




REVIEW ARTICLE



## Immunobiology and nanotherapeutics of severe acute respiratory syndrome 2 (SARS-CoV-2): a current update

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### ABSTRACT

The emergence of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) constitutes the most significant global public health challenge in a century. It has reignited research interest in coronavirus. While little information is available, research is currently in progress to comprehensively understand the general biology and immune response mechanism against SARS-CoV-2. The spike proteins (S protein) of SARS-CoV-2 perform a crucial function in viral infection establishment. ACE2 and TMPRSS2 play a pivotal role in viral entry. Upon viral entry, the released pro-inflammatory proteins (cytokines and chemokines) cause the migration of the T cells, monocytes, and macrophages to the infection site. IFN $\gamma$  released by T cells initiates a loop of pro-inflammatory feedback. The inflammatory state may further enhance with an increase in immune dysfunction responsible for the infection's progression. A treatment approach that prevents ACE2-mediated viral entry and reduces inflammatory response is a crucial therapeutic intervention strategy, and nanomaterials and their conjugates are promising candidates. Nanoparticles can inhibit viral entry and replication. Nanomaterials have also found application in targeted drug delivery and also in developing a vaccine against SARS-CoV-2. Here, we briefly summarize the origin, transmission, and clinical features of SARS-CoV-2. We then discussed the immune response mechanisms of SARS-CoV-2. Finally, we further discussed nanotechnology's potentials as an intervention strategy against SARS-CoV-2 infection. All these understandings will be crucial in developing therapeutic strategies against SARS-CoV-2.


### KEYWORDS

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## Introduction

Coronaviruses are a group of large, enveloped, positive-sense, single-stranded RNA viruses that belong to the order Nidovirales, family Coronaviridae, subfamily Coronavirinae. There are four genera (alpha, beta, gamma, and delta) of coronavirus. They are characterized by diverse antigenic cross-reactivity and genetic composition. The alpha- and beta-coronavirus genera are the strains known to be pathogenic to humans [1]. Coronavirus causes various diseases ranging from liver-based (hepatic), neurological, enteric, and respiratory diseases [2–4]. SARS-CoV-2 has affected over 131 million people since its emergence and had led to more than 2.8 million deaths globally as of 6 April 2021, according to World Health Organisation (WHO). The US is the country most severely affected in both infection and fatalities, with about 30 million and 551,000 confirmed cases and deaths, respectively. This is followed by Brazil, India, Russia, France, the United Kingdom, Italy, Turkey, Spain, and Germany. On the list of the high death tolls are the USA (551,769 deaths), Brazil (331,433 deaths), and Mexico, with more than 204,000 deaths. Furthermore, according to WHO, America (more than 56 million cases and over 1.3 million deaths) remained the most severely affected with SARS-CoV-2. This is followed by Europe (more than 46 million cases and 986,000 deaths) [5]. Thus, the two regions (Europe and American region) account for about 80% of all the cases and deaths.

The high mortality and morbidity rate seen in patients with SARS-CoV-2 pose a critical challenge to global health and demands urgent therapeutic intervention. Possible transmission route for SARS-CoV-2 is mainly through droplets from the respiratory organ, direct contact with inanimate objects, and faecal-oral transmission. [6–8]. As of date, it has not been outrightly established if the virus can be transmitted through faecal contamination. However, studies are gradually emerging reporting faecal-oral transmission and other plausible transmission routes. The Chinese Centre for Disease Control and Prevention (CCDC) recently reported the presence of SARS-CoV-2 in the stool sample of a patient with SARS-CoV-2 [9]. Wang et al. [10] also reported high SARS-CoV-2 RNA copy numbers in a stool sample of patients infected with SARS-CoV-2. Several other studies are also available reporting the transmission route of SARS-CoV-2 [11–21].

Furthermore, differences in symptomology and severity can be attributed to genetic differences in the

immune system [22]. An essential step in any virus's life cycle involves attachment and penetration into the host cell [23]. The attachment of SARS-CoV-2 is enhanced by an interplay between angiotensin-converting enzyme 2 (ACE-2) and the spike surface glycoprotein S [24,25]. ACE-2 is a membrane carboxypeptidase that is evenly distributed in a variety of human tissues [25,26]. It is worthy to note that the affinity between the S protein on the viral surface and the ACE-2 is excessively high compared to the interaction between S protein and SARS-CoV-1. Also, the expression of the ACE-2 depends on age, hereditary, and sex. It increases in certain conditions such as Cancer, existing acute cardiopulmonary disease, and immunosuppressive use. This affinity and interaction give insight into the low fatality rate (LFR) in paediatric patients compared to the high fatality rate in patients above 80 years. Apart from the S protein, several other receptors play a crucial role in their attachment and entry into the host cell [26–28]. ACE-2 is generally expressed in human organs that are vulnerable to SARS-CoV-2. These organs include the lung, heart, kidney, stomach, bladder, nasal mucosa, bronchus, ileum, etc. [28].

Generally, patients with SARS-CoV-2 often go through three stages: initiation, amplification, and consummation [29]. During initiation, the virus inside the host cell undergoes replication. Replication of the viral particle occurs in the upper respiratory tract, notably the mucus-secreting epithelial cells [30]. There is also the activation of chemokines at this stage. In the absence of a sufficient immunological response, infected patients enter the amplification stage. At this stage of the infection, there is excess production of inflammatory cytokines, increasing immunopathological processes. Multiplication occurs at the lower respiratory tract and the stomach's mucous membrane layer, containing glands and gastric pits [31]. Viral multiplication results in a moderate dose of viral particles in the bloodstream. Infection does not show distinctive symptoms, and only a few infections are controllable at this point. There have been reports where patients display signs that are not linked to respiratory infections. Such symptoms include acute liver and heart injury, diarrhoea, and kidney failure [28,32–34]. Consummation ensues when inflammatory mediators and subsequent multiple organ damage overwhelm the host's capacity [29]. The humoral immunological response plays a crucial role in SARS-CoV-2 infection establishment. The activation of the B cells upon viral entry leads to the production of several

immunoglobulins (IgA, IgM, IgG). There is also the production of neutralizing antibodies.

Finally, the innate and adaptive immune systems are stimulated by the cytopathic effect induced initially by the viral increase in pneumocytes and capillary endothelial cells [27,35,36]. There is a reduced number of T cells in the blood in older patients or those with high viral load and individuals who have two co-existing diseases or immunocompromised individuals (lymphopenia). The reduced number of T cells serves as a bioindication of advance (acute) infection [27,36]. Also, pneumonia is the major clinical sign associated with SARS-CoV-2. In certain patients, the immunological response could lead to multi-organ failure [37–39]. The overall incidence and the severity of SARS-CoV-2 depends on several factors, such as age and underlying diseases (e.g. Cancer, obesity, diabetes, cardiovascular diseases) [40–42].

Several promising therapeutic strategies are rapidly emerging for the treatment of coronavirus. The majority of the studies focussed on antiretroviral agents, steroids, immunosuppressive drugs, and anticoagulants therapy. Hippensteel et al. [43] reported Heparin (an anticoagulant) as a potential drug against SARS-CoV-2. Remdesivir, an inhibitor of the viral RNA-dependent, RNA polymerase has also been effective against SARS-CoV-2 [44]. A study also reported that Glucocorticoids, Dexamethasone, resulted in lower mortality compared to patients who received usual care alone [45]. Eculizumab was also reported as a potential treatment option for severe cases of SARS-CoV-2 [46]. More recently, Dallochio et al. [47] showed that the combination of a protease inhibitor and two nucleoside analogues drugs mostly used in treating HIV infection could be an effective way of treating SARS-CoV-2. Moreover, several vaccines have been developed while others are still in the developmental stage for treatment against SARS-CoV-2 (Table 1).

However, nanotechnology is a rapidly emerging area with potentials against several infectious diseases [48–51]. The field of nanotechnology is a multidisciplinary area that uses nano-sized particles (size range of 1–100nm) and devices for several applications not limited to diagnostics, targeted drug delivery, and the production of new therapeutic biomaterials [52,53]. The use of nanomaterials in the formulation of new drugs has been seen as a critical enabling technology, with the potentials to provide solutions targeting current and future medical needs. However, whether nanotechnology is ripe enough to address medical needs efficiently in the context of a pandemic is a question that needs to

be answered. Currently, the treatment approach that prevents ACE2-mediated viral entry and that reduces inflammatory response has been the focus since the emergent of SARS-CoV-2 [54]. Nanoparticles can be efficiently inserted into SARS-CoV-2 for neutralizing the viral particles. They can be used to control the proliferation and multiplication of the virus. Moreover, they can also be used to target the S protein preventing the virus from attaching to host cells. The development of nano compounds (encapsulation of the virus with nanomaterials) can also be an effective route to control viral growth and its attachment to host cells [55]. Nanotechnology can also be utilized to deliver antiviral drugs targeting SARS-CoV-2 and can also be used in the vaccine formulation.

