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Running Title: Classification of Coronavirus (COVID-19) Treatments and Drugs based on Mechanism of Action, Efficacy, and Safety

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ABSTRACT

The recently discovered coronavirus SARS-CoV-2 has forced countries into lockdown, people into quarantines, and economies to a standstill. Currently there are no FDA approved treatments for COVID-19, the disease caused by this new coronavirus strain. With over 2.8 million cases in the US as of July 3 and a death rate of approximately 5.9%, an effective treatment is urgently needed (Center for Disease Control [CDC], 2020). Promising drugs that are being developed explicitly to target COVID-19 vulnerabilities are 1-2 years away from broad use. Repurposed drugs that are FDA approved for other indications have known safety profiles and therefore could be used immediately. This paper presents drugs currently available for coronavirus and those in development to understand the benefits, costs, and mechanisms of actions of each drug. This paper highlights FDA approved drugs that can be repurposed and therefore used immediately to test for coronavirus efficacy, as well as novel drugs and vaccines that are in development to target COVID-19 vulnerabilities.

Introduction

COVID-19 is the disease caused by the SARS-CoV-2 virus, more commonly known as the coronavirus (Cui *et al.* 2019). One of many coronaviruses, SARS-CoV-2 is a specific variation of the MERS and SARS viruses that attacked the human population in the early 2000s (Stadler *et. al.* 2003). It originated in Wuhan, China, and spread rapidly to other parts of the world because of its contagious nature (Wu *et al.* 2020). It is primarily a respiratory illness, although other organs such as the heart, blood vessels, stomach, and intestines can also be impacted. The death rate is approximately 6%. The exact number of cases is difficult to estimate as many individuals have not presented severe symptoms or have been entirely asymptomatic. (CDC 2020). It has been estimated that approximately half of the SARS-CoV-2 positive patients are asymptomatic (Ghandi *et al.* 2020).

As a novel disease, there have been shortages of testing kits, and as of early July there is still no accepted standard of care (Padula 2020). Since the virus can be easily spread and is difficult to detect, vaccines are a promising prevention strategy. However, these vaccines are 12-18 months away from widespread use (Verch *et al.* 2018). Thus, there is an immediate need for both prevention strategies and curative therapies.

This paper presents the various drugs in development, as well as novel drugs and vaccines, to compare their mechanism of action and efficacy in defeating COVID-19. We introduce three different classes of drugs which can be used against the disease: antiviral drugs, vaccines, and anti-inflammatory drugs. Because anti-inflammatory drugs only treat the symptoms of COVID-19, we will focus on the development of vaccines and repurposing of antivirals in this paper.

Drug Classification

The drugs in development can be classified by a multitude of factors which include type, availability, the manufacturer of the drug, and the mechanism of action. Below we introduce each class and sort the drugs in their respective categories.

Classes of Drugs

As shown in Table 1, current therapies in clinical use or development can be sorted into three classes: vaccines, antiviral drugs, and anti-inflammatory drugs (Amant & Kramer 2020, Jean *et al.* 2020, Little 2020). Additionally, there are non-pharmacological therapies such as convalescent plasma appropriate for specific clinical situations.

A vaccine provides the body immunity to the virus by introducing a weakened form of the virus to engage the B cells and generate antibodies specific to viral antigens. Antiviral drugs prevent viral replication by prohibiting specific stages in the viral life cycle. An anti-inflammatory drug reduces the inflammatory side effects of the virus in hopes that the body's immune system will be able to fight off the virus on its own.

Table 1: Classes of COVID 19 drugs

Treatment	Mechanism of Action (Biology and Connection to virus)
Vaccines	● Provides active acquired immunity to virus as a preventative
Antiviral	● Prohibits virus from replicating or inhibits growth of the virus
Anti-inflammatory	● Reduces inflammation and pain ● Does not defeat virus; reduces symptoms

Brand new drugs being developed explicitly to treat COVID-19

Novel drugs have the advantage of having mechanisms of action that explicitly target some vulnerability or characteristic specific to SARS-CoV-2. However, they are new to humans, which means their safety profile, let alone efficacy, is not yet established. Several promising novel drugs and vaccines are shown in Table 2. Because they are still in early stages of clinical trials or pre-human testing, these drugs will be at least one to two years before clinical use. (Verch *et al.* 2018). As such, we will discuss generalized mechanisms of action rather than focus on the limited data on each individual drug.

