Drug targets for COVID-19 therapeutics: Ongoing global efforts

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The current global pandemic COVID-19 caused by the SARS-CoV-2 virus has already inflicted insurmountable damage both to the human lives and global economy. There is an immediate need for identification of effective drugs to contain the disastrous virus outbreak. Global efforts are already underway at a war footing to identify the best drug combination to address the disease. In this review, an attempt has been made to understand the SARS-CoV-2 life cycle, and based on this information potential druggable targets against SARS-CoV-2 are summarized. Also, the strategies for ongoing and future drug discovery against the SARS-CoV-2 virus are outlined. Given the urgency to find a definitive cure, ongoing drug repurposing efforts being carried out by various organizations are also described. The unprecedented crisis requires extraordinary efforts from the scientific community to effectively address the issue and prevent further loss of human lives and health.

Keywords. Coronavirus; Covid-19; drug discovery; drug repurposing; drug target; SARS-CoV-2

1. Introduction

The advent of the devastating COVID-19 pandemic in 2019 has left more than 5.5 million people infected and more than 340,000 deaths all over the world (Zhou et al. 2020a; https://www.who.int/emergencies/diseases/novel-coronavirus-2019). These numbers demonstrate the large-scale damage this virus has caused on a global scale. COVID-19, as the World Health Organization (WHO) has designated this disease, is caused by the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) (Du Toit 2020) (https://www.who.int/emergencies/diseases/novel-coronavirus-2019/technical-guidance/naming-the-coronavirus-disease-(covid-2019)-and-the-virus-that-causes-it). Since there is no absolute definitive drug or vaccine available that can contain the spread of this deadly virus, the management strategy for the disease is primarily aimed at treating the symptoms (Jin et al. 2020). Lack of treatment options has only led to an increased number of fatalities due to the disease (Abbas et al. 2020; Down et al. 2020).

Academic labs and drug discovery organizations world over are working tirelessly to evaluate compounds that can inhibit the spread of SARS-CoV-2 in humans. To achieve this it is essential to first identify drug targets and subsequently identify and evaluate compounds and biologics that can effectively engage these targets and inhibit the spread (Alexander et al. 2020a, b; Dong et al. 2020). However, such efforts can be arduous and involve a painstakingly long process. Therefore in parallel, we should also evaluate known antivirals and repurpose them either as single agents or in combinations so that they can effectively contain the spread of the virus (Ahn et al. 2020; Hijikata et al. 2020; Jeon et al. 2020). In order to do this, global concerted efforts are required, and rapid clinical trials need to be conducted to evaluate the role of potential candidate compounds in this particular disease and population setting.

Since the onset of this century, Coronaviruses have created a pandemic-like situation at least at two earlier
events. First was the Severe Acute Respiratory Syndrome (SARS) pandemic at the beginning of the 21st century and then the Middle East Respiratory Syndrome (MERS) outbreak almost a decade before (Al-Omari et al. 2019; Centers for Disease and Prevention 2013; Holmes 2003). Both these pandemics were caused by viruses belonging to the Coronavirus family of viruses (Benvenuto et al. 2020). In fact, the symptoms of SARS and the current COVID-19 pandemic patients are quite similar, reaffirming the fact that both these viruses are quite similar in their genomic constitution and mode of transmission (Kandeel et al. 2020; Kumar et al. 2020; Xie and Chen 2020a). However, since the SARS epidemic, the SARS-CoV-2 virus has undergone mutations (Becerra-Flores and Cardozo 2020; Biswas et al. 2020; Bzowka et al. 2020; Poterico and Mestanza 2020; Yin 2020) and thus the drugs developed against the SARS virus might not very effective in containing the virus spread. In order to understand the drug targets and appreciate the ongoing efforts directed towards the identification of therapies against SARS-CoV-2, it is important to understand the virus biology, mode of transmission and replication cycle. This is especially important since any effective therapy against SARS-CoV-2 should preferably target the stages in the virus life cycle.

In this review, the potential drug targets for drug candidates against SARS-CoV-2 are discussed and an overview of the current status of drug development against SARS-CoV-2 infection is provided. The equally important efforts towards vaccine development are excluded from this review, as this topic is covered in a separate in-depth review (Mukherjee 2020).

1.1 Classification of coronaviruses

SARS-CoV-2 is a member of the Coronavirus (CoV) class of viruses. CoV are essentially positive-stranded RNA viruses and display a crown-like appearance on the surface when observed under an electron microscope. It is due to the presence of this ‘crown-like structure’ that this class of viruses is called Coronaviruses (coronam being the Latin term for crown) (Alanagreh et al. 2020; Rehman et al. 2020). Structurally, these ‘crown-like structures’ are glycoprotein present on the viral envelope which facilitate virus entry in the host cells (Coutard et al. 2020). There are four known subfamilies of coronaviruses, classified as Alphacoronavirus, Betacoronavirus, Gammacoronavirus and Deltacoronavirus (Li et al. 2020a). Although the zoological evolution of coronaviruses is still an active research subject, it is widely accepted that Alpha- and Betacoronaviruses are predominant in bats and rodents whereas Delta- and Gammacoronavirus gene sources are the avian species (Brussow 2020a; Cascella et al. 2020; Coronaviridae Study Group of the International Committee on Taxonomy of 2020).

The causative virus of COVID-19 pandemic, SARS-CoV-2 virus is a part Betacoronavirus subfamily and is believed to have crossed the species barrier to infect humans due to zoonotic transmission (Mackenzie and Smith 2020; Zimmermann and Curtis 2020). The hallmark of coronavirus transcription is the production of multiple sub-genomic RNAs containing sequences corresponding to both genomic ends (Song et al. 2020). These viruses utilize RNA-dependent RNA synthesis to generate mRNAs transcribed by the host genome. Genetically, SARS-COV-2 is a positive-sense, single-stranded RNA virus with a genome size of 30 kb which encodes for two Open Reading Frames (ORFs) (Cer- aolo and Giorgi 2020; Dabravolski and Kavalionak 2020; Yang et al. 2005). These ORFs are designated as 1a and 1b, and code for protease 3ClPro and PLpro. These proteases then cleave the polypeptide into 16 non-structural proteins (Nsp) which are essentially viral enzymes involved in replication and packaging of the virus within the host cell and four structural proteins that contribute to the outer structure of the virus (Jean et al. 2020; McKee et al. 2020; van Boheemen et al. 2012). Like other Coronaviruses, the outer surface of the SARS-CoV-2 virus is made of Spike (S) protein, envelope (E) protein, membrane (M) protein and the Nucleocapsid (N) protein. The M and E proteins are involved in virus morphogenesis and assembly. The Spike protein (S) is at the forefront of infection and interacts with the ACE-2 receptor on the host cell surface thereby promoting virus-cell membrane fusion during initiation of viral infection. The Envelope (E) and Membrane (M) protein constitute the cover outside the viral genetic material. Inside the shell of M and E proteins is the RNA which is guarded by the Nucleocapsid protein (Glebov 2020; Nieto-Torres et al. 2011; Nieto-Torres et al. 2015).