Therefore, to properly tackle SARS-CoV-2 infection, predict the incidence of the disease, formulate drugs and vaccines with high potency against SARS-CoV-2 infection, an understanding of the biology, pathophysiology, immunological response mechanisms against SARS-CoV-2 and the role of nanotechnology as a therapeutic strategy is very crucial. In this review, the origin, transmission, and clinical features of SARS-CoV-2 were briefly summarised. We further discussed the immune response mechanisms of SARS-CoV-2. Finally, we discussed the potentials of nanotechnology as an intervention strategy against this rapidly ravaging SARS-CoV-2 infection.

### Brief history and origin

Coronaviruses have been present in humans for at least 500–800 years. They are known to take their origin in bats [56,57]. Coronaviruses have long been recognized as critical veterinary pathogens, causing respiratory and enteric diseases in mammals and birds. The first known coronavirus, the avian infectious bronchitis virus, was isolated in 1937 and was the causative agent of deadly infections in chicken. In 1965, Tyrrell and Bynoe [58] isolated the first human coronavirus from the nasal cavity and was propagated on human ciliated embryonic trachea cells *in vitro*. However, of the known coronavirus species, only six have been known to cause disease in humans: HCoV-229E, HCoV-OC43, HCoV-NL63, HCoV-HKU1, SARS-CoV, and MERS-CoV [59,60]. The first four are endemic locally; they have been associated mainly with the mild, self-limiting disease, whereas the latter two can cause severe illness. SARS-CoV and MERS-CoV are betacoronaviruses [61]. They are among the pathogens included in the World Health Organisation's list of

high-priority threats (A research and development blueprint for action to prevent epidemics) [62].

Generally, Coronaviruses are capable of adapting rapidly to new hosts through genetic recombination and mutation *in vivo*. As RNA viruses, coronaviruses rely on RNA-dependent RNA polymerase (RdRp) to replicate their genome. The intrinsic error rate of RdRp is approximately 1,000,000 mutation/site/replication, resulting in continuous point mutations. Point mutations alone are insufficient to create a new virus; however, this can only occur when the same host is concurrently infected with two coronavirus strains, enabling recombination. One coronavirus can gain a genomic fragment of hundreds or thousands of base-pair long from another strain when the two co-infect the same host, allowing the virus to increase its ecological niche [56]. This susceptibility enabled the emergence in approximately two decades of two new human coronavirus species with epidemic potential: SARS-CoV and MERS-CoV. Given the high prevalence and wide distribution of coronaviruses, their large genetic diversity, the frequent recombination of their genomes, and increasing activity at the human-animal interface, these viruses represent an ongoing threat to human health [63]. This fact again became evident in late 2019 and early 2020, when a novel coronavirus was discovered to cause a large and rapidly spreading outbreak of respiratory disease, including pneumonia, in Wuhan, China.

Therefore, it all started in December 2019, a group of unexplained viral pneumonia cases was reported in Wuhan, China. In a quest to identify the cause of this disease, many tests were carried out, which ruled out several causative agents that may cause similar symptoms. A new strain of coronavirus was identified as the causative agent and tentatively named 2019-nCoV by the World Health Organisation (WHO) on 12 January 2020 [64]. The virus was isolated and the viral genome sequenced. 2019-nCoV was characterized as a betacoronavirus, and thus became the seventh discrete coronavirus species capable of causing human disease. On January 20, Professor Zhong Nanshan, a SARS intervention specialist after a visit to Wuhan, confirmed that 2019-nCoV was spreading between people, which led to increased alertness by the Chinese government and people. On 30 January 2020, WHO declared the outbreak of novel coronavirus a public health emergency of international concern, the sixth public health emergency after H1N1 (2009), polio (2014), Ebola in West Africa (2014), Zika (2016), and Ebola in the Democratic Republic of Congo (2019). The International Committee

on Taxonomy of Viruses decided to rename 2019-nCoV as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), and the associated pneumonia as coronavirus disease 2019 (COVID-19) on 12 February 2020 [65,66]. The outbreak is ongoing and poses a great global challenge. Health workers, government workers, and the general public need to come together to prevent the further spread of COVID-19.

### Transmission

Genomic sequence analysis of COVID-19 showed 88% identity with two bat-derived severe acute respiratory syndromes (SARS)-like coronaviruses [29,67], postulating that mammals are the possible link between COVID-19 and humans. Several findings have suggested that person-to-person transmission is a likely route for spreading COVID-19 infection. These findings are backed up by cases that occurred within families and among people who did not visit Wuhan's wet animal market [68,69]. Person-to-person transmission occurs primarily via direct contact or end-to-end droplets spread by coughing or sneezing from an infected individual. In a small study conducted on women in their third trimester who were confirmed to be infected with the coronavirus, there was no evidence of possible transmission from mother to child. However, all pregnant mothers went through caesarean sections for delivery [70]. So, it remains unclear whether transmission can occur during vaginal birth. This is important because expectant mothers are relatively more susceptible to infection by respiratory pathogens and severe pneumonia [65].

The binding of a receptor expressed by host cells is the first step of viral infection accompanied by fusion with the cell membrane. It is, therefore, reasoned that the lung epithelial cells are the primary target of the virus. Thus, it has been reported that human-to-human transmissions of SARS-CoV occur by the binding between the receptor-binding domain of virus spikes and the cellular receptor, which has been identified as angiotensin-converting enzyme 2 (ACE2) receptor [67,71]. Furthermore, the sequence of the receptor-binding domain of COVID-19 spikes is similar to that of SARS-CoV. This data strongly recommends that entry into the host cells is likely through the ACE2 receptor [67]. Studies have shown the correlation between angiotensin II receptor blockers (ARBs) and an increase in the risk of SARS-CoV-2 infection. A recent study reported ARBs as predictors of SARS-CoV-2 infection [72]. However, the investigation diverges from most previous



findings, as ACE inhibitors did not influence the risk of SARS-CoV-2 infection and outcomes. Also, Fosbol et al. [73] reported that prior use of ACEI/ARBs was not significantly associated with SARS-CoV-2 diagnosis and mortality among patients with SARS-CoV-2.

Similarly, the SARS coronavirus was transmitted through large droplets and direct contact [74]. The virus can reach a concentration of about 100 million particles per ml in sputum [75]. It can survive on contaminated surfaces and objects at room temperature for up to 6 days [76].

### Clinical features

COVID-19 spreads primarily through the respiratory tract by droplets, respiratory secretions, and direct contact for a low infective dose [77]. Otherwise, it has been reported that a SARS-CoV-2 was isolated from faecal swabs of a severe pneumonia patient on 10 February 2020, from a critical case in the Fifth Affiliated Hospital, Sun Yat-Sen University Guangdong, China [78]. Likewise, Zhang et al. [79] have found SARS-CoV-2 in faecal swabs and blood, indicating the possibility of multiple routes of transmission. ACE2 protein presents in abundance on lung alveolar epithelial cells and enterocytes of the small intestine, which may help understand infection and disease manifestations' routes. The incubation period is 1–14 days, mostly 3–7 days based on the current epidemiological investigation [80]. The COVID-19 is contagious during the latency period [77]. It is highly transmissible in humans, especially in the elderly and people with underlying diseases. Patients' median age is 47–59 years, and 41.9–45.7% of patients were females [81,82]. As it is designated SARS-CoV-2, COVID-19 patients presented similar symptoms, such as fever, malaise, and cough [77]. Most adults or children with SARS-CoV-2 infection presented with mild flu-like symptoms. A few patients are in critical condition and rapidly develop acute respiratory distress syndrome, respiratory failure, multiple organ failure, and even deaths [28].

A recent study led by Prof. Nan-Shan Zhong's team, by sampling 1099 laboratory-confirmed cases, found that the common clinical manifestations included fever (88.7%), cough (67.8%), fatigue (38.1%), sputum production (33.4%), shortness of breath (18.6%), sore throat (13.9%), and headache (13.6%) [77]. A part of patients manifested gastrointestinal symptoms, with diarrhoea (3.8%) and vomiting (5.0%). The clinical manifestations were inconsistent with the previous data of 41, 99, and 138 patients' analyses in Hubei province [28,80]. Fever

and cough were the dominant symptoms, whereas upper respiratory signs and gastrointestinal symptoms were rare, suggesting the differences in viral tropism compared with SARS-CoV, MERS-CoV, and influenza [65]. The elderly and those with underlying disorders (i.e. hypertension, chronic obstructive pulmonary disease, diabetes, cardiovascular disease) developed rapidly into acute respiratory distress syndrome, septic shock, metabolic acidosis, and coagulation dysfunction, even leading to death [65]. Minor symptoms of SARS-CoV-2 that are often neglected but very important include dysgeusia [83], anosmia [84], and skin lesions [85].

