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Review

Prospect of SARS-CoV-2 spike protein: Potential role in vaccine and therapeutic development

Subodh Kumar Samrat [a], Anil M. Tharappel [a], Zhong Li [a], Hongmin Li [a,b,*]

[a] Wadsworth Center, New York State Department of Health, 120 New Scotland Ave, Albany, NY 12208, USA
[b] Department of Biomedical Sciences, School of Public Health, University at Albany, 1 University Place, Rensselaer, NY 12144, USA

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ABSTRACT

The recent outbreak of the betacoronavirus SARS-CoV-2 has become a significant concern to public health care worldwide. As of August 19, 2020, more than 22,140,472 people are infected, and over 781,135 people have died due to this deadly virus. In the USA alone, over 5,482,602 people are currently infected, and more than 171,823 people have died. SARS-CoV-2 has shown a higher infectivity rate and a more extended incubation period as compared to previous coronaviruses. SARS-CoV-2 binds much more strongly than SARS-CoV to the same host receptor, angiotensin-converting enzyme 2 (ACE2). Previously, several methods to develop a vaccine against SARS-CoV or MERS-CoV have been tried with limited success. Since SARS-CoV-2 uses the spike (S) protein for entry to the host cell, it is one of the most preferred targets for making vaccines or therapeutics against SARS-CoV-2. In this review, we have summarised the characteristics of the S protein, as well as the different approaches being used for the development of vaccines and/or therapeutics based on the S protein.

1. Introduction

In December 2019, Wuhan in the Hubei province of China became the center of an outbreak of pneumonia of unknown cause, which raised intense attention not only within China but internationally. Later, it was confirmed that the causative agent for this pneumonia-like disease is a coronavirus (CoV) belonging to the family *Coronaviridae* (Jiang et al., 2020a; C. C. Wang et al., 2020; Q. Wang et al., 2020; F. F. Wu et al., 2020; Y. Wu et al., 2020; Zhou et al., 2020). On February 11, 2020, the World Health Organization named the virus SARS-CoV-2 and renamed the syndrome from 2019-nCoV to COVID-19, short for coronavirus disease 2019 ("WHO. Novel Coronavirus(2019-nCoV) Situation Report – 22. February 11, 2020. https://www.who.int/docs/default-source/coronaviruse/situation-reports/20,200,211-sitrep-22-ncov.pdf. Accessed May27, 2020.," n.d.). COVID-19, a respiratory disease, has led to more than 22,140,472 confirmed cases and over 781,135 deaths globally as of August 19, 2020. In the USA alone, over 5,482,602 people are currently infected with SARS-CoV-2, which has caused more than 171,823 deaths ("Johns Hopkins University: https://coronavirus.jhu.edu/map.html. Accessed on August 19, 2020.," n.d.)

The first coronavirus pandemic of the 21 st century occurred in November 2002, when an infectious agent caused outbreaks of atypical pneumonia in Guangdong Province, southern China, and Southeast Asia, North America, and Europe. By the end of February 2003, the virus had spread to neighboring regions and countries. The disease caused by the virus was named severe acute respiratory syndrome (SARS), for which a global alert was issued by WHO on March 13, 2003 (Lee et al., 2003; Tsang et al., 2003; Zhong et al., 2003). SARS caused a global pandemic in 2002–2003, with approximately 10 % (774/8098) case fatality rate (CFR) ((Jiang et al., 2020a; Lee et al., 2003). The SARS-causing coronavirus SARS-CoV has not circulated in humans since 2004.

Another coronavirus, named MERS-CoV after the disease it causes (Middle East Respiratory Syndrome), was first reported in Saudi Arabia in 2012 and has continued to infect humans with restricted human-to-human transmission. WHO has reported a CFR of approximately 34.4 % (858/2494) in 27 countries for MERS-CoV ("WHO. Middle East respiratory syndrome coronavirus (MERS-CoV). August 2, 2019. https://www.who.int/emergencies/mers-cov/en/. Accessed on May 27, 2020.," n.d.).

The coronavirus was first identified as a cause of the common cold in 1960 (Al-Osail and Al-Wazzah, 2017). Coronaviruses belong to the subfamily *Coronavirinae* in the family *Coronaviridae* and the order *Nidovirales* (International Committee on Taxonomy of Viruses). Based on phylogenetic and genome structure, this subfamily is further divided

* Corresponding author at: Wadsworth Center, New York State Department of Health, 120 New Scotland Ave, Albany, NY 12208, USA.
E-mail address: Hongmin.li@health.ny.gov (H. Li).

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into four genera *Alphacoronavirus*, *Betacoronavirus*, *Gammacoronavirus*, and *Deltacoronavirus* (de Wilde et al., 2018). Alphacoronaviruses and betacoronaviruses usually cause respiratory illness in humans and gastroenteritis in animals. These two families include seven strains of human CoVs. The four viruses HCoV-NL63, HCoV-229E, HCoV−OC43, and HKU1 induce only mild upper respiratory diseases in immunocompetent hosts; however, some of them may cause severe complications in infants, young children and older people (Cui et al., 2019; Su et al., 2016). The other three highly pathogenic viruses, SARS-CoV, MERS-CoV, and SARS-CoV-2, cause severe respiratory syndrome, pneumonia, bronchiolitis, rhinitis, pharyngitis, sinusitis, and other systemic symptoms such as occasional watery diarrhea in humans of all ages. Based on current sequence databases, all human coronaviruses have animal origins. Five of them, SARS-CoV-2, SARS-CoV, MERS-CoV, HCoV-NL63, and HCoV-229E, originated from a bat, and the remaining two, HCoV−OC43 and HKU1, originated in rodents(Paules et al., 2020; Su et al., 2016).

The coronavirus genome is a single-stranded RNA of about 30 Kb, the largest among the RNA viruses (Masters, 2006). Coronaviruses usually infect their hosts in a species-specific manner, resulting in acute or persistent infections. The RNA genome contains a 5′ cap and 3′ poly-A tail, making it suitable for direct translation into a large size polyprotein. Structural protein occupies 10 kb of the genome, whereas non-structural protein occupies two-third of the genome. The virus has a spherical shape with a diameter of approximately 125 nm. The most striking feature of the coronavirus is the club-shaped spike protein projecting from the virion surface. These spike proteins serve as attachment proteins for the virus to enter host cells (Fehr and Perlman, 2015; Neuman et al., 2006).

The viral genome of the coronavirus encodes four structural proteins named spike (S), envelope (E), membrane (M), and nucleocapsid (N), 16 non-structural proteins (nsp1–16), and 8 accessory proteins (Jiang et al., 2020b; Siu et al., 2008). The S protein plays the most critical role in viral attachment, fusion, and entry into the target cell (D. E. C.J. Gordon et al., 2020;D.E. Gordon et al., 2020; Jiang et al., 2020b, 2020b)). It is a trimeric class I fusion protein that exists in a metastable prefusion conformation following translation. A substantial structural rearrangement of the S protein is required to fuse the viral membrane with the host cell membrane (Bosch et al., 2003; Hulswit et al., 2016). The size of the densely glycosylated S protein ranges between CoV species from approximately 1100–1600 amino acids length, with an estimated molecular mass of up to 220 kDa (Hulswit et al., 2016; Li, 2016). CoV particles are decorated with the club-shaped trimers of the S protein, which is 8–23-nm long (Hofmann et al., 2004). The S protein not only determines the host tropism but also is the crucial target for neutralizing antibodies produced by the immune system of the infected host (Hofmann et al., 2004; Walls et al., 2020).

The S protein is divided into S1 and S2 subunits. The S1 subunit contains two domains termed the N-terminal domain (NTD) and the C-terminal domain (CTD). The receptor-binding domain (RBD) is in the CTD. The S2 subunit contains the necessary elements required for membrane fusion, including an internal membrane fusion peptide (FP), two 7-peptide repeats (HR), a membrane-proximal external region (MPER), and a transmembrane domain (TM) (Li, 2016). The S1 and S2 subunits are separated by a cleavage site that is recognized by host proteases and undergoes proteolytic cleavage (Hoffmann et al., 2020; Li et al., 2003; Wrapp et al., 2020b). The S protein is primed by cellular protease TMPRSS2 (Glowacka et al., 2011; Matsuyama et al., 2010; Meng et al., 2020; Shulla et al., 2011), which cleaves the S protein at the S1/S2 and S2′ sites, leading to conformational changes of the S2 unit to allow fusion between the virus and host cell membranes to release viral RNA into the cytoplasm (Hoffmann et al., 2020; Meng et al., 2020). The S protein is also an excellent target for the development of therapeutic entry inhibitors, vaccines, and therapeutic antibodies (Amanat and Krammer, 2020; "An updated guide to the coronavirus drugs and vaccines in development," 2020; Du et al., 2009a; Kim et al., 2020; Zhao et al., 2018).

