial, Chan has recommended application of novel nanomaterials for rapid point-of-care tests, diagnostics for surveillance and monitoring, therapeutics, and vaccine development for COVID-19 [17].

1.3 **Objective and significance of the chapter**

In this chapter, we review the current state-of-the-art in novel bionanomaterials-based technologies used to combat COVID-19. We highlight the role of bionanoparticles (NPs) in the destruction of n-CoV-2. We first capture the key scientific discoveries made in the structural analysis of this new RNA virus to better understand the pathogen for designing novel combat strategies. We summarize the current technologies and potential of NPs as next-generation smart disinfectants against this pathogen. The key progresses made in the detection, therapy, and vaccination of SARS-CoV-2 with nanotechnology are highlighted as separate sections in this chapter. We conclude with a perspective on the most recent technological updates and biosafety measures for COVID-19. We also identify future bionanomaterial-based approaches and advances to combat this disease. We have aimed to provide key technological knowledge in NP-based disinfection, diagnostics, medicine, and vaccine against SARS-CoV-2 through this chapter to further facilitate emergent technologies and invention in this field. Nanoscience or nanobiotechnology approaches have been at the forefront in preparing sanitizer, mask materials, and effective and rapid methods to determine the pathogen or corresponding antibody, drugs, and biosensors for this new pathogen [10,18]. Detection, disinfection, drug delivery, and vaccinations are the essence to combat this pandemic, and scientists are on their way to develop nano-based materials for the detection and treatment of COVID-19.

2. **Disinfection**

The NPs are suitable for the destruction of n-CoV-2 pathogens because of their broad range of antiviral activity. Chemical disinfectants are required in high concentrations and large dosages that are harmful for both the environment and patients. In comparison, NPs are effective at small dosages and can reliably disinfect large areas from the pathogen [19,20]. They can enhance the effectiveness of personal protective equipment, surface cleaning, and filtration of airborne pathogens [21]. Coronaviruses have been known to have a capacity of persisting on surfaces [22]. To this end, personal protection equipment provides an essential line of defense against the widespread dissemination of SARS-CoV-2, especially for our healthcare personnel and immunocompromised population and in indoor settings. These equipment are generally used as disposable
short-term protection, as they lack an antimicrobial or antiviral coating. Our indoor air filters also suffer similar limitations. To this end, silver nanocluster/silica composite coating deposited via a patented cosputtering technique on facial masks has shown groundbreaking effect against n-CoV-2 pathogen [23]. These NP-enabled disinfection technologies can provide us with reliable protection against viral and microbial pathogens in nearby and indoor settings [24]. On the other hand, NanoTech Surface, Italy, has invented a durable and self-sterilizing titanium dioxide and silver ion formula for disinfecting the surfaces [25]. FN Nanotech, United States, has produced novel photocatalytic coatings based on titanium dioxide NPs that can destroy the organic compounds on surfaces and on exposure to light can damage the virus membranes [19]. Furthermore, nanomaterial disinfectants have the unique ability to generate reactive oxygen species (ROS). They possess size-controlled photodynamic and photothermal capabilities that cannot be achieved with bulk chemical disinfectants. However, it should be noted that biodegradable or polymeric nanomaterials are more environmentally friendly and safer for long-term use as disinfectant technology.

3. Detection and diagnostics

Fast and real-time detection of this new pathogen is an urgent requirement for us, as there are limited treatment options against SARS-CoV-2. Real-time reverse transcription—polymerase chain reaction (RT-PCR) and quantitative RT-PCR (RT-qPCR) are the standard procedures for detection and diagnosis of COVID-19, and they have been recommended by the CDC, the WHO, and the EU [26]. RT-PCR tests have been widely used in this pandemic to diagnose COVID-19 cases using respiratory samples from patients such as nasopharyngeal or oropharyngeal swabs, sputum, lower respiratory tract aspirates, bronchoalveolar lavage, and nasopharyngeal wash/aspirate or nasal aspirate. This test is used to assess the nucleic acids from SARS-CoV-2 and is used for both individual tests and tests of pooled samples from individuals. An outline is given here for the RT-PCR analysis of mRNA (Table 14.1).

However, testing is limited to certified laboratories with proper equipment capability, and the tests require six to 7 hours. These are some crucial impediments to the high volume of tests required during the pandemic. Therefore, there has been a major research thrust for alternative rapid diagnostic technologies and sensors to detect the SARS-CoV-2 pathogen from infected individuals (Table 14.2).

