COVID-19 update: The race to therapeutic development

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PII: S1368-7646(20)30063-7

DOI: https://doi.org/10.1016/j.drup.2020.100733

Reference: YDRUP 100733

To appear in: *Drug Resistance Updates*

Received Date: 15 September 2020

Revised Date: 19 October 2020

Accepted Date: 21 October 2020

Please cite this article as: { doi: https://doi.org/

COVID-19 update: The race to therapeutic development

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Abstract

The COVID-19 pandemic, caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), represents an unprecedented challenge to global public health. At the time of this review, COVID-19 has been diagnosed in over 40 million cases and associated with 1.1 million deaths worldwide. Current management strategies for COVID-19 are largely supportive, and while there are more than 2,000 interventional clinical trials registered with the U.S. National Library of Medicine (clinicaltrials.gov), results that can clarify benefits and risks of candidate therapies are only gradually becoming available. We herein describe recent advances in understanding SARS-CoV-2 pathobiology and potential therapeutic targets that are involved in viral entry into host cells, viral spread in the body, and the subsequent COVID-19 progression. We highlight two major lines of therapeutic strategies for COVID-19 treatment: 1) repurposing the existing drugs for use in COVID-19 patients, such as antiviral medications (e.g., remdesivir) and immunomodulators (e.g., dexamethasone) which were previously approved for other disease conditions, and 2) novel biological products that are designed to target specific molecules that are involved in SARS-CoV-2 viral entry, including neutralizing antibodies against the spike protein of SARS-CoV-2, such as REGN-COV2 (an antibody cocktail) and LY-CoV555, as well as recombinant human soluble ACE2 protein to counteract SARS-CoV-2 binding to the transmembrane ACE2 receptor in target cells. Finally, we discuss potential drug resistance mechanisms and provide thoughts regarding

clinical trial design to address the diversity in COVID-19 clinical manifestation. Of note, preventive vaccines, cell and gene therapies are not within the scope of the current review.

Keywords: COVID-19, SARS-CoV-2, virus life cycle, therapeutic targets, drug development, antivirals, immunomodulators, monoclonal antibodies, ACE2, spike protein, repurposed use, existing drugs

1. Introduction

The COVID-19 pandemic, caused by the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), continues to spread across the globe (Artese et al., 2020). The majority of people who become infected with SARS-CoV-2 experience mild to moderate respiratory illness. Older people, and those with underlying medical conditions (e.g., cardiovascular disease, diabetes, and hypertension) are likely to develop serious illness, including pneumonia, acute respiratory distress syndrome (ARDS), multi-organ failure, and death (World Health Organization, 2020a). As of 19 October 2020, more than 40 million cases of COVID-19 have been reported worldwide, resulting in more than 1,114,857 deaths (Johns Hopkins University, 2020). There are currently no approved vaccines or therapeutics for COVID-19, though many potential treatments are being evaluated in ongoing clinical trials. These include repurposing the existing drugs previously approved for other conditions, as well as novel biological products that are designed to target the key checkpoints in the SARS-CoV-2 lifecycle (Artese et al., 2020; Drożdżal et al., 2020). To facilitate COVID-19 drug development, the US Food and Drug Administration (FDA) has created a special emergency program for possible coronavirus therapies, the Coronavirus Treatment Acceleration Program (CTAP) (U.S. Food and Drug Administration, 2020b). The CTAP website provides information about how developers of COVID-19 therapeutics can interact with the FDA to obtain advice on progressing through development milestones to document whether their product is beneficial while maintaining due safeguards for patient safety. The FDA has also developed specific guidance to assist sponsors in the clinical development of drugs and biologics for the treatment or prevention of COVID-19 (U.S. Food and Drug Administration, 2020c).

2. The SARS-CoV-2 Life Cycle

The SARS-CoV-2 life cycle involves several critical checkpoints, which serve as potential therapeutic targets for COVID-19 treatments (FIG. 1). This includes virus binding and entry into host cells (involving angiotensin-converting enzyme 2 (ACE2) and transmembrane protease serine 2 (TMPRSS2)), RNA replication and transcription (involving helicase and RNA-dependent RNA polymerase (RdRp)), the translation and proteolytic processing of viral proteins (involving chymotrypsin-like and papain-like proteases), virion assembly, the release of new viruses through the exocytic systems, and the host's immune response to SARS-CoV-2 infection. Many clinical studies are underway to evaluate therapeutic candidates that are designed to target different stages in the virus life cycle. Therapeutic agents under development will be discussed in detail in later sections.

2.1. Viral binding and entry

SARS-CoV-2 is an enveloped, positive sense RNA virus. The genomic RNA is coated by the nucleocapsid (N) phosphoprotein, while the surrounding envelope contains several embedded structural proteins; including spike (S) glycoprotein, small envelope (E) glycoprotein, and membrane (M) glycoprotein. Viral entry begins with the binding of SARS-CoV-2 spike protein (S) to the host cell receptor, ACE2, which is widely expressed in the epithelial cells of lungs, liver, intestine, brain, heart, and kidneys (Hoffmann et al., 2020). The S protein consists of two functional subunits that facilitate binding with sugar- and protein-based receptors within the S1 unit and initiation of viral membrane fusion with S2 (Tai et al., 2020).

S protein interaction with ACE2 is an essential step in virus infection. The S1 receptor-binding domain (RBD) is responsible for recognizing and binding to ACE2, as one key factor in mediating virus entry. Thus, the RBD is currently one of the main targets for developing novel COVID-19 therapeutics (Tai et al., 2020). Upon binding to ACE2, the virus can either be endocytosed or the S protein can be immediately cleaved to mediate cell membrane fusion at the cell surface. The cell surface protease, TMPRSS2, is critical for initiating infection in bronchial epithelial cells, with the ability to cleave at the S1/S2 boundary, mediating fusion and release of genomic RNA into the cytoplasm (Hoffmann et al., 2020). Targeting TMPRSS2 to prevent the S1/S2 cleavage may potentially prevent viral entry into the host cells. In cells where the virus utilizes the endosomal pathway for entry, lysosomal proteases can be targeted (Ou et al., 2020; Shah et al., 2010), preventing the activation of S protein for membrane fusion (FIG. 1) (Hoffmann et al., 2020).

Fusion peptide (FP) and heptad repeat (HR) regions within the S2 subunit mediate membrane fusion and release of viral RNA. Therapeutic potential of these regions gained attention during previous efforts towards treatments of respiratory illness caused by the closely related coronavirus, SARS-CoV. It is important to note that the S2 subunit is less exposed than S1 and may only be accessible following conformational changes (Coutard et al., 2020; Xia et al., 2020). Nevertheless, examining virus binding and entry as a critical checkpoint within the virus life cycle reveals several targets that are likely beneficial to reducing virus spread within the host system.

