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.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.
COVID-19 update: The race to therapeutic development

Julianne D. Twomey¹, Shen Luo¹, Alexis Q. Dean¹, William P. Bozza¹, Ancy Nalli¹, Baolin Zhang¹,*

Office of Biotechnology Products, Center for Drug Evaluation and Research, Food and Drug Administration, Silver Spring, MD 20993, United States

ARTICLE INFO

Keywords: COVID-19 SARS-CoV-2 Virus life cycle Therapeutic targets Drug development Antivirals Immunomodulators Monoclonal antibodies ACE2 Spike protein Repurposed use Existing drugs

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 2000 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), 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.

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). Most 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 COVID19 have been reported worldwide, resulting in more than 1,114,857 deaths (Johns Hopkins University, 2020). There are currently no approved vaccines for COVID-19, and a single therapeutic approved at the time of publication, 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 life cycle (Artese et al., 2020; Drozdzal et al., 2020). To facilitate COVID-19 drug development, the U.S. 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).

¹ Corresponding author.
E-mail address: Baolin.zhang@fda.hhs.gov (B. Zhang).
ⁱ All authors contributed equally and agreed to the content of the manuscript.

https://doi.org/10.1016/j.drup.2020.100733
Received 15 September 2020; Received in revised form 19 October 2020; Accepted 21 October 2020
Available online 24 October 2020
1368-7646/Published by Elsevier Ltd. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).
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 on 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 Clerq, 2020). Blockade of these proteins with inhibitors, such as bocceprevir (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 undergo different forms of cell death, 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 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 the sites of infection (Fig. 1). The continuous activation of immune cells leaves damaging effects ranging from capillary damage to multiorgan failure. In severe cases, 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 (Remna 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 from 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; Drozdzal 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, 2020; Wang et al., 2020b), which prompted several clinical studies including the ACTT-1 trial sponsored by the U.S. National Institute of Allergy and Infectious Diseases (NCT04280705) and the SOLIDARITY trial sponsored by WHO (World Health Organization, 2020a). Preliminary report from randomized, double-blind, placebo-controlled phase-3 ACTT-1 trial showed that remdesivir shortened the recovery time in hospitalized patients with COVID-19. On 1 May 2020, remdesivir was granted EUA in the US for treatment of suspected or laboratory-confirmed COVID-19 in hospitalized adult and pediatric patients with severe disease (U.S. Food and Drug Administration, 2020a). About the same time, remdesivir also received
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-AEC2 interaction, and virus endocytosis | NCT04381936/RECOVERY (UK, 15,000), NCT04334382 (US, 1550) | (Hinton, 2020; Horby et al., 2020a; US National Library of Medicine, 2020; World Health Organization, 2020a) |
| Camostat | Small molecule | TMPRSS2 | Blocks S protein priming and viral entry | NCT04303507 (UK/Thailand, 40,000) | (US National Library of Medicine, 2020) |
| Azithromycin | Small molecule | Lysosome | Interferes with autophagy and virus endocytosis | NCT04381936/RECOVERY (UK, 15,000), 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, >12,000), NCT04292899/SIMPLE (international, 4891), NCT04292730/SIMPLE (international, 1113) | (Beigel et al., 2020; Goldman et al., 2020; Spinelli 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, >12,000), NCT04381936/RECOVERY (UK, 5040) | (RECOVERY Collaborative Group, 2020; World Health Organization, 2020a) |
| 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, 15,000), 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 | NCT04324621 (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 15 June 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 22 October 2020, FDA approved remdesivir (Veklury) for use in adults and pediatric patients (12 years of age and older and weighing at least 40 kg) for the treatment of COVID-19 requiring hospitalization.

Footnote: Selected clinical trials may have expanded or been withdrawn since publication as this is a rapidly expanding field.

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 can be continuously evaluated through ongoing trials. On 28 August 2020, based on new data from the ACTT-1 trial and an additional randomized, open-label clinical trial with moderate COVID-19 (Study GS-US-540-5774/NCT04292730), FDA broadened EUA for remdesivir to include all hospitalized COVID-19 patients, irrespective of their severity of disease (U.S. Food and Drug Administration, 2020c). On 22 October 2020, after analysis of the final report from the above-mentioned ACTT-1 trial (Beigel et al., 2020) and NCT04292730 (Spinelli et al., 2020) and NCT04292899 trials (Goldman et al., 2020), FDA approved remdesivir (Veklury®) as the first treatment for COVID-19 (U.S. Food and Drug Administration, 2020). 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 and also based on results from randomized open-label trials (Cao et al., 2020; RECOVERY Collaborative Group, 2020; World Health Organization, 2020d; Pan et al., 2020).

