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Review

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

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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 Coronaviruses (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, Gammacoronavorus 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) (Ceraolo 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

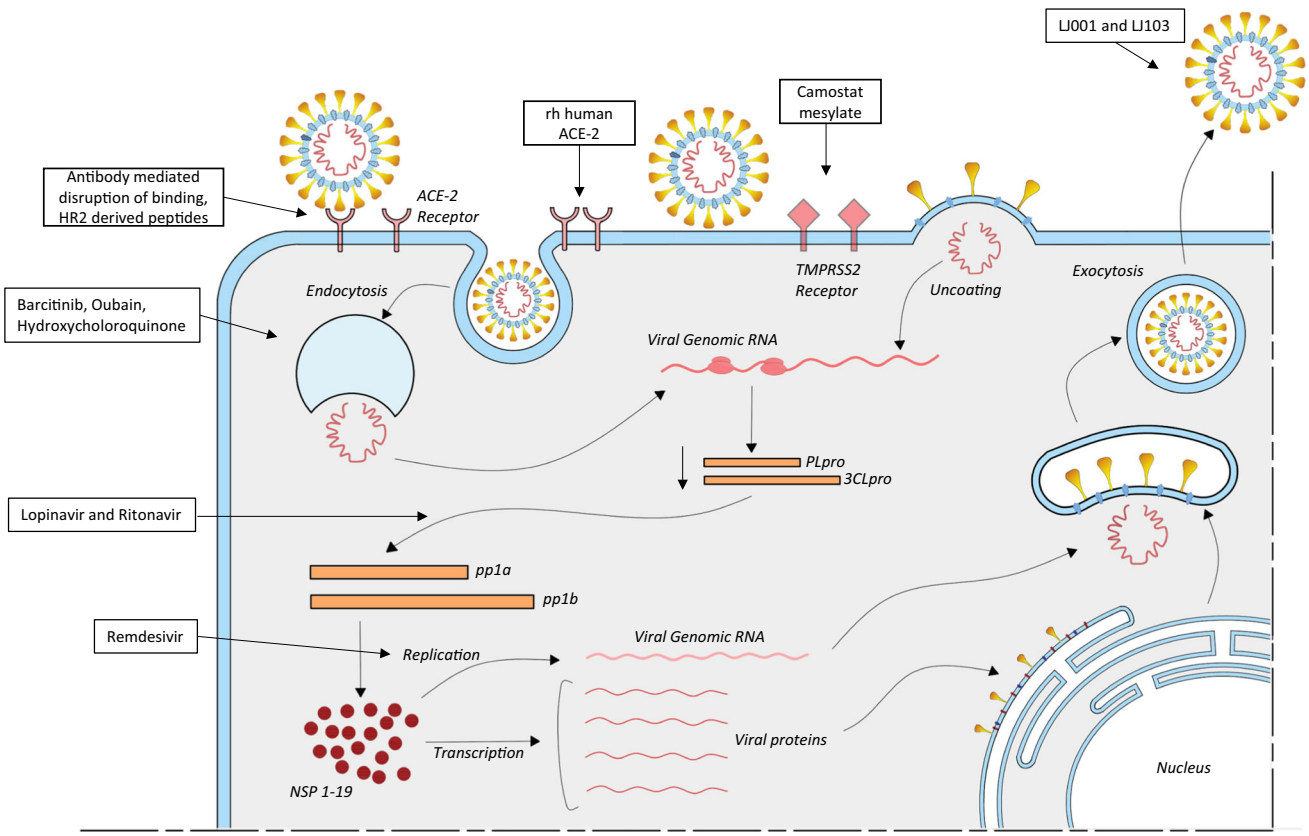

Figure 1. Stages of SARS-CoV-2 life cycle. Along with the stages arrows point to drugs and candidate drugs active against the drug targets.

ribonucleoprotein complex (RNP) (Cong *et al.* 2017; Gui *et al.* 2017; Narayanan *et al.* 2008; Narayanan *et al.* 2015).

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; Simmons *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; Hijikata *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 (Breckenridge 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. M oreover, 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

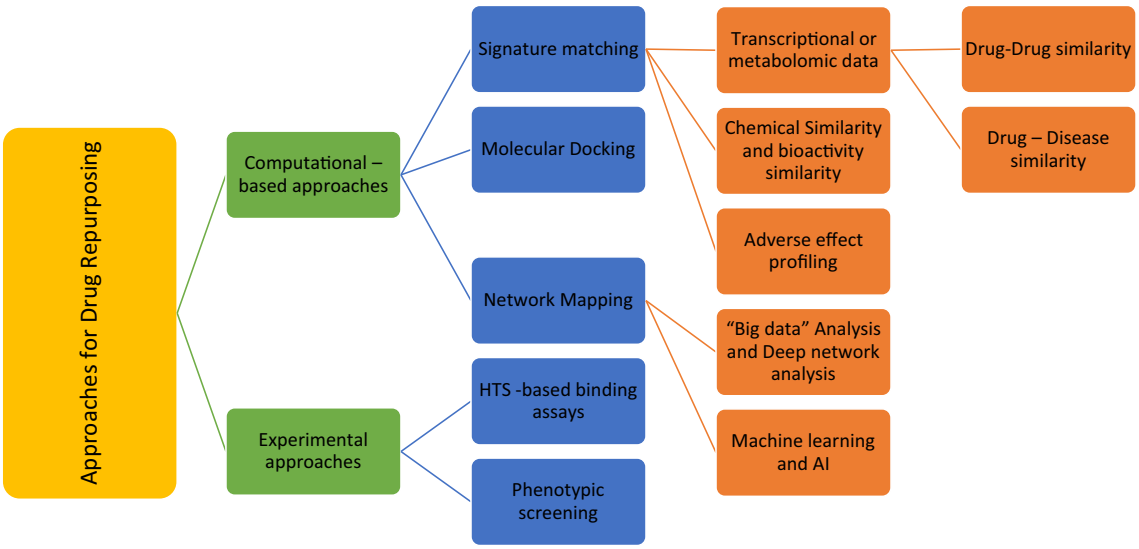

Figure 2. Hierarchical view of approaches for drug repurposing.

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.*

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 multiomics 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	Mechanismofaction	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 peptidel 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
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; Basit *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; Alia 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-C0V-2 viral progression (Keshtkar-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 Ribaviorin 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 Remdisivir, 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, Bictegravirand 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 hexamethylene amiloride (Pervushin *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 naïve 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

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 combination	III	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
Ascletis	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

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.

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 formidably 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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