COVID-19: The question of genetic diversity and therapeutic intervention approaches

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Abstract

Coronavirus disease 2019 (COVID-19), caused by the Severe Acute Respiratory Syndrome Coronavirus type 2 (SARS-CoV-2), is the largest pandemic in modern history with very high infection rates and considerable mortality. The disease, which emerged in China's Wuhan province, had its first reported case on December 29, 2019, and spread rapidly worldwide. On March 11, 2020, the World Health Organization (WHO) declared the COVID-19 outbreak a pandemic and global health emergency. Since the outbreak, efforts to develop COVID-19 vaccines, engineer new drugs, and evaluate existing ones for drug repurposing have been intensively undertaken to find ways to control this pandemic. COVID-19 therapeutic strategies aim to impair molecular pathways involved in the virus entrance and replication or interfere in the patients' overreaction and immunopathology. Moreover, nanotechnology could be an approach to boost the activity of new drugs. Several COVID-19 vaccine candidates have received emergency-use or full authorization in one or more countries, and others are being developed and tested. This review assesses the different strategies currently proposed to control COVID-19 and the issues or limitations imposed on some approaches by the human and viral genetic variability.

Keywords: COVID-19, therapeutic interventions, global health treat, virus diversity.

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Introduction

The scientific community considers the COVID-19 caused by the new coronavirus SARS-CoV-2 as the deadliest pandemic in recent human history. SARS-CoV-2 is a virus of the family Coronaviridae of the genus Betacoronavirus, with the subgenus Sarbecovirus. Many coronaviruses have been identified in several animal species, of which six infect human hosts, including the severe acute respiratory syndrome-related coronavirus (SARS-CoV-1) and the Middle East respiratory syndrome coronavirus (MERS-CoV) (Dietz et al., 2020; Guo et al., 2020). The genome of the new coronavirus was fully sequenced (NCBI Reference Sequence: NC_045512.2) (Wang et al., 2020). Its sequence presents about 82% identity to the bat SARS-like coronavirus WIV1 (bat SL-CoV-WIV1, GenBank: KF367457.1), and more than 85% identity with the bat SARS-like coronavirus ZC45 (bat SL-CoV-ZC45, GenBank: MG772933.1) (Li X et al., 2020; Yu et al., 2020).

SARS-CoV-2 is an enveloped, non-segmented positive-sense RNA virus with prominent stick-shaped protruding particles in their outer membrane (Peng et al., 2020; Yin et al., 2020). Similar to SARS-CoV-1 and MERS-CoV, the SARS-CoV-2 genome encodes nonstructural proteins (NSPs), such as 3-chymotrypsin-like protease, papain-like protease, helicase, and RNA-dependent RNA polymerase), structural and accessory proteins (Li Q et al., 2020). Among NSPs, NSP1 is the first protein of the polyprotein of SARS-CoV-2 and a leader protein, which acts as a potent inhibitor of gene expression of the virus carrier (Huang et al., 2011). Nonstructural protein 2 (NSP2) binds two other host proteins, prohibitin 1 and prohibitin 2 (PHB1 and PHB2), disrupting the host cell environment (Cornillez-Ty et al., 2009). NSP3, the papain-like proteinase protein, has multiple functions and is considered the most important protease of the virus (Báez-Santos et al., 2015).

This new coronavirus has four major structural proteins: the spike (S), small envelope (E), and membrane (M) glycoproteins, and nucleocapsid (N) protein, besides several accessory proteins. The trimeric S protein is indispensable for virus-cell receptor interactions during viral entry (Lu et al., 2020; Walls et al., 2020). SARS-CoV-2 targets cells through the S protein, which binds to the human angiotensin-converting enzyme 2 (ACE2) receptor and employs the cellular serine protease TMPRSS2 for S protein priming (Datta et al., 2020; Hoffmann et al., 2020; Letko et al., 2020; Tai et al., 2020). Notably, the ACE2 receptor is expressed in various tissues and organ systems throughout the body, including the central nervous system, gastrointestinal system, heart, lung, testes, and kidney (Baig et al., 2020; Zhang et al., 2021). In fact, in addition to oropharyngeal swabs, the viral RNA has also been detected in blood, urine, facial/anal swabs, semen, and vaginal secretion, suggesting other potential means of transmission (Peng et al., 2020). Ultimately, the S protein binding to the ACE2 receptor triggers a cascade of events leading to the fusion and releasing of the viral RNA genome into the host cell. The nonstructural proteins are subsequently synthesized to encode the viral replicase-transcriptase complex. The viral RNA is then synthesized by RNA-dependent RNA polymerase (Chen Y et al., 2020; Letko et al., 2020). Further, when the virus is in the cytosol, the non-structural viral proteins (nsp) 1-16 are produced and catalyze replication of the viral RNA genome, and inhibition of the host’s innate immune response (Thiel et al., 2003; Gildenhuys, 2020). The Mpro or NSP5 protease mediates the cleavage of the viral replicative proteins, RNA-dependent RNA polymerase (RpRp) and helicase (HEL) (Ziebuhr et al., 2000).

SARS-CoV-2 has one of the hardest outer protective shells among all coronaviruses. This feature is believed to result in more stable viral particles, resulting in greater resilience in body fluids (Goh et al., 2020). Another relevant and recurrent challenge imposed by this pandemic, is the emergence of distinct new-high transmissible variants around the globe; so far, five variants of concern (VOC) have already been identified, B.1.1.7, detected first in the UK, B.1.351, initially detected in South Africa, B.1.1.28.1 (also known as P1), first detected in Brazilian travellers in Japan, and more recently, B.1.427 and B.1.429, identified in USA (Centers for Disease Control and Prevention, CDC, 2021). These new variants prevent the body’s immune response by selecting and excluding pieces of the virus’s genetic sequence. In this sense, there was a need for further studies on the pathogenicity and replication of SARS-CoV-2.