3.2. Immunomodulators

Exogenous IFN treatments, which have been previously approved for multiple sclerosis, are being tested for their antiviral and immunomodulatory properties in COVID-19 patients. 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 (Manto 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 outcomes. 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).
Fig. 2. Therapies used in COVID-19 Clinical Trials. There are currently 2036 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.
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 arthritis, as well as cytokine release syndrome, and sarilumab cated for treatment of rheumatoid, giant cell, and juvenile idiopathic arthritis; (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 (NCT04322662) 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 also tested 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 or 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 (rhACE2) 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 transmembrane ACE2 for S protein binding (Table 2). Upon entering the bloodstream, the exogenous rhACE2 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). rhACE2 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 rhACE2 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 (Hemmes et al., 2018; Wang et al., 2020b). rhACE2 was reported to be safe in healthy subjects and in patients diagnosed with ARDS, which led to multiple rhACE2 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 rhACE2 in development is a recombinant bacterial carboxypeptidase (B38-CAP), an ACE2 receptor-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

---

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

| Primary Drug | Sponsor | Clinical Trials | Phase |
|--------------|---------|----------------|-------|
| rhACE2       | Kafrehsheik University | NCT04375046, NCT04382950 | Phase 1 |
| RhaCE2 APN01 | Apeiron Biologics | NCT043835136 | Phase 2 |
| SI-P019      | Systimmune, Inc. | n/a | Preclinical |
| COVIDTRAP (STI-4398) | Sorrento Therapeutics | n/a | Preclinical |
| AEC-MAB (STI-4920/ CMAB020) | Sorrento Therapeutics, Malpharm | n/a | Preclinical |
| Anti-COVID-19 DARPin® | Molecular Partners | n/a | Preclinical |
| LEAPS COVID-19 | CEL-SCI, University of Georgia Center for Vaccines and Immunology | n/a | Preclinical |
| Rhu-pGON | BioAegis Therapeutics Inc. | NCT04358406, NCT03466673 | 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.
ACE2, block protease activation of the spike protein, and are proposed to potentially block the binding of the spike protein 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 theseFc 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 (DiNobile 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 similar 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 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 (DiNobile et al., 2020; Yang et al., 2015). Controlling inflammation to decrease potential organ injury may be important to improve recovery from COVID-19 infection.

4.4. 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 in the body. 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 bloodstream (GT Biopharma, 2020). A similar approach involves a bi-specific antibody targeting the spike protein and the NKp46 NK cell receptor (Cytovia Therapeutics, 2020).
| Target | Primary Drug | Sponsor | Clinical Trials | Phase |
|--------|--------------|---------|----------------|-------|
| mAbs/ mAb cocktails/ polyclonal Abs | Spike Protein | AZD7442 (AZD8995 + AZD1061) | AstraZeneca, Vanderbilt University Medical Center | NCT04507256 | Phase 1 |
| | | BGB DXP593 | BeiGene | NCT04532294 | Phase 1 |
| | | COVI-GUARD (STI-1499) | Sorrento Therapeutics | NCT04551898 | Phase 2 |
| | | JS016 | Jumho Bioscience Co. and Eli Lilly | NCT04445398 | Phase 1 |
| | | LY-CoV555 (LY3819253) | Eli Lilly and Company and AbCellera Biologics Inc. | NCT04441918 | Phase 1 |
| | | | | NCT04411628 | Phase 1 |
| | | | | NCT04427501 | Phase 2 |
| | | | | NCT04537910 | Phase 2 |
| | | | | NCT04497987 | Phase 3 |
| | | | | NCT04518410 | Phase 2/Phase 3 |
| | | MW33 | Mabwell (Shanghai) Bioscience Co., Ltd. | NCT04533048 | Phase 1 |
| | | REGN-COV2 (REGN10933, REGN10987 antibody cocktail) | Regeneron Pharmaceuticals | NCT04519437 | Phase 1 |
| | | COVI-SHIELD (antibody cocktail containing COVI-GUARD) | Sorrento Therapeutics, Mount Sinai Health System | NCT04425629 | Phase 1/Phase 2 |
| | | COVI-AMG (STI-2020) | Sorrento Therapeutics, Mount Sinai Health System | NCT04426695 | Phase 1/Phase 2 |
| | | VIR-7831 (GSK4182136) | Vir Biotechnology, GlaxoSmithKline, Biogen, WuXi Biologics | NCT044381936 | Phase 1/Phase 2 |
| | | 47D11 | Utrecht University, Harbour BioMed, Erasmus MC, Mount Sinai Health System, and AbbVie | NCT04452318 | Phase 1/Phase 2 |
| | | 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 Lahn, 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 | FaizJourney 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 | 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 | Cellirion | NCT04525079 | Phase 1 |