The S proteins of different coronaviruses are so unique that some phylogenetically similar spike proteins bind to different receptors. In contrast, some phylogenetically different spike proteins can bind to a similar receptor (Li, 2015). MERS-CoV requires dipeptidyl peptidase 4 (DPP4) as its receptor (Li et al., 2003; Raj et al., 2013). Murine hepatitis virus (MHV), a β-coronavirus, uses carcinoembryonic antigen-related cell adhesion molecule 1 (CEACAM1) for entry (Dveksler et al., 1991; Williams et al., 1991). A few coronaviruses, including bovine coronavirus, recognize sugar for attachment and entry (Schultze et al., 1991). Some CoVs, including porcine respiratory coronavirus (PRCV), require recognition of aminopeptidase N (APN) (Godet et al., 1994), whereas transmissible gastroenteritis virus (TGEV) requires recognition of APN in addition to sugar for virus entry (Delmas et al., 1992; Krempl et al., 1997). The human angiotensin-converting enzyme 2 (ACE2) is the common receptor for SARS-CoV, SARS-CoV-2, and NL63, although the NL63 RBD has a structure significantly different from those of SARS-CoV and CoV-2 (Hofmann et al., 2005, p. 63; Letko et al., 2020; Li et al., 2003, p. 2; Lin et al., 2008; Tai et al., 2020). It has been shown that the receptor-binding domain of SARS-CoV-2 binds more strongly to the ACE2 receptor than that of SARS-CoV, making it a more suitable target for the development of virus attachment inhibitors, neutralizing antibodies, and vaccines (Tai et al., 2020; Q. C. Wang et al., 2020; Q. Wang et al., 2020). Strong binding of SARS-CoV-2 RBD to the ACE2 receptor is also a key reason for the higher infection rate in SARS-CoV-2 as compared to SARS-CoV and MERS-CoV ((Tai et al., 2020; Wrapp et al., 2020a) However, a recent paper by Shang and colleagues suggests that the full-length spike protein of SARS-CoV-2 has similar or lower affinity to hACE2 than SARS-CoV. This suggests that SARS-CoV-2 RBD is less exposed than SARS-CoV-RBD, and it is also less dependent on target cell protease since it is preactivated by proprotein convertase furin (Shang et al., 2020).

2. SARS-CoV-2 and the S protein as a potential vaccine target

The recent outbreak of SARS-CoV-2 is much more challenging to control because of its long incubation period. Recent studies have shown that the incubation time could range from 2 to 14 days with the median incubation period of 6.4 days (Backer et al., 2020; Lauer et al., 2020; Linton et al., 2020). It is estimated that only around 101 of every 10,000 people who contract SARS-CoV-2 are likely to develop symptoms after 14 days (Lauer et al., 2020). Therefore, most regulatory agencies suggest quarantine for at least 14 days. Some virus-carrying individuals do not develop any disease symptoms, but they can transmit the virus. One investigation in China suggested that the R0 of SARS-CoV-2 was as high as 4.7–6.6 before any infection control measures were applied (Sanche et al., 2020), suggesting that SARS-CoV-2 is highly contagious and more infectious than previously estimated. These findings are also supported by the fact that the SARS-CoV-2-RBD demonstrates 10–20 fold higher affinity to the human ACE2 receptor than SARS-CoV (Tai et al., 2020; Wrapp et al., 2020a).

To date, there is no approved drug for treatment of COVID-19, but an experimental antiviral drug with a known safety profile is currently being used for treatment of COVID-19 patients. It has been shown that the nucleotide analog Remdesivir can inhibit SARS-CoV and MERS-CoV in tissue culture and nonhuman animal models (Martinez, 2020). A clinical trial of Remdesivir is underway for treatment of Ebola virus infection. Recently clinical trials for Remdesivir have been started for SARS-CoV-2 as well (Cao et al., 2020; George Sakoulas, 2020; C. J. C.J. Gordon et al., 2020; D.E. Gordon et al., 2020). Despite much research and effort, there is no vaccine available for SARS-CoV-2 or any other coronaviruses. The diversity of the S-protein also renders any vaccines and nAbs unlikely to be cross-protective between existing and emerging CoVs.

3. Structure of the SARS-CoV-2 spike protein RBD bound with ACE2

The role of the S protein in binding with host receptors makes it a perfect target for vaccine and antiviral therapeutic development. Previous studies on SARS-CoV and MESR-CoV have revealed that vaccines based on the S protein can induce antibodies to block virus binding and fusion or neutralize virus infection ((Du et al., 2009a). Since the S protein plays a role in both virus entry and viral RNA release into the cytoplasm, a vaccine against the S protein should induce antibodies to block viral entry (Fig. 1). Previous reports suggest that immunization of mice with a trimeric form of MERS-CoV S protein RBD domain elicits potent neutralizing antibodies against MERS CoV (Coleman et al., 2017; Du et al., 2013; Mou et al., 2013; Tai et al., 2016);. Other studies show that immunization of rabbits with an RBD-Fc fusion protein elicits robust antibody responses, and the antisera can completely block SARS-CoV infection at different serum dilution (Chen et al., 2014; Coleman et al., 2014; Du et al., 2009b; He et al., 2004). Another study showed that immunization of mice with the S1 subunit of MERS-CoV actively induces neutralizing antibody production. Using the same strategy, the S1 subunit of SARS-CoV-2 can also induce S1-specific IgG in mice. However, further studies are required to verify the potency of the antibodies (Kim et al., 2020). Also, development of a vaccine targeting the S protein is always challenging, as a vaccine based on neutralizing antibodies may lead to antibody-dependent enhancement of secondary virus infection and vaccine-enhanced disease.

4. Antibody-dependent enhancement

It has been observed that COVID-19 pandemic intensity is different among regions. A country or region suffering the most may have been primed by exposure to one or more coronaviruses and encountered the effects of antibody-dependent enhancement (ADE) due to antigenic

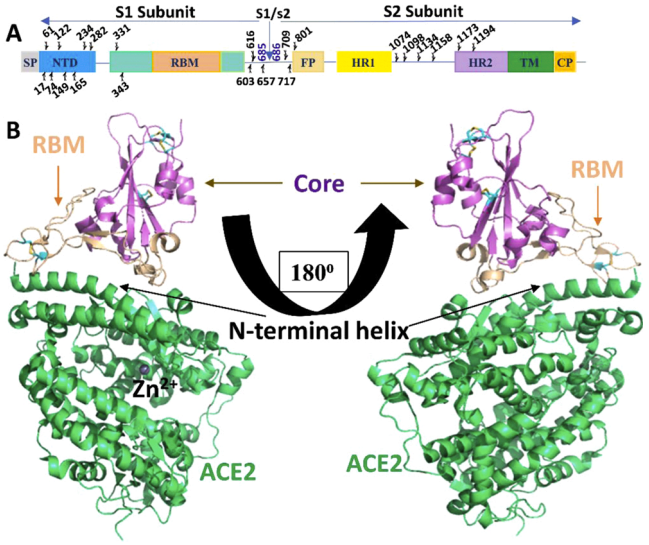

Fig. 1. Structure of SARS-CoV-2 Spike protein RBD bound with ACE2A. Schematic representation of SARS-CoV-2 Spike protein. Linear representation of the SARS-CoV-2 spike monomer. Its S1 subunit contains the N-terminal domain (NTD; 14–305 aa), receptor binding domain (RBD; 319–541 aa), and receptor binding motif (RBM; 437–508 aa). Its S2 subunit contains fusion peptide (FP; 788–806 aa), heptad repeat 1 (HR1;12–984 aa), heptad repeat 2 (HR2;1163–1213 aa), transmembrane domain (TM;1214–1237 aa), and cytoplasmic domain (CP; 1238–1273). The predicted glycosylation sites are indicated above the domain bars. **B.** Overall structure of the SARS-CoV-2 RBD bound to ACE2. ACE2 is shown in lime green. The SARS-CoV-2 RBD core is shown in purple and RBM in tint colour. The N-terminal helix of ACE2 responsible for binding is labelled (Lan et al., 2020).

epitope heterogeneity (Tetro, 2020). ADE is a phenomenon in which pre-existing non- or poorly neutralizing antibodies enhance the viral entry and replication in the host cell. ADE is more common in flaviviruses, especially in the dengue virus, which has four serotypes. It has been shown that when patients are infected with dengue virus for first time, specific neutralizing antibodies are produced. However, if they are later infected with a different serotype of dengue virus, the pre-existing antibodies from the previous infection do not have enough potency to neutralize the new virus, even though they can bind with the virus. These partially neutralizing antibodies help the virus to enter cells via an Fc-receptor (FcR)-mediated mechanism in addition to their natural entry route (Fig. 2A). The antibody-bound viruses bind via the antibody Fc-domain to FcR expressed on the surface of several immune cells, leading to enhancement of the virus entry and replication (Katzelnick et al., 2017; Khandia et al., 2018). ADE has also been reported in other viruses like HIV, Ebola, HCV, and Zika ((Gorlani and Forthal, 2013; Meyer et al., 2008; Takada et al., 2001; Willey et al., 2011). Vaccine-induced enhancement was first reported during the vaccine trial of RSV in 1969. In this trial, the administration of the formalin-inactivated vaccine RSV (FI-RSV) to naïve infants resulted in a much higher incidence rate of severe illness. It led to increased hospitalization in 80 % among vaccinated infants, compared to only 5% of the non-immunized infants (Kim et al., 1969). Unfortunately, two vaccinated infants also died because of enhanced RSV infections (Kim et al., 1969).