Regarding the diagnostic tools, the highly specific reverse-transcriptase polymerase-chain reaction (RT-PCR) technology is the gold standard test for COVID-19 and data from epidemiological evidence and clinical manifestations
combined with radiological images, such as computer tomography (CT), also have critical diagnostic value for COVID-19 (Li X et al., 2020). Clinically, COVID-19 presents a myriad of possible symptoms and outcomes, from asymptomatic carriage, flu-like symptoms including cough, fever, general weakness, myalgia, pneumonia-like characteristics, and respiratory failure requiring mechanical ventilation (Itelman et al., 2020). Although there are studies that point out that COVID-19 manifests itself as a respiratory tract infection, rising data have been demonstrating that COVID-19 should be treated as a systemic disease, involving the most diverse systems of the human body, such as gastrointestinal, cardiovascular, respiratory, renal, neurological, immunological and hematopoietic (Driggin et al., 2020; Mehta et al., 2020).

The transmission patterns of SARS-CoV-2 and its pathogenicity motivates the scientific community to work against the clock to improve the diagnostic, preventive and therapeutic management of the disease, and to identify the genetic risk factors. There is no current evidence to recommend any specific anti-SARS-CoV-2 treatment for patients with suspected or confirmed COVID-19. Diverse therapeutic interventions are being evaluated in clinical trials, and new approaches are being proposed regarding pharmacological therapy for COVID-19 (Saber-Ayad et al., 2020).

In the light of the actual scenario, the repurposing of drugs, the development of novel effective immunotherapies, and safe and effective long-lasting vaccines against the SARS-CoV-2 are essential strategies for coping with this pandemic. In this review, we aim to discuss the current status of therapeutic interventions against COVID-19 (Figure 1), highlighting them from a mechanistic point of view considering the role of microRNAs, viral characteristics, and host genetic determinants, as well as the feasibility of the available drugs. A review of the current research on these topics may help guide strategies to address the current COVID-19 pandemic and prepare us for future challenges.

**Genetic basis of COVID-19 clinical phenotypes**

The clinical heterogeneity observed in COVID-19 most likely results from the interaction of the immune responses and comorbidities presented by patients. The genetic background of patients certainly plays an essential role in this regard. Genetic variants of the cellular components that allow the interaction of the viral particle with the host cell and its entry are the most obvious candidates for investigation. Moreover, many of the components of the human innate and adaptive immune responses present genetic variants that may have functional impact. The genetic variability of the SARS-CoV-2 may provide additional factors modulating the disease manifestations (Hofmann et al., 2004; Li W et al., 2005, 2007; Cao Y et al., 2020; Pinto et al., 2020). Besides, hormonal factors inherent to sex can influence the risk of mortality in cases positive for SARS-CoV-2. Karlberg et al. (2004) studied the mortality rate from the Hong Kong SARS epidemic and observed a significant difference between men (21.9%) and women (13.2%). Coincidence or not, the ACE2 gene is located on the X chromosome (Xp22) (Li et al., 2003).

Oophorectomy or treatment of mice with an estrogen receptor inhibitor resulted in increased mortality in females infected with SARS-CoV-1 (Channappanavar et al., 2017). The other research front has concentrated efforts on the characterization of the different strains of SARS-CoV-2 to establish the viral subtypes and analyze the genetic variants associated with the different clinical phenotypes of COVID-19. In this case, the genomic regions whose products are responsible for the entry of SARS-CoV-2 in the host cells have been considered the principal candidates (Channappanavar et al., 2017; Benvenuto et al., 2020; Bezerra et al., 2020; Coutard et al., 2020; Licastro et al., 2020; Lu et al., 2020; Rehman et al., 2020; Sah et al., 2020; Shereen et al., 2020; Zhao et al., 2021). The analysis of a specific genomic signature of the SARS-CoV-2 strains can help in understanding the viral evolution since the first

![Figure 1](image-url) - Main routes for therapeutic intervention of the COVID-19. The article discusses four approaches that are being used in an attempt to treat patients with severe clinical evolution.
case reported in China (Fan et al., 2020). A computational tool was applied to identify and track numerous strains of SARS-CoV-2 circulating on different continents, especially those isolated from hospitalized patients, whether or not they needed intensive care and pulmonary ventilation (Zhao et al., 2021). The authors used a public database containing 4087 SARS-CoV-2 sequences and were able to define at least ten strains that infected patients in the United States, realizing that some of them are the same found in Asia and Europe. Such reports can help projects aiming to correlate SARS-CoV-2 strains with the clinical evolution of hospitalized patients.

Genetic diversity of the SARS-CoV-2

RNA viruses present higher mutation rates than DNA viruses, especially the single-stranded RNA (ssRNA) viruses, such as the SARS-CoV-2 (Peck and Lauring, 2018), although the SARS-CoV-2 and other related viruses perform proofreading during RNA replication, differently from most other RNA viruses (Romano et al., 2020). Data from the Global Initiative on Sharing All Influenza Data (GISAID) (Elbe and Buckland-Merrett, 2017) have indicated that the SARS-CoV-2 mutational rate (Shen Z et al., 2020) was similar to other coronaviruses (Eckerle et al., 2010; Son et al., 2020). The single nucleotide polymorphisms (SNPs) are the most frequent variants in the genome of the SARS-CoV-2 and are considered the leading cause of the genetic diversity and evolution of the virus, besides its virulence and transmissibility (Yin, 2020). The SNPs can be found in both coding and non-coding regions of the viral genome. SNPs located in coding regions have a high potential to contribute to the classification of new strains of SARS-CoV-2, calculate the rate of infection, and design vaccines and define effective doses for different population groups (Saha et al., 2020). One study carried out with virus isolates from Europe has shown that SNPs are more frequent in proteins related to viral replication (RNA polymerase) and ACE2 binding regions of the S protein. These genetic variants have been previously associated with the effectiveness of vaccines (Yin, 2020). Studies in other populations have described SNPs in the genes encoding NSP-2, and also RdRp and the S protein (Tabibzadeh et al., 2020).