Most patients with SARS-CoV-2 had regular or reduced white blood cell counts and lymphocytopenia in laboratory examination results [86]. In severe patients, the neutrophil count, D-dimer, blood urea, and creatinine levels were significantly higher, while the lymphocyte counts continued to decline. Additionally, inflammatory factors (interleukin (IL)-6, IL-10, tumour necrosis factor- $\alpha$  (TNF- $\alpha$ )) increase, signifying the immune status of patients. The data showed that ICU patients had elevated plasma levels of IL-2, IL-7, IL-10, granulocyte colony-stimulating factor (GCSF), 10 kD interferon-gamma-induced protein (IP-10), monocyte chemoattractant protein-1 (MCP-1), macrophage inflammatory protein 1- $\alpha$  (MIP-1 $\alpha$ ), and TNF- $\alpha$  [28]. Moreover, a lower lymphocyte count [87] and a high aspartate transaminase (AST)/alanine transaminase (ALT) ratio [88] at the moment of admission in the hospital has been associated with mortality rate. However, more studies are still required to confirm these parameters' capacity as a predictor of mortality in SARS-CoV-2.

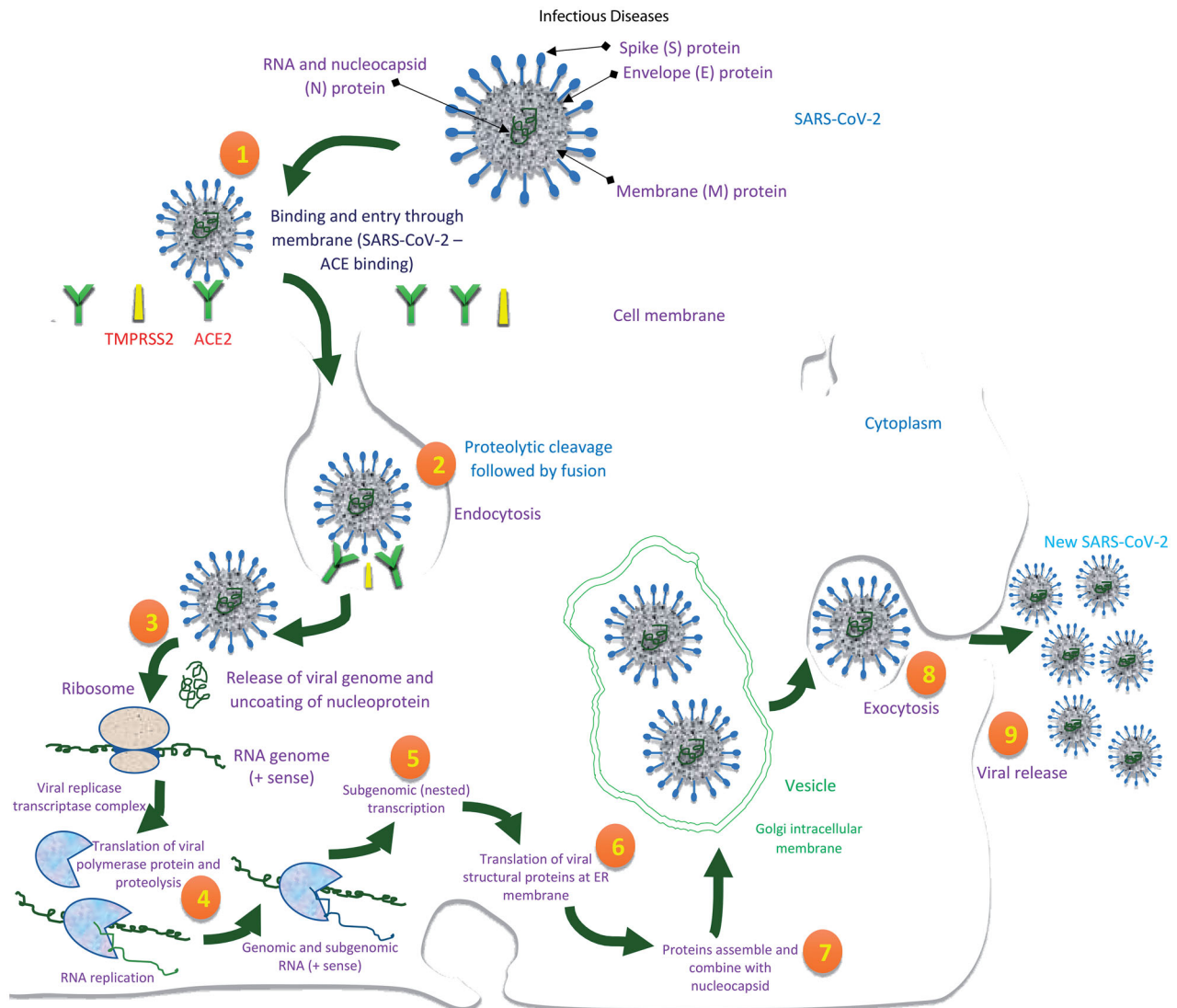
Also, the severity of lung involvement on chest X-rays and chest computed tomography (CT) in patients infected with SARS-CoV-2 can be a predictor of clinical progression [89]. Chest CT is highly sensitive for the diagnosis of SARS-CoV-2 [90]. It is the method of choice in the study of SARS-CoV-2 pneumonia. Most patients with SARS-CoV-2 have abnormal chest radiological findings, with more frequent ground-glass opacity and consolidation than patients with SARS and MERS [91]. However, studies are available reporting significant similarity in radiological findings between SARS-CoV-2 patients and those with complicated viral pneumonia, such as SARS and MERS [92,93].

### Viral entry and evasion of immunological responses

SARS-CoV-2 has a higher affinity for the human angiotensin-converting enzyme (ACE). It uses its envelope

spike proteins to bind to ACE2 receptors on host cells [94] (Figure 1). Organs with high expression of ACE2, such as kidney and intestines, heart, endothelium, and tongue, are its suitable targets [79,82]. ACE2 receptor is predominantly found in the human epithelia of the lung and small intestine. SARS-CoV-2 is more likely to infect the respiratory and gastrointestinal tracts [80,95]. Similarly, SARS-CoV-2 can infect cells genetically modified to express the ACE2 receptor solely [96,97]. The mucosa of the oral cavity is also a viral

invasion site [94]. Human dipeptidyl peptidase 4 (DPP4 or CD26) is also a potential binding target for the SARS-CoV-2 receptor-binding domain (RBD) of the S protein. DPP4 is expressed in human tissues such as the placenta, muscles, lungs, and the Central Nervous System (CNS). Other NK-cells, T cells, macrophages, and dendritic cells (DCs) also express the same protease DPP4 [94,98,99]. Wang et al. [82] also showed that the SARS-CoV-2 invade the cell utilizing CD147-spike protein.



**Figure 1.** The structure and pathophysiology of SARS-CoV-2. SARS-CoV-2 uses the ACE2 receptor and TMPRSS2 (transmembrane protease, serine 2) to enter the host. The SARS-CoV-2 viral protein binds to the host ACE2 receptor. This binding triggers viral entry. Upon entry into the host cell, there is the cleavage of the viral envelope. This proteolytic cleavage facilitates the release of the RNA genome in the cytoplasm. There is also the production of smaller RNA (subgenomic mRNAs). The translation of the mRNA produces many proteins (spike (S), envelope (E), and nucleocapsid (N) proteins, etc.) crucial for the formation of viral assembly. The three proteins (S, E, and M) enter the endoplasmic reticulum (ER). The combination of N protein and the positive strand of genomic RNA leads to a nucleoprotein complex formation. The nucleoprotein formation involves synthesizing a full-length RNA and the complete formation of the full-length genomic RNA. The complete generation of an entire virus particle (the assembly of protein and genomic RNA) occurs in the ER-Golgi apparatus chamber. This chamber is called the site of budding. The complete virus particles are then transported and released through the formation of the vesicle and the process of exocytosis. The summary of the entire process is as follows: (1) SARS-CoV-2 – ACE binding (2) proteolytic cleavage and subsequent fusion (3) the release of viral RNA and uncoating of nucleoprotein (4) translation and replication (5) transcription and RNA replication and packaging (6) translation (7) Assembly and budding (8) exocytosis (9) the release of the virus.

Upon entry into the host cell, genome RNA serves as mRNA for the first open reading frame (ORF1), which is translated into viral proteinases that are cleaved into smaller products by viral proteinase. These polyproteins are assembled on double-membrane vesicles and become a suitable site for viral replication (Figure 1). Through genome replication and viral subgenomic RNA transcription, the viruses evade the host immune response through their ability to stop PRR expression [22]. Suppression of type 1 IFN (IFN-1) and other proinflammatory cytokines can also occur in SARS-CoV-2 patients [100]. A similar invasion mechanism demonstrated in SARS, and MERS is employed by the SARS-CoV-2 virus [100–102], either through disturbance in RNA sensing and type 1 IFN production. SARS-CoV-2 restricts the production of type 1 IFN by inhibiting IFN signal transduction pathways such as IRF-3. IFN-1 response involves the ubiquitination and degradation of RNA sensor molecules and nuclear translocation of IFN regulatory factor 3 (IRF3), and the reduction of signal transducer and activator of transcription 1 (SATA1) phosphorylation [103–105].