Nanotechnology-based sensors have played a key role in these new and rapid detection technologies for COVID-19 [27–29]. Biosensors designed from NPs such as carbon nanotubes, quantum dots, gold, silver, and metal oxides have been known to be highly effective for the detection of other viral pathogens (e.g., human immune deficiency virus (HIV), H5N1 influenza virus, and Ebola). The NPs have high surface-to-volume ratios,
Table 14.1: Summary of preparation and the testing process of RT-PCR.

| Items | Corresponding sample handling and analysis steps |
|-------|-------------------------------------------------|
| **Upon receipt of r-RT-PCR panel reagent** | Protocol A |
| - Resuspend primer/probe | - Resuspend and aliquot n-CoV-polymerase chain |
| - Mix aliquot | - Store at $-20 \, ^\circ C$ (A) |
| - Store at $-70 \, ^\circ C$ (B) | - Selected from regions of the n-CoV-2 virus nucleocapsid gene |
| - Oligonucleotide primers used | **Protocol B** |
| **Upon obtaining sample** | 1. Extract sample RNA and HSC RNA |
| 2. Prepare master mix (15 μL) | 3. Prepare r-RT-PCR plate (5 μL RNA) |
| 4. Run assay on ABI7500FAST Dx | 5. Analyze data |
| 6. | **Report results** |

Table 14.2: Key nanotechnology-based COVID-19 diagnostics with potential for point-of-care use are summarized in this section.

| No. | Type of emergent diagnostic technology reported | Type of journal article | Type of NPs and biomaterials reported | Reference no. and Journal name |
|-----|-----------------------------------------------|-------------------------|--------------------------------------|--------------------------------|
| 1   | Analytical approaches | Review | Au, carbon nanotubes, superparamagnetic iron oxide, Ag, quantum dots, metal–organic frameworks, graphite, and immobilized proteins and DNA conjugates | [27], Analytical Methods |
| 2   | Biosensors | Review | Au, carbon nanotubes, graphene oxide, silica, metal oxide, aluminum, copper, magnetic NPs, and quantum dots | [28], TrAC Trends in Analytical Chemistry |
| 3   | RT with loop-mediated isothermal amplification coupled with NP-based biosensors | Review | Quantum dots, Au, and graphene | [29], Nano Express |
|     | • Electrochemical sensors | | | |
|     | • Chiral biosensors | | | |
| 4   | Chemiluminescent homogeneous biosensor | Research article | Phthalocyanine-dyed polystyrene and quantum dot-doped polystyrene | [30], Analytical Chemistry |
| 5   | Colorimetric assay for naked eye detection | Research article | Au NPs coated with antisense oligonucleotides | [31], ACS Nano |
Table 14.2: Key nanotechnology-based COVID-19 diagnostics with potential for point-of-care use are summarized in this section.—cont’d