Table 2: Novel therapies targeted to COVID-19.

Name	Type Novel Drugs / Treatments / Vaccines for COVID-19
convalescent plasma	non-pharmacological therapy
TAK-888 (Polyclonal hyperimmune globulin)	targeted antiviral drug
Antibodies from humanized mice	targeted antiviral drug
mRNA-1273	vaccine
BNT162	vaccine
AChAdOx1 nCoV-19	vaccine

Convalescent plasma involves the use of non-pharmacological blood plasma from patients who have recovered from the virus but is not a scalable approach to treatment. Vaccines like those shown in Table 2 are not likely as effective as treatments but could be used as preventatives.

Vaccines

The development of vaccines presents the most viable, effective, long-term preventative for the coronavirus. Because traditional vaccines are slow to develop, difficult to manufacture, and have a greater potential to be contaminated during manufacturing, scientists have turned to mRNA vaccines as an effective alternative (Pardi *et al.* 2018).

Mechanism of Action

Vaccines utilize the body's adaptive immune system to develop artificially acquired immunity. When a patient is exposed to a pathogen like a virus, the adaptive immune system will take days to develop naturally acquired immunity. A vaccine exposes the patient to a weakened form of the virus or specific shapes on the virus called antigens which the immune system can remember. Immune memory will protect the patient from the pathogen upon next exposure, provided that the pathogen has not mutated or changed the antigen which the body recognizes (Punt *et al.* 2019).

For mRNA vaccines, the genetic code of an antigen specific to the virus is sequenced and expressed in an mRNA template strand. This strand is injected into the patient through various methods. The mRNA strand in the body instructs the cells to make viral antigens. Once the non-self antigens in the mRNA strand are recognized by the

body's immune system, the body generates neutralizing antibodies. In this way, the mRNA strand is a template that generates a personalized vaccine for every individual (Versteeg *et al.* 2019).

Vaccine Built Specific for COVID-19

Scientists at Moderna, Pfizer, and other vaccine development companies have turned to the mRNA vaccines as a method to prevent the further spread of the coronavirus. mRNA vaccines have shown potential in generating antibodies against the coronavirus, even in animal models such as mice (Pardi *et al.* 2017, Bahl *et al.* 2017, Richner *et. al* 2017). Specifically, one study demonstrated that mice injected with the SARS coronavirus naturally developed neutralizing antibodies that were sufficient for prophylaxis of coronavirus (Subbarao *et al*. 2004).

The SARS-CoV-2 genome provides multiple potential targets for the development of an mRNA based vaccine. For the vaccine to be effective, it would need to target a gene which encodes for a protein necessary for viral replication or survival. The SARS-CoV-2 and SARS coronaviruses share 80% of their genomes, and the SARS spike (S) protein has 73% sequence similarity with the SARS-CoV-2 protein (Peng *et al* 2020). A 2004 study by Buchholz *et al.* showed that the spike protein is the only SARS-CoV antigen necessary and sufficient to produce neutralizing antibodies at high enough titer to protect the cells from viral infection.

Based on this, scientists have designed a synthetic mRNA strand that encodes the S protein of the coronavirus. This mRNA strand is injected as a vaccine into the body, and instructs immune cells to make copies of the foreign antigen. Once these proteins are expressed on the cell's surface and are recognized by the body's immune system, B cells bind to this antigen and generate antibodies in response to the foreign invader. T cells then destroy all infected cells with this virus. The memory B and T cells then remember this foreign antigen and prevent reinfection of the coronavirus, provided the virus has not mutated.

