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

SLAS Discovery
2021, Vol. 26(3) 311–329

DOI: 10.1177/2472555220979579
journals.sagepub.com/home/jbx
SAGE

Therapeutic and Vaccine Options for COVID-19: Status after Six Months of the Disease Outbreak

Dawid Maciorowski[1], Christian Ogaugwu[2], Subba Rao Durvasula[1], Ravi Durvasula[1], and Adinarayana Kunamneni[1]

Abstract

An outbreak of the coronavirus disease 2019 (COVID-19) caused by an infection of the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) occurred in Wuhan, China, in December 2019. This new virus belongs to the group of enveloped RNA beta-coronaviruses. Symptoms may differ in various infected persons, but major presentations include dry cough, nasal congestion, shortness of breath, fever, and general malaise. The disease appears to be more severe in patients above the age of 60 years and those with underlying conditions such as diabetes, cancer, cardiovascular diseases, chronic respiratory disease, and hypertension. There is still no approved vaccine against COVID-19, but more than a hundred are at different stages of development. It is known that the development of new drugs takes a relatively long time, so several known and already-approved drugs are being repurposed for the treatment of this disease. In this review, we explore the therapeutic and vaccine options that are available for COVID-19 6 months after its outbreak. Most noteworthy among the therapeutic options are dexamethasone, remdesivir, Avigan (favipiravir) and convalescent plasma.

Keywords

COVID-19, SARS-CoV-2, therapeutics, vaccines, drug repurposing

Introduction

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a novel human pathogenic virus; it belongs to the Coronaviridae family, whose members are named after their crown-like appearance caused by the surface glycoproteins that decorate the virus. This novel virus, also referred to as 2019-nCoV, is responsible for the coronavirus disease 2019 (COVID-19).[1,2] Coronaviruses including 229E, NL63, OC43, and HKU1 are common human pathogens that cause common cold-like symptoms. Other known pathogenic coronaviruses for humans include SARS-CoV (which causes the severe acute respiratory syndrome) and MERS-CoV (which causes the Middle Eastern respiratory syndrome). Coronaviruses are large (28–32 kb), single-stranded, positive-sense RNA viruses.[3] Within the phylogenetic subgroups of the family Coronaviridae, SARS-CoV-2 belongs to the beta-coronavirus, along with SARS-CoV and MERS-CoV.[4] Coronaviruses have similar proteins that are involved in replication at the 5′ end, and structural proteins encoded at the 3′ end of the genome.[3] The RNA script allows expression of the replicase, which is expressed as two polyproteins, pp1a and pp1ab. These can include up to 16 nonstructural proteins.[5] The nonstructural proteins are generated by processing of pp1a and pp1ab by two or three viral proteases encoded within the replicase. There are several accessory proteins that seem to be important for pathogenesis, but all are not functionally characterized.

Structural Proteins

A matured SARS-CoV-2 consists of four structural proteins, spike (S), envelope (E), nucleocapsid (N), and membrane (M), all of which constitute the complete structural

[1]Department of Medicine, Loyola University Medical Center, Maywood, IL, USA
[2]Department of Animal and Environmental Biology, Federal University Oye-Ekiti, Ekiti State, Nigeria

Received July 1, 2020, and in revised form Nov 15, 2020. Accepted for publication Nov 18, 2020.

Corresponding Author:
Adinarayana Kunamneni, Department of Medicine, Loyola University Medical Center, 2160 S 1st Avenue, Chicago, IL 60153, USA.
Email: akunamneni@luc.edu

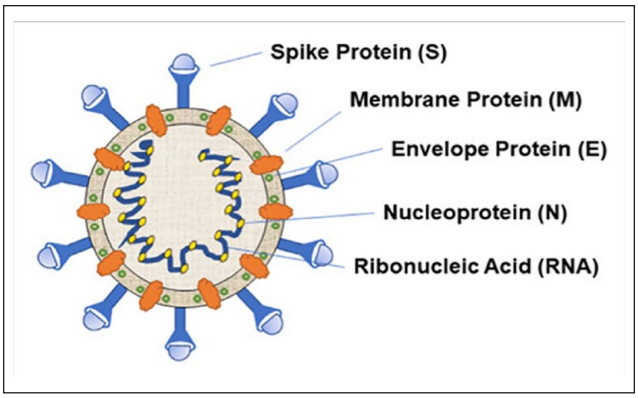


Figure 1. A schematic representation showing the structure of SARS-CoV-2.

viral particle[6] (**Fig. 1**). Each of these proteins plays a primary role in the structure of the viral particle.

The S protein mediates viral attachment to the host cell surface receptors and is responsible for the consequent fusion between the viral and host membranes to facilitate viral entry.[6,7] The S protein has two subunits: S1, which contains the receptor-binding domains (RBDs) that facilitate virus–host binding, which then transitions to the S2 for virus–host fusion.[1,8] Both SARS-CoV and SARS-CoV-2 recognize the human angiotensin-converting enzyme 2 (hACE2) as its host receptor binding to the S protein.[9] A novelty of the SARS-CoV-2 S protein is the presence of a furin cleavage site at the S1/S2 boundary of the protein, which is then cleaved during biosynthesis. The functionality of this is still not fully understood. It should be emphasized that the indispensable function of the S glycoprotein makes it a key target for therapeutic antibodies, diagnostics, and tentative vaccines. The coronavirus N protein packages viral genomic RNA into a ribonucleoprotein complex and serves as an RNA chaperone.[10] This protein localizes in the endoplasmic reticulum–Golgi region that is structurally bound to the nucleic acid material of the virus. The N protein is also involved in the host immunological response. It is also heavily phosphorylated, which may lead to structural changes enhancing the affinity for viral RNA.[11] The M structural protein is the most abundant and plays a prominent role in determining the shape of the virus envelope.[12] M is involved in facilitating interactions between all other structural proteins.[13] The M protein stabilizes the N proteins and promotes the completion of viral assembly by stabilizing the N protein–RNA complex within the virion, promoting viral assembly.[10] Finally, the E protein is the smallest structural protein and plays a role in the production and maturation of the virion.[14] The majority of this protein is located within sites of intracellular trafficking to participate in coronavirus assembly and budding.[15] The E protein is abundantly expressed inside infected cells, but minimal portions are incorporated within the envelope.[14] Both the M and E proteins constitute the viral envelope of the coronavirus family.[10,16]

Key Nonstructural Proteins

There are 29 proteins known to be produced by SARS-CoV-2.[17] Several of these proteins are critical nonstructural proteins that are valuable targets for antiviral drugs. Of these, the most druggable targets in this virus are several of its enzymes, some of which will be discussed below. The viral genome has 14 open reading frames, each of which encodes a variety of proteins. A viral replicase is used to translate most of the viral genomic RNA. From this, two polyproteins are synthesized (pp1a and pp1ab), which are further cleaved into nonstructural proteins.[3] These two polyproteins are processed by two proteases, papain-like protease (PLpro) and 3 chymotrypsin-like protease (3CLpro), which are both essential for generating functional replication complexes. PLpro cleaves the N-terminal region of the polyprotein to generate three nonstructural proteins (1/2/3) and is thought to have deubiquitinating activity.[18,19] 3CLpro cleaves 11 different sites of the polyprotein to produce a mature protein that anchors replication and transcription complexes and releases mature nonstructural proteins. RNA-directed RNA polymerase (RdRp) is critical for host cell RNA replication in RNA viruses due to its functionality of catalyzing the template synthesis of polynucleotides. This protein was found to be critical for the infection cycle of all RNA viruses. Chien et al. demonstrated the requirement of RdRp activity for SARS-CoV pathogenesis by showing that without RdRp, there is a complete disruption of SARS-CoV both in vitro and in vivo, as indicated by stopping RNA replication and halting viral growth.[20] These proteases have emerged as important drug targets because of their critical viral roles and low similarity with human proteases.[21,22] 2′-*O*-Methyltransferase (2′-O-MT) mediates mRNA cap 2′-*O*-ribose methylation of the 5′ cap of viral mRNAs, while 2′-*O* methylation is important for the host immune system to discern self-RNA from non-self-RNA. Viral helicase is essential for viral replication and therefore proliferation. Nonstructural uridylate-specific endoribonuclease (NendoU) is another nonstructural protein worth investigating as an antiviral target since its endoribonuclease is suspected to be similar in all coronaviruses.[23,24] Angiotensin-converting enzyme 2 (ACE2) is an antigen receptor recognition enzyme that is located on the host cell surface. To gain entry into a target cell, the SARS-CoV S protein binds to the ACE2 receptor.[25] hACE2 is present in a wide array of human tissues, including in the lung epithelia, kidney, testis, and small intestine.[25] The S protein consists of three sections, an ectodomain, a single-pass transmembrane anchor, and a short intracellular tail.[26] The ectodomain of the S protein consists of two subunits: S1 and S2. The S1 subunit contains an RBD residing on its C terminus

that is involved in the ACE2-binding process.[26] The SARS-CoV-2 S1 RBD has a substantially higher binding affinity to hACE2 in comparison with the SARS-CoV-1 RBD.[27] Both SARS-CoV-1 and SARS-CoV-2 rely on proteolytic processing from cell surface transmembrane serine protease 2 (TMPRSS2) and lysosomal endopeptidase enzyme (cathepsin L) for the preactivation of the S protein. TMPRSS2 cleaves the S protein, allowing for transmission of the virus via the ACE2 receptor, while cathepsin L activates membrane fusion.[9,28,29] There is strong evidence that SARS-CoV-2 has an additional novel preactivation mechanism through the proteasomal processing from proprotein convertase (PPC) furin.[27] A study has revealed that furin-mediated preactivation of the SARS-CoV-2 S protein enhances its ability to enter target cells.[27] This is significant as furin-mediated cleavage of the SARS-CoV-2 S protein allows SARS-CoV-2 to gain entry into cells with low expression of TMPRSS2 and/or cathepsin L.[27]

Drugs against SARS-CoV-2

There are many drugs that are either in development or in trial that target several of the SARS-CoV-2 structural and nonstructural candidates mentioned. Furthermore, there have been numerous reports of drug repurposing with the intent of finding already approved or nearly approved compounds that have efficient antiviral properties and are clinically safe. Repurposing is critical because it speeds up the amount of time for treatments to find their place in the clinical setting. Several compounds, such as remdesivir (RDV) and hydroxychloroquine (HQC), showed early promise, though opinions differ on HQC. **Table 1** shows several candidates that either target SARS-CoV-2 directly or serve to reduce COVID-19 pathology by targeting human receptors.