SARS-coV2 can also elude the host immune system through the irregular expression of genes associated with antigen presentation [106], such as the Major Histocompatibility Complex (MHC) depending on antigens' presentation [107]. MHC or HLA plays a dual role in SARS-CoV-2 infection. It either prohibits or aid infection [108–111]. Reports have also shown that CD147, a transmembrane glycoprotein of immunoglobulin superfamily involved in tumour progression and plasmodium invasion, can limit viral replication when its expression is halted [82]. Other mechanisms of SARS-CoV-2 invasion are the shedding of antibody–antigen complexes on cell surfaces, decrease Fc receptor expression, and limiting the complement regulatory components. SARS-CoV-2 can also evade identification by Immune cells. The role of viral entry is paramount at this vital stage, and it determines the entire health of a host. During viral entry, the infection can either be restricted with little or no clinical implication [94].

### SARS-CoV-2 infection and immunological response

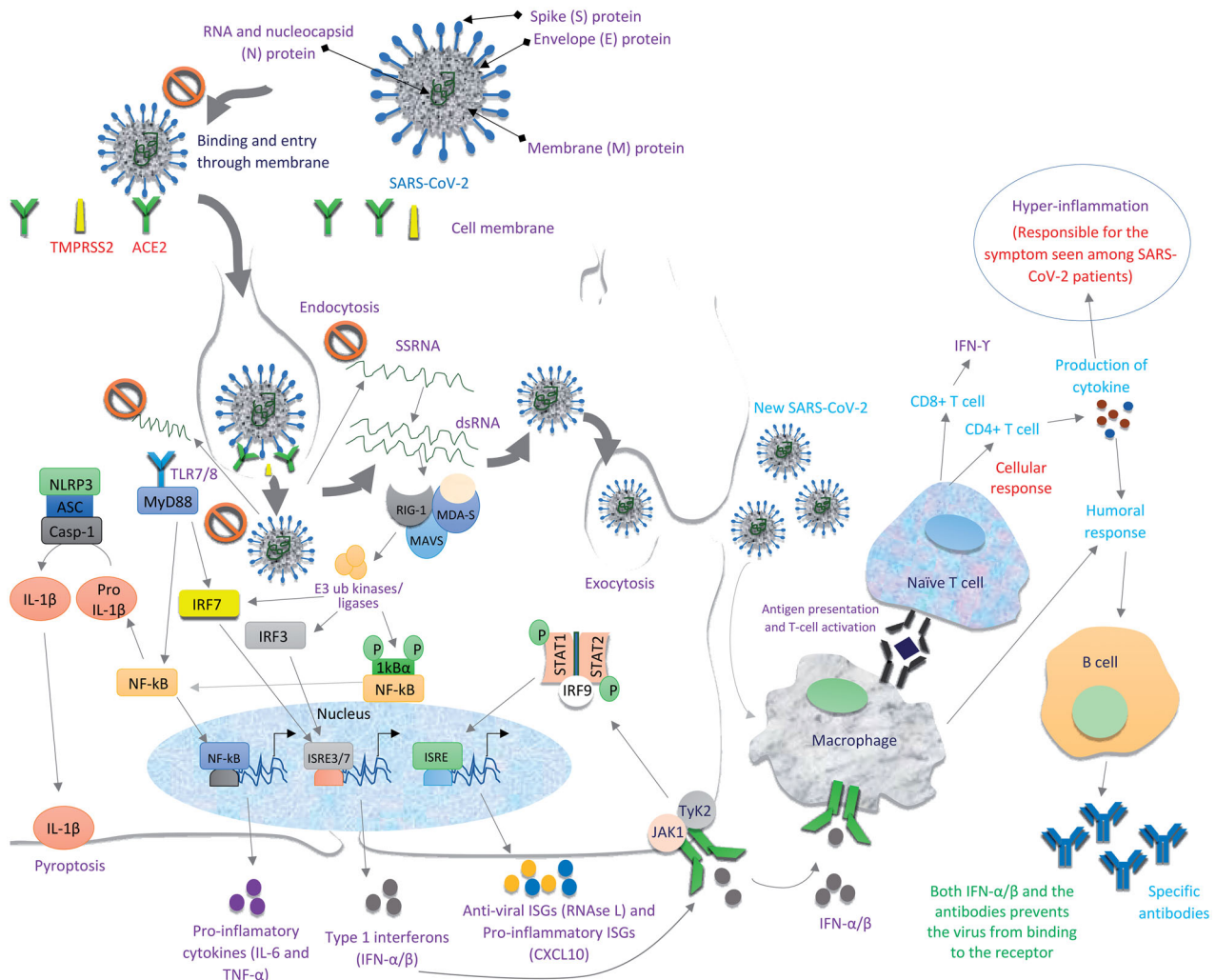
Innate immunity is the first-line defense mechanism against invading pathogens, including viral infection. It plays a vital role in the fight against diseases and infections through the complex interactions between cells and soluble mediators such as the macrophages, natural killer (NK) cells, monocytes, polymorphonuclear cells, dendritic cells, innate lymphoid cells, cytokines,

chemokines, and the complement system [112,113]. Invading pathogens are attacked almost immediately by the phagocytic processes and cytolysis. Innate response against pathogen invasion must be sensed first by the innate cells responsible for defense. In SARS-CoV-2, both the viral single-stranded RNA and double-stranded RNA must be recognized by pattern recognition receptors (PRRs) found on various innate immune cells, including antigen-presenting cells (APCs) [110]. They recognize pathogen-associated molecular patterns (PAMPs) of invading viral RNA, resulting in innate immune cells' activation [114,115]. Endosomal PRRs active in innate immunity such as Toll-like receptors (TLR-) 3, 7/8, and 9 found on macrophages or DCs are responsible for detecting SARS-CoV-2 [80,100,116,117].

Other receptors such as the RIG-I-like receptors (RLRs) [100], C-type lectin-like receptors (CLRs) [53], NOD-like receptor (NLR) such as NLRP3 inflammasome [118], and free molecule receptors such as STING, cGAS, IFI16, and DAI are active in recognition of viruses and mediation of immune response-related signalling pathway [81]. RLRs are comprised of the H family members RIG-I (DDX58), MDA5 (IFIH), and LGP2, which recognize the genomic structure of RNA viruses such as SARS-CoV-2 [100]. NLRs are divided into three classes, mainly the inflammasomes (NLRP1, NLRP3, NLRP6, NLRC4, NLRC5W, and AY2), the embryo regenerative and regulatory NLRs [80,118]. They are a subclass of PRRs made up of conserved NOD structure. CLRs are soluble PRRs expressed majorly in myeloid cells. They are responsible for phagocytosis, maturation of DCs, and chemotaxis. Moreover, Toll-like receptors (TLRs) recognize PAMPs, RIG-I-Like receptors recognize nucleic acids, C-type Lectin-like receptors (CLRs), and NOD-like receptors (NLRs) are pattern recognition receptors (PRRs) responsible for identifying the viral antigens [81]. RNA fragment of SAR-CoV-2 can activate RIG-1 and mitochondrial antiviral signalling (MAV) platforms in the cytosol [119].

Upon recognizing the invading pathogen, the inflammasomes (monocytes and the macrophages) activate the viral nucleic acids. There is also the activation of proteins through downstream inflammatory signalling pathways, such as the phosphorylation or the translocation of nuclear factor  $\kappa$ B (NF- $\kappa$ B), phosphoinositide 3-kinase, mitogen-activated protein kinase, and IFN regulatory factor 3 (IRF-3). The activations trigger an immune response and the production of type 1, 11, and 111 interferons (IFN) and the activation of genes coding for cytokines such as IL-1 $\beta$ , TNF- $\alpha$ , IL-6, and IL-18 [81,94,119–123]. The precursors are converted into active cytokines, which in