1.2 Molecular basis of disease transmission

It is a well-accepted fact that the SARS-CoV-2 transmission is facilitated by respiratory secretions in the form of droplet/aerosol when a person comes in close contact with the infected person (Guo et al. 2020a, b). Recent reports suggest that the infection can also spread through stool, urine, and respiratory secretions (Casanova et al. 2010; Ding et al. 2020; Wang et al. 2020b).
As soon as the SARS-CoV-2 virus enters the human body, it establishes a cycle of replication by binding to cell types such as enterocytes and pneumocytes. This virus can also infect tubular renal epithelial cells (Bao et al. 2020), immune cells (Annweiler et al. 2020) and cerebral neurons (Bilinska et al. 2020; Xie and Chen 2020b). The Spike protein present on the surface of SARS-CoV-2 is responsible for the primary establishment of host-protein interaction. The Spike protein binds to the Angiotensin-converting enzyme-2 (ACE-2) receptor present on the host cell plasma membrane (Annweiler et al. 2020; Hasan et al. 2020b). Post receptor recognition, the viral genome including the Nucleocapsid is released into the cytoplasm of the host cell as shown in figure 1. As mentioned above, the SARS-CoV-2 viral genome has two ORFs: 1a and 1b. These ORFs translate to two polypeptides (PP) Pp1a and Pp1b which in turn hijack the host cellular ribosomes for their own translational process, thereby making a replication-transcription complex (Bojkova et al. 2020; Dong et al. 2020).

The polypeptide is processed by proteases and this processing results in 16 Non-Structural Proteins (NSPs), and each of these has its own specific function in replication and transcription (Hillen et al. 2020; te Velthuis et al. 2012). NSP1 and 2 are involved in the suppression of host gene expression. NSP5 is involved in replication whereas NSP4 and 6 are transmembrane proteins (Kandeel et al. 2020; Stobart et al. 2013; Zhang et al. 2020b). NSP7 and 8 act as primases, while NSP9 is an RNA-binding protein. The dimeric form of NSP9 is critical for viral infection, and disruption of this dimerization could be a potential strategy to inhibit the infection. NSP10 is involved in replication and NSP12 is an RNA-dependent RNA polymerase. NSP12 has helicase activity, NSP14 demonstrates exonuclease activity, and NSP15 has endoribonuclease activity, while NSP16 possesses methyltransferase activity (Athmer et al. 2017; Hillen et al. 2020; Hu et al. 2009; Jia et al. 2019; Mirza and Froeyen 2020; Neogi et al. 2020).

These NSPs with the help of host machinery translate the RNA coding for the viral Spike, Envelope, Nucleocapsid and Membrane proteins. These proteins then enter the endoplasmic reticulum (ER) – golgi apparatus and are involved in viral assembly and packaging. The viral genome binds to the Nucleocapsid (N) protein and results in the formation of the

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Figure 1. Stages of SARS-CoV-2 life cycle. Along with the stages arrows point to drugs and candidate drugs active against the drug targets.
As depicted in figure 1, Coronaviruses exploit the host’s endosomal pathway to gain entry in the host cell. As such the virus entry into the host cell is an energetically unfavorable process (Brielle et al. 2020), but viruses are able to overcome this barrier due to the low pH environment and pH-dependent endosomal cysteine protease (Du et al. 2020; Simmonds et al. 2011; Zhang et al. 2019). Other host proteases, such as transmembrane protease serine 2 (TMPRSS2) and TMPRSS11D (also known as airway trypsin-like protease), are involved in the processing of the Spike protein into its constituent subunits S1 and S2 and promote virus entry at the plasma membrane of the host (Iwata-Yoshikawa et al. 2019; Maggio and Corsini 2020; Matsuyama et al. 2010). Agents that modify the pH or inhibit these proteases can be potential drug targets for anti-coronavirus therapy (Baglivo et al. 2020; Bein et al. 2020). Finally, the virus particle is assembled, and it again exploits the host’s exosomal pathway and fuses with the plasma membrane resulting in the release of virus particles into the extracellular region. Upon infection, the viral load increases in the host body and this results in an increase in pro-inflammatory cytokines (Alosaimi et al. 2020; Conti et al. 2020; Magro 2020) and chemokines (Alosaimi et al. 2020; Channappanavar and Perlman 2017; Gralinski et al. 2018; Skinner et al. 2019), which have the potential to damage the lung tissue (Tanaka et al. 2013), leading to deterioration of lung function, and finally lung failure (Brussow 2020b).

2. Approaches for drug discovery targeting SARS-CoV-2

Antiviral drugs targeting the SARS-CoV-2 can be classified into two major classes, with the first group targeting virus–host interactions or inhibiting viral assembly (Zhou et al. 2020b). The other approach would include drugs that modulate broad-spectrum host innate immune responses or interfere with signaling pathways involved in viral replication. These drugs may be capable of engaging host receptors or proteases utilized for viral entry or may impact the endocytosis pathway (2020; Channappanavar and Perlman 2017; Dong et al. 2020; Hiji kata et al. 2020; Jeon et al. 2020; Liu et al. 2020b; McKee et al. 2020; Sanders et al. 2020).