Of the several compounds tested as potential COVID-19 treatments, few have come out as front-runners, most notably, RDV, HQC, and lopinavir (LPV)/ritonavir (RTV). RDV is a broad-spectrum antiviral prodrug that is metabolized into its active form, GS-441524. This compound has shown antiviral properties against several viruses, including Ebola and MERS-CoV.[30] RDV does exhibit in vitro antiviral activity against SARS-CoV-2, warranting its use as a potential treatment for COVID-19.[31] More recently, RDV was shown to be efficacious in shortening the recovery time of hospitalized COVID-19 patients in a study spanning several countries.[32] RDV is a competitive inhibitor of RdRP, competing with adenosine triphosphate.[33] The RDV prodrug undergoes several metabolic steps within the cell in the formation of the active RDV–triphosphate (GS-441524) compound.[33] Recently, the claims of RDV's efficacy as a mortality-reducing drug by a small U.S. trial[32] were unfounded during a large trial by the World Health Organization (WHO)[34] where RDV had little effect on mortality reductions. HCQ is an aminoquinoline that is commonly used as an antimalarial agent, but it has also been used against lupus and rheumatoid arthritis.[35] It is an analog of chloroquine (CQ) in which one of the *N*-ethyl substituents of CQ is β-hydroxylated. The activity of HCQ against malaria is equivalent to that of CQ, and HCQ is preferred over CQ when high doses are required because of the lower level of ocular toxicity of HCQ.[36] HCQ has had promising in vitro data against SARS-CoV-2, suggesting its use as a possible COVID-19 treatment. Mechanistically, HCQ can pass through the host cell's membrane and aggregates within the host's intracellular compartments, including lysosomes and other vesicles. This accumulation results in the increase of the vesicular pH, which consequently does not allow the virus to release the vesicle into the cytoplasm, thus resulting in a minimized viral load within the host cell.[35] Also, HCQ might be involved in disruption of various enzymatic functions, including glycosylation of newly synthesized proteins.[37] Several other mechanisms have been proposed for how HCQ interacts with SARS-CoV-2; however, HCQ is no longer considered a therapeutic option as it does not reduce mortality.[38] LPV, commonly administered for treatment of HIV-1, is a retroviral protease inhibitor.[39] LPV is often combined with RTV, which acts as an inhibitor against cytochrome P450 metabolism of LPV.[39] LPV-RTV has also shown inhibitory activity against SARS-CoV-1 cysteine proteases, making it a drug of interest in combating SARS-CoV-2.[40] In regard to the inhibition of the SARS-CoV-2 3CLpro, it has been suggested that both LPV and RTV inhibit 3CLpro activity.[40]

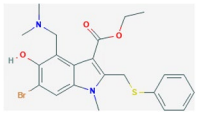
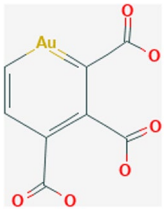
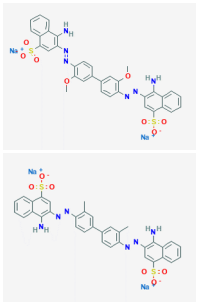
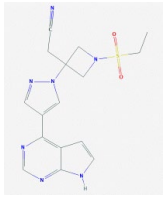
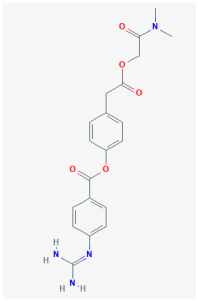
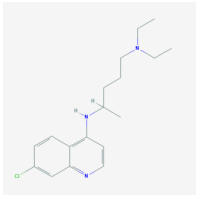
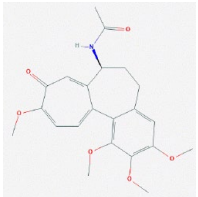
On June 16, 2020, a breakthrough repurposed drug was reported for critically ill hospitalized COVID-19 patients such as those on ventilators. The steroid, dexamethasone, was found to reduce deaths due to COVID-19 by one-third in a controlled clinical trial conducted in the UK.[41] So far, it is not advisable to use dexamethasone for patients who are not critically ill since the steroid showed no effect.[41]

The most recent promising drug alternative emanated from a study by Bouhaddou et al.,[42] who mapped the phosphorylation landscape of SARS-CoV-2 infection in Vero E6 cells and utilized the results to identify several drugs for treatment of the infection. Silmitasertib, gilteritinib, apilimod, dinaciclib, ARRY-797, and ralimetinib were among the compounds tested, and some of them were able to decimate 50% of coronavirus at a lower concentration than RDV.[42] While some of these compounds are already at different stages of clinical trials for other applications, it remains to be seen in the near future if they will perform equally well in human patients as they did in cells.

Antibody Treatments

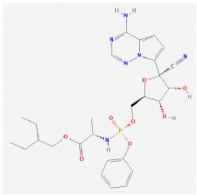
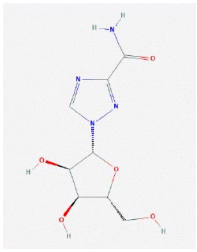
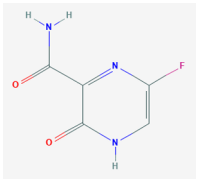
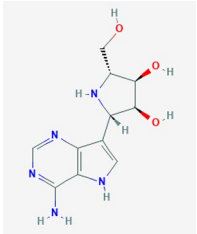
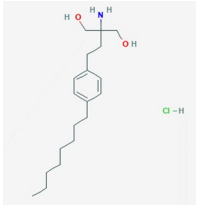
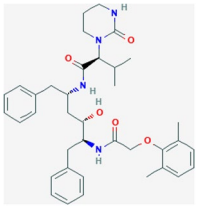
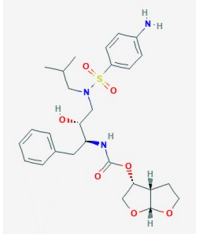
Antibodies have immense potential as treatments for COVID-19. This is because antibodies can neutralize the viral particle or target inflammatory factors, such as

Table 1. Drugs That Have Been Either Repurposed or Synthesized to Show Antiviral Activity against SARS-CoV-2.

Drug Name	2D Structures	Target	Mechanism	Novel (NV) or Repurposed (RP)	References
Arbidol		S glycoprotein and hACE2	Blocks viral entry	RP	Vankadari[73]
Aurine tricarboxylic acid		RdRp	Blocks viral replication	RP	Morse et al.[74]
Benzopurpurin B		Endoribonuclease NSP15	Causes viral RNA degradation	RP	Ortiz-Alcantara et al.[5]
Baricitinib		JAK kinase	Suppression of proinflammatory cytokines typically observed in people with COVID-19	RP	Richardson et al.[75]
Camostat mesylate		TMPRSS2	Blocks nucleocapsid entry from phagosome to cytoplasm	RP	Hoffmann et al.[9]
Chloroquine		Endosome/ACE2	Interferes with S protein processing by lysosomal enzymes as well as viral envelop assembly	RP	Vincent et al.[37]
Colchicine		Host tubulin	Suppression of proinflammatory cytokines typically observed in people with COVID-19	RP	Finkelstein et al.[76]

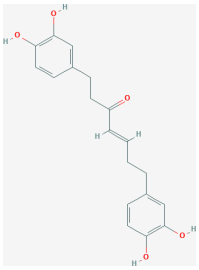
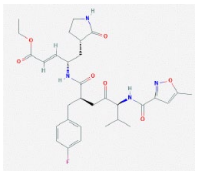
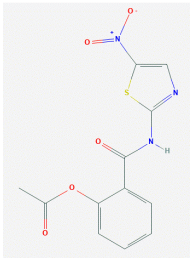
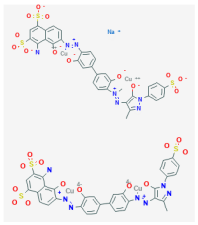
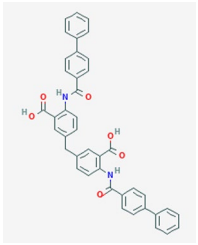
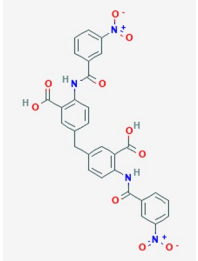
(continued)

Table 1. (continued)

Drug Name	2D Structures	Target	Mechanism	Novel (NV) or Repurposed (RP)	References
Remdesivir		RdRp	Blocks viral replication	RP	Agostini et al.[30]
Ribavirin		RdRp	Blocks viral replication	RP	Morse et al.[74]
Favipiravir (Avigan)		RdRp	Blocks viral replication	RP	Guo[77]
Galidesivir		RdRp	Blocks viral replication	RP	Warren et al.[78]
Gilenya (fingolimod)		Host sphingosine 1-phosphate receptor	Anti-inflamatory	RP	Torjesen[38]
Lopinavir		3CLpro and PLprop	Blocks viral replication by inhibiting polyprotein processing	RP	Sheahan et al.[4]
Darunavir		3CLpro and/or PLpro	Blocks viral replication by inhibiting polyprotein processing	RP	Liu et al.[79]

(continued)

Table 1. (continued)