2.2 Viral replication and release

After releasing viral RNA into the cytoplasm, the virus hijacks the host translational machinery to translate the RNA into two large polyproteins, which will ultimately produce the replicase-transcriptase complex (RTC) through viral protease cleavage (Hoffmann et al., 2020). The importance of viral replication proteins, particularly the viral proteases, main protease (Mpro), papain-like protease (PLpro), as well as RdRp activity of the RTC is evidenced by the functionality conservation across coronaviruses (Li and De Clercq, 2020). Blockade of these proteins with inhibitors, such as boceprevir (an inhibitor of Mpro) and antivirals that block viral RNA polymerase activity may alleviate SARS-CoV-2 infection (Choy et al., 2020; Ma et al., 2020). The RTC drives production of both negative sense RNA and positive sense RNA with RdRp and helicase functionality (Hoffmann et al., 2020; Thiel et al., 2003). Discontinuous transcription of negative sense RNA yields the subgenomic RNA (sgRNA) to be translated into viral accessory and structural proteins, including the S, M, N, and E proteins. Most of these proteins localize to the endoplasmic reticulum (ER) where they are folded and post-translationally modified before being transported to the ER-Golgi intermediate compartment (Fehr and Perlman, 2015). Mature virions are an assembly of nucleocapsid-coated genomic RNA and structural proteins that are released from the cell via exocytosis. Once released, virion particles may interact with other ACE2 expressing cells in various organs, including the heart, liver, and kidney (Li et al., 2020).

2.3 Immune response to SARS-CoV-2 infection

A critical approach to treating COVID-19 patients, particularly those with severe respiratory or cardiovascular complications may be through regulating the virus-mediated immunopathology and host immune response to the viral infection. The initial host immune response involves the activation of the type I and III interferon (IFN) responses, followed by activation of IFN-stimulated

genes (ISGs) as well as later release of pro-inflammatory cytokines and chemokines, which mount an antiviral defense against the viral infection (Cardone et al., 2020). However, coronaviruses, including the novel SARS-CoV-2, have been documented to employ strategies towards blocking and evading this response, resulting in dampening of antiviral mechanisms and increases in viral replication, titer, and spread (Blanco-Melo et al., 2020; Park and Iwasaki, 2020). Given the critical role of the IFN system in viral defense, exogenous IFN as a therapeutic has been explored and will be discussed in greater detail in the following sections.

Other mechanisms employed by the immune system to combat the virus can also play a role in disease severity (Cardone et al., 2020). With continuing viral replication, infected cells can become apoptotic, releasing increased levels of pro-inflammatory cytokines or damage-associated molecular patterns (DAMPs) , which may lead to increased tissue damage (Cardone et al., 2020). In some settings, the release of high levels of pro-inflammatory cytokines may be associated with severe symptoms and virus persistence (FIG. 1). Elevations have included IL-6, IL-1β, and TNF-α, with high levels of IL-7, IL-8, IL-9, IL-10, IFN-γ, TNF, MCP1, MIP1A, MIP1B, G-CSF, GM-CSF having also been observed in COVID-19 patient plasma (Huang et al., 2020a). In some patients, this event is believed to promote cytokine release syndrome (CRS) or "cytokine storm" resulting in the recruitment of hyperactive macrophages and monocytes to sites of infection (FIG. 1). The continuous activation of immune cells leaves damaging effects ranging from capillary damage to multiorgan failure. In severe patients, initial lung injury can progress into ARDS, a major contributor to COVID-19 mortality (Zhang et al., 2020). Thus, to mitigate the harmful effects of the host immune response, a considerable portion of therapeutic programs are aimed towards reducing the overproduction of pro-inflammatory cytokines and associated cytokine storm.

The current review highlights the potential therapeutic strategies for the treatment of COVID-19, including small molecule drugs and therapeutic proteins to target the SARS-CoV-2 viral entry, viral amplification or the host immune responses. However, preventive vaccines, cell and gene therapies are not within the scope of this review.

3. Repurposing of existing drugs for COVID-19

While treatment options that prevent infection or viral replication of SARS-CoV-2 are yet to be approved, the availability of therapeutics with antiviral, anti-inflammatory, or immunomodulatory

activities provide many potential candidates (Table 1). Using drugs previously approved for other indications takes advantage of existing detailed information on human pharmacology and toxicology to expedite clinical trials and regulatory review. Indeed, the majority of ongoing clinical trials for COVID-19 are aimed to evaluate the safety and efficacy of the existing drugs, previously approved for other conditions by at least one regulatory agency (FIG. 2A) (US National Library of Medicine, 2020). Repurposed agents used to treat a variety of other disease conditions (e.g., HIV, Herpes, Hepatitis C, and influenza) have been proposed as possible treatment options for COVID-19 (FIG 2B).

3.1. Antivirals

One way these drugs are being used is to target the endolysosomal pathway that SARS-CoV-2 uses to enter target cells. Chloroquine (CQ) and hydroxychloroquine (HCQ), the antimalarial drugs that increase pH in the endosome, lysosome, and Golgi apparatus have also been reported to alter ACE2 terminal glycosylation, impacting SARS-CoV binding to ACE2 (Fox, 1993; Liu et al., 2020; Mauthe et al., 2018; Vincent et al., 2005; Yao et al., 2020). Azithromycin, a broad-spectrum macrolide antibiotic that induces lysosomal alkalization, has been reported to have potential *in vitro* activity against H1N1 influenza virus by interfering with its internalization (Renna et al., 2011; Tran et al., 2019). To prevent S priming, camostat, a pancreatitis drug that inhibits TMPRSS2, was found to inhibit SARS-CoV-2 infection in human lung cells (Hoffmann et al., 2020). While camostat and azithromycin are currently under investigation, the potency of CQ/HCQ in COVID-19, which initially showed promise, was later challenged due to a lack of efficacy by larger studies (Boulware et al., 2020; Horby et al., 2020b; Kupferschmidt, 2020; World Health Organization, 2020d). An Emergency Use Authorization (EUA) for CQ and HCQ, which had been authorized by FDA to allow certain uses of those drugs in the context of initial reports of potential benefit and widespread expert interest, was revoked based on FDA's ongoing assessment of available scientific information associated with the emergency use of those products (Hinton, 2020). Specifically, FDA determined that CQ and HCQ are unlikely to be effective in treating COVID-19 for the authorized uses in the EUA. Additionally, in light of ongoing serious cardiac adverse events and other serious side effects, FDA determined that the known and potential benefits of CQ and HCQ no longer outweigh the known and potential risks for the authorized use.

Many clinical strategies to inhibit viral replication and release involve the use of repurposed antivirals (Artese et al., 2020; Drożdżal et al., 2020; Pawar, 2020). Drugs that have been under study for potential uses in COVID-19 include remdesivir, a broad-spectrum RdRp inhibitor that was previously studied for Ebola treatment, and favipiravir (obtained conditional marketing approval in Japan for the treatment of influenza), and the approved HIV protease inhibitor combination lopinavir/ritonavir (Beigel et al., 2020; Furuta et al., 2017; Grein et al., 2020; McMahon et al., 2020; Sheahan et al., 2017; Wang et al., 2020b).