| No. | Type of emergent diagnostic technology reported | Type of journal article | Type of NPs and biomaterials reported | Reference no. and Journal name |
|-----|-----------------------------------------------|--------------------------|--------------------------------------|--------------------------------|
| 6   | Dual-functional plasmonic photothermal biosensors | Research article         | Au nanoislands                       | [32], ACS Nano                 |
| 7   | Plasmonic device for femtomolar detection with standard bioassays | Research article         | Au nanorod on bovine serum albumin scaffold | [33], Nature Biomedical Engineering |
| 8   | Field-effect transistor-based biosensor        | Research article         | Graphene                             | [34], ACS Nano                 |
| 9   | Lateral flow immunoassay                      | Research article         | Lanthanide-doped polystyrene         | [35], Analytical Chemistry      |
| 10  | • Lateral flow assay                           | Review                   | Au and Au nanorods                   | [36], Biomedicine and Pharmacotherapy |
|     | • Enzyme-linked immunosorbent assay (ELISA)    |                          |                                      |                                 |
|     | • Colloidal gold immunochromatographic assay   |                          |                                      |                                 |
|     | • Chemiluminescent immunoassay                 |                          |                                      |                                 |
| 11  | • RT with loop-mediated isothermal amplification | Review                   | CRISPR, enzymes, and DNA-tagged aptamers or antibodies | [37], ACS Sensors |
|     | • Lateral flow assay                           |                          |                                      |                                 |
|     | • CRISPR based SHERLOCK                       |                          |                                      |                                 |
|     | • ELISA                                        |                          |                                      |                                 |
|     | • Proximity ligation assay                     |                          |                                      |                                 |
| 12  | Antibody test coupled with paper-based ELISA   | Research article         | Rabbit antihuman immunoglobulin conjugated with horseradish peroxidase CRISPR-Cas13a | [38], Analyst |
| 13  | CRISPR-Cas13a with cellular phone-based fluorescence plate reader for the detection of SARS-CoV-2 RNA | Research article         | Quantum dots, Au, Ag, metal oxides, graphene, Au nanoislands, and CRISPR-Cas13 | [39], Cell |
| 14  | • Biosensor                                    | Review                   |                                      | [40], Nature Materials          |
|     | • Field-effect transistor                      |                          |                                      |                                 |
|     | • Dual-functional photothermal sensor          |                          |                                      |                                 |
|     | • CRISPR-Cas lateral flow assay                |                          |                                      |                                 |
|     | • CRISPR-Cas fluorescence assay                |                          |                                      |                                 |
tunable optoelectronic properties, and larger active surfaces for binding. Therefore, the NP-based biosensors offer high specificity to the target biomolecule, rapid detection, and the capability to determine low concentrations of the target analyte as compared with the traditional techniques. For example, a phthalocyanine dye and quantum dot-doped polystyrene NP system has been developed as an enhanced chemiluminescent biosensor for detecting target analytes in low-volume biological samples [30]. This fluorescence resonance energy transfer-based biosensing system overcomes the common limitations of immunoassays such as the extensive washing steps required to prevent nonspecific binding of the target. These NP-based strategies have been applied toward designing faster, easily accessible, and cost-effective technologies for the detection of the new viral pathogen, SARS-CoV-2 to combat this pandemic.

Various NP-based sensors and kits are ready for SARS-CoV-2 tagging and simultaneous detections. Fig. 14.2 provides an overview of these sensors [24]. However, to improve the reproducibility and to eliminate some false-positive results, the researchers at Maryland University have developed a novel colorimetric determination system that is based on gold NPs capped with thiol-modified antisense oligonucleotides. These antisense oligomers are specific to N-genes of SARS-CoV-2, and this new AuNP-based assay can diagnose positive COVID-19 cases within 10 min from the separated RNA samples [31]. One of the challenges is the detection of low viral loads of SARS-CoV-2. This limitation has been addressed by a research team at ETH Zurich, Switzerland. They have invented a dual functional plasmonic biosensor chip containing two-dimensional Au nanoislands that combine a plasmonic photothermal effect and localized surface plasmon resonance sensing transduction to provide a remarkable method of detecting n-CoV-2 viruses up to concentrations as low as 0.22 pM [32]. Luan et al. have designed novel plasmonic nanoprobe addition units for standard bioassays to enhance the signal-to-noise ratio of these traditional assays for the detection of low sample volumes of biomarkers [33]. These multifunctional NP-based probes consist of a bovine serum albumin platform with fluorophores, gold nanorods as the plasmonic agent, and biotin as the component for the detection of biomarkers with high specificity and sensitivity. This novel NP add-on for common bioassays can bring breakthrough advancements in the detection of low volumes of SARS-CoV-2.

Another rapid and accurate detection method for SARS-CoV-2 developed by Seo et al. is a field-effect transistor (FET)—based biosensing device. The sensor consists of SARS-CoV-2 spike protein antibodies immobilized on a graphene FET via the 1-pyrene butyric acid N-hydroxysuccinimide ester (PBASE) linker to detect SARS-CoV-2 spike protein antigen in clinical samples even at low concentrations. The device can detect spike proteins as low as $1.31 \times 10^{-3}$ pM in clinical transport medium and shows no interference from MERS-CoV antigen. This new diagnostic device is unique in its specificity and sensitivity to the SARS-CoV-2 pathogen [34]. Another rapid and precise diagnostic method suitable
for large sample loads common in hospital settings is a novel lanthanide-doped polystyrene NP-based lateral flow immunoassay invented by Chen et al. [35]. It is an analytical procedure that uses lanthanide-doped NPs synthesized via miniemulsion polymerization from tris(1,3-diphenyl-1,3-propane dionato) (1,10-phenanthroline) europium-(III), styrene, acrylic acid, 2,2’azobis (isobutyronitrile), and cetyltrimethylammonium [30]. The lanthanum-doped NPs are dispersed in water (5% w/v) and stored at 4 °C before surface functionalization with mouse antihuman IgG antibody (M-H IgG) and rabbit IgG (R IgG). The lateral flow immunoassay for SARS-CoV-2 is
fabricated with these NPs via slight modification of a previously reported procedure [30]. The serum samples are diluted with assay buffer (1:1000), and 100/μL of the diluted sample is added to the sample well of the lateral flow immunoassay strip for analytical assessment. When the test solution migrates from the sample pad to the absorbent pad, the functionalized lanthanide-doped polystyrene NPs are accumulated at the test and control lines as shown in Fig. 14.3. After settling for 10 min, the test strip is uploaded to the