Drug Name	2D Structures	Target	Mechanism	Novel (NV) or Repurposed (RP)	References
Hirsutenone		3CLpro and/or PLpro	Blocks viral replication by inhibiting polyprotein processing	RP	Kumar et al.,[80] Zhou et al.[81]
Rupintrivir		3CLpro and/or PLpro	Blocks viral replication by inhibiting polyprotein processing	RP	Anand et al.[21]
Nitazoxanide		Unknown	Slows replication; unknown target	RP	Guo[77]
NSC-306711		Endoribonuclease NSP15	Viral genomic RNA degradation by host cellular innate immunity blocking	RP	Ortiz-Alcantara et al.[5]
C-473872		Endoribonuclease NSP15	Viral genomic RNA degradation by host cellular innate immunity blocking	RP	Ortiz-Alcantara et al.[5]
C-467929		Endoribonuclease NSP15	Viral genomic RNA degradation by host cellular innate immunity blocking	RP	Ortiz-Alcantara et al.[5]

cytokines. Research groups at universities and companies have used antibodies from recovered COVID-19 patients to treat new patients. Many of these are at the clinical stage, while others are still in preclinical phases. The most popular of these was the use of convalescent plasma developed early in the course of the COVID-19 pandemic.[43] Numerous case series and observational studies have since been published with variable results.[44–46] Two published randomized controlled trials were halted early, one due to concern of a lack of benefit and the other due to low enrollment.[47,48] To date, one randomized controlled trial has been completed but did not meet its composite endpoint of progression to severe disease or all-cause mortality at 28 days; the median time from symptom onset to administration was 8 days, and the median antibody titer was 1:40. The results of additional randomized controlled trials are forthcoming. Questions remain about the antibody titer that should be used when treating patients with COVID-19, and if timing of administration is an important consideration. In August 2020, the Food and Drug Administration (FDA) announced an Emergency Use Authorization (EUA) for convalescent plasma in patients with COVID-19. On September 23, 2020, the FDA issued an update on convalescent plasma therapy for COVID-19. The update included an analysis that supported the concept of an antibody dose–response effect; the FDA concluded convalescent plasma "may be effective." Another strategy is through using lab-synthesized antibodies that can neutralize the virus. Most often, antibodies are synthesized through genetically modified mice that are able to express various antibodies. Our laboratory uses a ribosome display method to synthesize antibodies against various pathogens, including the Zika virus, Ebola, and Marburg virus,[49,50] and most recently has focused on SARS-CoV-2. Antibody therapeutics are of critical importance in the fight against this pandemic, and thus, in the coming months, we expect rapid progress to be made through available synthesis methodologies.

Camelid-derived single-domain antibody fragments, also called VHHs or nanobodies (nAbs), offer several advantages over conventional antibodies as candidates for specific therapies. Despite being approximately one-tenth of the size of a conventional antibody, they retain specificity and affinity similar to conventional antibodies, while being far easier to clone, express, and manipulate. They are readily expressed in bacteria in large quantities and show high thermal stability and solubility, making them easily scalable and cost-effective. Their modularity means that they can be oligomerized to increase avidity or to increase serum half-life.[51] Critical to their use as antivirals in humans, they can easily be humanized with existing protocols.[52] Importantly, they have proven to be highly potent inhibitors of viral infections in vivo, particularly respiratory infections.[53,54]

nAbs may be an alternative source of treatment against COVID-19, and various avenues for antibody treatment (**Table 2**) are currently being explored, with a surge in research findings. Unfortunately, the poor cross-neutralizing efficacy of SARS-CoV-derived antibodies against SARS-CoV-2 has required additional input to generate new antibodies and improve existing ones. Thus, the shift in attention toward producing SARS-CoV-2-specific antibodies that have demonstrated higher neutralizing potential is timely and imperative. Antibodies such as REGN-COV, BD-23, CB6-LALA, SARSVHH-72, S309, 47D11, 311 mAb-31B5, and 311 mAb-32D4 appear to be particularly promising for combating the COVID-19 pandemic in view of their potent in vitro neutralizing activities and/or in vivo protection efficacies in animal models[55] (**Table 2**). Current structural and sequence comparison-based analyses have attempted to summarize the various possible mechanistic reasons why most SARS-CoV-2 and SARS-CoV-derived antibodies do not cross-react and/or cross-neutralize.[55] Gavor et al.[55] have offered some insights into what types of antibodies might cross-react and cross-neutralize SARS-CoV-2 and SARS-CoV, and these should be further addressed experimentally. Gavor et al.[55] have also provided a perspective on the impact of Asp614Gly and other mutations on the neutralizing effect of current antibodies.

Gavor et al.[55] have considered a platform to easily identify and choose antibodies that might be tested in a cocktail against COVID-19 to overcome escape mutant strains. For example, promising cocktails might include REGN-COV, 414-1 + 553-15, COV2-2196 + COV2-2130, CR3022 + CR3014, or B38 + H4. The prospect of combining monoclonal antibodies (mAbs) 553-15 and S309 with other antibodies in a cocktail is particularly attractive because these mAbs demonstrate a potent synergistic neutralizing effect with many of the other antibodies.[56,57] Moreover, mAb CR3022 might be combined with mAb COV21, C105, or B38 in a cocktail because CR3022 does not appear to compete with these three antibodies for binding to the SARS-CoV-2 S glycoprotein, and therefore might offer synergistic neutralizing effects.[58,59] Similarly, the potent NTD-binding nAb 4A8 might also be considered in a cocktail with RBD-binding antibodies because 4A8 binding to the NTD leaves the RBD region of the S glycoprotein free for co-binding antibodies that might offer additive neutralizing effects. Of note, in addition to cocktail antibody therapies, a cocktail with other antiviral drugs such as RDV might be therapeutically explored against COVID-19. Moving forward, because antibody-dependent enhancement (ADE) of COVID-19 cannot be reliably predicted after vaccination or antibody treatment, careful analysis of safety will need to be conducted in humans.

A lot of antibodies have also been repurposed for use against COVID-19. Many of these antibodies do not have mechanisms of action relevant to SARS-CoV-2, but rather to COVID-19 pathology. Researchers have shown that the infection of SARS-CoV-2 activates CD4+ T lymphocytes,

Table 2. Different Antibodies, Their Intended Targets, and Stages of Clinical Development.

Molecule/Description	Target	Neutralizing Mechanism	Stage	References
LY-CoV555	SARS-2 S	Blocks viral attachment and entry into human cells	Phase 2 trials	**NCT04427501**
REGN10987 and REGN10933 humanized and human mAb cocktail	REGN10933: RBM of SARS-2 REGN10987: RBD/S1BCD	Block hACE2-RBD binding ADCC and ADCP	Clinical	Hansen et al.,[82] Baum et al.[83]
S309 human mAb	SARS and SARS-2 RBD/S1BCD	Targets a conserved glycan-containing epitope within S protein and shows Fc-dependent effector mechanisms	Clinical	Pinto et al.[56]
4A8, 1M-1D2, and 0304-3H3 human mAbs	4A8: NTD of S1 1M-1D2: S1 domain 0304-3H3: S2 domain	Likely restrain conformational change in S protein	Preclinical	Chi et al.[84]
47D11 human mAb	SARS-2 and SARS RBD/S1BCD	Binds to the conserved epitope of RBD without compromising spike–receptor interaction	Phase 1 trials expected	Wang et al.[85]
CR3022 human mAb	SARS and SARS-2 RBD/S1BCD	Destabilizes and destroys the prefusion S trimer	Preclinical	Lan et al.,[86] Tian et al.,[87] Ter Meulen et al.[88]
S230 human mAb	SARS-RBD/RBM	Blocks hACE2-RBD binding	Preclinical	Walls et al.[89]
SARS-VHH-72 (HCAb) llama (camelid) mAb	SARS, SARS-2, and bat WIVI CoV RBD/S1BCD	Blocks hACE2-RBD binding Destabilizes the prefusion spike	Preclinical	Wrapp et al.[90]
ADI-55689 and ADI-56046 human mAbs	SARS, SARS-2, and bat WIV1 RBD/RBM/S1BCD	Block hACE2-RBD binding and induce S1 shedding	Preclinical	Wec et al.[91]
P2C-1A3 and P2C-1C10 human mAbs	SARS-2 RBD	Block hACE2-RBD binding	Preclinical	Ju et al.[92]
P2A-1A10 and P2A-1B3 human mAbs	SARS-2 RBD	Block hACE2-RBD binding	Preclinical	Ju et al.[92]
P2C-1F11 and P2B-2F6 human mAbs	SARS-2 RBD/RBM	Block hACE2-RBD binding	Preclinical	Ju et al.[92]
311mab-31B5 and 311mab-32D4 human mAbs	SARS-2 RBD/RBM	Block hACE2-RBD binding	Preclinical	Chen et al.[93]
B38 and H4 human mAbs	SARS-2 RBD/RBM/S1BCD, although at different sites	Block hACE2-RBD binding	Preclinical	Wu et al.[59]
CA1 and CB6 human mAbs	SARS-2 RBD/RBM	Block hACE2-RBD binding	Preclinical	Shi et al.[94]
BD-368-2, BD-218, and BD-23 human mAbs	SARS-2 RBD	Block hACE2-RBD binding	Preclinical	Cao et al.[95]
EY6A mouse mAb	Both SARS and SARS-2 RBD/S1BCD	Might engage multiple mechanisms	Preclinical	Tian et al.,[87] Zhou et al.[96]
COV21 human Ab	SARS and SARS-2	Blocks hACE2-RBD	Preclinical	Robbiani et al.,[58] Lan et al.,[86] Tian et al.,[87] Walls et al.,[89] Barnes et al.[97]
C121, C135, C144, and C105 human mAbs	SARS-2 RBD	Block hACE2-RBD binding	Preclinical	Robbiani et al.,[58] Lan et al.,[86] Tian et al.,[87] Walls et al.,[89] Barnes et al.[97]

(continued)

Table 2. (continued)