Preclinical studies have shown that remdesivir inhibited replication of SARS-CoV, MERS-CoV, and SARS-CoV-2 *in vitro* (Agostini et al., 2018; Brown et al., 2019; Sheahan et al., 2017; Sheahan et al., 2020; Wang et al., 2020b), which prompted several clinical studies including the ACTT trial sponsored by the U.S. National Institute of Allergy and Infectious Diseases (NCT04280705) and the SOLIDARITY trial sponsored by WHO (World Health Organization, 2020c). Preliminary report from randomized, double-blind, placebo-controlled phase-3 ACTT trial showed that remdesivir shortened the recovery time in hospitalized patients with COVID-19 (Beigel et al., 2020). As a result, remdesivir was granted EUA in the US (U.S. Food and Drug Administration, 2020a), Special Approval for Emergency in Japan (Pharmaceuticals and Medical Devices Agency, 2020), and Conditional Marketing Authorization in the EU (European Medicines Agency, 2020), where the safety and efficacy will be continuously evaluated through ongoing trials. However, the interim results from the randomized open-label SOLIDARITY trial reported little or no effect of remdesivir on overall mortality, initiation of ventilation and duration of hospital stay among hospitalized patients (Pan et al., 2020). Moreover, the lopinavir/ritonavir combination was reportedly ineffective in hospitalized COVID-19 patients also based on results from randomized open-label trials (Cao et al., 2020; RECOVERY Collaborative Group, 2020; World Health Organization, 2020d).

3.2 Immunomodulators

Exogenous IFN treatments, which have been previously approved for multiple sclerosis, are being tested for their antiviral and immunomodulatory properties. Clinical trials are focused on testing subcutaneous administration or nebulized IFN β, with direct inhalation into the lungs of patients, to stimulate an immune response. IFN β is an endogenously produced cytokine protein with antiviral effects, which may be deficient in lung cells of COVID-19 patients. Therefore, restoring

type I IFN levels might reduce the viral load in COVID-19 patients (Mantlo et al., 2020). However, the interim results from the WHO SOLIDARITY trial reported that IFN-β1a was ineffective in hospitalized patients (Pan et al., 2020). This has only been tested in small trials, with larger trials being necessary to fully understand the treatment results. Pegylated IFN λ, which is known for its antiviral activity independent of type I interferons, is being tested in clinical trials to prevent infection and to slow viral replication while reducing inflammatory damage (Prokunina-Olsson et al., 2020). IFN λ, may have a narrow therapeutic window due to the heightened risk of bacterial infections, impacting the duration or timing of administration (Broggi et al., 2020).

As described above, COVID-19 patients with severe illness often present increased levels of cytokines, chemokines, T lymphocytes, NK cells, and growth factors in plasma (Huang et al., 2020b). The use of immunomodulators to reduce serum levels of pro-inflammatory cytokines might be helpful in mitigating immune-related symptoms. Severe COVID-19 cases are also linked to high levels of serum IL-6, which can be a component of cytokine release syndrome (Filocamo et al., 2020; Wu et al., 2020a). Several clinical trials are evaluating the potential use of the existing anti-inflammatory therapeutic proteins (Guaraldi et al., 2020) including (i) IL-6R blockers tocilizumab (NCT04381936), indicated for treatment of rheumatoid, giant cell, and juvenile idiopathic arthritis, as well as cytokine release syndrome, and sarilumab (NCT04315298), indicated for rheumatoid arthritis (RA); (ii) IL-1R blocker anakinra (NCT04330638), a recombinant protein drug also treating RA; (iii) TNF-α blocker infliximab (NCT04344249), another biologic for RA; and (iv) IFN-γ blocker emapalumab (NCT04324021) approved for primary hemophagocytic lymphohistiocytosis treatment (Filocamo et al., 2020; Spinelli et al., 2020). However, recent results from a phase-3 trial of tocilizumab (Roche, 2020) and sarilumab (Sanofi, 2020) were both disappointing. Additional therapies that are commonly used for allergies or heartburn are being tested to potentially reduce cytokine storm in pulmonary tissues (Hogan et al., 2020). Histamine blockers (the H1 receptor antagonist Cetirizine and H2 receptor antagonist Famotidine) may control the hyper-immune response (Wu et al., 2020b).

Several small molecule drugs with anti-inflammatory activity are also being tested for COVID-19. Among these, the corticosteroid dexamethasone has been reported to decrease the risk of death in COVID-19 patients with severe respiratory complications (Horby et al., 2020a). The FDA recently added dexamethasone to the list of drugs for temporary compounding by outsourcing facilities and pharmacy compounders during the COVID-19 public health emergency to help prevent demand

and supply interruptions (U.S. Food and Drug Administration, 2020d; University of Oxford, 2020a). WHO also strongly recommends corticosteroids (i.e. dexamethasone, hydrocortisone or prednisone) for the treatment of patients with severe and critical COVID-19 (World Health Organization, 2020b). Other anti-inflammatory small molecule drugs include the anti-microtubule agent colchicine (NCT04322682) to block elongation of microtubules and interfere with cytokine and chemokine secretion, and the Janus kinase (JAK) inhibitors ruxolitinib and baricitinib (NCT04345289) to inhibit the release of pro-inflammatory cytokines (Spinelli et al., 2020).

Heparin, previously approved as a blood thinner, was originally used in COVID-19 clinical trials to limit lung injury and prevent blood clot formation (Ayerbe et al., 2020; Tang et al., 2020). Due to the affinity of the spike protein to cell surface glycans, Heparin, which is a secretory glycosaminoglycan (GAG), is now being tested as a decoy protein with administration in a spray and nebulized formulation (Dixon et al., 2020; Kim et al., 2020). By binding to the spike protein within the blood, heparin may prevent the interaction of S protein with ACE2 preventing initial infection or viral spread.

4. Biotechnology products for COVID-19

The development of novel biotechnology products mainly focuses on preventing viral entry through targeting the interaction between the S protein and the ACE2 host cell receptor (FIG. 2C, Table 2). Several strategies are under clinical investigation, including recombinant proteins and monoclonal antibodies against the key molecules involved in SARS-CoV-2 viral entry.