ADE has also been reported in SARS-CoV and MERS-CoV. It has been shown that anti-spike sera, which can neutralize SARS-CoV pseudo viral particles, can initiate virus entry in cells that do not express the ACE2 receptor for SARS-CoV. ADE is based on the expression of FcR on cells (Jaume et al., 2011; Wang et al., 2014). Another report suggests that ADE occurs through FcR in macrophages, but there are no changes in gene profiling, and virus replication has been shown to be abortive (Yip et al., 2016). A recent study has shown that MERS-CoV RBD-specific MAb and the SARS-CoV RBD-specific MAb can mediate the entry of their respective coronaviruses into FcR-expressing human cells. This study also suggests that a fully neutralizing antibody can also mediate ADE by functionally mimicking viral receptors from host cells (Wan et al., 2019). It has also been shown that passive transfer of anti-S IgG or serum from previously infected animals caused more severe lung injury in animal models (Liu et al., 2019a,b).

There are huge theoretical concerns of vaccine-induced ADE which can occur in several scenarios. It is possible that vaccine-induced antibodies against SARS-CoV-2 may bind to the virus without neutralizing it. Currently mutations on the viral Spike protein have been found in circulating clinical SARS-CoV-2 strains (Korber et al., 2020; Lu et al., 2020). If this happen, the non-neutralizing antibodies could produce ADE effect and enhance the viral entry into cells (Garber, 2020; Iwasaki and Yang, 2020; Tetro, 2020; Ulrich et al., 2020). In addition, significant sequence variations between the spike proteins of SARS-CoV and SARS-CoV-2 may cause ADE (Tetro, 2020). Moreover, it is also possible that a future SARS-related (SARSr)-CoV causes ADE in patients vaccinated with SARS-CoV-2, if the future SARSr-CoV shows significant sequence variations from SARS-CoV-2. Furthermore, insufficient concentration of neutralizing Ab may also cause ADE (Renner et al., 2018; Wan et al., 2019). Given the fact that neutralizing antibodies declined rapidly in some of COVID-19 patients (Long et al., 2020; Seow et al., 2020), this latter scenario is more troublesome. Nevertheless, based on the knowledge from research on SARS-CoV, several vaccine trials are ongoing for SARS-CoV-2.

5. Use of nanobodies against coronaviruses

Soon after the discovery of the nanobody in the camelid family by C. Hamers-Casterman and colleagues in 1993 (Hamers-Casterman et al., 1993), it became a potent tool as a neutralizing antibody. Several nanobodies have been screened and validated for binding against

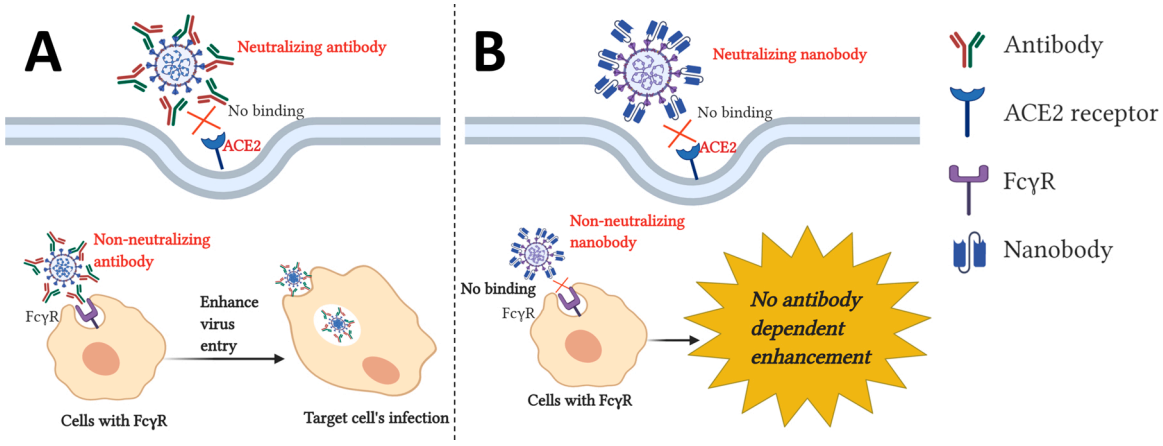

Fig. 2. Schematic representation of antibody-dependent enhancement and protection through nanobodies. A. Virus particles are detected by heterotypic antibodies from previous infection. This complex then binds to the Fcγ receptor on the surface of immune cells and is internalized. Further virus replication leads to an increased viral load. **B.** The nanobody lacks an Fc portion and is unable to bind to the Fcγ receptor, which protects the cell from antibody-dependent enhancement (created with BioRender.com).

different targets ranging from human melanoma cells to viruses. A nanobody against human melanoma cells targeting endothelin receptor type B has been recently identified, which will be helpful in the future to treat human melanoma (Ji et al., 2020). Besides, several nanobodies have been identified to block the ligand-receptor binding for primary immune cells. For example, nanobodies inhibiting PD1-PDL1 interaction, LIN28:let-7 interaction, and T cell marker CD3 are all promising candidates for targeting and activating cytotoxic T lymphocytes (CTLs) to induce anti-tumor responses. GRP78, CD38, and GPC3 expression on cancer cells have also been targeted for nanobody expression and purification, which provide useful cancer cell markers and potential therapeutic markers (Aghamollaei et al., 2020, p. 78; Hambach et al., 2020; Li et al., 2020; Moradi-Kalbolandi et al., 2020; L. L. Xia et al., 2020; S. Xia et al., 2020; C. J. Yu et al., 2020;C. Yu et al., 2020).

One drawback of use of nanobody is the absence of antibody-dependent cellular cytotoxicity (ADCC). Since nanobody lacks the Fc portion so it is unable to bind to immune cells to provide ADCC effect. It has been shown that non protective antibodies help in protection from HIV (Forthal et al., 2001; Haynes et al., 2012), herpes simplex virus (Kohl et al., 2000; Kohl and Loo, 1982, 1982), Ebola virus (Gunn et al., 2018; Saphire et al., 2018), and influenza virus (Greenberg et al., 1977; Jegaskanda et al., 2014), and SARS-CoV (Yasui et al., 2014) by mechanism of ADCC. Therefore, the use of nanobody has both benefits and drawbacks. Nanobody provides protection against ADE, however, it lacks ADCC. It is very important to balance the adverse effect of ADE and beneficial effect of ADCC. To this end, it is important to note that nanobody can be easily engineered to add different effector function such as Fc regions, toxins, liposomes, and other ligand binding scaffolds (Harmsen et al., 2005; Laursen et al., 2018; Schriewer et al., 2020). Recently, the European Medicines Agency (EMA) and the US Food and Drug Administration (FDA) have approved a bivalent nanobody, caplacizumab, for treatment of patients with thrombotic thrombocytopenic purpura (Hanlon and Metjian, 2020; Scully et al., 2019).

Several nanobodies have been reported to act as potential therapeutic agents against different viruses. Nanobodies against viruses work on the principle of inhibiting the ligand-receptor interaction (Fig. 2 A&B). A nanobody against HCV has been reported which blocks the E2-CD81 interaction and stops the virus-cell to cell transmission (Tarr et al., 2013). A replication-inhibiting nanobody against porcine reproductive and respiratory syndrome virus (PRRSV), which is a significant threat to the swine industry, has been identified and provides a novel antiviral drug for inhibition of PRRSV replication and controlling PRRSV disease (Duan et al., 2020; Wang et al., 2019). Another intracellular antibody directed towards human papillomavirus (HPV) oncoprotein E7 has shown great potential for therapy of HPV16-associated disease (Li et al., 2019). Nanobodies have also exhibited good antiviral effects against bovine viral diarrhea virus (Li et al., 2017).

Only limited studies have been performed on nanobodies against coronaviruses. A few groups investigated nanobody activity against the MERS-CoV S protein and successfully found nanobodies that could neutralize MERS-CoV in pseudo-viral particles and in a mouse model (Raj et al., 2018; Zhao et al., 2018). Recently, nanobodies against SARS-CoV have also been identified which have shown cross-neutralization activity, and therefore have excellent therapeutic potential against the SARS-CoV-2 virus (Wrapp et al., 2020a). Several other nanobodies have been identified recently that act against the SARS-CoV-2 receptor-binding domain (Chi et al., 2020; Walter et al., 2020; Y. F. Wu et al., 2020; Y. Wu et al., 2020).

6. Different vaccine strategies using the S protein against SARS-CoV-2

Protein-based subunit vaccines are probably one of the safest formats of vaccine, but immune responses generated with this kind of vaccine are heavily dependent on the adjuvant used. The S protein in different form including full-length S Protein, S1 RBD, RBD-Fc, and N-terminal, have shown nAb responses and protection in multiple animal models and nonhuman primates (Deng et al., 2018; Lan et al., 2015; Tse et al., 2020; Wang et al., 2017; Zhang et al., 2016).