![Figure 14.3](image)

Design and fabrication of the developed assay. (a) Lateral flow test strip. (b) Assay. Reproduced with permission from Z.H. Chen, Z.G. Zhang, X.M. Zhai, Y.Y. Li, L. Lin, H. Zhao, L. Bian, P. Li, L. Yu, Y.S. Wu, G.F. Lin, Rapid and sensitive detection of anti-SARS-CoV-2 IgG, using lanthanide-doped nanoparticles-based lateral flow immunoassay. Anal. Chem. 92(10) (2020) 7226—7231.
portable fluorescence reader for the measurement of fluorescence at an excitation wavelength of 365 nm and an emission wavelength of 615 nm with a delay time of 20 μs. The results are quantified from the areas of the fluorescence peaks of the test line, $A_t$, and the control line, $A_c$. The $A_t:A_c$ ratio (R) denotes the anti-SARS-CoV-2 IgG concentration in the serum. The optimum time for maximum fluorescence is 10 min for this lateral flow assay. The reproducibility or coefficient of variation of this immunoassay is 11.5%–14.63% (i.e., <15%). This rapid and sensitive method is comparable with RT-PCR and may be more accurate than RT-PCR for suspected SARS-CoV-2 patients [6,26].

Currently, the RT-PCR-based technology serves as a gold standard for the detection of SARS-CoV-2, but the method requires expert personnel, advanced instrumentation, and 4-6 h to generate results. Antibody-based testing is another key approach used in COVID-19 detection. The antibody tests are based on the detection of antibodies or immunoglobulins, i.e., Y-shaped proteins produced by the patients’ immune response as a defense against the SARS-CoV-2 virus. Several emerging points of care technologies for SARS-CoV-2 are using antibody-based tests coupled with immunoassays such as lateral flow, time-resolved fluorescence, or plasmonic nanoparticles [36,37]. For example, a paper-based ELISA with specific antigens has recently been designed for detection of SARS-CoV-2 antibody with colorimetric readout based on 3,3′,5,5′-tetramethylbenzidine-horseradish peroxidase reaction [38]. However, detectable limits of antibodies are not developed early in the disease. Patients who have recovered from SARS-CoV-2 also possess these antibodies, which defend them against further infection. These are some of the current issues limiting the efficacy of antibody-based detection. A recent model has highlighted the significance of frequent testing and fast turnaround of results over sensitivity of tests in combating the transmission of this virus [39].

Therefore, new clustered regularly interspaced short palindromic repeats (CRISPR)—based strategies have emerged for point-of-care diagnosis of COVID-19 [40]. CRISPR-Cas originally developed as an approach to minimize phage transmission in bacteria has now provided us with a key resource for viral RNA detection with a rapid turnaround of 1 h. Cas13 enzyme from the bacterial immune system can directly bind to single-stranded RNA. This Cas13 protein is conjugated with programmed CRISPR RNA to form a nuclease-inactive ribonucleoprotein complex, which on binding with its complementary RNA sequence can cleave any surrounding single-strand RNAs. The binding and cleavage of Cas13 can be rapidly detected via a single-strand RNA-fluorophore quencher pair. A preamplification of the target RNA is used to enhance the sensitivity of the CRISPR-Cas13 approach for the detection of SARS-CoV-2 in the SHERLOCK protocol. The CRISPR-Cas13-based DETECTR approach can avoid the conversion of amplified DNA back to RNA and has also been approved by the FDA. Both these CRISPR approaches are attractive as the point-of-care tests, as they can be read via lateral flow
paper assays. Recently, Fozouni et al. have reported a CRISPR-Cas13a-based direct and portable assay that does not require preamplification of the SARS-CoV-2 genome and can provide the detection results within 5 min of measurement via a mobile phone app [39]. This assay can detect up to ~100 copies/μL of SARS-CoV-2 RNA in 0.5 h, whereas the other two FDA-approved CRISPR methods require 1 h for detection. Thus, the CRISPR strategy has been a novel breakthrough for COVID-19 diagnostics with the potential for being developed into COVID medications.