Molecule/Description	Target	Neutralizing Mechanism	Stage	References
COV2-2196, COV2-2130, COV2-2196, and COV2-2381 mAbs	SARS-2 RBD/RBM	Block hACE2-RBD binding	Preclinical	Zost et al.[98]
2-15, 2-7, 1-57, 1-20, and 2-4 human mAbs	SARS-2 RBD	Block hACE2-RBD binding	Preclinical	Liu et al.[99]
H014 humanized mAb	SARS and SARS-2 RBD/S1BCD	Blocks hACE2-RBD binding	Preclinical	Lv et al.[100]
CC12.1 and CC6.33 human mAbs	SARS-2 RBD/RBM and SARS RBD	Block hACE2-RBD binding	Preclinical	Hansen et al.,[82] Rogers et al.,[101] Lei et al.,[102] Yuan et al.[103]
5C2 human scFv-Fc	SARS-2 S	Inhibits ACE2 from binding to S protein	Preclinical	Yuan et al.[104]
n3088 and n3130 human nAbs	SARS-2 RBD	Target a cryptic epitope situated in RBD	Preclinical	Wu et al.[105]
CV1/CV35 human mAb	SARS-2 RBD	Binds to an epitope distinct from the RBD	Preclinical	Seydoux et al.[106]
CV30 human mAb	SARS-2 S	Inhibits the S-ACE2 interaction	Preclinical	Seydoux et al.[106]
31B5, 32D4, COVA1-18, and COVA2-15 human mAbs	SARS-2 RBD	Perturb the ACE2-RBD interaction	Preclinical	Chen et al.,[93] Brouwer et al.[107]
P2B-2F6 human mAb	SARS-2 RBD	Competes with ACE2 for binding to the RBD	Preclinical	Ju et al.[92]
CB6 human mAb	SARS-2 RBD	Is overlapped with the binding epitopes of ACE2	Preclinical	Ju et al.[92]
H2 human mAb	SARS-2 RBD	Binds to the RBD but does not compete with ACE2 for RBD binding	Preclinical	Wu et al.[59]
B5 human mAb	SARS-2 RBD	Binds to the RBD but displays partial competition with ACE2	Preclinical	Wu et al.[59]
B38 and H4 human mAb	SARS-2 RBD	Show complete competition with ACE2 for binding to RBD	Preclinical	Wu et al.[59]
JS016 human mAb	SARS-2 RBD	Blocks SARS-CoV-2 RBD binding to ACE2	Phase 1 clinical	Shi et al.[94]
414-1 and 553-15 human mAbs	RBD and S ectodomain of SARS-2	Block hACE2-RBD binding	Preclinical	Wan et al.[57]

ADCC, antibody-dependent cell cytotoxicity; ADCP, antibody-dependent cellular phagocytosis.

which consequently become pathogenic T-helper cells generating various cytokines.[60] This then leads to high expression of interleukins (ILs) like IL-6 that accelerate inflammation. A report has shown that IL-6 levels in COVID-19 patients were significantly elevated,[61] suggesting that antibodies targeting the IL-6 receptor may reduce COVID-19 pathology. Actemra is one of the repurposed antibodies against COVID-19. Actemra was first approved in Japan in 2005 as a treatment for rheumatoid arthritis and cytokine release syndrome.[62] As severe cytokine release is part of COVID-19 pathology, Actemra may help reduce symptomatic expression of the disease. Kevzara is another antibody repurposed to treat COVID-19. It was first approved in the United States in 2017 for the treatment of rheumatoid arthritis.[63] Several Kevzara clinical trials are ongoing or are expected to start in the near future (i.e., NCT04315298, NCT043 21993, and NCT04324073).

Vaccines against SARS-CoV-2

A vaccine is of utmost importance to fully defeat the COVID-19 pandemic. Presently, there are more than 120 different vaccines being developed. There are different vaccine platforms that are currently being tested, some of which have not been tested in clinical settings before. Virus-like particle (VLP) vaccines consist of manipulated viral shells that mimic the viral structure but are not infectious because they lack the natural genetic material. They are used to prime the immune system by eliciting a strong immune response. Protein subunit-based vaccines consist of several viral proteins with an adjuvant that are expected to elicit an immune response, though several doses may be required. DNA- and RNA-based vaccines use modified nucleic acid scripts that encode a SARS-CoV-2 protein. Several of these vaccines encode and produce several copies of the SARS-CoV-2 S protein. There are also many vaccines that are viral vector based, including replicating viral vector and nonreplicating viral vector vaccine platforms. Replicating viral vector vaccines utilize weakened pathogens such as measles and horsepox, which can encode and express various structural proteins of the SARS-CoV-2 virus through viral replication. This methodology can provoke a strong immune response, but existing immunity to the viral vector can subdue the vaccine's efficacy. Nonreplicating vector vaccines are like the latter but utilize different vectors, such as adenoviruses, which do not induce a great immune response. Although no licensed vaccines use this methodology, adenoviruses have been widely used in gene therapy. Vaccines will be necessary both for individual protection and for the safe development of population-level herd immunity.

Public–private partnership collaborative efforts, such as the Accelerating COVID-19 Therapeutic Interventions and Vaccines mechanism, are key to rapidly identifying safe and effective vaccine candidates as quickly and efficiently as possible. **Table 3** shows several vaccines that are in preclinical or various phases of clinical trials. There are several more vaccines that are being developed that are in the preclinical phase. Several of these vaccines use methodologies that have never been used in a viral candidate, so there is uncertainty with regard to their utilization in the clinical sphere.

The vaccine mRNA-1273 was developed by the National Institute of Allergy and Infectious Diseases (NIAID) and the company Moderna. This vaccine uses messenger RNA to express SARS-CoV-2 proteins.[64] This was the first vaccine to be tested in clinical trials in the United States. The first participant was administered this investigational vaccine on March 16, 2020. The ChadOx1 nCoV-19 vaccine candidate was developed at the University of Oxford Jenner Institute.[65] This vaccine uses an adenovirus vector to induce a protective immune response. The ChadOx1 platform has been used to develop investigational vaccines against several different pathogens, including MERS-CoV. Recently, it was found that the vaccine was effective in tests on macaques and showed no viral replication within the lungs.[66] Ad5-nCoV was the first SARS-CoV-2 vaccine tested in Chinese clinical trials. This vaccine candidate is also adenovirus vector based (type 5 vector) and expresses the SARS-CoV-2 S protein.[67] It was developed by CanSino Biologics Inc. in Tianjin, China. The AAVCOVID vaccine candidate was developed in the laboratory of Luk Vandenberghe at Massachusetts General Hospital. This vaccine uses an adeno-associated virus (AAV) vector that expresses the SARS-CoV-2 S protein. AAV technology has been extensively used in the field of gene therapy, and this lab is a leader in the realm of AAV. This vaccine is expected to reach clinical trials by the end of 2020 (https://www.masseyeandear.org/news/press-releases/2020/05/mee-and-mgh-advancing-aavcovid-vaccine). In late June 2020, the clinical trial of an RNA-based vaccine, LNP-NCOVsaRNA, from Imperial College London started off in the United Kingdom (trial registration no.: SRCTN17072692). The self-replicating RNA vaccine relies on the encoded S protein from the envelope of SARS-CoV-2 and should induce immunity in recipients without causing COVID-19.

To date, just two coronavirus vaccines have been approved. Sputnik V—formerly known as Gam-COVID-Vac and developed by the Gamaleya Research Institute in Moscow—was approved by the Ministry of Health of the Russian Federation on August 11[68] (**Table 3**). Experts have raised considerable concern about the vaccine's safety and efficacy given it has not yet entered phase 3 clinical trials. A second vaccine in Russia, EpiVacCorona (ClinicalTrials.gov ID: NCT04527 575), has also been granted regulatory approval, also without entering phase 3 clinical trials (**Table 3**).

Several antibodies have been identified to target different domains of SARS-CoV-2 and are effective in neutralizing

(text continues on p. 16)

Table 3. Vaccine Candidates against SARS-CoV-2 and Clinical Phases.

Vaccine Type	Vaccine	Developer	Clinical Stage	Number of Doses	Timing of Doses	Route of Administration	Reported Results of Clinical Trials	References/Trial Registration Nos.
Inactivated vaccines	Inactivated	Institute of Medical Biology, Chinese Academy of Medical Sciences	Phase 1/2	2	0, 28 days	IM	Phase 1 data suggest the vaccine is safe and triggers an immune response, although a drop in neutralizing antibody titers from day 14 to day 28 is a potential cause for concern.	NCT04470609
	Inactivated	Wuhan Institute of Biological Products/ Sinopharm	Phase 3	2	0, 14 or 0, 21 days	IM	A phase 2 trial showed that the geometric mean titres of nAbs were 121 and 247 at day 14 after two injections in participants receiving vaccine on days 0 and 14 and on days 0 and 21, respectively. Moreover, 7-day adverse reactions occurred in 6.0% and 19.0% of the participants receiving injections on days 0 and 14 vs on days 0 and 21.	Xia et al.[108]
	Inactivated	Research Institute for Biological Safety Problems, Republic of Kazakhstan	Phase 1/2	2	0, 21 days	IM	The proportion of volunteers with increased levels of the immune response of specific neutralizing antibody titers in ELISA following the vaccination, compared with a placebo.	NCT04530357
	Inactivated SARS-CoV-2 vaccine with aluminum hydroxide	Sinovac	Phase 3	2	0, 14 days	IM	A phase 2 trial showed that two doses of 6 μg/0.5 mL or 3 μg/0.5 mL of the vaccine were well tolerated and immunogenic in healthy adults, with the 3 μg dose eliciting 92.4% seroconversion under the day 0, 14 schedule and 97.4% under the day 0, 28 schedule.	Zhang et al.[109]
	Inactivated	Beijing Institute of Biological Products/ Sinopharm	Phase 3	2	0, 14 or 0, 21 days	IM	A phase 2 trial showed that the vaccine at a dose of 5×10^{10} viral particles per mL was safer than the vaccine at 1×10^{11} viral particles and elicited a comparable immune response. However, high preexisting Ad5 immunity reduced the nAb response and influenced the T-cell immune response.	ChiCTR2000031809
	Whole-virion inactivated (BBV152A)	Bharat Biotech	Phase 2	2	0, 14 days	IM	N/A	NCT04471519, CTRI/2020/07/026300
RNA vaccines	mRNA	Curevac	Phase 2	2	0, 28 days	IM	N/A	NCT04449276, NCT04515147