7. DNA vaccines

DNA vaccines are composed of plasmid DNA molecules encoding one or more immunogens. A DNA vaccine is better than an mRNA vaccine in terms of the formulation required for its stability and ease of delivery. However, there is a risk that integration of the vaccine into the host genome may create mutations(Ledwith et al., 2000; Liu, 2019). Passive transfer of sera from mice immunized with DNA encoding the MERS-CoV S domain has been shown to protect naïve mice from MERS-CoV infection (Chi et al., 2017). Other research showed that the DNA encoding the S1 domain is superior to that with full length S protein in eliciting antibody and Th1/Th2 responses. Both DNAs encoding the S1 and S proteins were shown to induce cross-neutralizing Abs against multiple strains of MERS-CoV from human and camel origins (Al-amri et al., 2017). Another study showed that sera from mice immunized with S protein-encoding DNA detects SARS-CoV S protein (Zhao et al., 2004). Mice immunized with S protein-encoding DNA and booted with CD4+ and CD8 + T cell-specific peptides improves the

expression of several cytokines (Huang et al., 2007). Another report shows that DNA encoding the S protein from SARS-CoV elicits neutralizing antibodies, as measured by a Pseudotyped lentiviral vector reporter neutralization assay and S protein-specific CD4+ and CD8 + T-cell responses in all immunized volunteer (Martin et al., 2008). Recently, Yu and colleagues reported that DNA vaccine encoding the SARS-CoV-2 S protein can protect rhesus macaques after challenge with SARS-CoV-2 (J. J. Yu et al., 2020; C. Yu et al., 2020). Currently, two SARS-CoV-2 DNA vaccines are under development. Inovio Pharmaceuticals developed a DNA vaccine NCT043364, which is undergoing Phase 1 clinical trial. Several other companies are involved in the development of DNA vaccines, which is mentioned S protein-based DNA vaccine (Table 1).

8. Viral vector-based vaccines

Viral vector-based vaccines depend on the delivery of one or more antigens encoded by a modified viral vector. This technique has several advantages over other techniques in use. This technology uses replicating or non-replicating vectors. Upon delivery, antigens are expressed in the host cells, and host cells generate both humoral and cell-based immune responses against the targeted pathogen (Bouard et al., 2009; Rauch et al., 2018). Viral vectors that can tolerate a large fragment insertion in their genome can be manipulated to encode any antigen of choice. Several viral vectors have been used recently in the generation of vaccine candidates against SARS-CoV. Also, a rabies virus-based vaccine expressing the SARS-CoV S protein has been found to induce the production of high levels of SARS-CoV-neutralizing antibodies in mice in a single vaccination (Faber et al., 2005).

A live attenuated Modified Vaccinia Ankara (MVA) vector encoding a full-length S glycoprotein has been shown to generate a potent neutralizing antibody in mice, rabbit, and monkey (Chen et al., 2005). Other studies show that immunization of mice with recombinant adenovirus containing the S protein induces both neutralizing antibodies in serum as well as CD8 + T cells in lungs (Du et al., 2006, p.; Kobinger et al., 2007; Liu et al., 2005; Shim et al., 2012). Currently, different companies are involved in making replicating and non-replicating viral vector-based vaccines (Tables 2 and 3,

Table 1
S protein-based DNA vaccines.

Manufacturer	Strategy	Vaccine Name/ Stage	Ref
Inovio Pharmaceuticals/ International Vaccine Institute	DNA plasmid vaccine injected by intradermal (ID) injection followed by electroporation (EP) using a CELLECTRA® 2000 device in healthy adult volunteers	INO-4800/ Phase 1/2 NCT04336410 NCT04447781	("Inovio Pharmaceuticals/International Vaccine Institute. http://ir.inovio.com/news-releases/news-releases-details/2020/INOVIO-and-IVI-Partner-with-Seoul-National-University-Hospital-to-Start-Phase-12-Clinical-Trial-of-INOVIOs-COVID-19-DNA-Vaccine-INO-4800-in-South-Korea/default.aspx. Accessed July 29, 2020," n.d.)
Osaka University/AnGes/ Takara Bio	DNA plasmid vaccine + adjuvant	Phase 1/2 NCT04463472	("Osaka University/AnGes/Takara Bio. https://www.takarabio.com/about/bioview-blog/current-events/dethroning-king-coronavirus-with-novel-vaccines. Accessed July 29, 2020," n.d.)
Karolinska Institute / Cobra Biologics (OPENCORONA Project)	DNA vaccine delivered to patient's muscle by electroporation to generate a viral antigen on which the immune system then reacts	Pre-Clinical	("Cobra Biologics. Cobra Biologics and the Karolinska Institute collaborate to develop COVID-19 vaccine. 30th Mar 2020. https://www.cobrabio.com/News/March-2020/Cobra-Karolinska-Institutet-COVID-19-Vaccine. Accessed May 21, 2020," n.d.)
Takis/Applied DNA Sciences/Evvivax	DNA vaccine candidates created using the structure of the S protein	Pre-Clinical	("Takis. Takis, a biotech company in Castel Romano, Rome, announces that it is ready to test its Covid-19 vaccine on pre-clinical models. 17 March 2020. http://www.takisbiotech.it/index.php/en/news/209-rome-17-march-2020-takis-a-biotech-company-in-castel-romano-rome-announces-that-it-is-ready-to-test-its-covid-19-vaccine-on-pre-clinical-models. Accessed on May 21, 2020.," n.d.)
Immunomic Therapeutics, Inc./EpiVax, Inc./ PharmaJet, Inc.	Plasmid DNA delivered via PharmaJet's Tropis Needle-free Injection System, which precisely targets delivery of vaccine to the intradermal tissue depth	Pre-Clinical	("Pharmajet: Pharmajet partner with ITI and EpiVax to develop and deliver COVID-10 Vaccine. April 15, 2020. https://www.immunomix.com/pharmajet-partners-with-iti-and-epivax-to-develop-and-deliver-covid-19-vaccine/. Accessed May 21, 2020.," n.d.)
Zydus Cadila	DNA plasmid vaccine against the major viral membrane protein responsible for the cell entry of the novel coronavirus	Phase 1/2 CTRI/2020/07/026,352	("Zydus Cadila. Zydus Cadila accelerates COVID-19 vaccine research. 8 April 2020 https://www.pharmatutor.org/pharma-news/2020/zydus-cadila-accelerates-covid-19-vaccine-research. Accessed on May 21, 2020.," n.d.)
Genexine Consortium	DNA VVaccine (GX-19)	Phase 1/2 NCT04445389	("Genexine Consortium. https://pharmashots.com/press-releases/korean-biotech-firm-genexines-covid-19-deoxyribonucleic-acid-vaccine-pipeline-gx-19-is-ready-for-clinical-testing-as-soon-as-it-applies-to-the-drug-ministry-for-human-testing/. Accessed July 29, 2020," n.d.)
BioNet Asia	GENE-based vaccine (COVIGEN) encoding the SARS-CoV-2 S protein	Pre-Clinical	("BioNet. BioNet in Thailand is developing a COVID-19 GENE-based vaccine (COVIGEN) encoding the S (Spike) protein of SARS-CoV-2. http://www.bionet-asia.com/media/news-events/. Accessed on May 21, 2020.," n.d.)
University of Waterloo	DNA vaccine using a bacteriophage-based approach allowing it to replicate within bacteria already present in the body, delivering the vaccine to cells in targeted tissues and triggering production of a virus-like particle (VLP) that will induce an immune response	Pre-Clinical	("University of Waterloo. University of Waterloo developing DNA-based COVID-19 vaccine. April 16, 2020. https://uwaterloo.ca/stories/news/university-waterloo-developing-dna-based-covid-19-vaccine. Accessed May 21, 2020.," n.d.)
Symvivo Corporation	bacTRL-Spike contains different concentrations of live Bifidobacterium longum, which has been engineered to deliver plasmids containing synthetic DNA encoding spike protein from SARS-CoV-2	bacTRL-Spike/ Phase 1 (NCT04334980)	("Symvivo Corporation. Evaluating the Safety, Tolerability, and Immunogenicity of bacTRL-Spike Vaccine for Prevention of COVID-19. April 6, 2020. https://clinicaltrials.gov/ct2/show/NCT04334980. Accessed May 21, 2020.," n.d.)

Table 2
Replicating viral vector-based vaccines that encode for the S protein.