**Figure 2.** Host immune response during SARS-CoV-2 infection. When SARS-CoV-2 viral particles enter into the cell, they are recognized by innate immune receptors (TLR7/8, RIG1-MDA-5 (RNA sensors), and the NLRP3 (inflammasome sensor)). The RNA genome of the virus and other proteins interacts with MAVS (mitochondrial antiviral-signalling protein). This interaction triggers the activation of NF- $\kappa$ B. This activation is mediated by several signalling cascades involving several ligases and E3 ubiquitin kinase. The NF- $\kappa$ B subsequently enters the nucleus. In the nucleus, NF- $\kappa$ B functions as a transcriptional activator of several pro-inflammatory cytokines (IL-1 $\beta$  AND IL-6). When ubiquitin kinases phosphorylate IRF3 (IFN-regulatory factor 3), it homodimerizes. Subsequently, it enters the nucleus to ensure the activation of Type 1IFNs. Type 1IFNs uses both autocrine and paracrine mechanisms to induce the JAK-STAT signalling pathway. The JAK1 and TYK2 protein kinases ensure the phosphorylation of STAT1 and STAT2. Both STAT1 and STAT2 heterodimers enter the nucleus, where they help in the transcription of genes stimulated by IFN and genes that have an IFN-stimulated response element (ISRE) in their promoter. The strong antiviral activity of type 1IFNs helps to prevent the proliferation and progression of the virus. The activity of type1IFNs is further enhanced by the expression of ISGs (IFN-stimulated genes) (e.g. RNase L). So, both the pro-inflammatory cytokines and the type 1 IFNs ensure viral clearance and prevent infection. Therefore, the adaptive immune response is modulated by the cytokines produced by the infected cells. There is usually the recruitment and activation of macrophages, B cells, and T cells. These immune cells ensure the elimination of the virus from host cells. However, SARS-CoV-2 uses several tactics to shut down the immune signalling cascade and manoeuvre the immune system. The virus uses its structural proteins (M and N protein) and NSPs (NSP1, NSP3b, NSP6) along with PLpro to suppress the immune signalling cascade.

a complement system act against viral progression. Antiviral properties produced by IFN can truncate any of the viral life cycle steps [123]. Type 1 (IFN-1) [124] divided into IFN $\alpha$ , IFN- $\beta$ , and type 11 (IFN $\gamma$ ) is released by plasmacytoid DCs. In contrast, type 11 (IFN-111), which is the IFN- $\lambda$ , is released by epithelial cells of the gastrointestinal and the respiratory tract [119,125].

Furthermore, IFN-1 is a cytokine produced by most cells at viral invasion. However, the cells producing it

differ based on the type of viral infection. Plasmacytoid and myeloid DCs are major producers of IFN-1 [126]. Most immune cells produce IL-6 [127]. IL-6 is a pleiotropic cytokine that induces B cell proliferation and assists Cytotoxic T lymphocyte (CTL) activation [94]. It also plays a role in pro-inflammatory and anti-inflammatory reactions, inducing Th17 lineage cells and inhibiting regulatory T (Treg) cell proliferation [128,129]. Moreover, the interferon and the cytokines produced activate the



natural killer (NK) cells, which activates the major histocompatibility complex (MHC)-independent immune response capable of stopping the pathogenesis of SARS-CoV-2 at an early stage of infection [96]. IFNs, phagocytes, and other cytokines are produced by macrophages' immune response [121,130,131].

Once the disease is established, the DC initiates an immediate response by producing IFNs, 1L-6, and the stimulation of adaptive response. IFN type 1 activates IFN-transmembrane family proteins, which inhibit the viruses' entrance into host cells, replication, and other host cells' infection [132]. Apart from direct antiviral activity, the IFN-1 acts on cellular components of innate and adaptive immunity such as NK cells and T cells [94]. The complement system is part of the innate system. It is activated at the acute phase of the disease. However, it can be a one-step forward and a two-step backward process. This is because the anaphylatoxins c3a and c5a can activate immune cells, inducing the release of pro-inflammatory cytokines, other components fragments such as membrane attack complex (MAC), c3b, and c5b inducing arachidonic acid synthesis that acts in the inflammatory process [94] or negatively affects immune response by the dissemination of intracellular coagulation (DIC) that can cause organ failure [133,134]

The complement system's activation through either the alternative or the mannose lectin binding pathway inactivate virions and recruit immune cells. There are also viral opsonization, cytolysis, and B and T cell responses [119,135,136]. Glycoprotein S of the SARS-CoV-2 interacts with the mannose-binding lectin and activates the complement cascade [136,137] that eradicates invading viral pathogen directly through cytolysis or indirectly through immune complex-mediated viral clearance. [Figure 2](#) summarizes the host immune response during SARS-CoV-2 infection.

### **Adaptive immunity against SARS-CoV-2**

Generally, two cells play a major response in adaptive immunity. These are the T cell and the B cells.

#### ***T cell immunity***

DCs is a connecting bridge between the adaptive immune system and the innate immune system. DCs' activity results in an unselective pro-inflammatory response after its interactions with pathogens or acts as APCs, activating lymphocytes [119]. The SAR-CoV-2 envelope protein such as the S, E, and N have epitopes

recognized by DCs, while the binding between the DCs to the epitope triggers an adaptive immune response [36]. MHC class 1 usually presents antigen epitopes to CD8+ T lymphocytes, where cytotoxicity takes place. Similarly, the presentation of these epitopes by the MHC class to CD4+ T helper (h) cells stimulates the T cell receptors triggering differentiation of the T helper cells (Th) and finally resulting in the immunologic cascades [119,138].

#### ***B cell immunity***

After the differentiation of Th cells into Th1, Th2, Th17, Th22, Th9, and Th follicular (f) or T regulatory lymphocytes (Treg), the Th2 lymphocytes with the B cells aid the maturation of plasma cells and the secretion of antiviral antibodies IgM, IgG and IgA. Studies have shown that patients develop anti-SAR-CoV-2 IgM and or IgG at 15 days of infection onset [139]. Evidence is also available that these antibodies remain detectable and recovered from recovered patients after initial infection [140]. In the presence of another immunological mechanism, possible activation of the complement system and stimulation of immune cells such as monocytes and macrophages may be required in fighting SAR-CoV-2 viral infection.

### **Antiviral nanotechnology as an intervention strategy against SARS-CoV-2 infection**

Over several decades, drugs and vaccines' unavailability has hindered protection and intervention against emerging viral threats [141]. Thus, a rapid response in developing therapeutic strategies for SARS-CoV-2 and possible future epidemics remains a critical challenge. Several promising therapeutic strategies are rapidly emerging for the treatment of coronavirus. However, an essential step in combating SARS-CoV-2 is prompt, efficient testing and diagnosis of the virus. The current approach for SARS-CoV-2 diagnosis involves the throat and nasal swab of potentially infected persons. The swab sample is then analyzed using a reverse transcriptase-polymerase chain reaction (RT-PCR) test. Nanotechnology could be employed to prevent the spread of viruses, diagnose the virus, as an antiviral drug delivery system, and repress immunological response due to viral infection. The field of nanotechnology is a multidisciplinary area that uses nano-sized particles (size range of 1-100nm) and devices for several applications not limited to diagnostics, targeted drug delivery, and new therapeutic

production of biomaterials [142,143]. Nanoparticles can either be organic (e.g. liposomes, polymeric, micelles, ferritin) or inorganic (e.g. metal nanoparticles). Both types of nanoparticles have been efficient in treating several health conditions [144]. Organic nanoparticles have been used in some antiviral drugs (e.g. acyclovir, efavirenz, zidovudine, and dapivirine) to increase the bioavailability of drugs, enhance efficient drug delivery and improve antiviral activity [145,146].

Metallic nanoparticles have shown more promise due to their ability and their multi-target functions on microbes and less tendency for organisms to acquire resistance against them [147]. Many metallic nanoparticles (silver, zinc, gold, and copper, etc.) are already used as antimicrobial agents. Silver nanoparticles specifically have demonstrated excellent potentials against bacteria [148–150] and pathogenic fungi [51,151,152], and several viruses (including HIV-1) [153,154]. It is also an excellent candidate for capturing and immobilization of viral cells in personal protective devices (PPD). Copper nanoparticles effective against bacteria [155] and fungi [156] have also been reported to be effective against HuCoV-229E (different from SARS-CoV-2, although they share several similarities) [157]. It has also been recently reported to be useful in preventing SARS-coronavirus and influenza virus [158]. Gold nanoparticles are known to be antibacterial [159,160] and antifungal [159]. They have also been reported to exhibit antiviral activity [161]. Metallic oxide nanoparticles (e.g. Zinc oxide nanoparticles have also been shown to exhibit antiviral activity against H1NI and SARS-CoV replication [162,163]. Several other nanoparticles effective against a wide range of viruses were also reported by [164] in their recent review.