(continued on next page)
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, including RdRp and spike proteins (Pachetti et al., 2020; van Dorp et al., 2020). 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 changing viral genome to stay ahead of potential drug resistance and nudge RBD in different structural conformations (Huo et al., 2020). (Pachetti et al., 2020; van Dorp et al., 2020).

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, including RdRp and spike proteins (Pachetti et al., 2020; van Dorp et al., 2020). 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.

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.

Declaration of Competing Interest

The authors report no declarations of interest.

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], 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.

References

3DPrint, 2020. Prellis Biologies Pursues Bioprinted Lymph Nodes for Production of COVID-19 Antibodies (07/09/2020). https://3dprint.com/267101/prellis-biologie-s-pursues-bioprinted-lymph-nodes-for-production-of-covid-19-antibodies-d/.

CEL-SCI, 2020a. CEL-SCI Initiates Development of Immunotherapy to Treat COVID-19 Coronavirus Infection (09/15/2020). https://www.businesswire.com/news/home/20200915005826/en/CEL-SCIs-Initiates-Development-of-Immunotherapy-To-Treat-COVID-19-

CEL-SCI, 2020b. CEL-SCI To Develop LEAPS COVID-19 Immunotherapy in Collaboration With University of Georgia Center for Vaccines and Immunology. https://www.irdi.org/press-releases/cell-sci-initiates-development-of-leaps-covid-19-immunotherapy-in-collaboration-with-university-of-georgia-center-for-vaccines-and-immunology.

Bioaegis Therapeutics, 2020. Plasma Gelsolin to Protect Tissue/Organs in Severe Coronavirus Infection Without Compromising Pathogen Response. https://www.bioaegistherapeutics.com/covid-19-plasma-gelsolin-to-protect-tissue-organs-in-severe-coronavirus-infection-without-compromising-pathogen-response/.

De Santis, M., Mancini, N., Grazzini, F., Zanotti, I., 2020. Type III interferons disrupt the lung epithelial barrier upon viral recognition. Science p. eabc3545.

DiNubile, M.J., Levinson, S.L., Stossel, T.P., Lawrenz, M.B., Warawa, J.M., 2020. Plasma Gelsolin to Protect Tissue/Organs in Severe Coronavirus Infection Without Compromising Pathogen Response. https://www.bioaegistherapeutics.com/covid-19-plasma-gelsolin-to-protect-tissue-organs-in-severe-coronavirus-infection-without-compromising-pathogen-response/.

Kidney Int. 97, 829–838.

Lundgren, J., Babiker, A.G., Pettit, S., Neaton, J.D., Burgess, T.H., Bonnett, T., Benfield, T., Henry, H., Kortepeter, M.G., Atmar, R.L., Creech, G.B., Lundgren, J., Babiker, A.G., Pett, S., Neaton, J.D., Burgess, T.H., Bonnett, T., Green, M., Makowski, M., Osnisi, A., Nayar, S., Lane, H.C., 2020. Remdesivir for the treatment of Covid-19: final report. N. Engl. J. Med. 382, 1787–1799.

Lundgren, J., Babiker, A.G., Pettit, S., Neaton, J.D., Burgess, T.H., Bonnett, T., Benfield, T., Henry, H., Kortepeter, M.G., Atmar, R.L., Creech, G.B., Lundgren, J., Babiker, A.G., Pett, S., Neaton, J.D., Burgess, T.H., Bonnett, T., Green, M., Makowski, M., Osnisi, A., Nayar, S., Lane, H.C., 2020. Remdesivir for the treatment of Covid-19: final report. N. Engl. J. Med. 382, 1787–1799.

Lyon, S., Saha, D., Bandyopadhyay, S., 2015. Ono-4818: a novel oral drug for the treatment of Covid-19 - final report. N. Engl. J. Med. 373, 1919–1927.