The SARS-CoV-2 evolves in vivo after infection, which may affect its virulence, infectivity, and transmissibility (Shen Z et al., 2020). Indeed, several studies have analyzed the mutational profile of interhost and intrahost single nucleotide variants (iSNV). The analysis of large datasets has shown that SARS-CoV-2 presented a more significant proportion of G>T changes in both iSNVs and iSNPs compared to SARS-CoV-1 and MERS. Interestingly, the mutational profile of the iSNVs was more similar among SARS-CoV-2 and MERS-CoV than SARS-CoV-1 (Sapoval et al., 2021). Altogether, the data presented above indicated that genetic variations in the SARS-CoV-2 genome sequence could be critical to assist in the definition of the virus transmission pattern and to control the infection outbreak, as well as for epidemiological monitoring and tracking of the virus.

The A382 corresponds to the deletion of the nucleotide in the position 382 which truncates the ORF7b and removes the ORF8 transcription-regulatory sequence. This variant is associated with milder illness compared to the wild-type virus, probably due to reduced cytokine release during the acute phase of the disease. The mechanism of this attenuated variant suggests that ORF8 can be a target for therapeutic intervention (Young et al., 2020). Conversely, SARS-CoV-2 that bears the D614G mutation in the S protein is associated with a higher case fatality rate (Becerra-Flores and Cardoza, 2020), a fact that should be considered for design of therapeutic antibodies and prognosis.

Genetic diversity of the human host

Viral targets in the host cells, such as the ACE2 and TMPRSS2, have been considered molecular markers to determine the genetic susceptibility or resistance to COVID-19 (Mohammadpour et al., 2021). Several studies have shown that the presence of polymorphisms in the ACE2 gene can affect: (i) the modulation of intermolecular interactions with the SARS-CoV-2 S protein (Benetti et al., 2020; Gibson et al., 2020; Hussain et al., 2020; Lippi et al., 2020); (ii) the binding to the viral S protein (Li, Q et al., 2020; Stawiski et al., 2020); (iii) the structure and stabilization (Benetti et al., 2020), and the expression of the ACE2 receptors (Badawi, 2020; Cao Y et al., 2020; Delanghe et al., 2020). ACE2 variants usually alter the interaction between host cells and SARS-CoV-2 by showing lower affinity to the virus proteins that bind host cells’ surface, thus conferring decreased susceptibility to COVID-19 (Stawiski et al., 2020).

ACE2 expression differs on the basis of the biological age and sex of each individual (Goren et al., 2020; Ovsyannikova et al., 2020), and also according to the different geographic and ethnic distribution of the COVID-19 patients (McCoy et al., 2020; Sun et al., 2020). A large number of studies have described SNPs in patients of distinct countries affecting the molecular mechanisms cited above (Badawi, 2020; Benetti et al., 2020; Cao Y et al., 2020; Delanghe et al., 2020; Gibson et al., 2020; Hatami et al., 2020; Hussain et al., 2020; Lippi et al., 2020; Stawiski et al., 2020; Yamamoto N et al., 2020). According to Alfiano et al. (2020), these polymorphisms could explain in part the differences currently observed in COVID-19 incidence between countries around the world, despite the globalization of exchanges and travels. A gene homologous to ACE2, the human ACE1 gene that is mapped on chromosome 17, presents a polymorphic insertion (I) or deletion (D) of a 287-base pair (bp) Alu repeat sequence in intron 16 (Rieder et al., 1999), that has been shown to impact susceptibility to the disease as well as the frequency of recoveries and deaths (Delanghe et al., 2020; Hatami et al., 2020; Yamamoto N et al., 2020; Calabrese et al., 2021).

Other studies have reported the association of polymorphisms in other protein cell receptors, such as the TMPRSS2 receptor (Asselta et al., 2020; Hou et al., 2020; Russo et al., 2020; Senapati et al., 2020; Torre-Fuentes et al., 2021), as well as in the HLA genes (Nguyen et al., 2020; Lorente et al., 2021; Amoroso et al., 2021; Warren and Birol, 2021) and ABO blood group locus (Ellinghaus et al., 2020; Amoroso et al., 2021; Zhao et al., 2021), with the risk of acquiring COVID-19. These results suggest that HLA antigens may influence SARS-CoV-2 infection and clinical evolution of COVID-19, and confirm that blood group A individuals are at greater risk of infection. In most of these studies, the
variants observed were associated with the susceptibility to SARS-CoV-2 infection, as well as with the severity of the disease, such as the development of cardiovascular and respiratory complications (Ellinghaus et al., 2020; Hou et al., 2020; Amoroso et al., 2021; Lorente et al., 2021). A review of the possible impact of genetic factors involved in the immune responses on COVID-19 can be found in Anastassopoulou et al. (2020).

Variability in the human and viral miRNA network and the control of host response to SARS-CoV-2

MicroRNAs (miRNAs), a class of non-coding small RNA molecules, are important post-transcriptional regulators that have been associated with the development of several pathologies, including the ones caused by viral infections (Malthby et al., 2016; Trobaugh and Klimstra, 2017; Girardi et al., 2018; Stolzenburg and Harris, 2018; Dutta et al., 2019; Tribolet et al., 2020). Human (host) and viral miRNAs interact with each other and although these interactions are not yet completely elucidated, it is very likely to involve the regulation of cellular processes that affect virus pathogenicity and cellular response (Totura and Baric, 2012; Bruscella et al., 2017). The gene network associated with host responses can result from miRNA transcriptional regulation of a subset of mRNA targets that are critical components of signaling pathways, including the WNT, INK, PI3/AKT, MAPK, and NOTCH pathways (Barbu et al., 2020; Khan M et al., 2020).