Surfaces coated with substances containing nanomaterials have shown potential against SARS-CoV-2 [165,166]. They produce ions that disrupt microbial cells and have been reported to exhibit antiviral activity. The ability of SARS-CoV-2 to survive on several surfaces for an extended period is one of the significant challenges in overcoming the virus. Thus, synthesizing and engineering nanomaterials so that the release of ions is gradual is a crucial technique that can offer protection continuously even after just one treatment. The use of nanomaterials in the formulation of new drugs has been seen as a critical enabling technology, with the potentials to provide solutions targeting current and future medical needs. However, whether nanotechnology is ripe enough to address medical needs efficiently in the context of a pandemic is a question that needs to be

answered. Nanoparticles can be efficiently inserted into SARS-CoV-2 for neutralizing the viral particles. They can also be used to control the proliferation and multiplication of the virus. They can also be used to target the S protein preventing the virus from attaching to host cells. The development of nano compounds (encapsulation of the virus with nanomaterials) can also be an effective route to control viral growth and its attachment to host cells [55]. Nanotechnology can also be utilized to deliver antiviral drugs targeting SARS-CoV-2. Currently, available nanoparticulate antiviral systems include liposomes, polymeric NPs, micelles, solid lipid NPs (SLNs), nanostructured lipid carriers (NLCs), nanocapsules, nanotubes, quantum dots, dendrimers, emulsions, nanogels, vesicles, and cyclodextrin-based systems. They are nano-scale drug delivery systems that offer a slow-release and the delivery of drugs to the targeted cells (Figure 3)

### **Mechanism of action of nanomaterials against SARS-CoV-2 and potential targets for nanomaterials**

Metallic nanoparticles can prevent attachment of the virus to host cells, thereby inhibiting internalization and impairing replication. Nanomaterials containing silver, zinc, titanium, and gold have shown great promise against several viruses [167]. Nanoparticles' mechanism of action is based on their ability to bind to the viral protein, impairing their chances of interaction with the host and preventing their entry [168]. For example, the interaction of carbon quantum dots with the S protein of HCoV-229E has been reported to prevent the viral protein from interacting with the host cells. There was also a reduction in viral replication. Higher antiviral activity was also seen when the carbon quantum dots were functionalized with boronic acid [169]. Nanoparticles can also inhibit viral replication by disrupting the key enzyme facilitating the process. Their treatment efficiency depends on their shape, size, and surface charge [170].

As already stated, for SARS-CoV-2, the spike proteins (S protein) of SARS-CoV-2 (similar to that of SARS-CoV) perform a crucial function in viral infection establishment [96,171]. There are two S subunits (S1 and S2). The S1 subunit with human angiotensin-converting enzyme II (ACE2) serves as the entry receptor. The S2 subunit enhances viral fusion and penetration [96,172]. Subsequently, there is an infection establishment. In an attempt to eliminate the virus and facilitate tissue repair, there is an upregulation of inflammatory cytokines by

macrophages and monocytes [173] (Figure 2). However, the inflammatory state may further be exacerbated with an increase in immune dysfunction; a condition called cytokine release syndrome (CRS). The CRS is responsible for the progression of the infection evidenced by several symptoms seen in about 20% of the patients [28]. Therefore, a treatment approach that prevents ACE2-mediated viral entry and that reduces inflammatory response has been the focus since the emergence of SARS-CoV-2 [54].

Many antiviral drugs (including remdesivir) used for the early intervention against SARS-CoV-2 infection have shown potential activity [174,175]. However, only a few drugs target the late stage of the CRS-associated infection. Evidence is available that immunopathology caused by SARS-CoV-2 may be curbed by targeting IL-6 and granulocyte-macrophage colony-stimulating factor (GM-CSF) using monoclonal antibodies [97,176]. However, the complexity of cytokine interactions and the ease with which the cytokine targets multiply makes it challenging to suppress CRS [177].

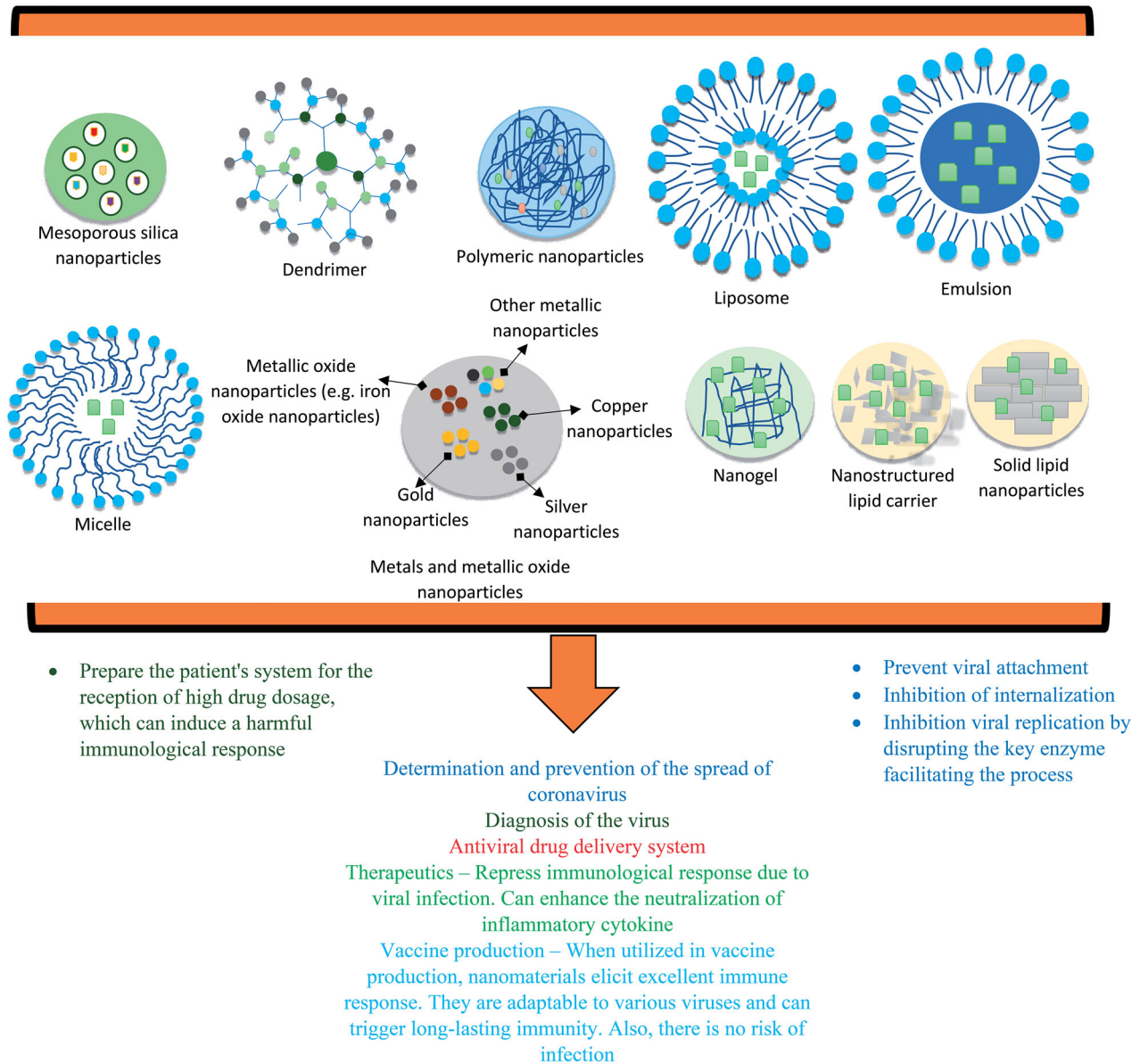
SARS-CoV-2 targets the upper respiratory tract and the lungs. The lung is, however, more critically affected. Nanomaterials as a potential biomaterial against coronavirus can penetrate the deep-lung, delivering drugs directly to the cells that SARS-CoV-2 uses for its dissemination into the biological system. Nanomaterials that can prevent viral interaction and binding to the cell membrane hold a great promise as this could be achieved using nanomaterials such as liposomes, polymers, and small molecules (Figure 3) – this could be implemented via aerosol. However, the important dilution of these materials can affect the effectiveness negatively. This setback, however, can be removed by using nanoparticles that target the virion. Nanomaterials can be delivered as immunosuppressive agents targeting immunological cells and organs and causing a decrease in dosage, distribution of drugs to non-target tissues and organs, and can also cause undesirable side effects. The possibility also abounds that nanotools can be specifically engineered to manoeuvre the immune cells and readjust and prepare the patient's system for the reception of high drug dosage, which can induce a harmful immunological response. Evidence is also available that nanodiamonds could be used to decrease macrophage infiltration – this process collectively leads to inflammation.

Therefore, nanotechnology is a rapidly emerging area with potentials against several infectious diseases [48–50,174,178]. Engineered liposomes, exosomes, and

nanosponges have shown the potential to neutralize bacterial toxins [179,180]. Cellular nanovesicles carrying proteins with orientation, structure, and activity have been synthesized with potential against viral particles [181–183]. Nanovesicles displaying ACE2 protein to compete with host cells for binding to the SARS-CoV-2 have recently shown great promise [184,185]. Nanovesicles have also been employed for cell membrane-coated nanoparticles to neutralize cytokines in SARS-CoV-2 infection [182,186].