4.1 Recombinant human soluble ACE2

Recombinant human soluble ACE2 (rhsACE2) protein represents a novel approach to preventing binding of SARS-CoV-2 to ACE2, by introducing a soluble form in excess to compete with endogenous membrane-bound ACE2 for S protein binding (Table 2). Upon entering the bloodstream, the exogenous rhsACE2 is intended to bind and neutralize circulating SARS-CoV-2 virions, serving as a scavenger or decoy (Monteil et al., 2020; Tai et al., 2020; Zhou and Zhao, 2020). rhsACE2 proteins were previously explored to treat acute lung injury, pulmonary hypertension, and ARDS, as a soluble additive protein to replace deficient ACE2 and as a potential soluble decoy protein to SARS-CoV (Hemnes et al., 2018; Imai et al., 2005). In addition to inhibiting virus infection, treatment with rhsACE2 may reduce interleukins and TNFα production, and supplement endogenous ACE2 enzymatic activity, contributing to the regulation of the renin-

angiotensin system (RAS) to prevent further lung injury (Hemnes et al., 2018; Wang et al., 2020b). rhsACE2 was reported to be safe in healthy subjects and in patients diagnosed with ARDS, which led to multiple rhsACE2 therapies advancing to later phase clinical trials (Table 2) (Haschke et al., 2013; Ju et al., 2020; Khan et al., 2017). A similar protein to rhsACE2 in development is a recombinant bacterial carboxypeptidase (B38-CAP), an ACE2 receptors-like enzyme that was explored previously for hypertension and cardiac dysfunction (Minato et al., 2020).

Expanding on soluble ACE2, Fc-ACE2 fusion proteins are being designed with IgG1 Fc portion to prolong the circulating half-life of the rhsACE2 and modulate the immune system response (Table 2) (Bian et al., 2020; Iwanaga et al., 2020). Engineering the Fc-ACE2 fusion protein with an Fc null portion may facilitate the passage of the protein through alveolar mucosa, through binding with FcRn. To increase spike protein binding potential, a bivalent ACE2 protein fused to an IgG1 Fc is under development (SI-F019) (SystImmune, 2020). An antiviral Fc conjugate (AVCs) is being explored for COVID therapies, based on previous studies of AVCs in the context of influenza (Balfour, 2020; Wrapp et al., 2020). The compound consists of an IgG1 Fc region fused to a potent antiviral small molecule, which binds the virus to neutralize it.

Designing a therapy to target multiple epitopes of the SARS-CoV-2 spike protein may increase the potential of binding and neutralizing the virus. The ACE-MAB bispecific fusion protein has two functional arms, with one arm being a fully human antibody targeting the spike protein, to prevent binding to ACE2, and the other arm being a truncated rhsACE2 protein (Cel-Sci, 2020a). Through targeting three parts of the spike protein, the anti-COVID-19 DARPin® fusion protein candidates are proposed to potentially block the binding of the spike protein to ACE2, block protease activation of the spike protein, and "cuff" the protein to prevent conformational changes (Balfour, 2020). Many of these Fc fusion proteins aim to not only be used as a treatment but to have prophylactic potential.

4.2 Other proteins and peptides

Small peptide-based therapies are also being developed that target the N protein and elicit cytolytic T cell response (Amawi et al., 2020; Cel-Sci, 2020a, b). By targeting N protein antigens, those agents may have a broader antiviral potential as the N protein shares 90% amino acid homology with SARS-CoV and 48% with MERS-CoV (Grifoni et al., 2020). Masking the sialic acid glycans on the host cell receptors in a patient's airway may reduce the binding of the spike protein and

lower the risk of SARS-CoV-2 infection, potentially offering prophylactic activity (Pneumagen, 2020). Preliminary data reported a reduction in SARS-CoV-2 infectivity with the multivalent carbohydrate binding molecule (mCBMs) Neumifil. Additional targeted therapies are under development, not specifically to prevent the viral infection, but to treat downstream pathology of COVID, such as acute lung injury, pneumonia, and ARDS. Recombinant human plasma gelsolin (rhu-pGSN) is under investigation to treat COVID-19-induced pneumonia (Bioaegis Therapeutics, 2020) and has been reported to reduce inflammation (DiNubile et al., 2020; Yang et al., 2015). Controlling inflammation to decrease potential organ injury may be important to improve recovery from COVID-19 infection.

4.3 Neutralizing antibodies

Neutralizing antibodies employ the same strategy as the decoy ligands, aiming to block the interaction of the virus with the ACE2 host cell receptor, thereby inhibiting viral entry (Jiang et al., 2020; Zhou and Zhao, 2020). Antibodies can also alter the conformation of a protein needed for viral entry or destroy infected cells through effector functions. Several antibodies are being developed against the spike protein (Table 3), with the aim of blocking receptor binding to the host cell membrane (Eli Lilly, 2020; Wong, 2020). Such antibodies have been designed based on convalescent serum isolated from patients who have recovered from severe SARS-CoV-2 infection, from phage display libraries, transgenic mice engineered to express the trimeric SARS-CoV-2 spike protein, B cell isolation, and 3D printed lymph nodes (3DPrint, 2020; BusinessWire, 2020; Hansen et al., 2020; Ju et al., 2020; Snyder, 2020; Wang et al., 2020a; Zimmer, 2020). Anti-SARS-CoV-2 antibodies are being isolated from wide populations of patients who have recovered from infection, with the hope of identifying a strong candidate that will effectively bind and neutralize the virus.

Using antibodies from patients who have recovered from SARS-CoV-2 infection as a molecular template follows a similar strategy as using convalescent serum from recovered patients; to provide a potential boost to the immune system or to provide a prophylactic immunity prior to infection. B cells are isolated, and a range of antibodies with different binding sites and mechanisms of action are screened for binding activity, binding competition with ACE2, SARS-CoV-2 neutralizing ability, and cross-reactivity to SARS-CoV and MERS-CoV (Ju et al., 2020; Wang et al., 2020a). Antibody cocktails can target different epitopes of the spike protein, expanding neutralization

potential which may also protect against future mutations in the virus (Table 3). These cocktails have demonstrated an activity to reduce viral load *in vitro* as well as in animal models with lung inflammation and injury (Hansen et al., 2020; Regeneron, 2020; Snyder, 2020; Zimmer, 2020). Antibody therapy development is advancing towards cocktails against all coronavirus strains, projecting past development for SARS-CoV-2 (Taylor, 2020).

Several antibody products are also being developed to control cytokine storm and treat COVID-19-induced pneumonia. These therapies include targeting of IL-6R (Levilimab) (NCT04397562), TLR4 (EB05) (NCT04401475), CXCL10 (EB06) and angiopoietin-2 (Ang2) (LY3127804) (NCT04342897). Targeting TLR4, which is upstream of IL-6, IL-8 and type I and type III interferons, or IL-6R may control the proinflammatory response in patients and suppress cytokine storm (Sallenave and Guillot, 2020). EB05 and Levilimab both aim to inhibit cytokine release through blocking the inflammatory signaling cascade. Anti-CXCL10 aims to reduce the high expressions of the chemokine CXCL10, which has been associated with long-term lung injury (Oliviero et al., 2020). Controlling excessive inflammation and cytokine release may reduce progression to ARDS in infected patients. Meplazumab, an anti-CD147 mAb, was developed to prevent the binding of the SARS-CoV-2 spike protein to CD147 host cells and to regulate cytokine secretion in patients with COVID-19 acquired pneumonia (Bian et al., 2020). CD147 was believed to be an additional host cell receptor to ACE2, which the virus utilized for internalization, though recent studies have demonstrated a lack of binding of CD147 to the spike protein (Shilts and Wright, 2020).