On the other hand, miRNAs from the virus can deregulate host miRNAs and facilitate the viral replication, induce the latency, prevent apoptosis, and/or cause immune evasion (Salmena et al., 2011; Scheel et al., 2016; Trobaugh and Klimstra, 2017; Damas et al., 2019; Mishra et al., 2020). SARS-CoV-2 genome mutations have also been reported to disrupt the binding sites of miRNAs and negatively impact the modulation of antiviral host defenses (Rad and McLellan, 2020), as well as viral miRNA sponges that can deplete specific host miRNAs (Bartoszewski et al., 2020; Srivastava et al., 2020).

In the infection by SARS-CoV-2, the identification of the potential virus-human miRNA-based interactions have been mostly conducted on computational miRNA prediction analysis (Arisan et al., 2020; Khan M et al., 2020; Nersisyan et al., 2020; Saçar and Adan, 2020; Sarma et al., 2020; Marchi et al., 2021). Based on the seed region specificity, Arisan et al. (2020) have compared SARS-CoV-2 sequences from different geographical regions to those from other viruses, such as SARS and MERS. Although the analyses revealed shared human miRNAs targeting the genome of these viruses, unique miRNAs were observed for SARS-CoV-2. The prediction analysis conducted by Sarma et al. (2020), identified 22 potential miRNAs from five genomes of SARS-CoV-2 linked with 12 human miRNAs. Finally, a comparison between the host miRNA binding profiles on 67 different SARS-CoV-2 genomes from 24 different countries revealed miRNAs associated with increased death rates of COVID-19. Recently, Centa et al. (2021) reported a significant association in the experimental expression analysis of two miRNAs, miR-26a-5p and miR-29b-3p, with the expression levels of inflammatory markers, such as IL-4, IL-6 and IL-8, in post-mortem lung cells of COVID-19 patients (Centa et al., 2021). These results showed the direct impact of miR deregulation in the endothelial dysfunction and inflammatory response in patients with SARS-CoV-2 infection and acute respiratory injuries.

Among the most common pathways and gene networks affected by the human-virus miRNA interactions are the ones associated with the ACE2 and TMPRSS2 genes (Arisan et al., 2020; Ghafouri-Fard et al., 2020; Hoffmann et al., 2020; Lukassen et al., 2020; Nersisyan et al., 2020; Paniri et al., 2021). The miRNAs that regulate the expression of these genes were deregulated in several cardiovascular and pulmonary diseases (Kohlstedt et al., 2013; Hu et al., 2014; Bao et al., 2015; Chen et al., 2015), such as the ones developed by many COVID-19 patients. These findings support miRNAs’ role in the development and progression of endothelial and vascular diseases (Ovchinnikova et al., 2015; Veger et al., 2017). Taken together, the data presented above show the role of miRNAs in modulating the immune- and other host response-related processes of SARS-CoV-2 infection, suggesting that they can be considered genetic factors for the observed differences in the response of the patients to the infection and in the severity of the disease. As the rich and valuable information obtained through in silico analysis becomes increasingly available, additional predictive viral-host miRNAs interactions are expected to be identified, which can lead to the potential identification of miRNAs as therapeutic targets for COVID-19 (Fernández-Hernando and Suárez, 2018; Prestes et al., 2020).

In the context of a pandemic, the polymorphisms as well as rare variants that impact disease susceptibility become quantitatively important since millions of people may be infected. Therefore, the knowledge of the genetic variation, at both individual and population levels, may further improve our understanding of the SARS-CoV-2 transmission and pathogenesis, enabling the identification of individuals at high risk of infection and subsequent disease sequelae. More broadly, this may provide valuable information for drug design and vaccine development (Sironi et al., 2020).

Molecular approaches for therapeutic interventions

The use of molecular tools, such as RNA interference (RNAi) is being considered in the search for treatment of COVID-19. The RNAi can directly disrupt the production of viral and/or host proteins involved in SARS-CoV-2 infection, therefore allowing the development of challenging but promising novel therapeutic approaches, which potentially result in specific depletion of key proteins involved in COVID-19 pathogenesis. The RNAi technology itself is simple; it consists of the use of synthetic short interfering RNAs (siRNAs), which can be directly introduced into the cell cytoplasm where they will trigger the degradation of specific mRNA targets. The FDA approval of the first drug based on siRNA (Patisiran), used to treat nerve damage caused by a genetic disease, is encouraging (Uludağ et al., 2020). The former studies focused on SARS-CoV-1 infection may guide the work in the current SARS-CoV-2 pandemic. Although RNAi can be directed against any protein, targeting essential viral proteins, such as S, E, M, and N proteins might represent more specific and efficient strategies. In the initial
studies applying RNAi against SARS-CoV-1, many efforts were performed with the use of siRNAs directed to the S-protein (Qin et al., 2004; Zhang et al., 2004; Wu et al., 2005), the Leader sequence (Li W et al., 2005), the non-structural protein 1 (Ni et al., 2005), the nucleocapsid N-protein (Zhao et al., 2005), theRpRp (He et al., 2003; Lu et al., 2004) and the E-protein (Meng et al., 2006) among others, and obtained considerable success in reducing viral load. Thus, RNAi technology warrants further exploration in order to verify its potential as an alternative strategy for SARS-CoV-2 infection treatment. Recently, several investigators suggested resume efforts focused on this direction (Asha et al., 2018; Ghosh et al., 2020).

Pharmacological interventions in cellular and animal models

In order to evaluate potential therapeutic intervention approaches, some strategies focused on ACE2, TMPRSS2, and S protein will be reported. Most of them use inhibitors to reduce the infection rate and the hypertensive and pro-inflammatory effects of Angiotensin II.