(continued)

Table 3. (continued)

Vaccine Type	Vaccine	Developer	Clinical Stage	Number of Doses	Timing of Doses	Route of Administration	Reported Results of Clinical Trials	References/Trial Registration Nos.
	mRNA-1273	Moderna/NIAID	Phase 3	2	0, 28 days	IM	A phase 1 study reported that the two-dose vaccine series was not seriously toxic, and it could elicit nAbs and Th1-biased $CD4^+$ T-cell responses.	Jackson et al.[64]
	mRNA	Arcturus/Duke-NUS	Phase 1/2	N/A	N/A	IM	Phase 1/2 preclinical data have shown highly promising results with 100% seroconversion for neutralizing antibodies after a single administration using a very low 2 μg dose. Neutralizing antibodies continued to increase for 60 days after dosing. Preclinical results also demonstrated robust $CD8^+$ T-cell induction and a Th1-biased T-helper cellular immune response.	NCT04480957
	LNP-nCoVsaRNA	Imperial College London	Phase 1	2	N/A	IM	N/A	SRCTN17072692
	mRNA	People's Liberation Army Academy of Military Sciences/ Walvax Biotech	Phase 1	2	0, 14 or 0, 28 days	IM	N/A	ChiCTR2000034112
	BNT162b1 (mRNA expressing a trimeric RBD) and BNT162b2 (mRNA expressing S protein)	Pfizer/Fosun Pharma/ BioNTech	Phase 3	2	0, 28 days	IM	A phase 1/2 study showed that the vaccine caused mild to moderate local and systematic symptoms in most vaccinators and geometric mean neutralizing titers after the 10 and 30 μg dose reached 1.8- to 2.8-fold that of the COVID-19 convalescent sera panel. Positive phase 3 study interim results showed >90% efficacy in preventing COVID-19 across study participants.	Mulligan et al.[110]
DNA vaccines	DNA plasmid vaccine with electroporation	Inovio Pharmaceuticals/ International Vaccine Institute	Phase 1/2	2	0, 28 days	ID	N/A	NCT04447781, NCT04336410
	DNA plasmid vaccine + adjuvant	Osaka University/ AnGes/Takara Bio	Phase 1/2	2	0, 14 days	IM	N/A	NCT04463472, NCT04527081
	DNA plasmid vaccine	Cadila Healthcare Limited	Phase 1/2	3	0, 28, 56 days	ID		CTRI/2020/07/026352
	DNA Vaccine (GX-19)	Genexine Consortium	Phase 1/2	2	0, 28 days	IM	N/A	NCT04445389
Nonreplicating viral vector	Replication defective simian adenovirus (GRAd) encoding S	ReiThera/LEUKOCARE/ Univercells	Phase 1	1	N/A	IM	N/A	NCT04528641

(continued)

Table 3. (continued)

Vaccine Type	Vaccine	Developer	Clinical Stage	Number of Doses	Timing of Doses	Route of Administration	Reported Results of Clinical Trials	References/Trial Registration Nos.
	ChAdOx1 nCoV-19	University of Oxford/ AstraZeneca	Phase 3	1	N/A	IM	A phase 1/2 trial reported that nAb responses were detected in 91% of participants after a single dose when measured in MNA80 and in 100% participants when measured in PRNT50. After a booster dose, all participants had neutralizing activity. Local and systemic reactions, including pain, fever, and muscle ache, could be reduced by paracetamol.	Folegatti et al.[111]
	Adenovirus type 5 vector	CanSino Biological Inc./ Beijing Institute of Biotechnology	Phase 3	1	N/A	IM/mucosal	A phase 2 trial showed that the vaccine at a dose of 5×10^{10} viral particles per mL was safer than the vaccine at 1×10^{11} viral particles and elicited a comparable immune response. However, high preexisting Ad5 immunity reduced the nAb response and influenced a T-cell immune response.	Zhu et al.[67]
	Adeno based (rAd26-S + rAd5-S) (Sputnik V)	Gamaleya Research Institute	Phase 3	2	0, 21 days	IM	A phase 1/2 trial showed that administration of both rAd26-S and rAd5-S caused the production of nAbs in 100% of participants on day 42 for both the lyophilized and frozen vaccine formulations. Cellular immune responses were detected in all participants at day 28. Moreover, the preexisting immune response to the vectors rAd26 and rAd5 did not influence the titer of RBD-specific antibodies.	Logunov et al.[68]
	Ad26COVS1	Janssen Pharmaceutical Companies	Phase 3	2	0, 56 days	IM	Preclinical trials showed that a single immunization with an Ad26 vector encoding a prefusion stabilized S antigen triggered robust nAb responses and provided complete or near-complete protection in rhesus macaques. The immunogen contains the wild-type leader sequence, the full-length membrane-bound S, mutation of the furin cleavage site, and two proline stabilizing mutations.	Mercado et al.[112]

(continued)

Table 3. (continued)

Vaccine Type	Vaccine	Developer	Clinical Stage	Number of Doses	Timing of Doses	Route of Administration	Reported Results of Clinical Trials	References/Trial Registration Nos.
	Ad5 adjuvanted oral vaccine platform	Vaxart	Phase 1	2	0, 28 days Oral	Oral	N/A	NCT04563702
Replicating viral vector	Measles-vector based	Institute Pasteur/ Themis/University of Pittsburgh CVR/Merck Sharp & Dohme	Phase 1	1 or 2	0, 28 days	IM	N/A	NCT04497298
	Intranasal flu-based RBD	Beijing Wantai Biological Pharmacy/Xiamen University	Phase 1	1	N/A	IM	N/A	ChiCTR2000037782
Protein subunit	Full-length recombinant SARS-CoV-2 glycoprotein nanoparticle vaccine adjuvanted with Matrix M	Novavax	Phase 2/3	2	0, 21 days	IM	N/A	NCT04533399, 2020-004123-16
	Adjuvanted recombinant protein (RBD–dimer)	Anhui Zhifei Longcom Biopharmaceutical/ Institute of Microbiology, Chinese Academy of Sciences	Phase 2	2 or 3	0, 28 or 0, 28, 56 days	IM	N/A	NCT04550351, NCT04466085
	RBD based	Kentucky Bioprocessing, Inc.	Phase 1/2	2	0, 21 days	IM	N/A	NCT04473690
	S protein (baculovirus production)	Sanofi Pasteur/GSK	Phase 1/2	2	0, 21 days	IM	N/A	NCT04537208
	Recombinant trimeric subunit S protein vaccine	Clover Biopharmaceuticals Inc./GSK/Dynavax	Phase 1	2	0, 21 days	IM	N/A	NCT04405908
	Recombinant S protein with Advax adjuvant	Vaxine Pty. Ltd./ Medytox	Phase 1	1	N/A	IM	N/A	NCT04453852
	Molecular clamp stabilized S protein with MF59 adjuvant	University of Queensland/CSL/ Seqirus	Phase 1	2	0, 28 days	IM	N/A	ACTRN12620000674932p, ISRCTN51232965
	S-2P protein + CpG 1018	Medigen Vaccine Biologics Corporation/ NIAID/Dynavax	Phase 1	2	0, 28 days	IM	N/A	NCT04487210
	RBD + adjuvant	Instituto Finlay de Vacunas, Cuba	Phase 1	2	0, 28 days	IM	N/A	IFV/COR/04
	Peptide	FBRI SRC VB VECTOR, Rospotrebnadzor, Koltsovo	Phase 1	2	0, 21 days	IM	N/A	NCT04527575

(continued)

Table 3. (continued)

Vaccine Type	Vaccine	Developer	Clinical Stage	Number of Doses	Timing of Doses	Route of Administration	Reported Results of Clinical Trials	References/Trial Registration Nos.
	RBD (baculovirus production expressed in Sf9 cells)	West China Hospital, Sichuan University	Phase 1	2	0, 28 days		N/A	ChiCTR2000037518
	SARS-CoV-2 HLA-DR peptides	University Hospital Tübingen	Phase 1	1	N/A	SC	N/A	NCT04546841
	S1-RBD-protein	COVAXX	Phase 1	2	0, 28 days	IM	N/A	NCT04545749
VLP	Plant-derived VLP adjuvanted with GSK or Dynavax adjuvants	Medicago Inc.	Phase 1	2	0, 21 days	IM	N/A	NCT04450004

ELISA, enzyme-linked immunosorbent assay; IM, intramuscular; N/A, not applicable/not available.

SARS-CoV-2 (**Table 2**). These antibodies may have the potential to treat SARS-CoV-2-infected patients, and future work to define these antibody epitopes will further aid vaccine development. The experimental and clinical results of some vaccine candidates, such as BBIBPCorV and PiCoVacc, were reported, with most vaccines showing neutralizing capacity.[69] For vaccine development, it is critical to generate protective T- and B-cell immune responses. The S protein has been shown to be the most potent antigen for SARS-CoV and MERS-CoV vaccines, and we hypothesize this may be similar for SARS-CoV-2 vaccines. However, the immunopathology induced by SARS-CoV or MERS-CoV vaccines was observed in animal models, which might be attributed to ADE, an aberrant Th2 response partially due to the N protein, as well as other unknown reasons.[69]

The mechanisms underlying this immunopathology deserve further investigation, which may provide instructive guidance for the future development of SARS-CoV-2 vaccines. Apart from immunopathology, other important questions remain to be addressed, such as how to protect the population vulnerable to lethal human CoVs, such as the elderly, and how best to provide protection against variant and heterologous CoV strains. Recently, hACE2 transgenic mice were developed that could be infected by SARS-CoV-2 and generated typical pathology that were similar to those of COVID-19 patients.[70,71] Rhesus macaques infected by SARS-CoV-2 also exhibited humoral and cellular immune responses and were protected from rechallenge.[72] In essence, it is equally important to identify the ideal animal model for evaluating potential SARS-CoV-2 vaccines.