Manufacturer	Strategy	Vaccine Name/ Stage	Ref.
Zydus Cadila	Codon-optimised proteins of the new coronavirus, expressed by replicating measles viral vector, will use reverse genetics to stimulate long-term neutralizing antibodies that protect against the infection	Pre-Clinical	("Zydus Cadila. Zydus Cadila looks to expedite Covid-19 vaccine development February 17, 2020. https://www.pharmaceutical-technology.com/news/zydus-cadila-covid-19-vaccine/, May 21, 2020.," n.d.)
Institute Pasteur/ Themis/ Univ. of Pittsburgh Center for Vaccine Research	The vaccine candidate consists of a replicating measles viral vector	Pre-Clinical	("CEPI. CEPI collaborates with the Institut Pasteur in a consortium to develop COVID-19 vaccine. March 19, 2020. https://cepi.net/news_cepi/cepi-collaborates-withthe-institut-pasteur-in-a-consortium-to-develop-covid-19-vaccine/. Accessed May 21, 2020.," n.d.)
Tonix Pharma/ Southern Research	Horsepox vector expressing S protein	Pre-Clinical	("Tonix Pharma. TNX-1800 Horsepox vector for S protein. April 26, 2020. https://covidvax.org/covid19-vaccine/Tonix/TNX-1800-Horsepox-vector-for-S-protein-Tonix-Pharma-Southern-Research. Accessed May 21, 2020.," n.d.)
BiOCAD and IEM	This viral vector vaccine based on attenuated influenza virus backbone (intranasal)	Pre-Clinical	("BIOCAD, 2020. https://gmpnews.net/2020/03/biocad-begins-developing-covid-19-vaccine/. Accessed May21, 2020.," n.d.)
University of Hong Kong	Influenza vector expressing RBD on its surface to induce immunogenicity against the SARS-CoV-2 virus; notably, can be administered as a nasal spray	Pre-Clinical	("University of Hong Kong. CEPI partners with University of Hong Kong to develop COVID-19 vaccine. March 18, 2020. https://cepi.net/news_cepi/cepi-partners-with-university-of-hong-kong-to-develop-covid-19-vaccine/. Accessed May 21, 2020.," n.d.)
IAVI/Batavia	Replication-competent VSV chimeric virus technology (VSVΔG) delivering the SARS-CoV-2 Spike (S) glycoprotein	Pre-Clinical	("IAVI and Batavia Biosciences Announce Collaboration on VSV-vector Based Epidemic Preparedness Vaccines: https://www.iavi.org/newsroom/press-releases/2020/iavi-and-batavia-announce-collaboration-vsv-vector-epidemic-preparedness-vaccines. March 5, 2020.," n.d.)
University of Western Ontario	VSV-S (Vesicular Stomatitis Virus-S) previously successfully used for the development of a vaccine for MERS	Pre-Clinical	("University of Ontario. Ontario Leading COVID-19 Research in Canada Province Announces First Phase of Research Projects to Fight COVID-19. May 21, 2020. https://news.ontario.ca/opo/en/2020/05/ontario-leading-covid-19-research-in-canada.html. Accessed May 21, 2020," n.d.)

respectively). The University of Oxford's non-replicating adenovirus-based ChAdOx1 nCoV-19 vaccine has shown protection in rhesus macaques after challenge with SARS-CoV-2(van Doremalen et al., 2020).

9. Subunit vaccines

Subunit vaccines use one or more antigens suitable for eliciting a robust immune response. In theory, the subunit vaccine is a very easy and safe vaccine, but in practice, it requires a suitable adjuvant to stimulate the host immune response. Several previous attempts were partially successful with SARS-CoV. Immunization of animals with the S1 RBD domain fused with the IgG1 FC portion (RBD-FC) induced highly potent antibodies which could bind with the RBD domain of the S1 domain, completely neutralize SARS-CoV, and inhibit SARS-CoV entry into Vero E6 cells (Du et al., 2009b, 2007; He et al., 2004). A similar approach is being used to develop a vaccine against the SARS-CoV-2 virus. Several companies, including the University of Queensland, are developing subunit vaccines based on the "molecular clamp" technology (Takashima et al., 2011). Trimer-tag technology is being used by Clover Biopharmaceuticals, Inc. to develop a vaccine against SARS-CoV-2 using mammalian cell-expressed Trimeric S protein ("Improvement of Pharmacokinetic Profile of TRAIL via Trimer-Tag Enhances its Antitumor Activity in vivo. - PubMed - NCBI," n.d.). Novavax, Inc. has several S protein-based nanoparticle vaccines which needs to be tested for its efficacy in the animal model. Johnson & Johnson, Pasteur Institute, and Chongqing Zhifei Biological Products Co., Ltd. have also started subunit vaccine development against SARS-CoV-2. Other companies involved in making subunit vaccines are listed in Table 4.

10. RNA vaccines

mRNA has been used as a template for endogenous expression of proteins selected as a vaccine candidate. An mRNA vaccine is a promising alternative because of its high potency, short production cycle, and low manufacturing cost. (Pardi et al., 2018; Yun et al., 2020). Currently, there is no mRNA vaccine in the market, so it will be challenging to pass the quality control and safety evaluation. Currently, mRNA-1273, a potential vaccine against

SARS-CoV-2 based on encoding for a prefusion stabilized form of the S protein, has been selected for evaluation by Moderna in collaboration with investigators at the NIAID Vaccine Research Center (VRC). This vaccine is currently the focus of a Phase 1 clinical trial (NCT04283461). Several other companies are also developing mRNA vaccines against SARS-CoV-2 (Table 5).

Table 3
Non-replicating viral vector-based vaccines that encode for the S protein.

Manufacturer	Strategy	Vaccine Name/ Stage	Ref.
CanSino Biological Inc./ Beijing Institute of Biotechnology	The Phase 2 clinical trial will evaluate immunogenicity and safety of Ad5-nCoV, which encodes for a full-length S protein of SARS-CoV-2	Phase1 ChiCTR2000030906 Phase 2 NCT04313127 ChiCTR2000031781	(Zhu et al., 2020)
University of Oxford	The ChAdOx1 platform consists of a transgenic nonreplicating chimp adenovirus-based vaccine that expresses, leading to host cell expression and display of the antigenic coronavirus spike protein upon immunization, thus prompting an immune response	COV001/ Phase 1/2 NCT04324606 Phase 2 2020-001,228-32 Phase 3 ISRCTN89951424	(Folegatti et al., 2020)
Gamaleya Research Institute	Adeno-based	Phase 1 NCT04436471 NCT04437875	("Gamaleya Research Institute. https://www.trialsitenews.com/gamaleya-research-institute-developed-covid-19-vaccine-clinical-trial-commences-across-russia/. Accessed on JUly 29, 2020.," n.d.)
GeoVax/BravoVax	The aim of this vaccine is prevention/ control of SARS-CoV-2, using its GV-MVA-VLPTM vaccine platform	Pre-Clinical	("GeoVax. GeoVax Progresses in Coronavirus (COVID-19) Vaccine Development Program. March 18, 2020. https://www.globenewswire.com/news- release/2020/03/18/2,002,611/0/en/GeoVax-Progresses-in-Coronavirus-COVID-19-Vaccine-Development-Program.html. Accessed May21, 2020.," n.d.)
Janssen Pharmaceutical Companies	Ad26 (alone or with MVA boost); leverages Janssen's AdVac® and PER.C6® technology, which provide the ability to rapidly upscale production of the optimal vaccine candidate	Pre-Clinical	("Johnson & Johnson. Johnson & Johnson Announces a Lead Vaccine Candidate for COVID-19; Landmark New Partnership with U.S. Department of Health & Human Services; and Commitment to Supply One Billion Vaccines Worldwide for Emergency Pandemic Use. March 30, 2020. https://www.jnj.com/johnson-johnson-announces-a-lead-vaccine-candidate-for-covid-19-landmark-new-partnership-with-u-s-department-of-health-human-services-and-commitment-to-supply-one-billion-vaccines-worldwide-for-emergency-pandemic-use. Accessed on May 21, 2020.," n.d.)
ReiThera	This vaccine targets the spike protein of SARS-CoV-2. The vaccine technology is based on a novel ReiThera-proprietary simian adenoviral vector with strong immunological potency and low pre-existing immunity in humans	Pre-Clinical	("ReiThera, LEUKOCARE and Univercells. ReiThera, Leukocare and Univercells announce fast-track development of a COVID-19 vaccine. APRIL 23, 2020. https://www.univercells.com/newsroom/reithera-leukocare-and-univercells-announce-fast-track-development-of-a-covid-19-vaccine/. Accessed on May 21, 2020.," n.d.)
DZIF – German Center for Infection Research	This vaccine will combine the spike protein with the MVA vector's genetic information, resulting in a viral vector able to penetrate human cells and consequently produce spike proteins	Pre-Clinical	("SARS-CoV-2: DZIF scientists and the development of vaccines https://www.dzif.de/en/sars-cov-2-dzif-scientists-and-development-vaccines Mar 9 2020.," n.d.)
Altimmune	The new intranasal vaccine is based on NasoVAX, the company's influenza vaccine candidate. Like NasoVAX, single intranasal dose would provide systemic immunity	Pre-Clinical	("Hannah Balfour: Biotech and academia collaborate on intranasal COVID-19 vaccine development:https://www.drugtargetreview.com/news/59182/biotech-and-academia-collaborate-on-intranasal-covid-19-vaccine-development/ 2 April 2020," n.d.)
Greffex	This genetically modified adenovirus-based vector vaccine will exploit GreVac(TM) Plug-And-Play technology to expedite the production of vaccine candidates	AdCOVID/ Pre-Clinical	("Greffex. Greffex completes COVID-19 vaccine, prepares for FDA animal testing. March 12, 2020. https://www.innovationews.com/Greffex-completes-COVID-19-vaccine-prepares-for-FDA-testing/ Accessed May 21, 2020.," n.d.)
Vaxart	The candidate is based on the company's VAASTT oral vaccines platform, which uses adenovirus type 5 (Ad5) as a delivery system for its treatment. Vaccine candidates will generate mucosal immune responses in addition to serum antibody responses	Pre-Clinical	("Vaxart. Vaxart Announces Additional Positive Pre-Clinical Data for its Oral COVID-19 Vaccine Program. April 30, 2020. https://investors.vaxart.com/news-releases/news-release-details/vaxart-announces-additional-positive-pre-clinical-data-its-oral/ Accessed May 21, 2020.," n.d.)
Centro Nacional Biotecnología (CNB-CSIC), Spain	MVA poxvirus vectors expressing S protein	Pre-Clinical	("Luis Enjuanes, Isabel Sola y Sonia Zúñiga. NOVEL HUMAN PATHOGENIC CORONAVIRUS: SARS-CoV-2. March 26, 2020. Centro Nacional de Biotecnología (CNB-CSIC), Madrid (Spain)," n.d.)
University of Manitoba	Dendritic cell-based vaccine	Pre-Clinical	("COVID-19 vaccine: Dendritic cell-based vaccine. https://covidvax.org/covid19-vaccine/ManitobaUni/Dendritic-cell-based-vaccine-University-of-Manitoba. Accessed May 26, 2020," n.d.)