Essentially, three general approaches can be utilized for screening of antiviral compounds capable of inhibiting the COVID-19 infection:

2.1 Repurposing of antiviral compounds

The first approach is to check existing antiviral compounds and molecules and estimate their effect on viral replication and packaging. Molecules like interferon alpha, beta and gamma, ribavirin and chemical inhibitors of cyclophilin 8 (Ma-Lauer et al. 2020; Zhang et al. 2020a) can be evaluated for their antiviral activities. These known antivirals have a strategic advantage since they are in active clinical use and their pharmacokinetic and pharmacodynamic properties are well studied. On the flip side, such drugs might lack specificity against SARS-CoV-2, and thus may have severe adverse effects (Ahn et al. 2020; Busquet et al. 2020).

2.2 High-throughput screening of compounds

The second approach involves screening of chemical libraries that constitute compounds targeting transcriptional machinery of various cell lines. High-throughput screening technology has the potential to screen large libraries of ‘drug-likely’ chemical compounds for chemical entities having antiviral effects. Even libraries of existing drugs can be screened to support drug repurposing efforts, thereby leading to the identification of new functions of many known drug molecules (Berdigaliyev and Aljofan 2020; de Wilde et al. 2014; Dyall et al. 2014; Kindrachuk et al. 2015; Lu et al. 2014). Marketed drugs like Lopinavir/ritonavir which was earlier intended to be used in anti-HIV therapy and was subsequently used to treat SARS have emerged as a result of the successful execution of such screening programs (Chu et al. 2004; Cvetkovic and Goa 2003). However, a serious disadvantage of this approach is that the ‘hits’ obtained from such screenings may have immunosuppressive or cytotoxic effects at higher concentrations. Another disadvantage is that the half-maximal effective concentration (EC50) of drugs required to be effective against the SARS-CoV-2 infection might exceed the highest serum concentration (Cmax) levels that can be achieved by pharmacological dosing (Mirza and Froeyen 2020).

2.3 Inhibition of SARS-CoV-2 replication mediated by siRNA

The third approach could involve the development of specific novel agents resulting from strong basic research around the genomic and biophysical
understanding of the SARS-CoV-2 life cycle. siRNA molecules or inhibitors that have the capability to inhibit specific viral enzymes involved in viral replication cycle, or monoclonal antibodies targeting the host receptor ACE-2 could be the result of such an endeavor (Hasan et al. 2020b). Such an approach has the potential to return a large number of virus-specific promising therapies against the SARS-CoV-2 virus. One of the major hurdles in such therapies is the specific drug delivery of these molecules and a lack of understanding of siRNA-based therapy (Lesch et al. 2019; Sohrab et al. 2018).

3. Approaches for drug repurposing

Due to the immense financial implications, resource implications and time implications involved in novel drug discovery process, pharmaceutical companies and researchers in the field are inclining towards and relying on ‘Drug Repurposing’ efforts (Ashburn and Thor 2004). As the name suggests, using this approach, a known drug or an investigational drug candidate drug is studied for new uses that are beyond their scope of original intended medical indication. Some researchers and institutions also term ‘Drug repurposing’ as Drug Repositioning, Drug re-profiling or Drug re-tasking depending on the final outcome of studies (Scannell et al. 2012).

This strategy can considerably lower the risk of failure of investigational drugs since the toxicity profile of the drug is already well evaluated and in most cases its adverse effects are well documented (Pammolli et al. 2011). More importantly, this strategy can help save time involved in Drug development since the preclinical testing, safety assessment and even formulation development has already been completed for repurposed drugs (Nosengo 2016). Also, since the drugs have undergone clinical trials earlier, repurposed drugs can potentially skip phases 1 and 2 trials, and based on therapeutic indication and adverse effect profile, repurposed drugs can be considered directly for large scale phase 3 trials (Brekenridge and Jacob 2019). Another important use of repurposed drugs is in drug combination therapy as the use of drugs can be modulated by effective novel drug combinations (Urquhart 2018). Also, initial drug repurposing experiments do not require elaborate laboratory settings and most often new indications and combinations can be postulated using in-silico approaches (Hurle 2013). At the same time, this exciting approach suffers from some pitfalls and cautious consideration is required before positioning a drug for a new therapeutic indication. Mostly drug repurposing studies are driven by drug targets and identified drug targets might demonstrate polypharmacology thereby leading to adverse side effects (Aguilera et al. 2019; Cheng 2019; Karuppasamy et al. 2019). Also in experimental screening studies, usually a higher dose is used and this might lead to misidentification of a compound as active while its corresponding pharmacological dose might be toxic. At the same time the effective plasma concentrations of drugs might be higher than the maximum tolerable pharmacological dose. Moreover, a substantial structural modification of a drug might change its toxicity profile thereby warranting fresh toxicity studies (Colson and Raoult 2016; Strittmatter 2014).

Many pharmaceutical companies are still shy of completely harnessing the potential of drug repurposing due to the attached intellectual property ‘burden’ and the associated costs (Farha and Brown 2019; Fetro and Scherman 2020; Talevi and Bellera 2020; Yildirim et al. 2016). Nevertheless, the drug repurposing approaches can be broadly divided into two broad categories: (1) the computational approach, here bioinformatics tools are used to identify new indications for drugs already in use and the approach relies on ‘Big data’ analysis and Artificial Intelligence (AI) (Issa et al. 2020; Ke et al. 2020; Lee and Chen 2020). (2) The experimental approach, this is a more traditional approach and relies on in vitro experiments to postulate new applications of drugs (Cha et al. 2018; Martorana et al. 2016). Figure 2 shows a hierarchical view of approaches being used for drug repurposing

3.1 Computational approach

Computational approaches for Drug repurposing are largely data-driven and involve a systematic analysis of gene expression, chemical structure, proteomic data or electronic healthcare records. The most commonly used computational approaches include Signature matching (Koudijs et al. 2019), computational molecular docking (Pinzi and Rastelli 2019; Trosset and Cave 2019), Genomic association analysis (Cheng et al. 2019; Nabirotchkin et al. 2020), Pathway or network mapping (Infante et al. 2020; Zhou et al. 2020b) and retrospective analysis using electronic health records of approved drugs (Karaman and Sippl 2019; Pereira et al. 2020; Shi et al. 2020b).