Summary

The spread of SARS-CoV-2 continues to cause problems to health systems and economies worldwide. There is currently no available vaccine against it that has passed the required clinical trials and received approval for use. However, only two drugs have emerged as effective treatments to combat it: the steroid drug dexamethasone, for critically ill patients on ventilators, and the antiviral drug RDV, for less critical cases, shortening the disease period. The international scientific community has intensified efforts on vaccines and therapeutic research at an unprecedented pace, and collaborations or formations of consortiums have allowed such speed in scientific advancement to take place. For antivirals against SARS-CoV-2, the development and clinical approval of novel compounds that specifically target SARS-CoV-2 will require an extended period of preclinical testing before they can enter clinical trials. The COVID-19 pandemic is a large-scale emergency and warrants the rapid use of already approved drugs that can be repurposed for its treatment. This strategy is what has facilitated the trials and uses of RDV, HQC, CQ, LPV, Avigan (favipiravir), and dexamethasone to treat COVID-19 in emergencies. It is expected that more effective drugs against SARS-CoV-2 will be found in the near future. Convalescent plasma may be used in the United States to treat hospitalized patients under an EUA or an Investigational New Drug (IND) application. "Adequate and well-controlled randomized trials remain necessary for a definitive demonstration of COVID-19 convalescent plasma efficacy and to determine the optimal product attributes and appropriate patient populations for its use," according to updated guidance issued by the FDA on September 2. While the world is transfixed by the high-stakes race to develop a COVID-19 vaccine, an equally crucial competition is heating up to produce targeted antibodies that could provide an instant immunity boost against the virus. Clinical trials of these mAbs, which could both prevent and treat the disease, are already underway and could produce signs of efficacy in the next few months, perhaps ahead of vaccine trials. In conclusion, we have listed the possible therapies, many of which are being tested in clinical trials and some that still need more testing.

Declaration of Conflicting Interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The authors received no financial support for the research, authorship, and/or publication of this article.

ORCID iD

Dawid Maciorowski https://orcid.org/0000-0002-4163-9535

References

1. Wrapp, D.; Wang, N.; Corbett, K. S.; et al. Cryo-EM Structure of the 2019-NCoV Spike in the Prefusion Conformation. *Science* **2020**, *367*, 1260–1263.
2. Wu, F.; Zhao, S.; Yu, B.; et al. A New Coronavirus Associated with Human Respiratory Disease in China. *Nature* **2020**, *579*, 265–269.
3. Wu, A.; Peng, Y.; Huang, B.; et al. Genome Composition and Divergence of the Novel Coronavirus (2019-NCoV) Originating in China. *Cell Host Microbe* **2020**, *27*, 325–328.
4. Sheahan, T. P.; Sims, A. C.; Leist, S. R.; et al. Comparative Therapeutic Efficacy of Remdesivir and Combination Lopinavir, Ritonavir, and Interferon Beta against MERS-CoV. *Nat. Commun*. **2020**, *11*, 1–14.
5. Ortiz-Alcantara, J.; Bhardwaj, K.; Palaninathan, S.; et al. Small Molecule Inhibitors of the SARS-CoV Nsp15 Endoribonuclease. *Virus Adapt. Treatment* **2010**, *2*, 125–133.
6. Naqvi, A.; Fatima, K.; Mohammad, T.; et al. Insights into SARS-CoV-2 Genome, Structure, Evolution, Pathogenesis and Therapies: Structural Genomics Approach. *Biochim. Biophys. Acta Mol. Basis Dis*. **2020**, *1866*, 165878.
7. Tortorici, M. A.; Veesler, D. Structural Insights into Coronavirus Entry. In *Advances in Virus Research*; Elsevier: Amsterdam, **2019**; Vol. 105, pp 93–116.

8. Walls, A. C.; Park, Y.-J.; Tortorici, M. A.; et al. Structure, Function, and Antigenicity of the SARS-CoV-2 Spike Glycoprotein. *Cell* **2020**, *181*, 281–*292*.e6.
9. Hoffmann, M.; Kleine-Weber, H.; Schroeder, S.; et al. SARS-CoV-2 Cell Entry Depends on ACE2 and TMPRSS2 and Is Blocked by a Clinically Proven Protease Inhibitor. *Cell* **2020**, *181*, 271–*280*.e8.
10. Narayanan, K.; Maeda, A.; Maeda, J.; et al. Characterization of the Coronavirus M Protein and Nucleocapsid Interaction in Infected Cells. *J. Virol*. **2000**, *74*, 8127–8134.
11. Zúñiga, S.; Sola, I.; Moreno, J. L.; et al. Coronavirus Nucleocapsid Protein Is an RNA Chaperone. *Virology* **2007**, *357*, 215–227.
12. de Haan, C. A. M.; Rottier, P. J. M. Molecular Interactions in the Assembly of Coronaviruses. In *Advances in Virus Research*; Elsevier: Amsterdam; **2005**; Vol. 64, pp 165–230.
13. Neuman, B. W.; Kiss, G.; Kunding, A. H.; et al. A Structural Analysis of M Protein in Coronavirus Assembly and Morphology. *J. Struct. Biol*. **2011**, *174*, 11–22.
14. Venkatagopalan, P.; Daskalova, S. M.; Lopez, L. A.; et al. Coronavirus Envelope (E) Protein Remains at the Site of Assembly. *Virology* **2015**, *478*, 75–85.
15. Nieto-Torres, J. L.; Verdiá-Báguena, C.; Jimenez-Guardeño, J. M.; et al. Severe Acute Respiratory Syndrome Coronavirus E Protein Transports Calcium Ions and Activates the NLRP3 Inflammasome. *Virology* **2015**, *485*, 330–339.
16. Corse, E.; Machamer, C. E. The Cytoplasmic Tails of Infectious Bronchitis Virus E and M Proteins Mediate Their Interaction. *Virology* **2003**, *312*, 25–34.
17. Kim, D.; Lee, J.-Y.; Yang, J.-S.; et al. The Architecture of SARS-CoV-2 Transcriptome. *Cell* **2020**, *181*, 914–921.e10.
18. Barretto, N.; Jukneliene, D.; Ratia, K.; et al. The Papain-Like Protease of Severe Acute Respiratory Syndrome Coronavirus Has Deubiquitinating Activity. *J. Virol*. **2005**, *79*, 15189–15198.
19. Kumar, S.; Sharma, P. P.; Shankar, U.; et al. Discovery of New Hydroxyethylamine Analogs against 3CLpro Protein Target of SARS-CoV-2: Molecular Docking, Molecular Dynamics Simulation and Structure-Activity Relationship Studies. *J. Chem. Inf. Model*. **2020**. DOI: 10.1021/acs.jcim.0c00326.
20. Chien, M.; Anderson, T. K.; Jockusch, S.; et al. Nucleotide Analogues as Inhibitors of SARS-CoV-2 Polymerase, a Key Drug Target for COVID-19. *bioRxiv* **2020**. DOI: 10.1101/2020.03.18.997585.
21. Anand, K.; Ziebuhr, J.; Wadhwani, P.; et al. Coronavirus Main Proteinase (3CLpro) Structure: Basis for Design of Anti-SARS Drugs. *Science* **2003**, *300*, 1763–1767.
22. Zhang, Y.; Xu, Q.; Sun, Z.; et al. Current Targeted Therapeutics against COVID-19: Based on First-Line Experience in China. *Pharmacol. Res*. **2020**, 104854.
23. Bhardwaj, K.; Guarino, L.; Kao, C. C. The Severe Acute Respiratory Syndrome Coronavirus Nsp15 Protein Is an Endoribonuclease That Prefers Manganese as a Cofactor. *J. Virol*. **2004**, *78*, 12218–12224.
24. Gupta, Y.; Maciorowski, D.; Jones, K.; et al. Bisindolylmaleimide IX: A Novel Anti-SARS-CoV2 Agent Targeting Viral Main Protease 3CLpro Demonstrated by Virtual Screening and In Vitro Assays. *Res. Square* **2020**. DOI: 10.21203/rs.3.rs-48709/v2.
25. Hamming, I.; Timens, W.; Bulthuis, M.; et al. Tissue Distribution of ACE2 Protein, the Functional Receptor for SARS Coronavirus. A First Step in Understanding SARS Pathogenesis. *J. Pathol*. **2004**, *203*, 631–637.
26. Li, M.-Y.; Li, L.; Zhang, Y.; et al. Expression of the SARS-CoV-2 Cell Receptor Gene ACE2 in a Wide Variety of Human Tissues. *Infect. Dis. Poverty* **2020**, *9*, 45.
27. Shang, J.; Ye, G.; Shi, K.; et al. Structural Basis of Receptor Recognition by SARS-CoV-2. *Nature* **2020**, *581*, 221–224.
28. Glowacka, I.; Bertram, S.; Muller, M. A.; et al. Evidence That TMPRSS2 Activates the Severe Acute Respiratory Syndrome Coronavirus Spike Protein for Membrane Fusion and Reduces Viral Control by the Humoral Immune Response. *J. Virol*. **2011**, *85*, 4122–4134.
29. Bosch, B. J.; Bartelink, W.; Rottier, P. J. M. Cathepsin L Functionally Cleaves the Severe Acute Respiratory Syndrome Coronavirus Class I Fusion Protein Upstream of Rather than Adjacent to the Fusion Peptide. *J. Virol*. **2008**, *82*, 8887–8890.
30. Agostini, M. L.; Andres, E. L.; Sims, A. C.; et al. Coronavirus Susceptibility to the Antiviral Remdesivir (GS-5734) Is Mediated by the Viral Polymerase and the Proofreading Exoribonuclease. *MBio* **2018**, *9*, e00221-18.
31. Choy, K.-T.; Wong, A. Y.-L.; Kaewpreedee, P.; et al. Remdesivir, Lopinavir, Emetine, and Homoharringtonine Inhibit SARS-CoV-2 Replication In Vitro. *Antiviral Res*. **2020**, *178*, 104786.
32. Beigel, J. H.; Tomashek, K. M.; Dodd, L. E.; et al. Remdesivir for the Treatment of Covid-19. *N. Engl. J. Med*. **2020**, *383*, 1813–1826.
33. Eastman, R. T.; Roth, J. S.; Brimacombe, K. R.; et al. Remdesivir: A Review of Its Discovery and Development Leading to Emergency Use Authorization for Treatment of COVID-19. *ACS Cent. Sci*. **2020**, *6*, 672–683.
34. Pan, H.; Peto, R.; Karim, Q. A.; et al. Repurposed Antiviral Drugs for COVID-19; Interim WHO SOLIDARITY Trial Results. *medRxiv* **2020**. DOI: 10.1101/2020.10.15.20209817.
35. Schrezenmeier, E.; Dörner, T. Mechanisms of Action of Hydroxychloroquine and Chloroquine: Implications for Rheumatology. *Nat. Rev. Rheumatol*. **2020**, *16*, 155–166.
36. Yam, J. C. S.; Kwok, A. K. H. Ocular Toxicity of Hydroxychloroquine. *Hong Kong Med. J*. **2006**, *12*, 294–304.
37. Vincent, M. J.; Bergeron, E.; Benjannet, S.; et al. Chloroquine Is a Potent Inhibitor of SARS Coronavirus Infection and Spread. *Virology J*. **2005**, *2*, 69.
38. Torjesen, I. Covid-19: Hydroxychloroquine Does Not Benefit Hospitalised Patients, UK Trial Finds. *BMJ* **2020**, *369*, m2263.
39. Ratia, K.; Pegan, S.; Takayama, J.; et al. A Noncovalent Class of Papain-Like Protease/Deubiquitinase Inhibitors Blocks SARS Virus Replication. *Proc. Natl. Acad. Sci. U.S.A*. **2008**, *105*, 16119–16124.
40. Nutho, B.; Mahalapbutr, P.; Hengphasatporn, K.; et al. Why Are Lopinavir and Ritonavir Effective against the Newly Emerged Coronavirus 2019? Atomistic Insights into the Inhibitory Mechanisms. *Biochemistry* **2020**, *59*, 1769–1779.
41. Ledford, H. Coronavirus Breakthrough: Dexamethasone Is First Drug Shown to Save Lives. *Nature* **2020**, *582*, 469–469.
42. Bouhaddou, M.; Memon, D.; Meyer, B.; et al. The Global Phosphorylation Landscape of SARS-CoV-2 Infection. *Cell* **2020**, *182*, 685–712.
43. Casadevall, A.; Pirofski, L. A. The Convalescent Sera Option for Containing COVID-19. *J. Clin. Invest*. **2020**, *130*, 1545–1548.