4.4 Multi-specific antibodies

Modulation of the immune system to selectively remove cells infected by SARS-CoV-2 may have potential in reducing the spread of the virus. A Tri-specific NK cell engager (TriKE) antibody is being developed, with the aim to engage NK cells and eliminate SARS-CoV-2 infected cells, before further virions are released into the blood stream (GT Biopharma, 2020). A similar approach involves a bi-specific antibody targeting the spike protein and the NKp46 NK cell receptor (Cytovia Therapeutics, 2020).

4.5 IgM and IgA antibodies

While most of the antibody therapeutics being developed are IgG, development of IgM and IgA therapies may potentially increase binding power as these antibodies have a greater number of

binding domains than IgG (IgM Bio, 2020). IgM and IgA antibodies are based on naturally occurring antibodies following severe SARS-CoV-2 infection produced from single B cells. These antibodies can undergo transport across mucosal membranes, which may have potential for treating infected lung tissue.

4.6 Single domain antibodies

Single-domain antibodies (sdAbs), or nanobodies, may potentially be used to neutralize the spike protein, through targeting a cryptic epitope in the trimeric spike protein interface (Table 3) (Wrapp et al., 2020; Wu et al., 2020c). These nanobodies, designed from screening nanobody libraries and shark variable domain of immunoglobulin new antigen receptor (VNAR) phage display libraries, are composed of the complementary determining regions with molecular weights of 12-15 kDa (Jaimes et al., 2020; Kupferschmidt, 2020; Wu et al., 2020c). Nanobodies are being developed against S protein and N protein to prevent viral protein-ACE2 receptor interactions. Nanobodies have demonstrated successful blocking of ACE2 binding and were shown to recognize RBD in different structural conformations (Huo et al., 2020). These therapies have been proposed for use as inhalation agents and may potentially neutralize the virus in a dose-dependent manner.

5. Perspectives

The concerted effort of the global scientific community to address the COVID-19 pandemic has been remarkable. This includes the rapid launch of a large volume of clinical trials to investigate potential therapeutics for COVID-19 treatment, as well as preventive vaccines (not included in this review). To mount an immediate response to the health crisis, many existing drugs are being tested for use in COVID-19. These include antiviral drugs and immunomodulators that were previously approved for the treatment of other disease conditions. These drugs have a regulatory record and established safety profiles which help expedite the development process. The novel targeted therapies, including neutralizing antibodies and Fc-fusion proteins, are mainly targeting the SARS-CoV-2 viral entry step. Some of these products may prove to be helpful in preventing the spread of the virus in the body, thereby accelerating recovery after infection or providing a means of prophylaxis.

Still, the SARS-CoV-2 virus remains novel and many aspects of transmission, infection, and treatment are yet to be unraveled. The current strategies under development mainly target ACE2 and S protein interaction for viral entry. Other potential therapeutic targets may include the sugar

moieties as additional receptors on the host cells (Qing et al., 2020), mediation of viral entry processes by accessory proteins, secondary infection to organs outside the respiratory system, and the dynamic immune response to the infection (Cheng et al., 2020; Fu et al., 2020; Liu et al., 2014). Further research into the pathophysiology of COVID-19 is needed to understand the mechanisms that result in severe manifestation of the disease. Since the beginning of the SARS-CoV-2 pandemic, the virus has been undergoing various mutations potentially impacting the effectiveness of the repurposed drugs or novel therapeutics, with constant surveillance identifying mutations in the RdRp and spike proteins (Pachetti et al., 2020; van Dorp et al., 2020). Therapeutic development for COVID-19 will need to monitor the changing viral genome to stay ahead of potential drug resistance and understand how the virus evades the human immune system (Pachetti et al., 2020; van Dorp et al., 2020).

Clinical trial design constitutes a critical component in the development of therapeutics against COVID-19. The FDA has established provisions for timely interaction and responses to sponsor inquiries and submissions to facilitate early discussion of efficient approaches to product development (U.S. Food and Drug Administration, 2020c). The course of COVID-19 disease is diverse, ranging from asymptomatic to fatal respiratory failure. It is therefore important to evaluate therapeutics in adequate and well-controlled clinical trials with defined populations to generate a safety and efficacy database that will best inform the clinical use of the drug or biologic.

Disclaimer

This article reflects the views of the authors and should not be construed to represent FDA's views or policies.

Conflict of Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Funding

This work was funded by the U.S. Food and Drug Administration. The funder had no role in the study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Limitations

As there is a huge volume of therapeutic approaches for COVID-19, we may not cover all available therapeutic development programs. In addition, research results are dynamic and change as new evidence emerges. Second, the clinical trial information was derived from the U.S. National Library of Medicine ClinicalTrials.gov, which was last accessed on 17 October 2020. Third, only articles/publications/translations from English were analyzed so some relevant international data might be missing.

Acknowledgements

The authors would like to thank Drs. Steven Kozlowski [Office of Biotechnology Products (OBP), CDER, FDA], Montserrat Puig [OBP, CDER, FDA], Daniela Verthelyi [OBP, CDER, FDA], Serge Beaucage [OBP, CDER, FDA], Adam Fisher [Office of Pharmaceutical Quality (OPQ), CDER, FDA] and Frank Weichold [Office of the Chief Scientist (OCS), Office of the Commissioner (OC), FDA] for their critical review and comments on the manuscript.

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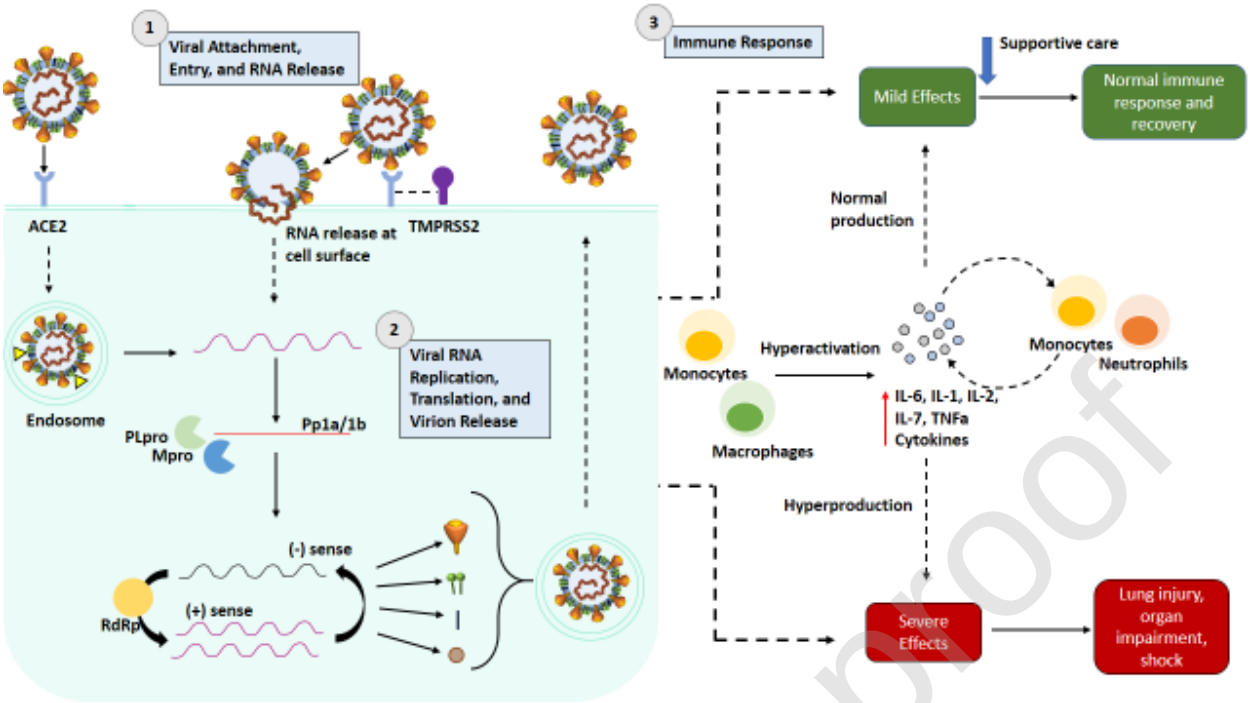