Furthermore, Rao et al. [185] showed that a decoy nanoparticle neutralizes coronavirus strain and subsequently neutralizes cytokine. The decoy nanoparticle (nanodecoy) was produced by fusing cellular membrane nanovesicles obtained from human monocytes and genetically manipulated cells. These cells were stably expressing angiotensin-converting enzyme II (ACE2) receptors. They also have an antigenic exterior the same as source cells. The host cells were effectively protected from Pseudoviruses and SARS-CoV-2 infection. This protection was due to competition between the nanodecoy and the host cells. Also, due to several cytokine receptors on the surfaces, there was the successful binding of the nanodecoys to the immune cells. This binding helps in the neutralization of inflammatory cytokines (IL-6) and GM-CSF. It also decreases immune disorder and lung injury in an acute pneumonia mouse model. Therefore, decoy nanoparticles promise to be an important biomaterial with potential against SARS-CoV-2. However, there's a need for optimization and scale-up in its production.

Understanding the potential SARS-CoV-2 drug target is crucial to design a drug against this virus. Due to similar sequence homology with other viruses, drugs useful for some viruses can be tested for their effect on SARS-CoV-2. For example, PLpro and 3CLpro are two viral proteases whose role is to cleave viral peptides into replication and packaging functional units. Therefore, drugs that target this protease can be studied. Even the enzyme responsible for the synthesis of viral RNA can be studied as possible drug targets. Also, synergistic coaggregation of nanoparticles with other substances (e.g. antiviral agents) can increase the antiviral compound's therapeutic potential and further reduce toxicity often associated with nanoparticles. Huang et al. [187] in a study involving MERS (the Middle East Respiratory Syndrome virus) show that the conjugation of gold nanorods with antiviral material (small  $\alpha$ -helix peptide) helped increase the therapeutic potential of the protein. Also, *in vivo* and *in vitro* analysis showed an



**Figure 3.** Various types of nanomaterials with potentials against coronavirus.

increase in biocompatibility, stability, and pharmaceutical potential of the material. Therefore, nanomaterials can be conjugated with already available antiviral agents and their possible anti-SARS-CoV-2 potential evaluated.

### Recent developments in the use of nanoparticles as a potential intervention strategy against SARS-CoV-2

As a drug delivery system, nanoparticles have great potential. The nano-based vaccine can be the solution to SARS-CoV-2 infection. Also, there is a sequence homology between SARS and MERS. This nanoparticle-based vaccine against SARS and MERS can be used as a blueprint to develop a vaccine targeting SARS-CoV-2 [188–191]. In a recent investigation, a vaccine

formulated with maltodextrin nanoparticles was found to be effective against SARS-CoV-2 [192]. Lipid nanoparticles have also been employed in RNA-based vaccines. It has been used in packaging the RNA molecule and delivering it within the body. Recently, a biotechnology industry, Moderna, based in the US with a major focus on mRNA therapeutics, rolled out its mRNA-1273 vaccine. The mRNA-1273 is an mRNA-based vaccine encapsulated in a lipid nanoparticle (LNP) (Table 1).

Antiviral NanoDiamonds technology masks with the potential to halt the spread of the SARS-CoV-2 are also under production at a company in Hong Kong. Additionally, using its proprietary recombinant nanoparticle vaccine technology, Novavax also kicks start the formulation of a vaccine for SARS-CoV-2. Researchers from the University of Washington's Institute for Protein



**Table 1.** List of developed vaccines and vaccine candidates against SARS-CoV-2 under WHO evaluation process.

S/No.	Name of vaccine	Manufacturer	Platform
1	BNT162b2/COMIRNATY Tozinameran (INN)	Pfizer	Nucleoside modified mRNA
3	AZD1222	SK BIO	Recombinant ChAdOx1 adenoviral vector encoding the spike protein antigen of the SARS-CoV-2
4	Covishield (ChAdOx1_nCoV-19)	Serum Institute of India	Recombinant ChAdOx1 adenoviral vector encoding the spike protein antigen of the SARS-CoV-2
5	Ad26.COV2.S	Janssen	Recombinant, replication-incompetent adenovirus type 26 (Ad26) vectored vaccine encoding the (SARS-CoV-2) spike (S) protein
6	AZD1222	AstraZeneca	Recombinant ChAdOx1 adenoviral vector encoding the spike protein antigen of the SARS-CoV-2
7	SARS-CoV-2 vaccine (Vero cell), Inactivated (InCoV)	Sinopharm/BIBP <sup>1</sup>	Inactivated, produced in Vero cells
8	SARS-CoV-2 vaccine (Vero cell), Inactivated mRNA-1273	SINOVAC Moderna	Inactivated, produced in Vero cells
9			mRNA-based vaccine encapsulated in lipid nanoparticle (LNP)
10	Sputnik V	The Gamaleya National Centre	Human Adenovirus Vector-based Covid-19 vaccine
11	Ad5-nCoV	CanSinoBio	Recombinant Novel Coronavirus Vaccine (Adenovirus Type 5 Vector)
12		NOVAVAX	–
13	EpiVacCorona	Vector State Research Centre of Virology and Biotechnology	Peptide antigen
14	Recombinant Novel Coronavirus Vaccine (CHO cell)	Zhifei Longcom, China	Recombinant protein subunit
15	SARS-CoV-2 Vaccine, Inactivated (Vero Cell)	IMBCAMS, China	Inactivated
16	Inactivated SARS-CoV-2 Vaccine (Vero Cell)	Sinopharm/WIBP <sup>2</sup>	Inactivated, produced in Vero cells
17	COVAXIN	Bharat Biotech, India	SARS-CoV-2 Vaccine, Inactivated (Vero Cell)
18	SCB-2019	Clover Biopharmaceuticals	Novel recombinant SARS-CoV-2 Spike (S)-Trimer fusion protein

Design are currently manufacturing nanoparticles to formulate a more efficient vaccine against SARS-CoV-2 using computational models to predict and engineer self-assembling proteins. A group of researchers from the University of Lille and Ruhr-University Bochum recently showed that incorporating AuNPs and carbon quantum dots (CQDs) to the cell culture medium before and during SARS-CoV-2 infection extensively suppressed the infection rate of the cells. By applying its nanorod technology, Sona Nanotech created a lateral-flow screening test to identify SARS-CoV-2 in less than 15 min [193].

Currently, gold nanoparticles used to bind antibodies are a new and less expensive approach still in their infant stage. In the presence of the antibodies, the nanoparticles cluster and subsequently change the colour of the swab. This approach provides a means for diagnosing the virus, especially in resource-limited settings. Additionally, biosensing devices (graphene-based field-effect transistors (FET) coupled to a specific antibody against SARS-CoV-2 S protein are also a promising and cost-effective means of diagnosing the virus. AuNPs can be used as nano biosensors in the detection of the particular whole viral cell. The nanoparticle combines its optical and electrical features with biological or synthetic molecules used as receptors in this process. During the process, the specific antibodies conjugated to gold nanoparticles react with cell surface proteins. Although all these approaches are relatively infancy,

they hold great promise in the fight against SARS-CoV-2 and future epidemics and pandemics.

More recently, the European Commission and the Spanish Ministry of Science and Innovation announced their plan to fund a research project (CONVAT). The project is aimed at developing a rapid SARS-CoV-2 test using nanobiosensors. The project will provide a new device using optical biosensor nanotechnology that will permit the detection of SARS-CoV-2 directly from the patient's sample within about 30 min, thus making testing in centralized medical laboratories non-useful. The new biosensor device will also be used for detecting the different SARS-CoV-2 present in animals and humans to check for possible evolutions of the new SARS-CoV-2 strain and prevent future outbreaks. Furthermore, nanoparticle-infused fabric that can be utilized in medical masks, personal protective materials, and other hospital materials has also been developed by Sonovia, an Israeli company. Nanopolymer-based disinfectants that can kill viruses and other microbial cells with up to 21 days of effectiveness are currently undergoing testing in Prague's public transport for use against SARS-CoV-2. A similar study utilizing antimicrobial polymer coating is also underway at the Hong Kong University of Science and Technology [193].

Furthermore, according to a report by Nanowerk, iron oxide nanoparticles have been reported as a potential agent for SARS-CoV-2 diagnosis. Iron oxide nanoparticle

is well known for its antibacterial [194] and antifungal activity [195]. Even nano-gold kit based on IgM/IgG antibody assay has shown promise in the early detection of SARS-CoV-2 [196]. However, more effort is needed to develop cost-effective kits for accurate and rapid diagnosis of SARS-CoV-2. Several other products currently under development for potential against SARS-CoV-2 can be seen in the Nanotechnology products database 2020 [193].

Finally, several vaccines have been developed for treating SARS-CoV-2. Within WHO EUL/PQ evaluation process, the vaccines that have been finalized and those still undergoing developmental stage and clinical trials are summarised in Table 1.