Zhu, P., 2020. Meplazumab treats COVID-19 pneumonia: an open-labelled, concurrent controlled add-on clinical trial. medRxiv.
bacteria-derived ACE2-like enzyme that suppresses hypertension and cardiac dysfunction. Nat. Commun. 11, p. 1058.

Monteiro, J., Kwon, H., Kim, E., Hagedijk, A., Wimmer, R.A., Stahl, M., Leopoldi, A., Garreta, E., Hurtado del Pozo, C., Prosper, F., Romero, J.P., Wirsinger, G., Zhang, H., Slutsky, A.S., Conder, B., Montserrat, N., Mirazimi, A., Penninger, J.M., 2020. Inhibition of SARS-CoV-2 infections in engineered human tissues using cell-adhesive sialic acid inhibitors. Cell 181, p. 1071.e10.

Oliviero, A., de Castro, F., Coperchini, F., Chiovato, L., Rotondi, M., 2020. COVID-19 pulmonary and olfactory dysfunctions: is the chemokine CXCL10 the common denominator? Neurosci. Lett. 697. https://doi.org/10.1016/j.neulet.2020.134255.

Ou, X., Liu, Y., Lei, L., Li, P., Li, M., Ren, L., Guo, L., Guo, R., Chen, Z., Xu, J., Xiang, Z., Ma, Z., Chen, X., Chen, J., Hu, K., Jin, Q., Wang, J., Qian, Z., 2020. Characterization of spike glycoprotein of SARS-CoV-2 on virus entry and its immune cross-reactivity with SARS-CoV. J. Virol. 94, p. e01705-20.

Pachetti, M., Marini, B., Benedetti, F., Giudici, F., Mauro, E., Storici, P., Masciovecchio, C., Angetti, S., Ciccozzi, M., Gallo, R.C., Zella, D., Ippolito, R., 2020. Emerging SARS-CoV-2 mutation hot spots include a novel RNA-dependent-RNA polymerase mutant. J. Med. Virol. 92, p. 1607-1620.

Pan, H., Rito, A., Abboad Karim, Q., Alelaidinia, M., Henaoo Restrepo, A.M., Hernandez Garcia, C., Kiemy, M.P., Malekzadeh, R., Murthy, S., Preisot, M.P., Reddy, S., Moses, R., Sathiayamaorthy, V., Rottingen, J.A., Swaminathan, S., 2020. Repurposed antivirals for COVID-19: an interim WHO SOLIDARITY trial results. medRxiv. p. 2020.10.20209817.

Park, A., Iwasaki, A., 2020. Type I and III IFN responses – induction, signaling, evasion, and application to combat COVID-19. Cell Host Microbe 27, 870-878.

Pawar, A.Y., 2020. Combating devastating COVID-19 by drug repurposing. Int. J. Antimicrob. Agents. 105984.

Pharmaceuticals and Medical Devices Agency, 2020. Special Approval for Emergency on Remdesivir for Emergencies on COVID-19. https://www.pmda.go.jp/english/int-activities/00084.pdf.

Pneumag, 2020. Pneumag Ltd Announces Positive Anti-Viral Activity for Novel Glycan Approach in Preventing COVID-19 Infections (07/09/2020). https://www.pneumag.com/news/18/70/Pneumag-Ltd-Announces-Positive-Aniti-Viral-Activity-for-Novel-Glycan-Approach-in-Preventing-COVID19-Infections.html.

Preuk.Usage, L., Cihlar, T., Jordan, R., Denison, M.R., Baric, R.S., 2017. Broad-spectrum antiviral GS-5734 inhibits both epidemic and zoonotic coronaviruses. Sci. Transl. Med. 10, p. 179.

Prokunina-Olsson, L., Alphonse, N., Dickenson, R.E., Durbin, J.E., Glenn, J.S., Greenbaum, D.C., Smith, A.B., Bates, P., Diamond, S.L., 2010. A small molecule inhibitor of human protease 3 inhibits SARS coronavirus and other members of the family Coronaviridae. J. Virol. 84, p. 10435-10445.

Qing, E., Hantak, M., Perlman, S., Gallagher, T., 2020. Characterization of spike glycoprotein of SARS-CoV-2 on virus entry and its immune cross-reactivity with SARS-CoV. J. Virol. 94, p. e01705-20.

Shilts, J., Wright, G.J., 2020. No evidence for basigin/CD147 as a direct SARS-CoV-2 receptor. https://www.fiercebiotech.com/biotech/sars-cov-2-cdc-fauci-project-final.pdf.