3.1.1 ‘Signature’ matching: Every drug or investigational drug candidate possesses some unique
characteristics or ‘signature’ like its transcriptomic effect profile, structural or adverse effect profile and by matching these characteristics/signatures with another disease or drug, repurposing can be achieved (Karaman and Sippl 2019; Koudijs et al. 2019). Using this approach for drug repurposing researchers rely on either drug–disease comparison or drug–drug comparison. In the first case, ‘signatures’ of a particular drug’s gene expression profile before and after treatment is compared with the differential gene expression profile obtained similarly by comparing profiles of healthy with the diseased (Jhamb et al. 2019; Khosravi et al. 2019). One such drug repurposing example that has taken this approach is the topiramate which is normally used as an antiepileptic drug and acts as an agonist for Gamma amino Butyric acid (GABA) activity (Dudley 2011; Dudley et al. 2011). Based on studies by Dudley and co-workers using the drug-disease approach, it was established that topiramate can also be used for inflammatory bowel disease (IBD) as it had signatures comparable to prednisolone, the treatment of choice for IBD (Dudley 2011). The drug–drug similarity approach identifies a common mechanism of action for drugs that belong to different classes and are usually structurally dissimilar (Bakal et al. 2019; Wu et al. 2019; Yang et al. 2019).

3.1.2 Computational molecular docking: Computational molecular docking is an indispensable tool for Drug repurposing activities (Chen et al. 2012; Cicaloni et al. 2019). Here, by using structure-based computational strategy, binding efficiency is predicted between the drug and the target molecule (Elfiky 2020). With this method large- and small-scale screens can be conducted with known drugs against a disease target (Brindha et al. 2016; Kitchen et al. 2004). However, this technique has its own limitations, such as, for many targets 3D structure is not elucidated or there is a lack of available screen-able macromolecular database that can provide structural information for a varied molecular class of drug (Xia 2017; Zhou et al. 2019).

3.1.3 Network mapping: Molecular Pathway or Network mapping is one of the most commonly used methods for drug repurposing. Many identified drug targets are not directly druggable as their direct inhibition might lead to severe adverse effects and thus network mapping can inform about the upstream or downstream druggable targets thereby enabling drug repurposing (Oulas et al. 2019; Zhou et al. 2020b). Based on Gene expression pattern and disease pathology, drug and disease networks can be created using network mapping tools (Gns et al. 2019; Janardhan et al. 2018). Such maps and networks can open enormous possibilities for drug repurposing.

3.2 Artificial intelligence and drug repurposing

Advances in Information technology with Artificial Intelligence (AI) and ‘Big-data analysis’ are revolutionizing drug repurposing efforts and studies (Mucke 2018). With the help of machine learning tools, computational algorithms can be developed that can predict new drug target engagement with far greater accuracy than earlier used methods (Alvarez-Machancoses et al. 2019).
2020; Kuang et al. 2019; Luscher Dias et al. 2020; Nabirotchkin et al. 2020). Huge data generated by High-throughput Next Gen Sequencing (NGS) from numerous patients when combined with disease characteristics and treatment options can lead to the identification of new disease biomarkers and drug targets (Stupnikov et al. 2018; Zai et al. 2018). AI-driven supervised machine learning algorithms can implement multomics and multitask learning to facilitate drug response elicited by engagement of multiple drug targets (Nascimento et al. 2019; Nath et al. 2018; Saberian et al. 2019; Zhao and So 2019). The impact of this technology can be appreciated by evaluating a recent study where a computational methodology was developed that can utilize heterogeneous data from previously described Drug Target interactions to predict new interactions with even greater accuracy. The methodology known as ‘deepDTnet’ can integrate networks connecting multiple drugs with drug targets and disease database with the help of deep learning (a form of machine learning based on AI) (Brasil et al. 2019; Monteiro et al. 2020; Wen et al. 2017; Zeng et al. 2020).

3.3 Drug repurposing in antiviral drug discovery

The approaches for drug repurposing can also be utilized to scout for drugs that can be effective antivirals. By screening the database of small molecules against viral drug targets using computational methods, drugs or molecules can be identified may possess antiviral activity (Pizzorno et al. 2019). Essentially three different scenarios can be discussed to facilitate antiviral drug repurposing: (1) Known target/new virus: In this scenario, an established antiviral drug targeting a specific protein/pathway is found to possess antiviral activity against other viruses. Known viral RNA polymerase Favipiravir and sofosbuvir were initially developed for the treatment of *Influenza virus* and *Hepatitis C virus* (HCV) infection and were repurposed for treatment of *Ebola virus* (Bai and Hsu 2019; Du et al. 2020; Johansen et al. 2015; Muthaiyan et al. 2020; Salata et al. 2019; Veljkovic et al. 2015) and *Zika virus* infection (Abbasi 2016; Bernatchez et al. 2020; Montes-Grajales et al. 2020; Mumtaz et al. 2017). (2) Known target/new indication: In this scenario, the pharmacological target is implicated to be affected in a new pathogenic infection. In such cases, drugs targeting these proteins can be repurposed as effective antiviral agents. One such example is about the repurposing of anti-cancer agent Imatinib. Cellular Abelson (ABL) kinase is the target of Imatinib and the same was shown to be active against coronaviruses (Ananthula et al. 2018; Coleman et al. 2016; Giuliani et al. 2018). (3) New target/new indication: This scenario occurs when an approved drug with a specific target is found to target additional viral proteins or targets. Many antimicrobial agents like teicoplanin (Aziz et al. 2018; Zhou et al. 2016), ivermectin (Chaccour and Rabinovich 2019; Rabinovich 2018), itraconazole (Alhakamy and Md 2019; Pace et al. 2016; Schloer et al. 2019; Tsubamoto et al. 2017) and nitazoxanide (Cao et al. 2017; Rossignol 2016) were also found to be active against some viral infections.