4. Medicine

A vaccine will help end this deadly COVID-19 pandemic. However, until its discovery and availability to the public, doctors all over the world are making tremendous efforts to treat the enormous numbers of COVID-19 patients and to cure them. To this end, there is constant research for medicine against this deadly pathogen. Hydroxychloroquine, the antibiotic azithromycin, anti-HIV combined drug lopinavir-ritonavir, antiinflammatory antibody, tocilizumab, antiviral drug remdesivir, a combination of remdesivir and baricitinib, and convalescent plasmas from cured patients have been used as a treatment for this disease [41–44]. The use of one of these drugs considered suitable for the respective patient along with oxygen support have been applied as the treatment protocol for COVID-19 by doctors all over the world. Nanotechnology can assist in galvanizing the potency and efficiency of COVID-19 drugs as NPs can be targeted to the diseased cells, have a longer circulation time in vivo, and can accumulate in the macrophages [45,46]. Nanomedicines can also be administered via inhalation or intravenous injection. Therefore, nanomedicines can bring breakthrough advancements in efficacy against SARS-CoV-2. They offer key advantages in drug availability and drug activity compared with their bulk counterparts, which can facilitate enhanced lifesaving capacity against this pathogen. It is now established that dexamethasone (6 mg/day), administered orally or through intravenous injection for 10 days, improves the condition of fatal patients by 35%. This has been discovered through one of the world’s largest randomized trials on COVID-19 patients. This drug also reduces the hospitalization time and chances of fatality in nonventilated patients. Lammers et al. have proposed that a new nanoformulation consisting of dexamethasone liposomal NPs will bring further groundbreaking improvements in the efficiency of this drug [41]. Liposomal dexamethasone has been a successful drug for several diseases including myeloma, multiple sclerosis, liver fibrosis, and rheumatoid arthritis. Reformulation of this drug in the nanoform has been shown to outperform the dexamethasone itself. However, nanoformulations are costlier and achieving economic viability as well as timely regulatory approval are some of the impediments of nanomedicine [47–51]. On the other hand, the fact that corticosteroids such as dexamethasone are well-known antiinflammatory drugs to prevent inflammation and propagation of phagocytic cells in the lungs is a key advantage in terms of cost and
regulatory approval of the nanoformulation. Cortisol is both cheap and an easily available standard drug [47]. A combination of cortisol and the antiviral drug is used in some cases by physicians to treat SARS-CoV-2 infections. At present, scientists also suggest that nitrous oxide inhalation is a supportive avenue for COVID-19 patients [52]. Inhaled nitrous oxide is approved by the US FDA for the treatment of patients requiring long-term oxygen therapy and pulmonary hypertension in newborns. The equipment to facilitate nitrous oxide inhalation in patients is inexpensive, relatively noninvasive as compared with the mechanical ventilation units, and can be arranged at home. Therefore, the therapy is significantly attractive as a cost-effective and efficient treatment option for SARS-CoV-2-infected patients. This treatment has recently shown tremendous results for a COVID-19 patient with pulmonary arterial hypertension. Another novel approach for COVID-19 medicine has focused on the infected host cells instead of targeting the pathogen [53]. This innovative technology is based on a new nanosponge formulation synthesized from membranes of human cells (e.g., human lung epithelial cells and macrophages), which are typically targeted by SARS-CoV-2. The nanosponge is surface-functionalized with the same protein receptors used by SARS-CoV-2 for entry to human cells. These nanospomes can successfully neutralize the n-CoV-2 pathogen and incapacitate it from attacking the host cells. Thus, there is an ongoing global search through innovation, experimentation, and trial and error for the invention of supportive medicines for COVID-19 infections [54].