44. Shen, C.; Wang, Z.; Zhao, F.; et al. Treatment of 5 Critically Ill Patients with COVID-19 with Convalescent Plasma. *JAMA* **2020**, *323*, 1582–1589.
45. Zhang, B.; Liu, S.; Tan, T.; et al. Treatment with Convalescent Plasma for Critically Ill Patients with Severe Acute Respiratory Syndrome Coronavirus 2 Infection. *Chest* **2020**, *158*, e9–e13.
46. Duan, K.; Liu, B.; Li, C.; et al. Effectiveness of Convalescent Plasma Therapy in Severe COVID-19 Patients. *Proc. Natl. Acad. Sci. U.S.A*. **2020**, *117*, 9490–9496.
47. Gharbharan, A.; Jordans, C. C. E; GeurtsvanKessel, C.; et al. Convalescent Plasma for COVID-19. A Randomized Clinical Trial. *medRxiv* **2020**. DOI: 10.1101/2020.07.01.20139857.
48. Li, L.; Zhang, W; Hu, Y; et al. Effect of Convalescent Plasma Therapy on Time to Clinical Improvement in Patients with Severe and Life-Threatening COVID-19: A Randomized Clinical Trial. *JAMA* **2020**, *324*, 460–470.
49. Kunamneni, A.; Clarke, E. C.; Ye, C.; et al. Generation and Selection of a Panel of Pan-Filovirus Single-Chain Antibodies Using Cell-Free Ribosome Display. *Am. J. Trop. Med. Hyg*. **2019**, *101*, 198–206.
50. Kunamneni, A.; Ye, C.; Bradfute, S. B.; et al. Ribosome Display for the Rapid Generation of High-Affinity Zika-Neutralizing Single-Chain Antibodies. *PloS One* **2018**, *13*, e0205743.
51. Bannas, P.; Hambach, J.; Koch-Nolte, F. Nanobodies and Nanobody-Based Human Heavy Chain Antibodies as Antitumor Therapeutics. *Front. Immunol*. **2017**, *8*, **1603**.
52. Vincke, C.; Loris, R.; Saerens, D.; et al. General Strategy to Humanize a Camelid Single-Domain Antibody and Identification of a Universal Humanized Nanobody Scaffold. *J. Biol. Chem*. **2009**, *284*, 3273–3284.
53. Cardoso, F. M.; Ibañez, L. I.; Van den Hoecke, S.; et al. Single-Domain Antibodies Targeting Neuraminidase Protect against an H5N1 Influenza Virus Challenge. *J. Virol*. **2014**, *88*, 8278–8296.
54. Detalle, L.; Stohr, T.; Palomo, C.; et al. Generation and Characterization of ALX-0171, a Potent Novel Therapeutic Nanobody for the Treatment of Respiratory Syncytial Virus Infection. *Antimicrob. Agents Chemother*. **2016**, *60*, 6–13.
55. Gavor, E.; Choong, Y. K.; Er, S. Y.; et al. Structural Basis of SARS-CoV-2 and SARS-CoV Antibody Interactions. *Trends Immunol*. **2020**, *41*, 1006–1022.
56. Pinto, D.; Park, Y. J.; Beltramello, M.; et al. Cross-Neutralization of SARS-CoV-2 by a Human Monoclonal SARS-CoV Antibody. *Nature* **2020**, *583*, 290–295.
57. Wan, J.; Xing, S.; Ding, L.; et al. Human-IgG Neutralizing Monoclonal Antibodies Block the SARS-CoV-2 Infection. *Cell Rep*. **2020**, *32*, 107918.
58. Robbiani, D. F.; Gaebler, C.; Muecksch, F.; et al. Convergent Antibody Responses to SARS-CoV-2 in Convalescent Individuals. *Nature* **2020**, *584*, 437–442.
59. Wu, Y.; Wang, F.; Shen, C.; et al. A Noncompeting Pair of Human Neutralizing Antibodies Block COVID-19 Virus Binding to Its Receptor ACE2. *Science* **2020**, *368*, 1274–1278.
60. Zhou, Y.; Fu, B.; Zheng, X.; et al. Aberrant Pathogenic GM-CSF $^{+}$ T Cells and Inflammatory CD14^{+} CD16^{+} Monocytes in Severe Pulmonary Syndrome Patients of a New Coronavirus. *Biorxiv* **2020**. DOI: 10.1101/2020.02.12.945576v1.
61. Chen, X.; Zhao, B.; Qu, Y.; et al. Detectable Serum SARS-CoV-2 Viral Load (RNAaemia) Is Closely Associated with Drastically Elevated Interleukin 6 (IL-6) Level in Critically Ill COVID-19 Patients. *Clin. Infect. Dis*. **2020**, *17*, 1937–1942.
62. Oldfield, V.; Dhillon, S.; Plosker, G. L. Tocilizumab: A Review of Its Use in the Management of Rheumatoid Arthritis. *Drugs* **2009**, *69*, 609–632.
63. Huizinga, T. W. J.; Fleischmann, R. M.; Jasson, M.; et al. Sarilumab, a Fully Human Monoclonal Antibody against IL-6Rα in Patients with Rheumatoid Arthritis and an Inadequate Response to Methotrexate: Efficacy and Safety Results from the Randomised SARIL-RA-MOBILITY Part A Trial. *Ann. Rheum. Dis*. **2014**, *73*, 1626–1634.
64. Jackson, L. A.; Anderson, E. J.; Rouphael, N. G.; et al. An mRNA Vaccine against SARS-CoV-2—Preliminary Report. *N. Engl. J. Med*. **2020**, *383*, 1920–1931.
65. Folegatti, P. M.; Ewer, K. J.; Aley, P. K.; et al. Safety and Immunogenicity of the ChAdOx1 nCoV-19 Vaccine against SARS-CoV-2: A Preliminary Report of a Phase 1/2, Single-Blind, Randomised Controlled Trial. *Lancet* **2020**, *396*, 467–478.
66. van Doremalen, N.; Lambe, T.; Spencer, A.; et al. ChAdOx1 NCoV-19 Vaccination Prevents SARS-CoV-2 Pneumonia in Rhesus Macaques. *bioRxiv* **2020**. DOI: 10.1101/2020.05.13.093195.
67. Zhu, F.-C; Guan, X. H.; Li, Y. H.; et al. Immunogenicity and Safety of a Recombinant Adenovirus Type-5-Vectored COVID-19 Vaccine in Healthy Adults Aged 18 Years or Older: A Randomised, Double-Blind, Placebo-Controlled, Phase 2 Trial. *Lancet* **2020**, *396*, 479–488.
68. Logunov, D. Y.; Dolzhikova, I. V.; Zubkova, O. V.; et al. Safety and Immunogenicity of an rAd26 and rAd5 Vector-Based Heterologous Prime-Boost COVID-19 Vaccine in Two Formulations: Two Open, Non-Randomised Phase 1/2 Studies from Russia. *Lancet* **2020**, *396*, 887–897.
69. Dong, Y.; Dai, T.; Wei, Y.; et al. A Systematic Review of SARS-CoV-2 Vaccine Candidates. *Signal Transduct. Target. Ther*. **2020**, *5*, 237.
70. Sun, S. H.; Chen, Q.; Gu, H. J.; et al. A Mouse Model of SARS-CoV-2 Infection and Pathogenesis. *Cell Host Microbe* **2020**, *28*, 124–*133*.e4.
71. Jiang, R. D.; Liu, M. Q.; Chen, Y.; et al. Pathogenesis of SARS-CoV-2 in Transgenic Mice Expressing Human Angiotensin-Converting Enzyme 2. *Cell* **2020**, *182*, 50–*58*.e8.
72. Chandrashekar, A.; Liu, J.; Martinot, A. J.; et al. SARS-CoV-2 Infection Protects against Rechallenge in Rhesus Macaques. *Science* **2020**, *369*, 812–817.
73. Vankadari, N. Arbidol: A Potential Antiviral Drug for the Treatment of SARS-CoV-2 by Blocking Trimerization of the Spike Glycoprotein. *Int. J. Antimicrob. Agents* **2020**, *56*, 105998.
74. Morse, J. S.; Lalonde, T.; Xu, S.; et al. Learning from the Past: Possible Urgent Prevention and Treatment Options for Severe Acute Respiratory Infections Caused by 2019-NCoV. *Chembiochem* **2020**, *21*, 730–738.
75. Richardson, P.; Griffin, I.; Tucker, C.; et al. Baricitinib as Potential Treatment for 2019-NCoV Acute Respiratory Disease. *Lancet* **2020**, *395*, e30.
76. Finkelstein, Y.; Aks, S. E.; Hutson, J. R.; et al. Colchicine Poisoning: The Dark Side of an Ancient Drug. *Clin. Toxicol. (Phila.)* **2010**, *48*, 407–414.
77. Guo, D. Old Weapon for New Enemy: Drug Repurposing for Treatment of Newly Emerging Viral Diseases. *Virol. Sin*. **2020**, *35*, 253–255.