Angiotensin II-converting enzyme (ACE2) receptor inhibitors

ACE2 inhibition has been suggested as a promising approach to attenuate the damage in lung cells caused by SARS-CoV-2 infection (Lopes et al., 2020). Captopril, enalapril, losartan and valsartan, which are all ACE2 antagonists, seem to inhibit the receptor and were able to avoid pneumonia caused by SARS-CoV-2 infection (Zhou et al., 2020). Further, docking assays and crystallography analysis of virus’ receptor (Benitez-Cardoza and Vique-Sánchezen et al., 2020; Xia et al., 2020) are being explored to support the development of new inhibitory compounds (Tai et al., 2020; Yan et al., 2020) and small peptides that potentially prevent the interaction between the SARS-CoV-2 S protein and ACE2 (Xiu et al., 2020).

Subunit protein TMPRSS2 Inhibitors

Nafamostat and camostat are serine proteases inhibitors proved to interfere in vitro with protein-mediated fusion of SARS-CoV-2 and the host cell (Kang et al., 2015; Yamamoto M et al., 2020). Camostat can also inhibit TMPRSS2 in the human lung cells infected with SARS-CoV-2 (Hoffmann et al., 2020). Clinical trials have been conducted to evaluate the efficacy and safety of camostat mesilate in treating COVID-19. Among those trials is possible to highlight some examples in which the drug was used alone (NCT04583592 (CAMELOT, England); NCT04662073 (USA); NCT04355052 (Israel); NCT04662086 (USA); NCT04644705 (Belgium); NCT04321096 (Denmark); NCT04470544 (England); NCT04652765 (USA); NCT04750759 (NICCAM; Germany); NCT04340349), and preliminary results from NCT04405999 demonstrated that prophylaxis using this drug reduced the rate of symptomatic COVID-19. Aprotinin, enalaprilat, genistein, and estradiol are examples of others TMPRSS2 inhibitors, which were active in vitro using different cell types, however, informations about such effect in vivo are still missing (Royston, 2015; Bestle et al., 2020; Wang et al., 2020).

Furin protease inhibitors

After binding to the ACE2 receptor, the S-protein must be cleaved by the host protease furin for priming the S2 fusion machinery for triggering the fusion of viral and host cell membranes (Bosch et al., 2004). Once furin processing is a required step for membrane fusion, furin inhibition could effectively reduce SARS-CoV-2 cell entrance in host cells (Shang et al., 2020). Darinaparsin, a currently used anticancer drug, showed a high binding-affinity to furin and could be a hopeful therapy approach for SARS-CoV-2 infection (Chowdhury et al., 2020). Estradiol and vitamin D were also able to affect furin’s activity in rat, mouse, and human cells (Glinsky, 2020). The treatment with Vitamin D is still controversial, while some studies have found negative correlation between vitamin D levels and COVID-19 cases (Ilie et al., 2020) other hypothesis an alleviation on lung inflammation caused by SARS-CoV-2 because vitamin D seems upregulated ACE2 human receptor and decreasing inflammatory cytokines (Xiao et al., 2021). Since, Vitamin D is known to enhance the rate of melanin synthesis; and this may concurrently regulate the expression of furin expression both vitamin D and melanin may have significant impact in management of COVID-19 (Paria et al., 2020). Additionally irisin, luteolin, and nafamostat have demonstrated inhibitory activity against furin (Peng et al., 2017; de Oliveira et al., 2020; Yamamoto M et al., 2020). Thus, several known compounds have shown a favorable potential to attack this critical step of SARS-CoV-2 entrance in host cells and reduce infection effectiveness.

VeroE6 cells are a well-known in vitro model system that produces high virus titers and displays visual cytopathic effects associated with viral infections. These cells are commonly used in in vitro antiviral assays, including for coronavirus (Matsuyama et al., 2010, 2020; Fintelman-Rodrigues et al., 2020; Unal et al., 2021). Past studies demonstrated that the messenger RNA expression level of TMPRSS2 in VeroE6/ TMPRSS2 cells is ∼10-fold higher than in normal human lung tissue and other human cell lines. SARS-CoV-2 uses the same receptor, ACE2, as SARS-CoV, and ACE2 expression is very high in VeroE6 cells (Matsuyama et al., 2020). In addition, recent studies verified that human Caco-2 colon epithelial cells as well as the lung cell line A549 stably expressing ACE2 and TMPRSS2 (Grobe et al., 2021).

Bromhexine and its metabolite ambroxol are mucolytic drugs that inhibit TMPRSS2, frequently used as a mucolytic agent in respiratory diseases. In vitro studies have shown that these drugs hamper the TMPRSS2 effect to activate a zymogen precursor of tissue plasminogen activator and ameliorate the cytokine storm induced by SARS-CoV-2 (Beeh et al., 2008; Furgala-Wojas et al., 2020). Clinical studies have been carried out using bromhexine (NCT04273763; NCT04355026 and NCT04340349), and preliminary results from NCT04405999 demonstrated that prophylaxis using this drug reduced the rate of symptomatic COVID-19. Aprotinin, enalaprilat, genistein, and estradiol are examples of others TMPRSS2 inhibitors, which were active in vitro using different cell types, however, informations about such effect in vivo are still missing (Royston, 2015; Bestle et al., 2020; Wang et al., 2020).
Fusion proteins inhibitors

The development of membrane fusion inhibitors prevents the specific fusion of the viral S2 protein domain, blocking the delivery of viral genetic material into the host cell (Yan et al., 2020). The EK1 peptide was able to inhibit SARS-CoV-2 fusion and a novel modified peptide (EK1 C4) showed an even higher inhibitory activity against the viral membrane fusion pathway (Xia et al., 2020). Lipopeptides (IPB01 and IPB02), designed on the basis of the S-protein S2 fusion domain, demonstrated the ability to inhibit SARS-CoV-2 fusion to host cells (Zhu Y et al., 2020). Imatinib might also be involved in the blockage of membrane fusion during coronavirus infection (Sisk et al., 2018).