4. Lessons from SARS: pharmacological interventions

Lessons from SARS and MERS epidemic can be used to develop some therapies for SARS-CoV-2 infection (Zumla et al. 2016). Previously used antiviral drugs like oseltamivir, peramivir, zanamivir, ganciclovir, acyclovir and ribavirin are not recommended for COVI-19 treatment (Li et al. 2020c; Wang et al. 2020b). Also, systemic corticosteroid treatment such as methylprednisolone is not appreciated as a treatment option for SARS-CoV-2 infected patients (Veronese et al. 2020). In such a scenario, given the similarity of SARS-CoV and MERS virus along with the SARS-CoV-2 virus, an insight into the treatment options available for SARS and MERS could provide valuable inspirations for Drug discovery and repurposing (Zumla et al. 2016). However, for both SARS and MERS, no specific treatment was recommended; rather WHO recommended managing the disease based on patients’ symptoms (Graham et al. 2013).

4.1 Ribavirin and corticosteroids

In the year 2003, the SARS pandemic, like COVID-19, caught the world by surprise. Early days in the SARS pandemic patients in Hong Kong and Canada were treated with a combination of ribavirin and corticosteroids (Rainer 2004; Tsang et al. 2003). However, subsequent reports indicated towards ribavirin’s high rate of toxicity and lack of ability to control the infection spread (Booth and Stewart 2005; Sung et al. 2004; Wong et al. 2003). Use of corticosteroid, methylprednisolone is controversial as far as SARS was concerned. In multiple cases, dose-related toxicity was observed. The lower dose of methylprednisolone,
250–500mg/day demonstrated some improvement on a subset of critical SARS patients however a prolonged usage in the absence of any specific antimicrobial agent predisposed the patients to disseminated fungal infection (Chan et al. 2003a, b; Tsang and Seto 2004; Tsang and Lam 2003) and avascular necrosis (Chan et al. 2003a, b). Based on localized, single-center uncontrolled clinical studies, it was recommended that Corticosteroids should only be used as a ‘rescue therapy’ and not as a treatment as it might impair the host viral clearance (Sung et al. 2004).

4.2 Interferons

Viral infections such as hepatitis B and C have been successfully treated by Interferon treatment (Christian et al. 2004). Since Interferon is also broad-spectrum antiviral, it was used in some single-center, open-labelled, uncontrolled clinical settings against SARS. In these small trials, patients were stable post-treatment with Interferon in combination with corticosteroids. The results pointed out that perhaps with interferon treatment the lung deterioration can be delayed (although this could not be proven statistically) (Zhao et al. 2003). Also, post this treatment, improved oxygen saturation levels and lower creatine phosphokinase levels were observed in critically ill patients. However, this warranted properly designed clinical trials globally (Loutfy et al. 2003).

4.3 Ritonavir and lopinavir

A combination of viral protease inhibitor, ritonavir 400 mg and lopinavir 100 mg, when administered orally with 12 h interval for 10 to 14 days as standard therapy, yielded the most promising outcome in Hong Kong–based clinical studies (Chan et al. 2003a, b). Here the subjects showed a reduction in steroid dependency and nosocomial infections. At the same time reduction in viral load and concomitant increase in peripheral lymphocyte count was observed. This combination appears to be promising and even for COVID-19 as well this combination is being tested in clinical trials. However, some serious adverse effects were also reported from patients undergoing treatment for SARS infection with this combination. Subjects were observed to suffer from pancreatitis, diarrhea, abdominal pain and liver dysfunction among other associated discomforts like abdominal pain, asthenia, headache, nausea, insomnia and skin rash (Chu et al. 2004).

5. Key CoV targets for drug development and available therapies

As of date, no specific and definite antiviral drug is available for the treatment of CoV-associated pathologies (Barlow et al. 2020; Martinez 2020a; McKee et al. 2020; Wu et al. 2020a). However, some therapeutic agents based on the biology of the virus and some potential drug targets have been identified.

Since the onset of previous global coronavirus pandemics like MERS and SARS, considerable research has gone into the search for suitable drug targets and subsequent drug candidates (Lou et al. 2020). Based on this and life cycle stages of SARS-CoV virus, the therapies that have the potential to act on coronaviruses can be divided into five broad categories/approaches:

1. Inhibition of virus binding to the host receptor by either chemical compounds or monoclonal antibodies. These agents can block or effectively engage the host’s cell surface receptor thereby preventing virus binding and subsequent internalization (Li et al. 2019; Salata et al. 2019; Shang et al. 2020; Tortorici and Veesler 2019).

2. Target the viral endocytosis. This process enables the virus to enter the host cell and release its genetic material for further replication and therefore blocking virus-mediated endocytosis is a logical target for antiviral therapy (Baglivo et al. 2020; Delvecchio et al. 2016; Glebov 2020; Omotade and Roy 2019; Praveen et al. 2020).

3. Neutralize the virus particle. This can be accomplished by the compounds and antibodies acting on enzymes or functional proteins critical to virus replication and multiplication (Algaissi and Hashem 2020; Goo et al. 2020; Pinto et al. 2020; Wang et al. 2020a; Wu et al. 2020b).

4. Targeting the viral structural proteins like the membrane, envelope and Nucleocapsid protein thereby blocking virus repackaging (Hijikata et al. 2020; Kato et al. 2019; Mirza and Froeyen 2020; Saha et al. 2020; Zhang et al. 2020b).

5. Restoration of host’s innate immunity by the agents capable of producing virulent factors (Azkur et al. 2020; Casanova et al. 2020; Encinar and Menendez 2020; Gemmati et al. 2020; Mantlo et al. 2020; Tufan et al. 2020).

Table 1 summarizes the drug targets and compounds active against SARS-CoV-2, their current development status and the pros and cons of the proposed therapy.
**Table 1. List of probable drug targets against SARS-CoV-2 and compounds/agents effective against these targets**