78. Warren, T. K.; Wells, J.; Panchal, R. G.; et al. Protection against Filovirus Diseases by a Novel Broad-Spectrum Nucleoside Analogue BCX4430. *Nature* **2014**, *508*, 402–405.
79. Liu, C.; Zhou, Q.; Li, Y.; et al. Research and Development on Therapeutic Agents and Vaccines for COVID-19 and Related Human Coronavirus Diseases. *ACS Cent. Sci*. **2020**, *6*, 315–331.
80. Kumar, V.; Shin, J. S.; Shie, J.-J.; et al. Identification and Evaluation of Potent Middle East Respiratory Syndrome Coronavirus (MERS-CoV) 3CLPro Inhibitors. *Antiviral Res*. **2017**, *141*, 101–106.
81. Zhou, Y.; Vedantham, P.; Lu, K.; et al. Protease Inhibitors Targeting Coronavirus and Filovirus Entry. *Antiviral Res*. **2015**, *116*, 76–84.
82. Hansen, J.; Baum, A.; Pascal, K. E.; et al. Studies in Humanized Mice and Convalescent Humans Yield a SARS-CoV-2 Antibody Cocktail. *Science* **2020**, *369*, 1010–1014.
83. Baum, A.; Fulton, B.O.; Wloga, E.; et al. Antibody Cocktail to SARS-CoV-2 Spike Protein Prevents Rapid Utational Escape Seen with Individual Antibodies. *Science* **2020**, *369*, 1014–1018.
84. Chi, X.; Yan, R.; Zhang, J.; et al. A Neutralizing Human Antibody Binds to the N-Terminal Domain of the Spike Protein of SARS-CoV-2. *Science* **2020**, *369*, 650–655.
85. Wang, C.; Li, W.; Drabek, D.; et al. A Human Monoclonal Antibody Blocking SARS-CoV-2 Infection. *Nat. Commun*. **2020**, *11*, **2251**.
86. Lan, J.; Ge, J.; Yu, J.; et al. Structure of the SARS-CoV-2 Spike Receptor-Binding Domain Bound to the ACE2 Receptor. *Nature* **2020**, *581*, 215–220.
87. Tian, X.; Li, C.; Huang, A.; et al. Potent Binding of 2019 Novel Coronavirus Spike Protein by a SARS Coronavirus-Specific Human Monoclonal Antibody. *Emerg. Microbes Infect*. **2020**, *9*, 382–385.
88. Ter Meulen, J.; van den Brink, E. N.; Poon, L. L.; et al. Human Monoclonal Antibody Combination against SARS Coronavirus: Synergy and Coverage of Escape Mutants. *PLoS Med*. **2006**, *3*, e237.
89. Walls, A. C.; Xiong, X.; Park, Y. J.; et al. Unexpected Receptor Functional Mimicry Elucidates Activation of Coronavirus Fusion. *Cell* **2019**, *176*, 1026–*1039*.e15.
90. Wrapp, D.; De Vlieger, D.; Corbett, K. S.; et al. Structural Basis for Potent Neutralization of Betacoronaviruses by Single-Domain Camelid Antibodies. *Cell* **2020**, *181*, 1004–1015.
91. Wec, A. Z.; Wrapp, D.; Herbert, A. S.; et al. Broad Neutralization of SARS-Related Viruses by Human Monoclonal Antibodies. *Science* **2020**, *369*, 731–736.
92. Ju, B.; Zhang, Q.; Ge, J.; et al. Human Neutralizing Antibodies Elicited by SARS-CoV-2 Infection. *Nature* **2020**, *584*, 115–119.
93. Chen, X.; Li, R.; Pan, Z.; et al. Human Monoclonal Antibodies Block the Binding of SARS-CoV-2 Spike Protein to Angiotensin Converting Enzyme 2 Receptor. *Cell. Mol. Immunol*. **2020**, *17*, 647–649.
94. Shi, R.; Shan, C.; Duan, X.; et al. A Human Neutralizing Antibody Targets the Receptor Binding Site of SARS-CoV-2. *Nature* **2020**, *584*, 120–124.
95. Cao, Y.; Su, B.; Guo, X.; et al. Potent Neutralizing Antibodies against SARS-CoV-2 Identified by High-Throughput Single-Cell Sequencing of Convalescent Patients' B Cells. *Cell* **2020**, *182*, 73–84.
96. Zhou, D.; Duyvesteyn, H.; Chen, C. P.; et al. Structural Basis for the Neutralization of SARS-CoV-2 by an Antibody from a Convalescent Patient. *Nat. Struct. Mol. Biol*. **2020**, *27*, 950–958.
97. Barnes, C. O.; West, A. P., Jr.; Huey-Tubman, K. E.; et al. Structures of Human Antibodies Bound to SARS-CoV-2 Spike Reveal Common Epitopes and Recurrent Features of Antibodies. *Cell* **2020**, *182*, 828–842.
98. Zost, S. J.; Gilchuk, P.; Case, J. B.; et al. Potently Neutralizing and Protective Human Antibodies against SARS-CoV-2. *Nature* **2020**, *584*, 443–449.
99. Liu, L.; Wang, P.; Nair, M. S.; et al. Potent Neutralizing Antibodies Directed to Multiple Epitopes on SARS-CoV-2 Spike. *Nature* **2020**, *584*, 450–456.
100. Lv, Z.; Deng, Y. Q.; Ye, Q.; et al. Structural Basis for Neutralization of SARSCoV-2 and SARS-CoV by a Potent Therapeutic Antibody. *Science* **2020**, *369*, 1505–1509.
101. Rogers, T. F.; Zhao, F.; Huang, D.; et al. Isolation of Potent SARS-CoV-2 Neutralizing Antibodies and Protection from Disease in a Small Animal Model. *Science* **2020**, *369*, 956–963.
102. Lei, C.; Qian, K.; Li, T.; et al. Neutralization of SARS-CoV-2 Spike Pseudotyped Virus by Recombinant ACE2-Ig. *Nat. Commun*. **2020**, *11*, **2070**.
103. Yuan, M.; Liu, H.; Wu, N. C.; et al. Structural Basis of a Shared Antibody Response to SARS-CoV-2. *Science* **2020**, *369*, 1119–1123.
104. Yuan, A. Q.; Zhao, L.; Bai, L.; et al. Isolation of and Characterization of Neutralizing Antibodies to Covid-19 from a Large Human Naïve scFv Phage Display Library. *BioRxiv* **2020**. DOI: 10.1101/2020.05.19.104281.
105. Wu, Y.; Li, C.; Xia, S.; et al. Identification of Human Single-Domain Antibodies against SARSCoV-2. *Cell Host Microbe* **2020**, *27*, 891–898.e5.
106. Seydoux, E.; Homad, L. J.; MacCamy, A. J.; et al. Analysis of a SARS-CoV-2-Infected Individual Reveals Development of Potent Neutralizing Antibodies with Limited Somatic Mutation. *Immunity* **2020**, *53*, 98–105.e5.
107. Brouwer, P. J. M.; Caniels, T. G.; van der Straten, K.; et al. Potent Neutralizing Antibodies from COVID-19 Patients Define Multiple Targets of Vulnerability. *Science* **2020**, *369*, 643–650.
108. Xia, S.; Duan, K.; Zhang, Y.; et al. Effect of an Inactivated Vaccine against SARS-CoV-2 on Safety and Immunogenicity Outcomes: Interim Analysis of 2 Randomized Clinical Trials. *JAMA* **2020**, *324*, 951–960.
109. Zhang, Y.-J.; Zeng, G.; Pan, H.-X.; et al. Immunogenicity and Safety of a SARS-CoV-2 Inactivated Vaccine in Healthy Adults Aged 18-59 Years: Report of the Randomized, Double-Blind, and Placebo-Controlled Phase 2 Clinical Trial. *medRxiv* **2020**. DOI: 10.1101/2020.07.31.20161216.
110. Mulligan, M. J.; Lyke, K. E.; Kitchin, N.; et al. Phase 1/2 Study of COVID-19 RNA Vaccine BNT162b1 in Adults. *Nature* **2020**, *586*, 589–593.
111. Folegatti, P. M.; Ewer, K. J.; Aley, P. K.; et al. Safety and Immunogenicity of the ChAdOx1 nCoV-19 Vaccine against SARS-CoV-2: A Preliminary Report of a Phase 1/2, Single-Blind, Randomised Controlled Trial. *Lancet* **2020**, *396*, 467–478.
112. Mercado, N. B.; Zahn, R.; Wegmann, F.; et al. Single-Shot Ad26 Vaccine Protects against SARS-CoV-2 in Rhesus Macaques. *Nature* **2020**, *586*, 583–588.