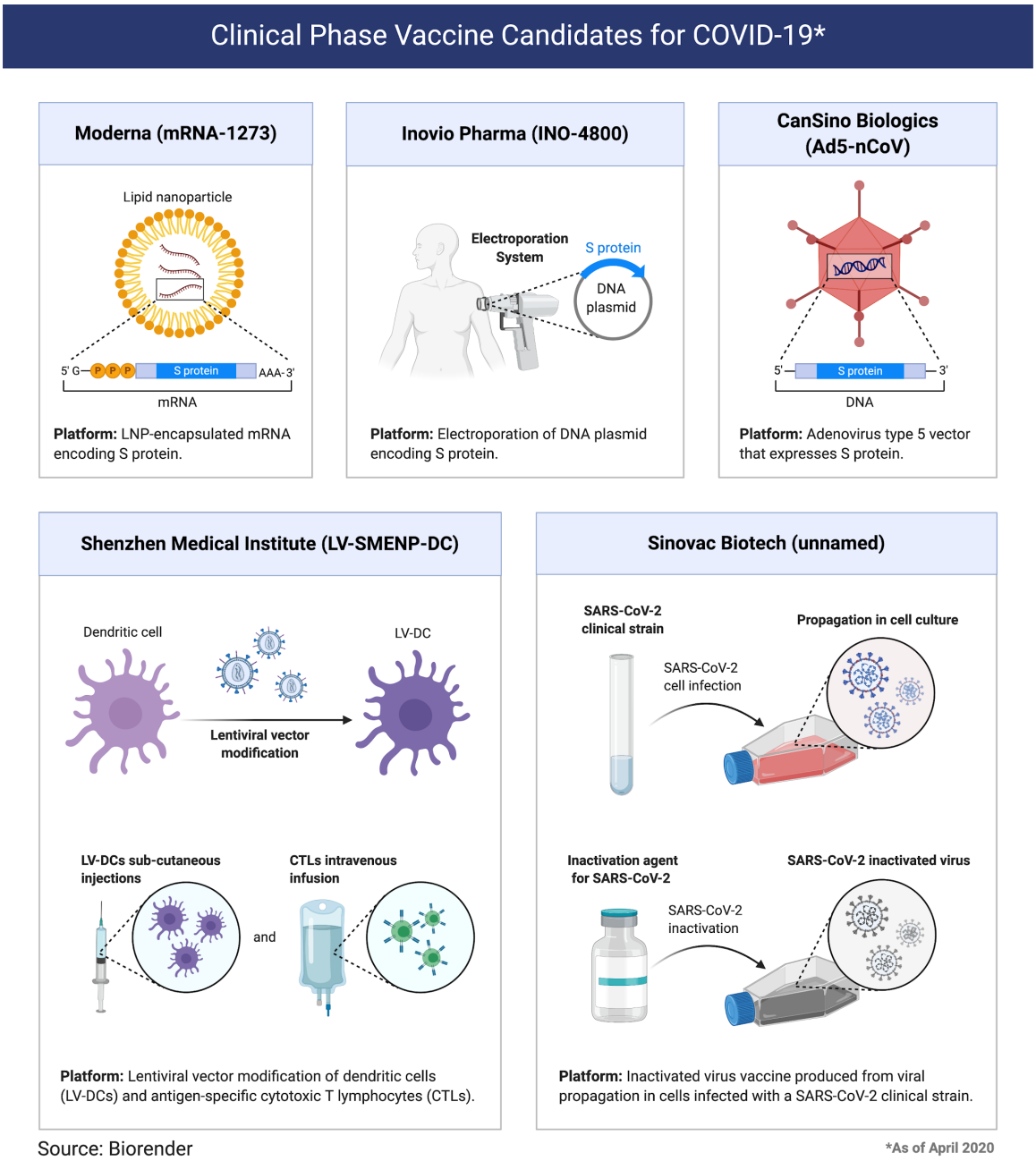

Figure 1: **Clinical Phase Vaccine Candidates for COVID-19.** The basic design of candidate therapies and mode of delivery are shown for mRNA-1273 (A), INO-4800 (B), Ad5-nCoV (C), LV-SMNEP-DC (D) and Sinovac Biotech's unnamed vaccine (E).

Problems and Risks with vaccines

Vaccines are traditionally used as preventives rather than for treatment of viruses because it takes time to establish initial adaptive immunity via immune memory cells (Punt *et al.* 2019). Thus, mRNA vaccines are not a viable option if patients have not successfully generated their own antibodies specific to the SARS-CoV-2 virus within a week or two.

Moreover, there have been no mRNA vaccines with proven clinical results. Currently, proof of concept studies is needed to establish efficacy of these vaccines. Thus, the vaccine needs to be tested on animals and undergo clinical trials for safety and efficacy. However, various drug development companies have been given special exemptions to begin with human testing rather than in preclinical models. This strategy is high risk/high reward due to the immediate need for effective treatment and prevention (Lurie, et. al. 2020). Lastly, the optimal treatment dosage and time for the vaccine is unknown. Scientists also do not know how long the immunity by the vaccine will last because the mutation rate of the virus has not been sufficiently established (Lurie, et. al. 2020).