Figure 1. Potential therapeutic targets for COVID-19 treatment. 1) SARS-CoV-2 attachment to host receptor ACE2, and release of genomic RNA, through cleavage with TMPRSS2 or endo-/lysosomal proteases characterizes initial infection. Several agents can be employed to inhibit these interactions including neutralizing antibodies, recombinant human soluble ACE2 (rhsACE2), protease inhibitors, and endosomal pH modulators (Fehr and Perlman, 2015). 2) Replication and translation of genomic RNA into structural proteins to assemble mature virions for release results in viral amplification and increases in infection. Antivirals inhibiting viral proteases and RdRp are being evaluated against this checkpoint (Fehr and Perlman, 2015). 3) Due to viral replication, host immune responses are triggered that can cause hyperactivation of immune cells and constant production of pro-inflammatory cytokines, resulting in more severe disease presentation (Cardone et al., 2020; Huang et al., 2020b). Novel and repurposed immunomodulators are under investigation to mitigate harmful immune responses. Angiotensin-converting enzyme 2 (ACE2); Transmembrane protease serine 2 (TMPRSS2); RNA-dependent RNA polymerase (RdRp); Main protease (Mpro); Papain-like protease (PLpro); IL (interleukin); Tumor necrosis factor α (TNFα)

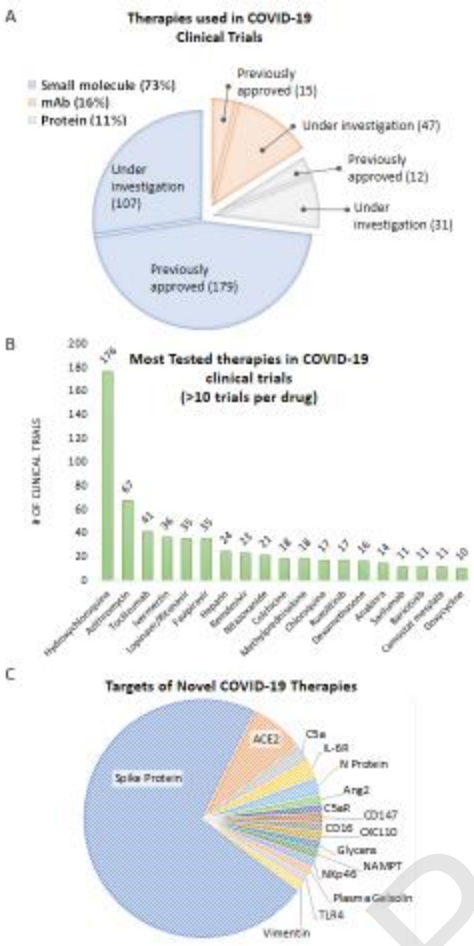

Figure 2: Therapies used in COVID-19 Clinical Trials. There are currently 2,036 clinical trials that are registered as of 17 October 2020 with clinicaltrials.gov for interventional study for patients who have been diagnosed with COVID-19. (A) These trials list 396 different therapeutics as interventions, with the majority of the tested therapies of the small molecule family (73%). Many of these drugs have been previously approved for other indications by at least one regulatory agency (e.g. US FDA, SFDA, EMEA, Health Canada, Japan MHLW, Ministry of Health of the Russian Federation, etc.). (B) Of the repurposed drugs, hydroxychloroquine (including hydroxychloroquine sulfate) is being studied in 176 clinical trials. (C) Novel therapeutics that are being developed, focus on preventing viral entry into the host cell through targeting the spike protein-ACE2 interaction with recombinant human soluble ACE2 proteins or anti-spike protein antibodies. A detailed listing of the therapies under clinical trial and development can be found in Tables 1 and 2. Data shown were derived from the U.S. National Library of Medicine ClinicalTrials.gov (access date 17 October 2020, search terms on interventional studies of "SARS-CoV-2" and "COVID-19"). Data of listed clinical trials do not delineate between those that have been initiated, stopped, or have not started enrollment.

Table 1. Examples of existing drugs proposed for repurposed use for COVID-19 treatment