11. Spike protein-based therapeutics

Two S-protein-based methods that show promise as therapeutics for SARS-CoV-2 include those facilitating peptide interference with RBD-ACE2 interaction, as well as those using mAbs that target the S-protein. A previous study has shown that hexapeptide ^{438}YKYRYL^{443} from the S protein of SARS-CoV virus binds to ACE2 with a binding affinity of K_D =46 μM and blocks the entry of SARS-CoV into Vero E6 cells (Struck et al., 2012). A peptide from the RBD domain of the S protein (aa 471–503) can inhibit the binding of ACE2 to SARS-CoV RBD and block SARS-CoV entry into Vero cells with an EC50 of 41.6 μM (Hu et al., 2005). Similarly, a combination of two peptides from ACE2 motif aa

Table 4
Vaccines based on protein subunits.

Manufacturer	Strategy	Vaccine Name/Stage	Ref.
Anhui Zhifei Longcom Biopharmaceutical/Institute of Microbiology, Chinese Academy of Sciences	Adjuvant recombinant protein (RBD-Dimer	Phase 1 NCT04445194 Phase 2 NCT04466085	("Anhui Zhifei Longcom Biopharmaceutical/Institute of Microbiology, Chinese Academy of Sciences. 2020 https://covidvax.org/covid19-vaccine/AnhuiZhifei/Adjuvanted-recombinant-protein-Anhui-Zhifei-Longcom-Biopharma-Institute-of-Microbiology-Chinese-Acad. Accessed on July 29, 2020.," n.d.)
Vaxine Pty Ltd/Medytox	Recombinant spike protein with Advax adjuvant	Phase 1 NCT04453852	("Vaxine Pty Ltd/Medytox. https://www.biospectrumasia.com/news/37/16000/vaxine-announces-covid-19-vaccine-collaboration-with-medytox.html. Accessed on July 29, 2020.," n.d.)
Kentucky Bioprocessing, Inc	RBD-Based	Phase 1 NCT04473690	("Kentucky Bioprocessing, Inc. https://www.kentucky.com/news/coronavirus/article241709386.html. Accessed on July 29, 2020.," n.d.)
AdaptVac (PREVENT-nCoV consortium)	AdaptVac's universal viral Capsid-Like Particle (CLP) will be employed to deliver an optimal vaccine against the SARS-CoV-2 virus (COVID-19)	Pre-Clinical	("ADPVAC, 2020. https://www.adaptvac.com/news. Accesses May 21, 2020.," n.d.)
ExpreS2ion	Drosophila S2 insect cell expression system VLPs. This vaccine uses AdaptVac's capsid VLP technology and ExpreS2ion's ExpreS2 technology, which has the potential to mimic a virus to the body's immune system, giving the optimal stimulus to generate a fast, long-lasting immune response that offers a highly efficacious protection	Pre-Clinical	("ExpreS2ion. ExpreS2ion Announces Bavarian Nordic Enters Agreement with AdaptVac to Advance the COVID-19 Vaccine. May 06 2020. https://expres2ionbio.com/investor/international-press-releases/. Accessed May 21, 2020.," n.d.)
IMV Inc	DPX-COVID-19 is a formulation of the DPX platform with peptide epitopes from S proteins of the novel coronavirus (SARS-CoV-2)	DPX-COVID-19/ Pre-Clinical	("IMV. DPX-COVID-19 at a glance. April 15, 2020:https://imv-inc.com/clinical-trials/dpx-covid-19/. Accessed May 21, 2020.," n.d.)
WRAIR/USAMRIID	Ferritin nanoparticle from H. pylori are used to attach a small part of the coronavirus S protein binding receptor onto the ferritin nanoparticle shell which is surrounded by proprietary lipid ring around the shell that acts as an accelerant or booster	Pre-Clinical	("Eric Niiler: The US Army's Virus Research Lab Gears Up to Fight Covid-19. April 01, 2020. https://www.wired.com/story/the-us-armys-virus-research-lab-gears-up-to-fight-covid-19/ Accessed on May21, 2020.," n.d.)
National Institute of Infectious Disease, Japan	Vaccines rely on genetic engineering to create recombinant proteins that will serve as an antibody against the virus	Pre-Clinical	("Shionogi Inc. Shionogi Accelerates Development of Potential COVID-19 Treatments and Vaccine. April 28, 2020. https://www.shionogi.com/us/en/news/2020/4/shionogi-accelerates-development-of-potential-covid-19-treatments-and-vaccine.html. Accessed May21, 2020.," n.d.)
Osaka University/ BIKEN/ National Institutes of Biomedical Innovation, Japan	VLP-recombinant protein + Adjuvant	Pre-Clinical	("BIKEN foundation, 2020. https://www.osaka-u.ac.jp/en/news/info/corona/corona_info/cooperation. Accesses May 21, 2020.," n.d.)
Clover Biopharmaceuticals Inc./ GSK/Dynavax	Clover uses Trimer-Tag© technology to produce an S-Trimer subunit vaccine (resembling the native trimeric viral spike via a rapid mammalian cell culture-based expression system) which will be combined with GSK's pandemic adjuvant system to check vaccine efficacy	COVID-19 S-Trimer/ Phase 1 NCT04405908	("Clover Biopharmaceuticals Inc./GSK/Dynavax. https://www.fiercebiotech.com/biotech/using-gsk-dynavax-tech-clover-kickstarts-covid-vax-trial-data-drop-august. Accessed on July 29, 2020.," n.d.)
Univ. of Pittsburgh	The vaccine candidate is based on unique and patent protected signal peptide technology utilizing Vaxil's proprietary VaxHit™ bioinformatics platform	Pre-Clinical	("COVID-19 Vaccine Candidate Shows Promise: April 02, 2020. https://www.upmc.com/media/news/040,220-falo-gambotto-sars-cov2-vaccine. Accessed May21, 2020.," n.d.)
Vaxil Bio	The Vaccine Candidate is based on unique and patent protected signal peptide technology, utilizing Vaxil's proprietary VaxHit™ bioinformatics platform.	Pre-Clinical	("Vaxil. Vaxil commences preclinical COVID-19 vaccine trial and files an additional COVD-19 patent. March 27, 2020. https://vaxil-bio.com/vaxil-commences-preclinical-covid-19-vaccine-trial-and-files-an-additional-covid-19-patent/ Accessed May 21, 2020.," n.d.)
Biological E Ltd.	Adjuvanted protein subunit (RBD)	Pre-Clinical	("Biological E Ltd, 2020. https://www.livemint.com/news/india/covid-19-six-indian-companies-working-on-coronavirus-vaccine-11587016987400.html. Accessed May 27, 2020.," n.d.)
Flow Pharma Inc	FlowVax vaccines utilize Flow Pharma's patented Size Exclusion Antigen Presentation Control (SEAPAC(TM)) technology based on the benefits of making vaccine microspheres the same size as human white blood cells. This vaccine relies on killer T-cells rather than antibodies to fight virus infections	FlowVax Covid-19/ Pre-Clinical	("Flow Pharma: Flow Pharma Announces Strategic Partnership with Oakwood Labs for GMP Manufacturing of FlowVax COVID-19 Vaccine. April 15, 2020. https://www.accesswire.com/585181/Flow-Pharma-Announces-Strategic-Partnership-with-Oakwood-Labs-for-GMP-Manufacturing-of-FlowVax-COVID-19-Vaccine. Accessed May 21, 2020.," n.d.)
AJ Vaccines	The vaccine candidate will use technology to raise strong immune responses while being well tolerated and to meet potential global demand in 2021	Pre-Clinical	("AJ Vaccines, 2020. https://ajvaccines.com/news/. Accessed May 21, 2020.," n.d.)
Generex/EpiVax	Generex Biotechnology Corporation will use EpiVax expertise and computational tools to	Pre-Clinical	("Generex. Generex Signs Contract with EpiVax to Develop Ii-Key Peptide Vaccines to Address the