Main protease inhibitors

More than four thousand approved commercial drugs were screened in silico as potential main protease (Mpro) inhibitors of SARS-CoV-2 infection (Biembengut and de Souza, 2020; Jiménez-Alberto et al., 2020). The results evidenced the potential use of several of them in COVID-19 treatment. Drug design recognized the Michael acceptor inhibitor N3 as a potent and irreversible inhibitor of SARS-CoV-1 Mpro (Yang et al., 2005). In vitro experiments verified that it also inhibited SARS-CoV-2 replication in Vero cells (Jin et al., 2020). Furthermore, chemical modifications of Mpro inhibitory groups caused a pronounced lung tropism in mice (Khan S et al., 2021, Zhang et al., 2021). Peptidomimetic aldehydes also inhibited SARS-CoV-2 replication in Vero E6 cells and showed low toxicity in Sprague-Dawley rats and Beagle dogs (Dai et al., 2020). Several natural compounds were also identified as inhibitor candidates of Mpro (Gentile et al., 2020; Gurung et al., 2020; Khan S et al., 2021; Olubiyi et al., 2020).

RNA-dependent RNA polymerase (RpRp) inhibitors

The RDPRD can also be a target for pharmacological intervention directed to specifically hinder the function of this enzyme complex (Zhu W et al., 2020). A known candidate is favipiravir, which binds to the catalytic domain of RdRp hindering nucleotide inclusion during RNA synthesis (Furuta et al., 2017). Some drugs such as ribavirin, remdesivir, sofosbuvir, galidesivir and tenofovir are good candidates as inhibitors of the RNA-polymerase mediated replication (Elfiky, 2020; Soufi and Irvani, 2021). Ribavirin and favipiravir were able to restrain the SARS-CoV-2 RpRp enzymes (Huang et al., 2020). Buonaguro et al. (2020) described that some commercial drugs with inhibitory activity against the RpRp, including NHC EIDD1931, have suppressed SARS-CoV-2 replication in vitro and a preclinical animal model, revealing this pathway as a promising target for therapeutic intervention.

Nanotechnology to boost pharmacological therapy

Nanotechnology-based approaches can provide specific drug delivery, enhanced drug bioavailability, low toxicity and improved antiviral activity. Carbon quantum dots inhibited the replication of the human coronavirus (Lopezchini et al., 2019). Diphyllin loaded polymeric nanoparticles demonstrated targeted inhibition of the S protein from the feline coronavirus (Hu et al., 2017). Glutathione-capped Ag2S nanoclusters also showed antiviral properties by obstructing viral RNA synthesis and budding of porcine epidemic diarrhea virus (PEDV) as a model of coronavirus (Du et al., 2018).

Clinical trials for drug repurposing

Drug repurposing or repositioning is a strategy for identifying new applications for approved or investigational drugs outside the first medical indication (Ashburn and Thor, 2004). Given the high decline rates, high costs, and slow new drug discovery and development’s timeframe, repurposing drugs is frequently becoming an attractive proposition. The rationale is that most of the process includes preclinical tests, safety assessment, and, in some cases, the development of the formulation has already been achieved. Besides, the risk of failure and the timeframe for drug development are almost non-existent (Pushpakom et al., 2019).

Until April 2021, more than 5,000 clinical trials were being performed worldwide, evaluating antivirals, corticosteroids, antibiotics, among other drugs against COVID-19 as summarized in Table 1. In the present review, we focus on studies published in journals where publication only occurs after the peer-review process. Here, we emphasize hydroxychloroquine (HCQ), chloroquine, and dexamethasone clinical trials.

Hydroxychloroquine is used to treat malaria, rheumatoid arthritis, and lupus. Some studies point to its antiviral activity against the human immunodeficiency virus (HIV), inhibiting the entry of the virus in host cells and promoting post-translation alteration of newly synthesized proteins via glycosylation inhibition (Rosa and Santos, 2020). Hydroxychloroquine was tested in a retrospective multicenter cohort study of 1438 patients with laboratory confirmation of SARS-CoV-2 infection admitted to 25 hospitals. Four different treatments were evaluated, (1) hydroxychloroquine and azithromycin, (2) hydroxychloroquine, (3) azithromycin, and (4) neither of these drugs. Initially, this study showed that patients who received hydroxychloroquine and azithromycin had a higher incidence of heart failure than the group without treatment. Furthermore, no significant reduction of mortality in the groups of patients receiving any of the treatments compared with the non-treated group (Rosenberg et al., 2020).

A randomized multicenter study involving 150 patients with moderate-stage COVID-19 in two arms, with or without hydroxychloroquine treatment, found no difference in the evolution of patients who used this drug or not. However, adverse effects related to the use of hydroxychloroquine were reported (Tang W et al., 2020). Corroborating this result, Mercuro et al. (2020) showed, in a cohort study of 90 patients with COVID-19, that individuals using hydroxychloroquine had an increased risk QT interval prolongation. Also, in a randomized study of patients with severe COVID-19, a high dose of chloroquine alone or with azithromycin/oseltamivir was not recommended due to potential safety hazards related to QT prolongation and increased lethality (Borba et al., 2020). A randomized, double-blind, placebo-controlled study tested hydroxychloroquine as post-exposure prophylaxis and concluded that it did not significantly reduce the severity of symptoms in outpatients presenting mild and early COVID-19 (Boulware et al., 2020).