Conclusions on vaccines

If no hindrances are observed, an mRNA vaccine will likely be the long-term solution for the prevention of SARS-CoV-2. It is easily manufactured and lowers the possibility of contamination. However, this vaccine will take at least one to two years for development before the vaccine is proven effective in multiple trials (Verch *et al.* 2018). As a result, for immediate use, we are faced with the prospect of repurposing drugs (Sanders *et al.* 2020).

Drugs with Prior Human Use

Drugs that have prior human use experience are approved for other diseases and indications are being repurposed to treat COVID-19 symptoms and/or target the virus directly. There are many advantages to using repurposed drugs. Their effect on the human body is well known because of the prior human testing. Most importantly, the safety profile is established. It is advantageous to test repurposed drugs in the interest of time as they are able to skip phase one of clinical trials.

However, clinical testing to demonstrate efficacy of these drugs against COVID-19 needs to be established first before wide usage (Carlucci et. al 2020). Table 3 shows specific repurposed drugs which are undergoing clinical testing for COVID-19 treatment. (Harrison 2020 and Clinical Trials 2020)

Table 3: Various Repurposed COVID 19 drugs. Clinical trial data was current as of July 3, 2020. Data was compiled from ClinicalTrials.gov with additional information from Harrison 2020

Drug / Cocktail	Originator Company	Mechanism/Status	Clinical trials
ritonavir/ ASC09/ lopinavir-ritonavir	Abbvie; Ascletis; Pharmstandard	ASC09: experimental HIV-1 protease inhibitor; ritonavir and lopinavir: protease inhibitors for HIV/AIDS; umifenovir: entry inhibitor against influenza	At least 81 studies
ASC09/oseltamivir /ritonavir	Ascletis, Gilead, AbbVie	See above; oseltamivir: sialidase inhibitor for influenza	17
Various combinations of baloxavir marboxiil/favipiravir and lopinavir/ritonavir	Shionogi Toyama Chemical	Baloxavir marboxil: Cap-dependent endonuclease inhibitor; favipiravir: guanine analog RNA dependent RNA polymerase inhibitor for influenza A and B; see above	17 trials

combinations of darunavir/cobicistat alone or with lopinavir/ritonavir and thymosin alpha 1	Janssen Gilead	Darunavir: HIV-1 protease inhibitor; cobcist: inhibitor of cytochrome P450, in combination for HIV-1/AIDS ; Thymosin alpha: immune response boosting agent	9 trials
Remdesivir	Gilead	prodrug of an adenine analog for ebola and marburg virus; Emergency use authorization	35 trials
Chloroquine/ Hydroxychloroquine	Shanghai Zhongxi PHaramceutical Shanghai Ziyan Pharmaceutical, wuhan wuyao pharmaceutical	Endosomal acidification fusion inhibitor; Emergency use authorization revoked June 15, 2020.	312 total trials
Methylprednisolone	Generic	Synthetic corticosteroid that binds to nuclear receptors to dampen proinflammatory cytokines	27 trials
Interferon α-2b alone or in combination with lopinavir/ritonavir and ribavirin	Biogen Merck	Interferon α-2b: recombinant cytokine with antiviral properties; ribavirin: guanine derivative; See above	2 trials
Camrelizumab and thymosin	Incyte, Shanghai Hengrui PHarmaceutical	humanized monoclonal antibody targeting PD-1	3 trials (for thymosin)
Tocilizumab	Chugai Pharmaceutical, Zhejiang Hisun Pharmaceutical, JIangsu Qyun Bio-Pharmaceutical	Humanized monoclonal antibodies targeting interleukin-6	59 trials

A key characteristic of any drug is its mode of action, the method by which the drug treats the disease. For the case of an antiviral drug, its primary mechanism of action is blocking viral replication. To create an antiviral drug to inhibit viral replication, it is critical that we study the virus life cycle stages, as was done for MERS and SARS (Zumla et. al 2016).