| Targeted viral components | Examples | Mechanism of action | Status | Pros | Cons |
|----------------------------|----------|---------------------|--------|------|------|
| **Inhibition of SARS-CoV-2 fusion/entry** | | | | | |
| RBD of the S1 subunit of S | REGN3051 and REGN3048 mAbs | Antibodies target the RBD domain of the S1 subunit | Preclinical | Efficacy demonstrated *in vitro* | Narrow spectrum |
| S2 subunit of S | HR2P and P1 peptides | Antiviral peptides that inhibit fusion of S with host cell receptor | Preclinical | anti-HIV peptid has been marketed | Narrow spectrum |
| TMPRSS2 | Camostat Mesylate | TMPRSS2 inhibitor that blocks the TMPRSS2-entry pathway | Marketed | Promising results *in vitro*. Effect on patients need to be tested | Broad spectrum. Developed for therapy against SARS |
| **Inhibition of endocytosis** | | | | | |
| Endosomal acidification | chloroquine | An antimalarial that sequesters protons in lysosomes to increase the intracellular pH | Marketed | Broad spectrum; many SARS-CoV-2 affected patients show good recovery | No concrete clinical data to suggest efficacy |
| Clathrin-mediated endocytosis | Oubain | ATP1A1- binding steroids; inhibits clathrin-mediated endocytosis | Marketed | Active against MERS-CoV | May have risk of cardiac toxicity |
| **Inhibition of Viral Enzymes** | | | | | |
| 3CLpro | Lopinavir | Inhibits 3CLpro activity | Marketed | Broad spectrum | Toxicity Adverse impact on immune system |
| PLpro | GRL0617 | Inhibits PLpro activity | Preclinical | Narrow spectrum | No animal or clinical data available Side effects are common and may be severe with high dose regimens |
| RdRp | Remdesivir | Nucleotide analogue; Broad spectrum: many viral infections, inhibits viral RNA synthesis | Marketed | Active against SARS-CoV and MERS-CoV at high doses *in vitro* | Side effects are common and may be severe with high dose regimens |
| **Inhibition of Viral envelope (E), membrane (M), Nucleocapsid (N) and accessory proteins** | | | | | |
| E and M Protein | siRNA | Short chains of dsRNA that interfere with the expression of SARS-CoV proteins | Preclinical | Promising *in vitro* studies. | Optimal delivery method in humans uncertain |
| N Protein | Pj34 | Impairs viral replication | Preclinical | Narrow spectrum Effective *in vitro* and in animal studies | Optimal delivery method in humans is uncertain |
| Membrane and Accessory proteins | Lj001 and JL103 | Induces membrane damage | Preclinical | Broad spectrum | Anti-CoV activity yet to be demonstrated Unstable physiologically and photo dependent |

Also, the present development stage as well as the pros and cons of therapies are listed

5.1 **Inhibition of SARS-CoV-2 fusion/entry**

SARS-CoV-2 utilizes the spike protein present on the viral surface to gain entry into the host cells. The protein–protein interaction that takes place between the subunits of the spike protein and the active site of the ACE-2 receptor can be targeted to identify an effective treatment strategy (Wrapp 2020). Like other viruses, the coronaviruses also outsmart drugs targeted against them by constantly mutating the active site of spike protein (Becerra-Flores and Cardozo 2020; Chang et al. 2020; Goo et al. 2020; Qing et al. 2020). As a
result, the SARS-CoV-2 spike protein recognizes the ACE-2 receptor more efficiently than the previously studied SARS virus (Albini et al. 2020; Chen et al. 2020; Dediego et al. 2008; Hasan et al. 2020a; Mathewson et al. 2008). Specifically, the Receptor Binding Domain (RBD) of the spike protein is a critical target for antibody-mediated disruption of binding. Many antibodies demonstrating the ability to disrupt this binding are in preclinical stages of development (Chen et al. 2020; Tai et al. 2020; Tian et al. 2020). Another strategy is to engage and overwhelm the ACE-2 receptor with recombinant human ACE-2 which is normally present on the cell surface. So delivering an excess of the soluble ACE2 helps to neutralize the virus, by competitively binding to SARS-CoV-2 (rhACE2; GSK2586881) (Ameratunga et al. 2020). An open-labeled, randomized, controlled pilot clinical trial is in progress to evaluate this approach (NCT04287686).

Apart from the ACE-2 receptor, cellular serine protease TMPRSS2 also plays an important role in facilitating the entry of the virus in host cells (Hoffmann 2020). A clinically proven chemical inhibitor of TMPRSS2, Camostat Mesylate is also able to significantly reduce infection in cell lines of human lung origin (McKee et al. 2020; Rahman et al. 2020; Shirato et al. 2013; Sternberg et al. 2020). In addition to this, the heptad repeat 1 (HR1) and heptad repeat 2 (HR2) present on the SARS-CoV-2 have also been implicated in the facilitation of cell membrane fusion. HR2-derived peptides exhibit effective fusion inhibitory activity (Bosch et al. 2008; Huang et al. 2019; Wang et al. 2019; Xia et al. 2019a; Xia et al. 2019b).

5.2 Inhibition of endocytosis

It is known that post fusion of the spike protein with ACE-2 receptor, the virus is ingested in the cells in a pH and receptor-dependent endocytosis (Chu et al. 2006; Glebov 2020). Targeting endocytosis can be another potential strategy towards developing potential drug candidates against SARS-CoV-2. Clathrin-mediated endocytosis is regulated by AP-2-associated protein kinase 1 (AAK1) (Uitdehaag et al. 2019). Based on library screening, Janus kinase inhibitor Baricitinib was identified as a possible candidate drug for SARS-CoV-2 (Baglivo et al. 2020; Cantini et al. 2020; Lo Caputo et al. 2020). Also, Oubain, another inhibitor of clathrin-mediated, is being tested for its efficacy in drug trials for SARS-CoV-2 positive patients (Sisk et al. 2018). Recently, Chloroquine and its derivative hydroxychloroquine have garnered great interest as a therapy against SARS-CoV-2 infection (Alexander et al. 2020a; Ali and Grant-Kels 2020; Arnold and Buckner 2020; Ballout et al. 2020; Costanzo et al. 2020). Several clinical trials are underway to assess the contribution of chloroquine therapy in inhibiting SARS-COV-2 viral progression (Keshhtkar-Jahromi and Bavari 2020). Also, it was shown in vitro, that a derivative of Chloroquine, hydroxychloroquine (EC50 = 0.72μM) is far more potent in inhibiting SARS-CoV-2 infection than Chloroquine (EC50 = 5.47 μM) (Savarino et al. 2003; Yao et al. 2020). Although the exact molecular mechanism of hydroxychloroquine in the treatment of COVID-19 remains elusive, it is believed that hydroxychloroquine may impair endosome-mediated viral entry or the late stages of viral replication (Devaux et al. 2020).