(*continued on next page*)

Table 4 (*continued*)

Manufacturer	Strategy	Vaccine Name/Stage	Ref.
	predict epitopes that can be used to generate peptide vaccines against SARS-CoV-2 using the patented NuGenerex Immuno-Oncology (NGIO – Formerly Antigen Express) Ii-Key technology		Coronavirus Pandemic. March 04, 202. https://epivax.com/news/press-release-generex-signs-contract-with-epivax-to-develop-ii-key-peptide-vaccines-to-address-the-coronavirus-pandemic. Accessed May 21, 2020.," n.d.)
EpiVax/Univ. of Georgia	Sequence will be predicted based on EpiVax computational tool	Pre-Clinical	("EpiVax. EpiVax Accelerates COVID-19 Vaccine Development with UGA's Center for Vaccines and Immunology. May 04, 2020. https://epivax.com/news/press-release-epivax-accelerates-covid-19-vaccine-development-with-ugas-center-for-vaccines-and-immunology. Accessed May 21, 2020.," n.d.)
Sanofi Pasteur/GSK	Sanofi will contribute its recombinant DNA technology-based S-protein COVID-19 antigen expressed using baculovirus expression platform, and GSK will contribute its proven pandemic adjuvant technology	Pre-Clinical	("Sanofi and GSK. Sanofi and GSK to join forces in unprecedented vaccine collaboration to fight COVID-19. April 14, 2020. https://www.sanofi.com/en/media-room/press-releases/2020/2020-04-14-13-00-00. Accessed May 21, 2020.," n.d.)
Novavax	Full length recombinant SARS-CoV-2 glycoprotein nanoparticle vaccine adjuvanted with Matrix M	NVX-CoV2373/ Phase 1/2 NCT04368988	("Novavax. https://ir.novavax.com/news-releases/news-release-details/novavax-initiates-phase-12-clinical-trial-covid-19-vaccine. Accessed on July 29, 2020.," n.d.)
Heat Biologics/ Univ. Of Miami	Heat's gp96 vaccine platform activates CD8 T cells, antigen presenting cells and natural killer cells, and induces mucosal immunity, which could make it an ideal vaccine for COVID-19	Pre-Clinical	("Heat Biologics. Heat Biologics Announces Research Collaboration with University of Miami to Develop Vaccine Designed to Protect Against COVID-19 Coronavirus. Match 05, 2020. https://www.heatbio.com/news-media/news-releases/detail/649/heat-biologics-announces-research-collaboration-with. May 21, 2020.," n.d.)
University of Queensland /GSK/Dynavax	Subunit vaccine consisting of a SARS-CoV-2 spike protein stabilized with a protein "molecular clam"	ACTRN12620000674932p	("University of Queensland /GSK/Dynavax. https://advance.qld.gov.au/covid-19-fast-facts. Accessed on July 29, 2020.," n.d.)
Baylor College of Medicine/Texas Children's Hospital/Path	Based on RBD of Spike protein	Pre-Clinical	("Baylor College of Medicine, 2020 https://www.bcm.edu/coronavirus-preparedness/covid-19-research. May 21, 2020.," n.d.)
iBio/CC-Pharming	Subunit protein is produced in a plant. The aim of this company is to deliver vaccine candidates for rapid production at iBio's FastPharming manufacturing facility	Pre-Clinical	("Fast-Farming Pharma. How plants could speed up vaccine manufacture to tackle the COVID-19 pandemic? April 17, 2020. https://themedicinemaker.com/manufacture/fast-farming-pharma. Accessed May 21, 2020.," n.d.)
Saint-Petersburg scientific research institute of vaccines and serums	Recombinant protein, nanoparticles (based on S-protein and other epitopes)	Pre-Clinical	("Saint-Petersburg scientific research institute of vaccines and serums. May22, 2020. https://www.who.int/who-documents-detail/draft-landscape-of-covid-19-candidate-vaccines. Accessed May 25, 2020.," n.d.)
Innovax/Xiamen Univ./GSK	COVID-19′s series of truncated S will be screened during the preclinical testing process; ultimate lead candidate will be determined by immunogenicity data	COVID-19 XWG-03/ Pre-Clinical	("GSK. GSK Joins Xiamen Innovax Biotech to Support COVID-19 Vaccine Development & Expands Activity to Fight War against Pandemic. April 06, 2020. https://www.trialsitenews.com/gsk-joins-xiamen-innovax-biotech-to-support-covid-19-vaccine-development-expands-activity-to-fight-war-against-pandemic/. Accessed May 21, 2020.," n.d.)
VIDO-InterVac, University of Saskatchewan	Adjuvanted microsphere peptide-based vaccine	Pre-Clinical	("USask. USask VIDO-InterVac awarded $23 M for COVID-19 vaccine research. April 23, 2020. https://news.usask.ca/articles/research/2020/usask-vido-intervac-awarded-23m-for-covid-19-vaccine-research.php. Accessed May 21, 2020.," n.d.)
OncoGen	Concept of personalized vaccination. Multiepitope peptide vaccine candidates were identified against nCov that can potentially trigger both CD4+ and CD8 + T cell immune response	Pre-Clinical	("OncoGen. OncoGen researchers propose personalized vaccinomics strategy for the novel China coronavirus: https://oncogen.ro/oncogen-vaccine-design-for-coronavirus/. Accessed May 21, 2020.," n.d.)
MIGAL Galilee Research Institute	Oral, *E. coli*-based protein expression system of S and N proteins	Pre-Clinical	("MIGAL's Coronavirus Vaccine Project:https://www.migal.org.il/en/node/7010. Accessed May 21, 2020.," n.d.)
University of Alberta	Spike-based	Pre-Clinical	("WHO. Draft landscape of COVID-19 candidate vaccines. May 30, 2020. https://www.who.int/who-documents-detail/draft-landscape-of-covid-19-candidate-vaccines. Accessed May 30, 2020.," n.d.)

22–44 and 351–357 linked together by glycine blocks entry of SARS pseudoparticles in HeLa cells expressing ACE2 protein with EC_{50} of 100 μM (Han et al., 2006). Recently it has been shown that a 23-mer spike binding peptide 1 (IEEQAKTFLDKFNHEAEDLFYQS) derived from human ACE2 a1 helix binds SARS-CoV-2-RBD with low nanomolar affinity (dissociation constant, KD = 47 nM), potentially inhibiting the entry of the virus into human cells (G. L. Zhang et al., 2020; G. Zhang et al., 2020). Another study showed that the lapidated form of peptide EK1, EK1C inhibits SARS-CoV-2 mediated cell-cell fusion at the concentration of 2.5 μM and with an IC_{50} of 48.1 nM. This study also suggests that lipidation, as well as linker length, plays an essential role in the overall activity of lipopeptides. (S. L. Xia et al., 2020; S. Xia et al., 2020). This would be a potential candidate for therapeutic development. However, its efficacy against SARS-CoV-2 still needs to be validated using an *in vivo* model (Table 6).

Several monoclonal antibodies targeting the S protein against SARS-CoV have been identified that inhibit the virus entry to cells (Sui et al., 2004; ter Meulen et al., 2006, 2004; Traggiai et al., 2004; Zhu et al.,

Table 5
S protein-based RNA vaccines.