Drug	Type	Target	Hypothesized role in COVID-19 treatment	Selected clinical trials (location, estimated/actual enrollment)	References
Hydroxychloroquine/ Chloroquine*	Small molecule	Endosome, lysosome, and Golgi apparatus	Interferes with ACE2 glycosylation, virus-ACE2 interaction, and virus endocytosis	WHO SOLIDARITY trial (international, >12000), NCT04381936/RECOVERY (UK, 4716), NCT04334148 (US, 2000), NCT04303507 (UK/Thailand, 40000)	(Hinton, 2020; Horby et al., 2020b; US National Library of Medicine, 2020; World Health Organization, 2020c, d)
Camostat	Small molecule	TMPRSS2	Blocks S protein priming and viral entry	NCT04321096 (Denmark, 580)	(US National Library of Medicine, 2020)
Azithromycin	Small molecule	Lysosome	Interferes with autophagy and virus endocytosis	NCT04381936/RECOVERY (UK, 15000), NCT04334382 (US, 1550)	(University of Oxford, 2020b; US National Library of Medicine, 2020)
Remdesivir**	Small molecule	RNA-dependent RNA polymerase	Inhibits viral replication	NCT04280705/ACTT (international, 1062), WHO SOLIDARITY trial (international, >12000), NCT04292899/SIMPLE (international, 4891), NCT04292730/SIMPLE (international, 1113)	(Beigel et al., 2020; U.S. Food and Drug Administration, 2020a) (Goldman et al., 2020; Spinner et al., 2020; World Health Organization, 2020c)
Favipiravir	Small molecule	RNA-dependent RNA polymerase	Inhibits viral replication	NCT04411433 (Turkey, 1000), NCT04356495 (France, 338)	(US National Library of Medicine, 2020)
Lopinavir/ Ritonavir	Small molecule	HIV proteases	Inhibits viral replication	WHO SOLIDARITY trial (international, >12000), NCT04381936/RECOVERY (UK, 5040)	(RECOVERY Collaborative Group, 2020; World Health Organization, 2020c)
Sarilumab	mAb	IL-6 receptor	Anti-inflammation	NCT04315298 (US, 1912)	(US National Library of Medicine, 2020)
Tocilizumab	mAb	IL-6 receptor	Anti-inflammation	NCT04381936/RECOVERY (UK, 15000), NCT04320615/COVACTA (international, 450)	(Roche, 2020; University of Oxford, 2020b)
Infliximab	mAb	TNF-α	Anti-inflammation	NCT04344249 (France, 850)	(US National Library of Medicine, 2020)
Emapalumab	mAb	IFN-γ	Anti-inflammation	NCT04324021 (Italy, 54)	(US National Library of Medicine, 2020)
Anakinra	Protein	IL-1 receptor	Anti-inflammation	NCT04330638 (Belgium, 342)	(Maes et al., 2020)
Dexamethasone	Small molecule	Multiple inflammatory cytokines	Anti-inflammation	NCT04381936/RECOVERY (UK, 6425)	(Horby et al., 2020a)
Colchicine	Small molecule	Tubulin	Anti-inflammation	NCT04322682 (US/Canada/Spain, 6000)	(US National Library of Medicine, 2020)
Baricitinib	Small molecule	JAK	Anti-inflammation	NCT04421027 (international, 600)	(US National Library of Medicine, 2020)

* On June 15, 2020, the U.S. FDA revoked emergency use authorization that allowed for chloroquine and hydroxychloroquine to be used to treat certain hospitalized patients with COVID-19 when a clinical trial was unavailable, or participation in a clinical trial was not feasible.

** On October 1, 2020, the U.S. FDA reissued emergency use authorization with revisions to allow for remdesivir to be used only to treat adults and children with suspected or laboratory confirmed COVID-19 administered in an in-patient hospital setting.

Footnote: Selected clinical trials may have expanded or been withdrawn since publication as this is a rapidly expanding field. mAb, monoclonal antibody; ACE2, Angiotensin converting enzyme 2; RNA, ribonucleic acid; TMPRSS2, transmembrane serine protease 2; HIV, human immunodeficiency virus; IL, interleukin; TNF, tumor necrosis factor; IFN, interferon; JAK, Janus kinase.

Table 2: Examples of novel protein therapies proposed to treat COVID-19

Primary Drug		Sponsor	Clinical Trials	Phase
rbACE2	Recombinant Bacterial ACE2 receptors -like enzyme of B38-CAP	Kafrelsheikh University	NCT04375046, NCT04382950	Phase 1 Phase 1
RhACE2 APN01		Apeiron Biologics	NCT04335136	Phase 2
SI-F019	ACE2 fusion protein	Systimmune, Inc.	n/a	Preclinical, End of 2020
COVIDTRAP (STI-4398)	ACE2 fusion protein	Sorrento Therapeutics	n/a	Preclinical
ACE-MAB (STI-4920/ CMAB020)	Bispecific fusion protein of truncated ACE2 and anti-Spike Protein mAb	Sorrento Therapeutics, Mabpharm	n/a	Preclinical
Anti-COVID-19 DARPin®	Trispecific protein targeting spike protein	Molecular Partners	n/a	Preclinical
LEAPS COVID-19	Peptides targeting the N protein	CEL-SCI, University of Georgia Center for Vaccines and Immunology	n/a	Preclinical
Rhu-pGSN	Recombinant human plasma gelsolin	BioAegis Therapeutics Inc.	NCT04358406, NCT03466073	Phase 2
Cloudbreak Antiviral Fc conjugates (AVCs)		Cidara Therapeutics	n/a	Preclinical
Neumifil	Multivalent carbohydrate binding molecules	Pneumagen Ltd.	n/a	Preclinical

Footnote: Listed therapeutics and clinical trials may have expanded or been withdrawn since publication as this is a rapidly expanding field. Therapeutics have been identified from Clinicaltrials.gov and publicly available literature searches. ACE2, Angiotensin converting enzyme 2; n/a indicates that a clinical trial has not been registered with ClinicalTrials.gov

Table 3: Examples of novel antibody therapeutics proposed to treat COVID-19

	Target	Primary Drug	Sponsor	Clinical Trials	Phase
mAbs/ mAb cocktails/ polyclonal Abs	Spike Protein	AZD7442 (AZD8895 + AZD1061)	AstraZeneca, Vanderbilt University Medical Center	NCT04507256	Phase 1
		BGB DXP593	BeiGene	NCT04532294 NCT04551898	Phase 1 Phase 2
		COVI-GUARD (STI-1499)	Sorrento Therapeutics	NCT04454398	Phase 1
		JS016	Junshi Bioscience Co. and Eli Lilly	NCT04441918	Phase 1
		LY-CoV555 (LY3819253)	Eli Lilly and Company and AbCellera Biologics Inc.	NCT04411628 NCT04427501 NCT04537910 NCT04497987 NCT04518410 NCT04501978	Phase 1 Phase 2 Phase 2 Phase 3 Phase 2/Phase 3 Phase 3
		MW33	Mabwell (Shanghai) Bioscience Co., Ltd.	NCT04533048	Phase 1
		REGN-COV2 (REGN10933, REGN10987 antibody cocktail)	Regeneron Pharmaceuticals	NCT04519437 NCT04425629 NCT04426695 NCT04381936 NCT04452318	Phase 1 Phase 1/ Phase 2 Phase 1/ Phase 2 Phase 2/ Phase 3 Phase 3
		SCTA01	Sinocelltech Ltd, Chinese Academy of Sciences	NCT04483375	Phase 1
		TY027	Tychan Pte Ltd.	NCT04429529	Phase 1
		COVI-SHIELD (antibody cocktail containing COVI-GUARD)	Sorrento Therapeutics, Mount Sinai Health System	n/a	Phase 1 trials expected in Q3 2020
		COVI-AMG (STI-2020)	Sorrento Therapeutics, Mount Sinai Health System	NCT04584697	Phase 1/Phase 2
		HLX70	Hengenix	NCT04561076	Phase 1
		HLX71	Hengenix	NCT04583228	Phase 1
		BRII-196	Brii Biosciences, Tsinghua University, and Third People's Hospital of Shenzhen	NCT04479631	Phase 1
		BRII-198	Brii Biosciences, Tsinghua University, and Third People's Hospital of Shenzhen	NCT04479644	Phase 1