5. Vaccine development

It is suggested that SARS-CoV-2 S shares 98% sequence identity with the S protein from the bat coronavirus RaTG13 and it is evident that understanding the nanoscale and atomic-level structure of 2019-nCoV spike proteins will help in the development of a vaccine. Daniel Wrapp et al. have determined the structure of the 2019-n CoV spike in the prefusion conformation. They can provide a 3.5-angstrom resolution structure of 2019-nCoV S protein trimer in the perfusion conformation via cryo-TEM [16]. All these atomic-level structural information will support precision vaccine invention and the discovery of the correct antiviral therapeutics. Scientists throughout the world are engaged in vaccine preparation. It is now in focus that the S-protein is the most reliable target for the development of the COVID-19 vaccine [55]. This pandemic has galvanized innovations and next-generation technologies for accelerated vaccine development as it is a new target virus. North America, Europe, China, Asia, and Australia have led the endeavors in vaccine development with active engagement from public and private sector firms, multinational companies, as well as academia. The Coalition for Epidemic Preparedness Innovations (CEPI) has created an R&D database and vaccine development landscape to support and expedite the invention of a vaccine against this deadly disease. More than 200 vaccines are in the line of action to prove their efficacy. mRNA and DNA-based vaccines offer the advantage of an enhanced level of engineering of the antigen and can be
developed faster. Viral vectors are another attractive platform for vaccine candidates, as they provide high stability and strong immune response. Vaccines based on recombinant proteins effective for other viral diseases can make use of the already existing large-scale production process. We have mentioned at least eight of them, which have begun their human trial or comprehensive efficacy trial [56,57].

- Pfizer-BioNTech COVID-19 vaccine by Pfizer Inc., United States, that has been approved for emergency use for prevention of COVID-19 in individuals of age 16 and above
- mRNA-1273 vaccine by Moderna (Cambridge, Massachusetts, United States)
- Oxford University-AstraZeneca and Covishield vaccine are on the third human trial. They started their human trial on April 16, 2020
- ENSEMBLE, Johnson & Johnson’s single-dose COVID-19 vaccine has recently completed its Phase 3 trial over multiple countries
- COVAXINTM by Bharat Biotech in collaboration with the Indian Council of Medical Research (ICMR), India
- Altimmune’s intranasal coronavirus vaccine (Gaithersburg, Maryland, United States)
- INO-4800 by INOVIO Pharmaceuticals, United States
- Avian coronavirus infectious bronchitis virus (IBV) vaccine by MIGAL (Israel)

Biohybrid NPs play a key role in multiple aspects of COVID-19 vaccine development. They can help in vaccine design, delivery, and administration [58,59]. Nanovaccines essentially apply NPs as carriers or adjuvants for the biological components of the vaccine. For example, the NPs can act as a stabilizer for the antigen during the administration process and can enable the synthesis of multivalent antigens [10]. They can serve as a platform for targeted delivery of the antigen to boost up the patient’s response. An mRNA vaccine developed by ModernaTX Inc. is among the first to be approved for emergency use against COVID-19. The vaccine encodes a prefusion spike glycoprotein of SARS-CoV-2. One of the key components of this vaccine is the liposomal NP used to encapsulate the mRNA for efficient circulation and delivery in vivo. No mRNA or DNA vaccine has been approved so far for any disease, as the delivery of nucleic acid requires a NP platform to restrict its degradation inside the body [60]. The liposomal NPs have now been approved for RNA delivery. In the long run, nanotechnology will be highly beneficial as an immune-mediated approach against the nCoV-2 or COVID-19 pathogen.

6. Perspective

The NPs offer a wide range of transport, biointeraction, optical, magnetic, and electronic properties that are not available in macroscale or molecular materials [9,61]. The surfaces of nanocarriers can be readily functionalized with multiple peptides and biomarkers to both detect and treat the pathogen [13]. These properties can be exploited to advance
novel innovations in target-specific drugs, sensors, rapid point-of-care diagnostics, disinfecting agents, and vaccines against the SARS-CoV-2 pathogen [62,63]. A fundamental understanding of bionanointeractions can be used to uncover the mechanisms of interaction of the SARS-CoV-2 virus for designing reliable medicines and vaccines against the pathogen. Nanoformulations of glucocorticoids have the potential to further boost the efficacy of this antiinflammatory drug against SARS-CoV-2 and can bring breakthrough advancements in the search for supportive medicine for COVID-19 infections. Two mRNA vaccines with liposomal NPs as their delivery agents are among the first approved prophylactic measures against the novel SARS-CoV-2 pathogen [64,65]. The positively charged lipid NP encapsulation prevents disintegration of the mRNA in vivo, enhanced circulation, and efficient delivery.