Coronavirus Life Cycle

Viruses rely on the host cell to carry out the replication and translation of viral parts. The coronaviruses have a positive sense-RNA genome and contain four main structural proteins important for the viral life cycle: spike protein (S), membrane protein (M), nucleocapsid protein (N), and envelope protein (E). To replicate and make more viruses, the virus must undergo six stages (Fehr *et al.* 2015).

Steps 1 and 2) Attachment and Entry

In order for a virus to enter the cell, its surface protein must bind to a host cell receptor. Both the SARS coronavirus and the SARS-CoV-2 virus share the same surface protein, the spike (S) protein, that is used to unlock the cell. Once the S protein has attached to the receptor, the virus fuses with the cell membrane via endocytosis. Its viral parts, including viral DNA, are then emptied in the cytoplasm.

Step 3) Translation

Using its ribosomes, the RNA strand translates two viral replicases. These translated replicases form polypeptides which are then cleaved into 16 different proteins. Such nonstructural proteins are used to code for various other polymerases, including RdRp (RNA dependent RNA polymerase).

Step 4) Transcription using RdRp

RdRp is used to make more copies of the virus' single stranded RNA. A complementary negative RNA strand is made from the positive sense RNA genome. These RNAs are then translated to synthesize structural proteins.

Step 5) Assembly using viral proteins (S, E, M, N)

After the RNA is synthesized, the viral proteins S, E, and M are translated and enter the endoplasmic reticulum. Here the M and S proteins work together to assemble the viral parts.

Step 6) Release of the virus

After all viral structures have been manufactured, the M protein encloses the viral contents including the RNA and proteins into a mature virion. The production of the outer covering of the virion is directed by the E protein. S proteins are inserted inside the virion, as it will allow for subsequent binding to receptors of other host cells once released.

After the virus is assembled, the virions fuse with the cell membrane and exit the cell via exocytosis, releasing viruses into the body. Here the S protein also directs the fusion between the cell membrane and the viral membrane, as well as fusions between infected cells and healthy cells to avoid detection by human antibodies. Once in circulation, the virus goes on to infect more cells.

Mechanism of Action of Antiviral Drugs

The goal of many antiviral coronavirus drugs is to inhibit the replication of the coronavirus. In order to prevent viral growth, it is necessary that a drug hinders at least one of the stages in the virus' replication cycle. Figure 2 shows the molecular target of several current and developmental therapies for COVID-19 (Magden et. al 2004).

The first step to viral entry is the binding of the spike protein to the cell receptor. Monoclonal antibodies, camostat mesylate, and convalescent plasma are examples of drugs that prevent the viral S protein from fusing onto the cell receptor, and thus block attachment of the virus to the cell (Kupferschmidt 2020).

If the virus is successful in binding to the cell receptor, it enters the cell through the endosomal pathway using endocytosis. Drugs such as chloroquine and hydroxychloroquine target the pathway's dependence on a strict pH range by raising the endosomal pH, which hinders the maturation of the virus particles. Some studies also suggest that chloroquine and hydroxychloroquine prevent virus particles from binding to the cell receptor (Devaux et al 2020).

As previously discussed, during proteolysis, the virus converts the viral proteins into components for the virus structure. If the viral proteins are unable to be formed, the virus cannot reassemble to infect other cells. One repurposed drug, lopinavir-ritonavir, exploits the virus' dependence on the synthesis of proteins, and targets two viral proteases (PL pro and 3CL pro). In particular, lopinavir-ritonavir is a repurposed HIV drug that inhibits the HIV protease enzyme, which spurs the production of harmless virions and prevents the spread of the viral infection. However, because of the difference in proteases, some studies have shown that lopinavir-ritonavir is not effective in combating COVID-19 (Slomski 2020).

Moreover, the SARS-CoV and the SARS-CoV-2 RNA-dependent RNA polymerase (RdRp) sequences are 96% identical, which suggests that RdRp-focused drugs can be effective for the coronavirus. Two drugs that inhibit RdRp are remdesivir and favilavir (Zheng 2020). Specifically, Remdesivir is an analogue for the nucleotide adenosine. The polymerase confuses the analog adenosine triphosphate (remdesivir) with the actual adenosine triphosphate. Once the polymerase attaches remdesivir on the virus's replicated strand, RNA synthesis is hindered and cannot continue. (Ko et. al 2020) Without the virus' genetic material, the virus is unable to mature and exit the cell.