Tai, W., He, L., Zhang, X., Pu, J., Voronin, D., Jiang, S., Zhou, Y., Du, L., 2020. Characterization of the receptor-binding domain (RBD) of 2019 novel coronavirus: implication for development of RBD protein as a viral attachment inhibitor and vaccine. Cell. Mol. Immunol. 17, 612-622.

Tang, N., Bai, H., Chen, X., Gong, J., Li, D., Sun, Z., 2020. Anticoagulant treatment is associated with decreased mortality in severe coronavirus disease 2019 patients with coagulopathy. J. Thromb. Haemost. 18, 1094-1099.

Taylor, N.P., 2020. Celltrion Plans July COVID-19 Trial, Advances ‘super Antibody’. https://www.fiercebiotech.com/biotech/celltrion-plans-july-covid-19-trial-supber-antibody.

Thiel, V., Ivanov, A.K., Paric, A., Hertzig, T., Schelle, B., Bayer, S., Weilbirich, B., Snijder, E.J., Rabenau, H., Doerr, H.W., Gorbalenya, A.E., Ziebuhr, J., 2003. Mechanisms and enzymes involved in SARS coronavirus genome expression. J. Gen. Virol. 84, 2305-2315.

Tran, D.H., Sugham, R., Hirose, T., Suzuki, S., Noguchi, Y., Sugawara, A., Ito, F., Yamamoto, T., Kowachi, S., Akagawa, K.S., Osimura, S., Suzuki, T., Ito, N., Mimaki, M., Suzuki, K., 2019. Azithromycin, a 15-membered macrolide antibiotic, inhibits influenza A(H1N1)pdm09 virus infection by interfering with virus internalization process. J. Antimicrob. Chemother. 74, 759-766.

U.S. Food and Drug Administration, 2020a. Coronavirus Disease 2019 (COVID-19) Update: FDA Issues Emergency Use Authorization for Potential COVID-19 Treatment. https://www.fda.gov/news-events/press-announcements/coronavirus-disease-2019-update-fda-issues-emergency-use-authorization-potential-covid-19-treatment.

U.S. Food and Drug Administration, 2020b. Coronavirus Disease 2019 (COVID-19) Update: FDA Coronavirus Treatment Acceleration Program (CTAP). https://www.fda.gov/drugs/coronavirus-covid-19-drugs/coronavirus-treatment-acceleration-program-ctap.

U.S. Food and Drug Administration, 2020c. FDA Guidance for Industry - COVID-19: Therapeutics for Treatment or Prevention. https://www.fda.gov/media/137926/download.

U.S. Food and Drug Administration, 2020d. Temporary Policy for Compounding of Certain Drugs for Hospitalized Patients by Outsourcing Facilities During the COVID-19 Public Health Emergency (09/15/2020). https://www.fda.gov/media/138276/download.

U.S. Food and Drug Administration, 2020e. COVID-19 Update: FDA Broadens Emergency Use Authorization for Veklory (remdesivir) to Include All Hospitalized Patients for Treatment of COVID-19. https://www.fda.gov/newsevents/press-announcements/covid-19-update-fda-broadens-emergency-use-authorization-veklory-remdesivir-in-virus-including-all-hospitalized.

University of Oxford, 2020a. Dexamethasone Reduces Death in Hospitalised Patients With Severe Respiratory Complications of COVID-19. University of Oxford, 2020b. This National Clinical Trial Aims to Identify Therapies That May Be Beneficial for People Hospitalised With Suspected or Confirmed COVID-19. https://www.recoverytrial.net.

US National Library of Medicine. 2020. U.S. National Library of Medicine ClinicalTrials.gov. https://clinicaltrials.gov/.

van Dorp, L., Acman, M., Richard, D., Shaw, L.P., Ford, C.E., Ormond, L., Owen, C.J., Zhang, H., Slutsky, A.S., Bernasconi, E., Le Turnier, P., Chang, S.C., Scopetra, D., Hyurka, Y., Denison, R.R., Shim, S.A., Hogg, A., Babusis, D., Clarke, M.O., Spahn, J.E., Bauer, L., Sellers, S., Porter, D., Zhang, H., Voronin, D., Jiang, S., Zhou, Y., Du, L., 2020. Characterization of spike glycoprotein of SARS-CoV-2 on virus entry and its immune cross-reactivity with SARS-CoV. J. Virol. 94, p. e01705-20.