	VIR-7831 (GSK4182136)	Vir Biotechnology, GlaxoSmithKline, Biogen, WuXi Biologics	NCT04545060	Phase 2, Phase 3
	47D11	Utrecht University, Harbour BioMed, Erasmus MC, Mount Sinai Health System, and AbbVie	n/a	Pre-clinical
	anti-COVID-19 PolyTope mAb Therapy	ImmunoPrecise Antibodies and EVQLV	n/a	Pre-clinical
	Anti-SARS-CoV-2	Hemogenyx/ Immugenyx	n/a	Pre-clinical
	Anti-SARS-CoV-2	Affinity Biosciences Pty Ltd.	n/a	Pre-clinical
	Anti-SARS-CoV-2	Amgen, Adaptive Biotechnologies	n/a	Pre-clinical
	Anti-SARS-CoV-2	Twist Biosciences, Proteona, Heidelberg University Hospital, Tübingen University Hospital, the German Cancer Research Center (DKFZ), the NMI Natural and Medical Sciences Institute, NUS Enterprise, and 10x Genomics	n/a	Pre-clinical
	Anti-SARS-CoV-2	Abound Bio, University of Pittsburgh, SaudiVax	n/a	Pre-clinical
	Anti-SARS-CoV-2	Adimab, Adagio Therapeutics	n/a	Pre-clinical
	Anti-SARS-CoV-2	Jecho Labs, Shanghai Jiao Tong University, People's Hospital of Henan Province, and Wuhan Virology Institute (Chinese Academy of Science)	n/a	Pre-clinical
	Anti-SARS-CoV-2	Ablexis, AlivaMab Discovery Services, and Berkeley Lights Collaborate	n/a	Pre-clinical
	Anti-SARS-CoV-2	AstraZeneca, VUMC, Chinese Academy of Sciences, USAMRIID, and the University of Maryland School of Medicine	n/a	Pre-clinical
	Anti-SARS-CoV-2	Centivax (Distributed Bio)	n/a	Pre-clinical
	Anti-SARS-CoV-2	FairJourney Biologics and Iontas	n/a	Pre-clinical
	Anti-SARS-CoV-2	Medicago and Laval University's Infectious Disease Research Center	n/a	Pre-clinical
	Anti-SARS-CoV-2	Prellis Biologics	n/a	Pre-clinical
	Anti-SARS-CoV-2	Yumab with Corona Antibody Team (CORAT)	n/a	Pre-clinical

		Anti-SARS-CoV-2	Virna Therapeutics, University of Toronto	n/a	Pre-clinical
		Anti-SARS-CoV-2	Y Biologics, Genexine	n/a	Pre-clinical
		Anti-SARS-CoV-2	AbClon Inc	n/a	Pre-clinical
		Anti-SARS-CoV-2 mAb	YUMAB/Boehringer Ingelheim	n/a	Pre-clinical
		Anti-SARS-CoV-2 program	Xbiotech	n/a	Pre-clinical
		AR-701	Aridis Pharmaceuticals, Inc.	n/a	Pre-clinical
		CT-P59	Celltrion	NCT04525079	Phase 1
		DXP-593	Beigene, Singlomics Biopharmaceuticals, and Peking University	NCT04551898 NCT04532294	Phase 2 Phase 1
		HFB30132A	HiFiBiO Therapeutics	n/a	Pre-clinical
		IDB003	VVC-VUMC, AstraZeneca, and IDBiologics	n/a	Pre-clinical
		MTX-COVAB	Memo Therapeutics AG	n/a	Pre-clinical
		Super-antibody or antibody cocktail to target potential mutations of SARS-CoV-2	Celltrion	n/a	Pre-clinical
		Anti-SARS-CoV-2	VUMC, AstraZeneca, and Twist Bioscience/Twist Biopharma	n/a	Preclinical, Summer 2020
	IL-6R	Levilimab	Biocad	NCT04397562	Phase 3
	IL-6R	TZLS-501 (NI-1201)	Tiziana Life Sciences/NovImmune	n/a	Pre-clinical
	TLR4	EB05	Edesa Biotech Inc, Light Chain Bioscience (NovImmune), JSS Medical Research Inc.	NCT04401475	Phase 2/Phase 3
	CXCL10	EB06	Edesa Biotech, Light Chain Bioscience (NovImmune)	n/a	Preclinical
	CD147 (EMMPRIN)	Meplazumab	Tang-Du Hospital	NCT04275245, NCT04369586 NCT04586153	Phase 1/ Phase 2 Phase 1 Phase 2/ Phase 3
	Angiopoeitin 2 (Ang2)	LY3127804	Eli Lilly and Company	NCT04342897	Phase 2
	C5a	BDB-001	Staidson Biopharmaceuticals Co., Ltd	NCT04449588	Phase 2/ Phase 3
	C5aR	IPH5401 (Avdoralimab)	Innate Pharma SA	NCT04371367	Phase 2
	Vimentin	Pritumumab	Nascent Biotech, Inc.	NCT04396717	Phase 1
	Nicotinamide phosphoribosyltransferase (NAMPT)	ALT-100 (Enamptcumab)	Aqualung Therapeutics, Fusion Antibodies	n/a	Pre-clinical
mAb TriKE	SARS-CoV-2, CD16	TriKE anti-SARS-CoV-2	GT Biopharma, Inc.	n/a	Pre-clinical

mAb bispecific	Spike Protein, NKp46	anti-SARS-CoV-2 and anti-NKp46 bispecific antibody	Cytovia Therapeutics, Inc.	n/a	Pre-clinical
IgM and IgA	Spike Protein	Novel IgM and IgA antibodies	Atreca, BeiGene, and IGM Biosciences	n/a	Pre-clinical
sdAbs	Spike protein and N protein	Nanobodies	Beroni Group & Tianjin University	n/a	Pre-clinical
	Spike Protein	Linked nanobody antibody	University of Texas at Austin/ US National Institutes of Health/ Ghent University	n/a	Pre-clinical
	Spike Protein	sdAbs	Ossianix	n/a	Pre-clinical
	Spike Protein	sdAbs	Abcore	n/a	Pre-clinical
	Spike Protein	Nb11-59	Shanghai Novamab Biopharmaceuticals Co., Ltd.	n/a	Pre-clinical
	Spike Protein	Aeronab 6	University of California, San Francisco	n/a	Pre-clinical
	Spike Protein	VHH72-Fc	ExeVir Bio, The University of Texas at Austin, and VIB-Ghent University	n/a	Pre-clinical

Footnote: Listed therapeutics and clinical trials may have expanded or been withdrawn since publication as this is a rapidly expanding field. Therapeutics have been identified from Clinicaltrials.gov and publicly available literature searches. ACE2, Angiotensin converting enzyme 2; mAbs, monoclonal antibodies; IgM, Immunoglobulin M; IgA, Immunoglobulin A; sdAbs, single domain antibodies; IL-6R, interleukin-6 receptor; TLR4, Toll-like receptor 4 protein; CXCL10, C-X-C motif chemokine 10; C5a, complement component 5a; TriKE, Tri-specific NK cell Engager; n/a indicates that a clinical trial has not been registered with ClinicalTrials.gov