5.3 Inhibition of viral enzymes

As a result of aggressive antiviral drug development and discovery programs undertaken in the past, multiple drugs have been developed against viral proteases, polymerases and helicases (Martinez 2020b). Drugs developed against other viral diseases such as Remdesivir (Wang 2020), Flavipiravir (Li et al. 2020b), Lopinavir/Ritonavir (Beck et al. 2020; Costanzo et al. 2020; Gyebi et al. 2020; Schoergenhofer et al. 2020) are presently being evaluated in clinical trials for their efficacy in containing the COVID-19 pandemic. Remdesivir, an antiviral drug developed against Ebola, is an adenosine analog which inserts into viral RNA chains by RNA-dependent RNA polymerases (RdRps) and results in premature transcription termination (Cao et al. 2020; Gordon et al. 2020). Similarly, Favipiravir and Ribavirin are guanine analogs and are approved for some viral diseases (Costanzo et al. 2020; Fan et al. 2020). EIDD-2801 is another oral antiviral drug that acts as a nucleotide analog, like Remdesivir, albeit with lower EC50, and is orally administrable (Agostini et al. 2019). Other antiviral compounds Lopinavir and Ritonavir are protease inhibitors that target 3C–like protease (3CLpro) of SARS-CoV-2 (Bhatnagar et al. 2020). The main coronavirus protease, 3CLpro is responsible for processing the polypeptide to NSPs. Using high-throughput screening for compounds against 3CLpro, four molecules, viz. Prulifloxacin, Tegobuvir, Bictegravir and Nelfinavir, were identified (Barnard et al. 2006; De Clercq 2006; Liu et al. 2020b).
5.4 Inhibition of viral envelope, membrane, nucleocapsid and accessory proteins

SARS-CoV-2 envelope (E), membrane (M) and Nucleocapsid (N) protein are critical for virus survival and propagation, and therefore such structural proteins are the best drug targets. Since these viral proteins are structurally very different from the host proteins, drug targeting these proteins will have minimal adverse effects. Apart from protecting the viral genome, these structural proteins are also involved in suppressing the host immune system, thereby providing the virus a strategic advantage over the host (Bojkova et al. 2020; Borgio et al. 2020; Cherian et al. 2020). The N protein acts to suppress RNA silencing and suppresses RNA interference-mediated by siRNA. Therefore many siRNA based therapeutics target viral E, M and N protein translation and inhibit viral replication, at least in vitro (Nur et al. 2015; Sohrab et al. 2018; Song et al. 2019). However, siRNA-based therapies are still not available for human use due to inherent stability issues and the unavailability of reliable delivery methods (De Clercq 2006).

The E protein also serves as an ion channel and this action is inhibited by hexamethylenamine amiloride (Per-vushin et al. 2009). Another chemical inhibitor PJ34 targets the unique ribonucleotide-binding pocket at the N-terminal domain of N protein (Lin et al. 2014). It is important to note that most of these inhibitors were designed against the SARS virus; due to the mutations in the SARS-CoV-2 virus, such inhibitors may not be as effective in fighting against the ongoing COVID-19 pandemic.

LJ001 and LJ003 are broad-spectrum antiviral compounds that not only inhibit viral entry in the host cells but also damage the viral membrane by producing singlet oxygen molecules. Unfortunately, LJ001 is physiologically unstable and is photo-dependent (Barlow et al. 2020). Nevertheless, LJ001 defines a new class of antiviral compounds, and further research into this class of compounds will yield encouraging results.

5.5 Suppression of excessive inflammatory response

A well-orchestrated cytokine response is critical for the host immune response. It has been reported that some SARS-CoV-2 infected patients demonstrate a hyper-inflammatory response, possibly due to deregulated cytokine response. It was reported that COVID-19 patients in the ICU had high cytokines in plasma when compared with non-ICU patients, suggesting that cytokine dysregulation is involved in the severe form of COVID-19 disease (Channappanavar and Perlman 2020; Liu et al. 2020c). Additionally, SARS-CoV-2-infected patients admitted in ICU display increased levels of GM-CSF and IL6+CD4+T cells when compared to ICU naı¨ve patients (Boettcher et al. 2007). The above facts point to the possibility that inhibition of excessive inflammatory response might reduce the severity of COVID-19 disease. Corticosteroids are known to have excellent pharmacological potential in suppressing systemic inflammation (Liu et al. 2020a; Zha et al. 2020). However, their use in COVID-19 patients is still debatable and requires a detailed study.

It has been demonstrated that after the onset of SARS-CoV-2 infection, CD4+T Cells are activated to produce GM-CSF and other inflammatory cytokines, thus resulting in further induction of CD14+CD16+ monocytes with high expression of interleukin 6 (IL-6) (Conti et al. 2020; Liu et al. 2020a). This observation leads to the possibility that by blocking the IL-6 receptor we could potentially reduce immune stress caused by SARS-CoV-2. In line with this observation, a multicenter, randomized, controlled clinical trial is currently underway using an IL-6 receptor-specific antibody Tocilizumab (Li et al. 2020d) (NCT04315480).

Another recent advance in COVID-19 treatments is the Convalescent plasma treatment. With infection rates growing and no specific therapy available, therapy with convalescent plasma (CP) has been proposed as a principal treatment. In this therapy, the plasma obtained from a donor recovered from the disease is used to develop humoral immunity against SARS-CoV-2-infected patients. The plasma from the donor patient acts as a source of human antibodies against the infection (Jawhara 2020; Shi et al. 2020a, b). However, large scale human trials need to be conducted to better understand and evaluate CP as a method of treatment for COVID-19.