The RECOVERY study compared a variety of possible treatments with the usual care in patients hospitalized with...
| Drug                      | Participants                                                                 | Design                                                                                   | Intervention                                                                                       | Conclusion                                                                                                                                                                                                 |
|--------------------------|------------------------------------------------------------------------------|------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Chloroquine              | Adults who had household or occupational exposure to someone with confirmed SARS-CoV-2 infection. | Randomised, double-blind, placebo-controlled trial                                        | Oral hydroxychloroquine (400 mg on day 1, followed by 200 mg daily for up to 10 days) or placebo. | Hydroxychloroquine did not prevent illness compatible with COVID-19 when used as post-exposure prophylaxis within 4 days after exposure. Hydroxychloroquine did not substantially reduce symptom severity in outpatients with early, mild COVID-19. |
| Hydroxychloroquine       | Adults admitted to hospital with laboratory-confirmed SARS-CoV-2 infection, and evidence of lower respiratory tract infection. | Randomised, double-blind, placebo-controlled trial                                        | Oral hydroxychloroquine (600 mg on day 1, followed by 400 mg daily for up to 4 additional days). | Hydroxychloroquine did not prevent illness compatible with COVID-19 when used as post-exposure prophylaxis within 4 days after exposure. Hydroxychloroquine did not substantially reduce symptom severity in outpatients with early, mild COVID-19. |
| Remdesivir               | Adults who were hospitalized with COVID-19 and had evidence of lower respiratory tract infection. | Randomised, double-blind, placebo-controlled trial                                        | Remdesivir was superior to placebo in shortening the time to recovery in adults with severe COVID-19, no benefit was observed with remdesivir treatment beyond 10 days. | Remdesivir was superior to placebo in shortening the time to recovery in adults with severe COVID-19, no benefit was observed with remdesivir treatment beyond 10 days. |
| Lopinavir and Ritonavir   | Hospitalised adult patients with confirmed SARS-CoV-2 infection.              | Randomised, double-blind, placebo-controlled trial                                        | Lopinavir and Ritonavir was not associated with statistically significant benefits or contraindications. | Lopinavir and Ritonavir was not associated with statistically significant benefits or contraindications. |
| Dexamethasone            | Patients with non-severe COVID-19 and no risk factors for severe disease.     | Randomised, double-blind, placebo-controlled trial                                        | Among patients receiving a single 800 mg dose of dexamethasone within 24 h of receipt of oxygen alone, there was no difference in the proportion of patients who survived. | Among patients receiving a single 800 mg dose of dexamethasone within 24 h of receipt of oxygen alone, there was no difference in the proportion of patients who survived. |
| Ivermectin               | Patients were randomised 1:1 to receive oral, single dose of 400 μg/kg, followed by 200 μg/kg daily for 5 days. | Randomised, double-blind, placebo-controlled trial                                        | Ivermectin was not associated with statistically significant benefits or contraindications. | Ivermectin was not associated with statistically significant benefits or contraindications. |
| Nitazoxanide             | Adult patients presenting up to 3 days after onset of COVID-19 symptoms.      | Randomised, double-blind, placebo-controlled trial                                        | Nitazoxanide was not associated with statistically significant benefits or contraindications. | Nitazoxanide was not associated with statistically significant benefits or contraindications. |
| Dexamethasone            | Patients were randomised 1:1 to receive either standard care or standard care alone. | Randomised, double-blind, placebo-controlled trial                                        | Dexamethasone was not associated with statistically significant benefits or contraindications. | Dexamethasone was not associated with statistically significant benefits or contraindications. |
| Hydroxychloroquine       | Adults with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. | Randomised, double-blind, placebo-controlled trial                                        | Hydroxychloroquine did not prevent illness compatible with COVID-19 when used as post-exposure prophylaxis within 4 days after exposure. Hydroxychloroquine did not substantially reduce symptom severity in outpatients with early, mild COVID-19. | Hydroxychloroquine did not prevent illness compatible with COVID-19 when used as post-exposure prophylaxis within 4 days after exposure. Hydroxychloroquine did not substantially reduce symptom severity in outpatients with early, mild COVID-19. |
| Remdesivir               | Adults admitted to hospital with laboratory-confirmed SARS-CoV-2 infection, with an interval from symptom onset to enrolment of 12 days or less, and evidence of severe respiratory tract infection. | Randomised, double-blind, placebo-controlled trial                                        | Remdesivir was superior to placebo in shortening the time to recovery in adults with severe COVID-19, no benefit was observed with remdesivir treatment beyond 10 days. | Remdesivir was superior to placebo in shortening the time to recovery in adults with severe COVID-19, no benefit was observed with remdesivir treatment beyond 10 days. |
| Dexamethasone            | Patients were randomised 1:1 to receive either standard care or standard care alone. | Randomised, double-blind, placebo-controlled trial                                        | Among patients receiving a single 800 mg dose of dexamethasone within 24 h of receipt of oxygen alone, there was no difference in the proportion of patients who survived. | Among patients receiving a single 800 mg dose of dexamethasone within 24 h of receipt of oxygen alone, there was no difference in the proportion of patients who survived. |
| Ivermectin               | Patients were randomised 1:1 to receive oral, single dose of 400 μg/kg, followed by 200 μg/kg daily for 5 days. | Randomised, double-blind, placebo-controlled trial                                        | Ivermectin was not associated with statistically significant benefits or contraindications. | Ivermectin was not associated with statistically significant benefits or contraindications. |
| Nitazoxanide             | Adult patients presenting up to 3 days after onset of COVID-19 symptoms.      | Randomised, double-blind, placebo-controlled trial                                        | Nitazoxanide was not associated with statistically significant benefits or contraindications. | Nitazoxanide was not associated with statistically significant benefits or contraindications. |
COVID-19. The authors examined the daily use of 6 mg of dexamethasone for ten days (2104 patients) versus usual care alone (4321 patients). The preliminary results indicated lower 28-day mortality among patients receiving invasive mechanical ventilation or oxygen alone, but not among those who did not receive respiratory support at randomization (RECOVERY Collaborative Group, 2021).