In addition, NP-based biosensors can assist in the detection and epidemiological surveillance against this pathogen to curb the global pandemic [66]. For example, a biosensor based on oligomer-coated plasmonic Au NPs has been used as a facile point-of-care colorimetric assay to detect SARS-CoV-2 [31]. Recently, lateral flow assays with novel AuNP tracers designed for the detection of immunoglobulins specific to SARS-CoV-2 have shown promising results comparable with those obtained from PCR [67]. Therefore, there is a huge scope to extend the NP-based diagnostics for SARS-CoV-2 beyond AuNPs using quantum dots and carbon-based materials. A key advantage of these technologies will be their point-of-care capability and cost-effectiveness as compared with the RT-PCR and CT scan-based laboratory approaches. Recently, CRISPR-Cas13 has also evolved as an emergent strategy that has galvanized the point-of-care detection of SARS-CoV-2. The SARS-CoV-2 genome is fast evolving through various mutations in different regions of the globe resulting in new variants. Detection of low viral loading present at the early stages of the disease and limiting all cross-reactivity with viral strains other than SARS-CoV-2 also pose two main challenges for scientists. Therefore, innovative solutions will have to be designed to meet the challenge of prompt point of care detection of this RNA virus [40,68]. Jarrom et al. have suggested the significance of an evidence-based approach in designing strategic framework and standards for COVID-19 testing [69]. The use of single-molecule nanopore sequencing used to characterize long-sized DNA or RNA can also serve as an emergent possibility for the diagnosis of SARS-CoV-2 [70].

One of the methods for the transmission of the SARS-CoV-2 virus to humans is through contaminated surfaces or fomites. To this end, the importance of NP-based antiviral coatings has been suggested as a key resource to combat viral transmission. These smart coatings can serve as innovative solutions for improving our PPE against the virus. NPs such as gold, silver, titanium dioxide, zinc oxide, carbon nanotubes, and biohybrid chitosan can provide next-generation smart antiviral surface coatings through their unique mechanisms of interaction with the pathogen including production of reactive oxygen
species, inhibition of enzyme activity, energy transmission, and DNA damage [71]. Global interdisciplinary collaborations between materials scientists, environmental engineers, biomedical engineers, chemists, and nanoscientists will be the key to engineering these novel surface coatings against SARS-CoV-2.

Ruiz-Hitzky et al. have highlighted the emerging patents on NP-based technologies applied to COVID-19 responses [72]. Recently, new strains of the SARS-CoV-2 pathogen have been detected in Europe. New strains of the pathogen with spike aspartic acid–614 to glycine (D614G) substitution have replaced the parent SAR-CoV-2 virus. Research so far indicates that this new D614G variant has increased transmissibility in humans compared with the ancestral strain but has not evolved in pathogenicity [73]. Current vaccines are believed to show the same efficacy against this SARS-CoV-2 variant. As scientists, doctors, and engineers around the globe search for new avenues to fight this pandemic, several mechanistic insights remain unknown about SARS-CoV-2 [74]. Nanotechnology can continue to bridge this gap in knowledge about the pathogen through structural analysis, new diagnostics, therapeutics, and vaccines. For example, biomimetic 3D human lung models can be designed using hydrogels, pluripotent stem cells, and polydopamine via 3D bioprinting. These 3D models can be used instead of human subjects for understanding the preliminary mechanisms of interaction of SARS-CoV-2 with the new biohybrid NP-based therapeutic and detections agents [70]. Ongoing research on this new pathogen and biohybrid nanomaterials to combat the RNA virus will be critical in preventing surge of new cases and saving lives worldwide [75].

At the same time, biosafety should be of key importance. Regulatory guidance for the general public as well as handling, sample preparation, and analysis of this highly transmittable pathogen are regularly provided through CDC and global regulatory agencies. These guidelines are updated based on the most current research findings. SARS-CoV-2 cell culture, separation, and initial analysis of the samples should be conducted in a biosafety level 3 (BSL-3) laboratory with appropriate regulatory approvals. Samples for testing should be handled in a BSL-2 laboratory with a biosafety hood and with BSL-3 precautions including respiratory protection and proper personal protective equipment. Biosafety needs should be continuously assessed, and new experiments on NP–pathogen interactions should be performed with required regulatory approvals for continued global safety [76].

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