### **Challenges in the use of nanomaterial as an intervention strategy against SARS-CoV-2**

Nanotechnology is a critical player in antiviral therapy development and could be a major player in some antiviral agents' low bioavailability drawbacks [197,198]. The small size of nanoparticles enables its use as a drug delivery system across biological barriers [199–201]. The small size allows drug delivery across impermeable barriers. Also, the large surface area enhances improved efficiency, and there are also slim chances of emergent drug resistance. However, recent evidence is emerging of microbes developing resistance to nanoparticles.

Generally, several factors affect the production of novel antiviral drugs. The rapid increase in drug resistance is one of the significant factors. Moreover, the multiplication of viruses using host cell machinery makes it difficult to target specific viral metabolic pathways without impacting the host cell. Also, the fact that each virus has a unique biosynthetic pathway makes the formulation of drugs targeting a wide range of viruses highly difficult. Viral replication is dependent on the biosynthetic machinery of the host cell [202]. Thus, only a limited number of virus-specific metabolic functions that antiviral drugs can target without any damage to the host cells. Also, each virus has a specific role. This attribute hinders the formulation of a broad-spectrum antiviral agent that causes similar symptoms. Even some drugs that can cure acute illness are not effective during latent infection. This can lead to recurrent or chronic disease, which always poses some treatment difficulties [201]. Thus, drug preparation or dosage manipulation that targets physicochemical and bio-pharmaceutical features of antiviral materials should be a new therapeutic tactic.

Furthermore, following oral administration, nanoparticles can be degraded in the gut. Inability to penetrate the mucous barrier can also reduce its internal absorption [203]. Opsonisation, reduction in plasma half-life, and macrophage uptake can also result from its interaction with biological fluids [204]. Off-target absorption may trigger apoptosis with damage to the cell membrane, which subsequently triggers an adverse immunological response [205]. The renal system's inability to clear the nanoparticles prevents degradation and subsequent accumulation, leading to cytotoxicity [206]. Scaling up is another issue associated with nanoparticles, in addition to the associated high cost.

It is important to emphasize that for any nanomaterial to be used as an antimicrobial agent, the material must be biocompatible, biodegradable, and non-toxic to host cells. PEG can exhibit various charges, sizes, and shapes. It also enhances nanoparticle tolerability, clearance reduction, and an increase in circulation time. The distribution of nanoparticles is influenced by size. Therefore, ideal candidates for nanoparticle design must be materials with a size of less than 200 nm.

Due to the limitations (multiple administration routes, weak immunogenicity, and unstable nature) associated with conventional vaccines, nanoparticles have proven superior, with an additional increase in shelf life and easy recognition by immune cells. However, for efficient utilization of nano-based therapy as a future therapeutic strategy against SARS-CoV-2, there is a need for optimization, scale-up practices based on good manufacturing practice, regulatory guidelines, cost-effective formulation, and high-quality formulation. To provide an effective and safe antiviral agent, all the above features need to be considered. Safety concern, however, remains one of the pressing issues in the use of nanoparticles as an agent against pathogens.

Finally, with their small size, nanoparticles can penetrate various parts of the body. The potential toxicity and unforeseen side-effects raise several questions as regards their use as agents against SARS-CoV-2. Thus, there is a need for a full assessment of the safety of these biomaterials. Regulatory bodies are needed to ensure that these materials possess the lowest possible side effects on end-users. Devices with nanomaterials need to be adequately evaluated for any possible side effects. There is also a need to establish validated techniques to assess nanomaterials' exposure and detect and characterize nanomaterials' hazards. Much remain to be done before the establishment of comprehensive regulatory standards for Nanomedicines. The readers are

referred to other articles discussing the role of nanotechnology in the fight against SARS-CoV-2 [207–213].

## Conclusions

We summarise by stating that cells infected with SARS-CoV-2 undergo pyroptosis and produce several molecules that induce epithelial and endothelial cells and also macrophages. The production of pro-inflammatory proteins (cytokines and chemokines) causes T cells, macrophages, and monocytes to migrate to the site of infection. The released IFN $\gamma$  from T cells triggers a loop of pro-inflammatory feedback. The successful immunological response involves (1) the T cell-mediated elimination of the infected cells (2) antibody-mediated inactivation of the SARS-CoV-2. These antibodies are produced by B cells. (3) Recognition of the infected cells by macrophages and subsequent phagocytosis. However, multiple organ damage (dysfunctional immunological response) can result from (1) excess immunological response due to excessive infiltration of cells of the immune system and (2) an increase in a cytokine storm (IL-6, IL-2, IP-10, IL-10, IFN $\gamma$ , G-CSF, TNF, MIP1 $\alpha$ ) due to the excessive infiltration. The production of the non-neutralising antibody by B cells can lead to the viral infection's ADE (antibody-dependent enhancement). Although the information is rapidly emerging, the exact underlying mechanism of immunological reactions against SARS-CoV-2 remains elusive. The source of the several inflammatory reaction evidence during the reaction is unknown. More studies are urgently needed to understand the interplay between SARS-CoV-2 and the immune system comprehensively.

Furthermore, the development of an effective vaccine and other efficient therapeutic measures against SARS-CoV-2 remains the primary goal of pharmaceutical companies. The major therapeutic strategies against SARS-CoV-2 include (1) targeting cellular signalling pathways, (2) modulation of immune defense, (2) blocking viral cell entry and targeting various antiviral mechanisms, (4) targeting viral RNA-dependent RNA polymerase, (5) blocking polyprotein posttranslational processing, (6) endocytic pathway interference, (7) oligonucleotide gene therapy, (8) vaccine. Also, the strategies currently explored as vaccines for SARS-CoV-2 include (1) protein subunit vaccines, (2) nanoparticle or virus-like particle vaccines, (3) inactivated virus vaccines, (4) live-attenuated virus vaccine (5) mRNA and DNA vaccines (6) virus-vectored vaccines.

Currently, there are insufficient data as regards standard care. As research intensifies, several treatments for the early stage of the disease and as the disease progresses are available. Inflammatory assault on the lungs and several organs is a big issue among critically ill patients. Some patients also have multiple blood clots, while others require dialysis to support their faltering kidneys. Some of the common treatment strategies include the use of a ventilator (for respiratory failure), oxygen (for hypoxia), fluid, rest and acetaminophen (for fever, cough and loss of smell). Chloroquine and hydroxychloroquine have also been used on SARS-CoV-2 patients. A randomized trial has shown that they effectively improve pneumonia symptoms and decrease the progression of severe conditions [214].

Monoclonal antibodies have also shown promises of reducing the risk of hospitalization in outpatients at high risk of severe disease. Also, the antiviral remdesivir has been used in hospitalized patients with favourable outcomes [215]. Studies are in progress to evaluate its efficacy in combination with other therapies. Anticoagulants have also been used to prevent blood clots frequent in SARS-CoV-2 infected patients, although the risk of gastrointestinal and intracranial bleeding remains a big call for concern [216]. Immunosuppressant drugs (Dexamethasone and tocilizumab) have also been reported to reduce mortality in large clinical trials of hospitalized patients [217–219]. It has recently been recommended by the National Institutes of Health (NIH) for treating hospitalized patients experiencing respiratory distress. However, definitive evidence is lacking regarding the timing of treatment, routes of administration, and how best to use the drugs. Several clinical trials are currently ongoing as regards treatment guidelines. However, antiviral therapy is a promising option. Drugs that can suppress the exact cellular signals driving inflammation hold a promise.

As of 31 March 2021, about 13 different vaccines have been rolled out in different countries. According to WHO, a total of 604,032,357 vaccine doses have been administered as of 5 April 2021. Moreover, more than 200 additional vaccine candidates are under development. About 60 of the 200 are in clinical development, according to WHO. Also, several vaccines are currently at different stages in the process of being assessed for WHO emergency use listing [220] (Table 1). Although there are available vaccines, it remains unclear whether the vaccines can efficiently protect against SARS-CoV-2 and infection and transmission of the SARS-CoV-2 to others. The degree of effectiveness of the vaccines also

remains elusive. Also, the nano-based vaccine's potential has already been seen in mRNA-1273 developed by Moderna company. Thus, the nano-based approach could bring a new perspective and be a crucial strategy for attenuating the SARS-CoV-2 infection globally. However, studies are needed to understand the exact mechanism of action of nanoparticles against SARS-CoV-2. This is important for the rational design of an efficient and highly reliable therapeutic agent.

The establishment and development of protocols for the characterization, evaluation, and control of nanomaterials could help position nanotechnology as an integral approach in the quest for a solution to SARS-CoV-2 and even possible future outbreaks. During nanomaterials design, host cells' response to these materials needs to be thoroughly investigated. Therefore, to introduce an appropriate and efficient combination of nanoparticle therapeutic agents against SARS-CoV-2, multidisciplinary research-oriented efforts are highly needed. With the available genomic sequencing knowledge in addition to the structural modelling of proteins, nanotechnology offers a great promise as an intervention strategy against SARS-CoV-2.

## Disclosure statement

No potential conflict of interest was reported by the author(s).

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