Although Remdesivir failed to treat the ebola virus, it was shown to be successful in animals infected with SARS-CoV and MERS-CoV, two other coronaviruses (Wit et. al 2020). Remdesivir also successfully treated COVID-19 *in vitro* in monkey cells (Wang et al 2020).

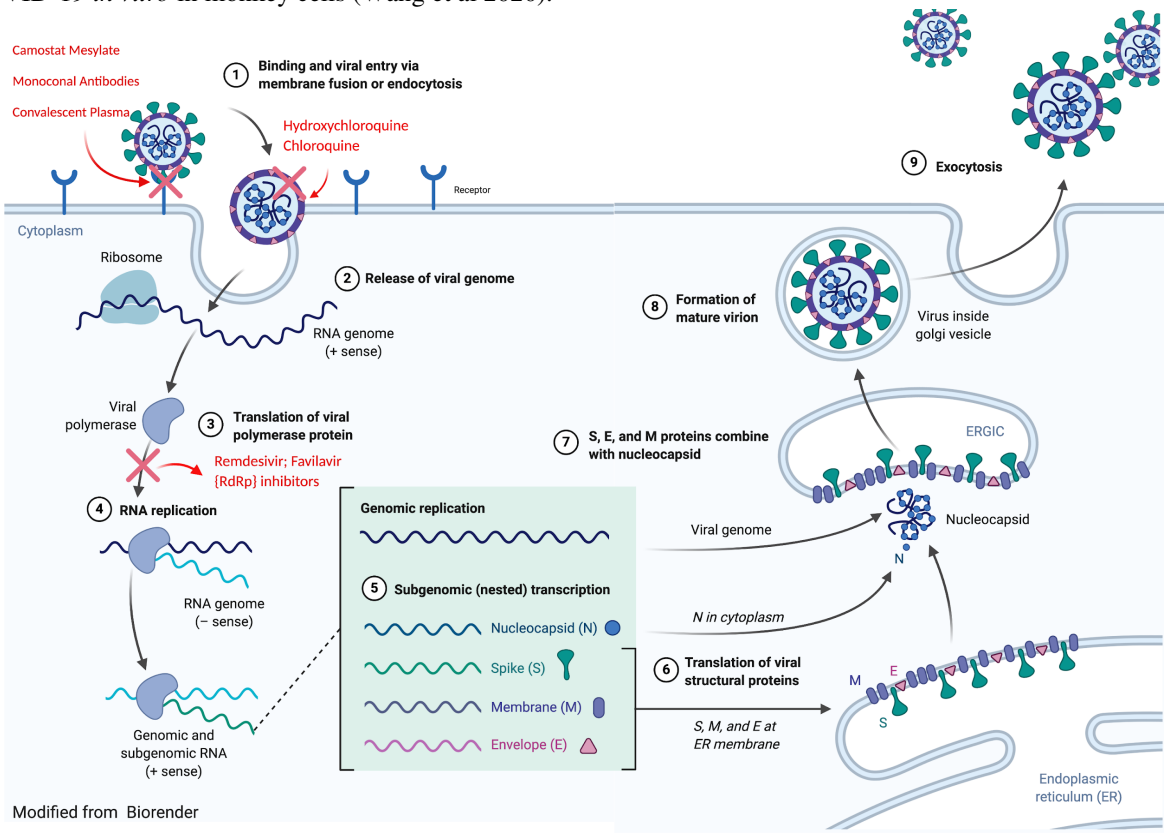

Figure 2: Drugs that inhibit the viral life cycle

Table 4: List of leading COVID 19 drugs and treatments under development

Therapy	Type	Producer	Mechanism of Action
Remdesivir	antiviral	Gilead	Remdesivir looks so similar to Adenosine that the viral polymerase can mistakenly insert into viral DNA to prevent the virus from replicating
Favilavir	antiviral	Zhejiang Hisun Pharmaceutical Company	Attacks RNA viruses by inhibiting RdRp, RNA-de-pen-dent RNA poly-merase, to prevent virus replication
Chloroquine	antiviral	Recipharm	Drugs prevent virus binding to host cells by increasing endosomal pH
TAK-888; Poly-clonal hyperim-mune globulin:	antiviral	Takeda	Antibodies are collected from recovered COVID-19 patients and are transferred to new patients to spur production of healthy antibodies to fight off virus
Kevzara:	anti-inflammatory	Regeneron/ Sanofi	Blocks IL-6 receptors. This lessens in-flammatory response, potentially milden-ing the overactive symptoms
mRNA-1273:	vaccine	Moderna	synthetic strand mRNA that induces body cells to produce antibodies against the vi-rus
convales-cent plasma	antiviral	N/A	Direct blood transfer between recovered patients and newly infected patients- the plasma from the recovered patients con-tains healthy antibodies