6. Current efforts from top pharmaceutical companies

Many pharmaceutical giants have now jumped into the race to find a drug for SARS-CoV-2 infected patients. Given the high number of fatalities across the globe, even regulatory authorities are giving rapid approvals to conduct clinical trials for promising candidate drugs. Table 2 shows a list of companies that are conducting clinical trials or are seeking approval from regulatory
authorities to conduct trials. Since the onset of the SARS epidemic, much knowledge was generated about drug targets and some candidate molecules were developed as well (Kumar et al. 2017). However, these molecules could not be taken to clinical trials since there were not enough patients suffering from SARS virus by the time these drugs were developed. Nevertheless, this information is of tremendous use since SARS–CoV and SARS-CoV-2 share striking similarities in the genome, replication cycle and even symptoms experienced by patients (Su and Lai 2020). Systemic genomic comparisons have revealed a striking 79% similarity at the nucleotide level between SARS-CoV-2 and SARS-CoV. However, only 72% nucleotide similarity was observed in the spike (S) protein of both the viruses (Zhang and Holmes 2020). At the biochemical level both the virus display preferential binding to the ACE-2 receptor. Even at the clinical level, the chest X-rays of patients infected with either SARS-CoV or SARS-CoV-2 display multilobar ground glass like opacities. Similarly the CT scan of patients infected with either virus display lobar consolidations (Ceccarelli et al. 2020).

However, since the SARS epidemic, the virus has mutated considerably, and as a result, it now has the Spike protein which is quite different from the previous version. This fact makes efforts to find drugs that inhibit virus entry to host cells quite difficult.

### Table 2. List of companies actively involved in finding a drug to treat SARS-CoV-2 patients

| Company/organization | Candidate drug            | Development phase | Current status and plans                                                                                                                                                                                                 | Timelines                           |
|----------------------|---------------------------|-------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------|
| Gilead               | Remdesivir                | III               | Remdesivir is now being tested in five Covid-19 clinical trials that have been set up at lightning speed                                                                                                                   | CT is anticipated to be completed by end of April 2020 |
| Sanofi               | Hydroxychloroquine        | Preclinical       | Conduct additional CTs and supply millions of doses of an existing anti-malaria product                                                                                                                                       | N.A.                                |
| Abbvie               | Lopinavir/ritonavir        | Preclinical       | Collaboration ongoing with select health authorities and institutions globally to determine antiviral activity against SARS-CoV-2                                                                                     | N.A.                                |
| Regeneron            | Monoclonal antibody therapy | Preclinical       | Aiming to select the top 2 antibodies for a cocktail therapy, which can either be administered to at-risk -vaccine naïve population or as treatment for those already infected                                                  | Potential to enter human CT by early summer 2020 |
| Ascleitis            | Combination of two antivirals | I                | The Chinese company is testing a combination of antivirals, developed against HIV and the other approved for hepatitis C                                                                                                 | N.A.                                |
| Takeda               | Polyclonal antibody therapy | Preclinical       | Collaboration with several health and regulatory agencies and health care partners across the globe on polyclonal antibody TAK-888                                                                                   | Program initiated in March 2020     |
| Lilly                | Antibody drug             | Preclinical       | Eli Lilly developing antibody treatments for coronavirus infection. Using a blood sample from a coronavirus survivor Partner company AbCellera identified more than 500 antibodies that might protect against the virus | CTs in humans to be started in the next four months of 2020 |

The information was collected from the company web sites or press release. CT Clinical Trial, N.A. status not known
Companies are also relying on drug repurposing (Beck et al. 2020; Wang et al. 2020), like chloroquine from Sanofi is planned to be tested in Coronavirus patients world over. Meanwhile, other companies like Abbvie, Gilead and Regeneron are testing known antiviral in combinations in patients affected with the SARS-CoV-2 virus (https://www.abbvie.com/coronavirus.html). This approach provides a strategic advantage to the ongoing efforts, as the pharmacological effect of single drugs is well-studied on the human body. Also, we know the exact mechanism of action and dose regimen for these antivirals. Now using them in combination to inhibit more than 2 drug targets can be a winning combination (Borges do Nascimento et al. 2020). Globally, scientists and health authorities are eagerly waiting to interpret the results obtained from these trials. In the meantime, companies like Takeda and Lilly are working on antibody therapy, and evaluating the efficacy of therapeutic molecules at breakneck speed. Under the aegis of WHO, ‘SOLIDARITY’ clinical trial is underway to evaluate the treatment opportunities available for COVID-19 patients. The trial is being conducted simultaneously in 30 countries and under this trial, four treatment options are being compared against the standard care options for SARS-CoV-2-infected patients. The trial will test the efficacies of Remdesivir and Chloroquine or Hydroxychloroquine as single agents, Lopinavir in combination with Ritonavir, and Lopinavir with Ritonavir plus Interferon beta-1a (https://www.who.int/ emergencies/diseases/novel-coronavirus-2019/global-research-on-novel-coronavirus-2019-ncov/solidarity-clinical-trial-for-covid-19-treatments).

7. Conclusion

Unfortunately, at the time of writing this article there are more than 22,00,000 confirmed patients suffering from SARS-CoV-2 with more than 152,000 reported deaths across the globe.

Novel infectious diseases resulting from the zoonotic transmission of ever-evolving and mutating coronaviruses will continue to pose a global threat to people’s lives and the global economy. Today, despite having suffered from two major coronavirus-related outbreaks like SARS and MERS, the world remains underprepared to formidable accept the challenge of a global pandemic like COVID-19. We are still clueless about the handling of the disease and far away from a definite line of treatment against the SARS-CoV-2 virus. It is extremely critical that a concerted effort across the globe is undertaken to find a robust cure for coronaviruses-related illness. Given the arduous and cost-sensitive road map for novel drug development, it is of utmost importance to develop broad-spectrum antivirals that act on common features of the coronavirus lifecycle. Drug repurposing should be broadened, and more combination drugs should be evaluated in patient trials to allow inhibition of the disease through more than one target. Although there is a lot to learn from the SARS and MERS epidemic, and a lot of research has been performed to develop a suitable cure, the same cannot be applied to COVID -19 due to viral evolution. Across the globe, serious efforts are ongoing to find compounds and drugs that can decrease COVID-19 progression and it is likely that all such prospects have not been covered in this review. WHO in collaboration with Microsoft maintains an active database of ongoing trials and compounds active against SARS-CoV-2 (https://www.who.int/ictrp/search/en/).

Extraordinary collaborations and technology exchange in the area of antiviral drug discovery and clinical trials will expedite patient access to more reliable drugs with improved therapeutic potential. This will also considerably reduce time-to-market for candidate drugs. The current ongoing research should lead to more collective drug discovery efforts, where partnership between research institutes and industries will be of paramount importance.

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