Manufacturer	Strategy	Vaccine Name/ Stage	Ref
Fudan University /Shanghai JiaoTong University/RNACure Biopharma	LNP-encapsulated mRNA cocktail encoding VLP for induction of neutralizing antibodies, as well as producing virus-like particles similar to SARS-CoV-2	Pre-clinical	("Fudan University. Towards an effective mRNA vaccine against 2019-nCoV: March 7, 2020. https://www.fudan.edu.cn/en/2020/0307/c1092a104281/page.htm. Accessed May 21, 2020.," n.d.)
Moderna/NIAID	Lipid nanoparticle (LNP)-encapsulated mRNA-based vaccine encoding a full-length, prefusion stabilized S protein of SARS-CoV-2	mRNA-1273/ Phase 1 NCT04283461 Phase 2 NCT04405076 Phase 3 NCT04470427	(Jackson et al., 2020)
Centro Nacional Biotecnología (CNB-CSIC), Spain	Replicating defective SARS-CoV-2- derived RNAs	Pre-clinical	("Centro Nacional Biotecnología (CNB-CSIC). TYPE: RNA vaccine:https://www.lykeo.com/ replicating-defective-sarscov-2-derived-rnas-centro-nacional-biotecnologia-cnb-csic-spain. Accessed May 21, 2020.," n.d.)
University of Tokyo / Daiichi-Sankyo	LNP-encapsulated mRNA	Pre-clinical	("University of Tokoyo and Daiichi Sankyo. Our Company's Efforts to Limit the Spread of the Virus that Causes COVID-19 Accessed May 21, 2020.," n.d.)
BIOCAD	Liposome-encapsulated mRNA to produce disease-specific antigens and trigger a regular immune response	Pre-clinical	("BIOCAD, 2020. https://gmpnews.net/2020/03/biocad-begins-developing-covid-19-vaccine/. Accessed May21, 2020.," n.d.)
China CDC/Tongji University/Stermina	mRNA	Pre-clinical	
Arcturus/Duke-NUS	Self replication of mRNA with LUNAR®, a leading nanoparticle non-viral delivery system, to produce proteins inside the human body. Provokes a vaccine response at much lower doses compared to traditional mRNA vaccines	Phase 1/2 NCT0448057	("Arcturus/Duke-NUS, 2020 https://www.duke-nus.edu.sg/about/media/media-releases/media-releases/arcturus-therapeutics-duke-nus-clinical-trials-for-covid-19-vaccine-candidate-approved-to-proceed. Accessed on July 29, 2020.," n.d.)
BioNTech/Fosun Pharma/Pfizer	This includes four vaccine candidates, each representing a different combination of mRNA format and target antigen	Phase 1/22020−001038-36 ChiCTR2000034825 Phase 3 NCT04368728	("BioNTech/Fosun Pharma/Pfizer. https://www.genengnews.com/covid-19-candidates/biontech-pfizer-and-fosun-pharma-bnt162/. Accessed on July 29, 2020.," n.d.)
Imperial College London	Self-amplifying RNA vaccine will deliver genetic instructions to muscle cells to make the 'S' protein on the surface of the coronavirus. This should provoke an immune response and create immunity to COVID-19	Phase 1 ISRCTN17072692	("Imperial College London. https://www.clinicaltrialsarena.com/news/imperial-college-covid-vaccine/. Accessed on July 29, 2020.," n.d.)
Curevac	mRNA	NCT04449276	("Curevac. https://www.curevac.com/news/curevac-receives-regulatory-approval-from-german-and-belgian-authorities-to-initiate-phase-1-clinical-trial-of-its-sars-cov-2-vaccine-candidate. Accessed on July 29, 2020.," n.d.)
Saiba GmbH	Virus-like particle, based on RBD displayed on virus-like particles of plant virus Cucumber Mosaic Virus (CMV)	Pre-clinical	("Saiba Biotech. Saiba proprietary technology has enabled scientists to generate a vaccine candidate against COVID-19 with preclinical proof-of-concept. https://www.saiba-biotech.com/. Accessed May 21, 2020.," n.d.)

2007). Although RBD of the S protein is the prime target for neutralizing antibodies, antibodies can recognize different epitopes on RBD and work synergistically. The SARS-CoV neutralizing antibodies CR3014 and CR3022 bind noncompetitively to the SARS-CoV RBD and synergistically neutralize the virus (ter Meulen et al., 2006). A recent report revealed that although a SARS-CoV-neutralizing antibody m396 showed promising binding with SARS-CoV-2 RBD in computational modeling, it only showed slight binding at the highest measured concentration (2.0 μM) in an experimental condition. Another study found that plasma samples from SARS-CoV-convalescent patients can neutralize SARS-CoV, but cannot cross-neutralize SARS-CoV-2, even though they can bind SARS-CoV-2 (Lv et al., 2020). These results suggest that monoclonal antibodies that bind with SARS-CoV S protein are unable to bind SARS-CoV-2. These results suggest an urgent need to develop novel monoclonal antibodies that could bind specifically to SARS-CoV-2 (Tian et al., 2020).

11.1. Small molecule inhibitor

Another area of research which can provide immediate control of SARS-CoV-2 spreads is the small molecule inhibitors. Several previous reports have suggested that small molecule compound can successfully inhibit the interaction between SARS-CoV spike protein and ACE2, leading to block the virus entry into the cells (Adedeji et al., 2013; Huentelman Matthew J. et al., 2004; Kao et al., 2004). Similar study in SARS-CoV-2 suggest that small molecule can inhibit the interaction between SARS-CoV-2 and ACE2. Hanson et. al., have performed a drug repurposing screen against 3384 small molecule drugs using a proximity -based assay which measure the binding of SARS-CoV2 spike protein Domain (RBD) and ACE2, and found 25 high quality small molecule hits that can be evaluated for its efficacy in future (Hanson et al., 2020). Even though druggable pockets are absent in spike protein and ACE2 in their unbound states, bound states have well defined pockets for drug development. Using computer modeling, Patil et al. has shown that several antiviral compound against HCV and HIV viruses e.g. Atazanavir, Grazoprevir, Saquinavir, Simeprevir, Telaprevir and Tipranavir could be potential candidate inhibitors for immediate future investigation (Patil et al., 2020).

12. Conclusions and futures perspectives

The emergence of the COVID-19 pandemic has underscored the necessity to find therapeutics and/or vaccines to control the spread of infection and save infected people. From recent and previous studies of SARS-CoV, MERS-CoV, and SARS-CoV-2, it is well known that the S protein plays a vital role in virus-host interaction and its entry into human cells. Still, we need to know more about the fundamental nature of SARS-CoV-2, for example, mechanisms of pathogenesis, cellular and humoral immune response in the host after virus infection, etc., to make a successful therapeutics and/or vaccine.

Table 6
Inactivated Virus based vaccines.

Manufacturer	Strategy	Vaccine Name/ Stage	Ref
Sinovac	Inactivated	Phase 3 NCT04456595 Phase 1 NCT04383574 NCT04352608	(Gao et al., 2020)
Wuhan Institue of Biological Products/ Snopharm	Inactivated	Phase 3 ChiCTR2000034780 Phase1 ChiCTR2000031809	("Wuhan Institue of Biological Products/ Snopharm. https://www.fiercepharma.com/pharma-asia/china-s-sinopharm-touts100-antibody-response-for-covid-19-vaccine-it-s-already-giving. Accessed on July 29, 2020.," n.d.)
BEJING Institute of Biological Products/ Sinopharma	Inactivated	Phase 3 ChiCTR2000034780 Phase1 ChiCTR2000032459	("BEJING Institute of Biological Products/Sinopharma, 2020 https://www.fiercebiotech.com/research/inactivated-covid-19-vaccine-by-china-s-sinopharm-clears-animal-tests. Accessed on July 29, 2020.," n.d.)
Institute of Medical Biology, Chinesee Academy of Medical Sciences	Inactivated	Phase 1/2 NCT04470609 Phase 1 NCT04412538	("Institute of Medical Biology, Chinesee Academy of Medical Sciences. http://english.nmpa.gov.cn/2020-06/22/c_502093.htm. Accessed on July 29, 2020.," n.d.)
Bharat Biotech	Inactivated (Whole-Virion Inactivated		("Bharat Biotech, 2020 https://www.deccanchronicle.com/lifestyle/health-and-wellbeing/270720/bharat-biotechs-covaxin-shows-encouraging-results-in-phase-i.html. Accessed on July 29, 2020.," n.d.)

In this review, we summarised different approaches using the S protein to generate a vaccine, therapeutics, or neutralizing antibodies targeting SARS-CoV-2. Several neutralizing antibodies have been detected that act against SARS-CoV or MERS-CoV, but with limited success. Many of the neutralizing antibodies or vaccines identified cause ADE or vaccine-enhanced disease, respectively. There is a rising concern about ADE effect by sub-optimal antibody generated by vaccine under development against SARS-CoV-2. Because of these risks, it is crucial to perform large-scale clinical trials to assess vaccine or therapeutic efficacy and safety before approving any for widespread use. It is also essential to find a neutralizing antibody which can neutralize different strain of viruses and yet not cause antibody-induced enhancement. Use of nanobodies is one of the options that can successfully avoid the ADE effect. Since the virus is still spreading globally, a vaccine is the preferred means to control COVID-19. Development, testing, and clinical trials are ongoing with a focus on identifying a potential drug/ vaccine to prevent or treat SARS-CoV-2-associated disease.

Recent studies have shown that SARS-CoV-2 is actively evolving. Recently, it was found that a clinical strain of SARS-CoV-2 containing a D614 G mutation within the viral spike protein is now dominant in many countries (Korber et al., 2020). It has been reported in several studies that this mutation is not causing patient sicker but has higher rate of infectivity than the wild-type virus (Daniloski et al., 2020; Eaaswarkhanth et al., 2020; Ogawa et al., 2020;). D614 G did not alter the virus's response to antibodies from patients infected with the wild-type virus, which suggests that vaccines currently under development based on the original viral spike protein will be still effective against the new strain (Grubaugh et al., 2020; L. L. Zhang et al., 2020; G. Zhang et al., 2020). However, in order to fully establish the safety, cross-challenging studies of the new strain in vaccinated animals should be performed to evaluate the biosafety of vaccines.

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