Promising Non-Pharmacological Treatment

As an up and coming therapy for treating COVID-19, convalescent plasma serum is a transfer of a high titer of neutralizing antibodies from a recovered patient to another individual. That individual may either be a sick patient, a high-risk individual such as a health care worker, or someone with no symptoms (Casadevall et al 2020). This method is already approved for emergency use by the FDA. (Food and Drug Administration [FDA], 2020a).

Mechanism of Action of Convalescent Plasma

Plasma is the liquid component taken from recovered patients. The blood of the recovered patients contains neutralizing antibodies which protect the donor from a second infection. Based on the principle of passive immunity, these neutralizing antibodies fight the virus by preventing entry to the cells and thus impeding virus replication in the recipient. The antibodies will thwart the spread of the virus as long as they remain in circulation. Because the donor's plasma and memory B cells are not provided to the recipient, the immunity is only temporary or until the patient can recover sufficiently to generate their own immune response (Punt *et al.* 2019). The convalescent plasma is more useful for prophylaxis in high risk patients than the treatment of disease.

Unknowns and Risks of Convalescent Plasma Therapy

As convalescent plasma therapy trials for the treatment of COVID 19 are ongoing, many unknowns exist and risks have yet to be discovered. The optimal dosage and treatment duration of convalescent plasma therapy is still not known. Some known risks of this therapy include serum sickness (low risk), the possible transmission of a pathogen, and transfusion related acute lung injury (Casadevall 2020). Moreover, convalescent plasma therapy does not provide the active immunity that the body naturally attains after fighting a virus. If the coronavirus is successful in mutating, then the convalescent therapy is rendered useless and will not prevent patients from re-infection. However, by that time, it is likely a vaccine will be available.

Applications of Convalescent Plasma Therapy

Convalescent plasma therapy treats people with symptoms at an early stage. According to one study, 58.3% of patients with SARS who were treated with convalescent plasma therapy within 14 days recovered and were discharged from the hospital, whereas only 15.6% treated after 14 days were discharged from the hospital on the same day (Cheng et al 2004).

One potential application for convalescent plasma serum is temporary immunity for healthcare workers. Individuals who work in the healthcare industry perform vital roles during the coronavirus pandemic. Thus, convalescent plasma may be a critical method for workers to obtain passive immunity to the virus without falling ill. It can also help family members with infected relatives to avoid the virus themselves (Casadevall et al 2020).

Conclusion

In this article, we compare the types and mechanisms of action of potential COVID-19 treatments to determine which drug is best suited to inhibiting the viral disease, with a specific focus on repurposed drugs. In particular the drugs in development that have been most successful thus far in inhibiting the virus were antiviral, repurposed drugs with a track record of safety in treating previous diseases.

Although developing therapies have been highlighted in this article, the need for an effective, safe drug is urgently needed. As of July 2020, no drugs or therapies have been approved by the Food and Drug Administration (FDA) due to insufficient data and adverse side effects from many drugs. For example, emergency use authorization of chloroquine and hydroxychloroquine has been revoked (FDA 2020b).

Remdesivir was shown to be the most promising therapy, as it successfully treated SARS-CoV-2 in vitro, MERS in mice, and SARS-CoV-2 patients in specific case studies. Convalescent plasma serum is an emergency therapy currently that is useful for individual cases, but is not easily scalable. Although an mRNA vaccine is in the making, the possible mutation of SARS-CoV-2 limits the applicability.

In the long term, a study can be focused on the efficacy of remdesivir, hydroxychloroquine, and convalescent plasma therapy, or an mRNA vaccine if the virus were to mutate and cause a second wave of infections. In the future, longitudinal studies that measure long term clinical improvement and immunity could be used to quickly develop novel therapies for future pandemics. The lessons of drug development in this scenario should be applied to future drug design.

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