Wrapp, D., De Vlieger, D., Corbett, K.S., Torres, G.M., Wang, N., Van Breedam, W., Cihlar, T., Jordan, R., Denison, M.R., Baric, R.S., 2020. Emerging SARS-CoV-2 mutation hot spots include a novel RNA-dependent-RNA polymerase mutant. J. Med. Virol. 102, p. 1778-1784.

Yamamoto, T., Kawachi, S., Akagawa, K.S., Omura, S., Sunazuka, T., Ito, N., Leist, S.R., Pyrc, K., Feng, J.Y., Trantcheva, I., Bannister, R., Park, Y., Babusis, D., Hanslmayr, S., Graham, B.S., Callewaert, N., Helmann, J.D., Twomey et al. 2020. JAK inhibitors in the management of COVID-19. Sci. Immunol. 5.

Zhang, H., Slutsky, A.S., Bernasconi, E., Le Turnier, P., Chang, S.C., Scopetra, D., Hyurka, Y., Denison, R.R., Shim, S.A., Hogg, A., Babusis, D., Clarke, M.O., Spahn, J.E., Bauer, L., Sellers, S., Porter, D., Zhang, H., Voronin, D., Jiang, S., Zhou, Y., Du, L., 2020. Characterization of spike glycoprotein of SARS-CoV-2 on virus entry and its immune cross-reactivity with SARS-CoV. J. Virol. 94, p. e01705-20.
neutralization of betacoronaviruses by single-domain camelid antibodies. Cell 181, 1004–1015 e1015.
Wu, C., Chen, X., Cai, Y., Xia, J., Zhou, X., Xu, S., Huang, H., Zhang, L., Zhou, X., Du, C.,
Zhang, Y., Song, J., Wang, S., Chao, Y., Yang, Z., Xu, J., Zhou, X., Chen, D.,
Xiong, W., Xu, L., Zhou, F., Jiang, J., Bai, C., Zheng, J., Song, Y., 2020a. Risk Factors
Associated With Acute Respiratory Distress Syndrome and Death in Patients With
Coronavirus Disease 2019 Pneumonia in Wuhan, China. JAMA Intern. Med.
Wu, C., Liu, Y., Yang, Y., Zhang, P., Zhong, W., Wang, Y., Wang, Q., Xu, Y., Li, M., Li, X.,
Zheng, M., Chen, L., Li, H., 2020b. Analysis of therapeutic targets for SARS-CoV-2
and discovery of potential drugs by computational methods. Acta Pharm. Sin. B 10,
766–788.
Wu, Y., Li, C., Xia, S., Tian, X., Kong, Y., Wang, Z., Gu, C., Zhang, R., Tu, C., Xie, Y.,
Yang, Z., Lu, L., Jiang, S., Ying, T., 2020c. Identification of human single-domain
antibodies against SARS-CoV-2. Cell Host Microbe 27, 891–898 e895.
Xia, S., Zhu, Y., Liu, M., Lan, Q., Xu, W., Wu, Y., Ying, T., Liu, S., Shi, Z., Jiang, S., Lu, L.,
2020. Fusion mechanism of 2019-nCoV and fusion inhibitors targeting HR1 domain
in spike protein. Cell. Mol. Immunol. 17, 765–767.
Yang, Z., Chiou, T.T., Stossel, T.P., Kobzik, L., 2015. Plasma gelsolin improves lung host
defense against pneumonia by enhancing macrophage NOS3 function. Am. J.
Physiol. Lung Cell Mol. Physiol. 309, 111–16.
Yao, X., Ye, F., Zhang, M., Cai, C., Huang, B., Niu, P., Liu, X., Zhao, L., Dong, E., Song, C.,
Zhan, S., Lu, R., Li, H., Tan, W., Liu, D., 2020. In vitro antiviral activity and
projection of optimized dosing design of hydroxychloroquine for the treatment of
severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Clin. Infect. Dis.
Zhang, S., Li, L., Shen, A., Chen, Y., Qi, Z., 2020. Rational use of Tocilizumab in the
treatment of novel coronavirus pneumonia. Clin. Drug Investig. 40, 511–518.
Zhang, S., Zhao, Q., 2020. Perspectives on therapeutic neutralizing antibodies against the
Novel Coronavirus SARS-CoV-2. Int. J. Biol. Sci. 16, 1718–1725.
Zimmer, K., 2020. First Antibody Trial Launched in COVID-19 Patients (07/09/2020).
https://www.the-scientist.com/news-opinion/first-antibody-trial-launched-in-covid
-19-patients-67604.