Ivermectin has been recently proved, in an in vitro experiment, to produce reduction in the RNA of SARS CoV-2 at 48 h of its single addition (Caly et al., 2020). Among patients with non-severe COVID-19 and no risk factors for severe disease receiving a single 400 mcg/kg dose of ivermectin, Chaccour and colleagues (2021) have found no difference in the proportion of PCR positives. There was however a marked reduction of self-reported anosmia/hyposmia, a reduction of cough and a tendency to lower viral loads and lower IgG titers which warrants assessment in larger trials.

Nitazoxanide, a clinically approved and commercially available antiparasitic drug, has been found to have broad-spectrum antiviral activity, including against coronaviruses, influenza viruses, and hepatitis B and C viruses (Amadi et al., 2002). In patients with mild Covid-19, symptom resolution did not differ between nitazoxanide and placebo groups after 5 days of therapy. However, early nitazoxanide therapy was safe and reduced viral load significantly (Rocco et al., 2021).

Besides inflammation, COVID-19 patients may present hypercoagulability, characterized by elevation of fibrinogen levels and D-dimers, and may develop disseminated intravascular coagulation (DIC) (Helms et al., 2020; Tang N et al., 2020). Evidence confirms that thrombotic events are associated with higher mortality (Helms et al., 2020). Therefore, the Brazilian Society of Thrombosis and Hemostasis (BSTH) and the Thrombosis and Hemostasis Committee of the Brazilian Association of Hematology, Hemotherapy, and Cellular Therapy (ABHH) recommend that all patients hospitalized for suspected or confirmed COVID-19 should receive pharmacologic thromboprophylaxis in the absence of absolute contraindications.

Immunotherapies: driving the immune response against SARS-CoV2

Anti-Interleukin 6

Considered one of the most potent cytokines of the inflammatory response, and due to its pleiotropic activity, IL-6 mediates a series of physiological functions, including proliferation, differentiation, activation, and survival of immune response cells (Scheller et al., 2011; Tanaka and Kishimoto, 2014; Schaper et al., 2015; Murakami et al., 2019). Synthesized mainly by lymphocytes, monocytes, and macrophages (Scheller et al., 2011; Schaper and Rose-John, 2015), as well as stimulated by other cytokines, especially IL-1 and TNF-α (Garbers et al., 2012), IL-6 is directly involved in the exacerbation of inflammation (Scheller et al., 2011), known as a “hyper-inflammatory state”, which causes intense acute lung injury in severe COVID-19 patients, which can progress to acute respiratory distress syndrome (ARDS) (Swaroop et al., 2016). In an attempt to eliminate SARS-COV-2, this exacerbated and continuous inflammatory reaction, also named “cytokine storm”, essentially has a positive feedback between proinflammatory molecules (mainly IL-6 and TNF-α) and lymphocytes, and also natural killer cells and macrophages (Huang et al., 2020; McGonagle et al., 2020; Mehta et al., 2020; Pedersen and Ho, 2020).

To stop this inflammatory process that is harmful to the patient, some studies (Wu R et al., 2020; Xu et al., 2020; REMAP-CAP Investigators, 2021) have shown that blocking (tocilizumab or sarilumab) of IL-6 functions promotes a significant clinical improvement and better prognosis for COVID-19 patients with ARDS. Among the main benefits of this treatment, stand out: the reappearance of normal temperature, improvement of oxygenation, reduction of lung injuries, and the return of a healthy percentage of peripheral lymphocytes (Zhang et al., 2021). Although basic science suggests rationale for administration of IL-6 receptor antagonists to patients with COVID-19, the clinical evidence regarding the efficacy and safety of tocilizumab remains observational only, according to Cortegiani et al. (2021), who investigated 3 indirect pre-clinical and 28 clinical studies. Another difficulty for developing countries is the high cost of this drug.

Convalescent plasma and neutralizing antibodies-based therapies

Neutralizing antibodies (Nabs) represent an immediate possibility to solve SARS-CoV-2 infection. Therefore, therapy-based studies have also focused on this approach. Nabs target the proteins of the viral surface, impairing its attachment to host cells. Therefore, the ACE2 receptor-binding domain S1 of the SARS-CoV-2 S protein has been pointed out as a major target for Nabs-based strategies by several in vitro and in vivo models (Duan et al., 2020; Wang et al., 2020; Wrapp et al., 2020; Wu R et al., 2020; Zeng et al., 2020).

In this context, convalescent plasma-based therapies are potential strategies to treat SARS-CoV-2 infection, since patients recovered from COVID-19 can present high levels of Nabs (Chen L et al., 2020). Historically, passive immunotherapy through the collection and transfusion of convalescent plasma, was first used in the late 19th century (Simon, 2007; Marano et al., 2016). During the Spanish flu, the use of these immune derivatives showed effective clinical potential (Bogardus, 1919), reducing the mortality (Luke et al., 2006). More recently, convalescent plasma was used during the H1N1 influenza pandemic in 2009 and 2013 during the Ebola outbreak in West Africa. However, the antibody levels in COVID-19 convalescent plasma are highly variable, and assays to determine the effective antibody titers remain limited (Brown and McCullough, 2020).

Some studies have demonstrated a reduction in viral load in COVID-19 patients treated with convalescent plasma (Ahn et al., 2020; Duan et al., 2020; Shen C et al., 2020; Ye et al., 2020; Zhang et al., 2021). Almost all patients showed improvement in the clinical, laboratory and imaging parameters. However, it was not possible to attribute the favorable clinical response to convalescent plasma, as the
multiplicity of drugs used and the lack of controls prevented this conclusion (Ye et al., 2020).

**Anti-complement approaches**

The inhibition of critical inflammatory components of the complement cascade seems to be very useful because, at the same time that it blocks the adaptive immune response, it can control the tissue damage associated with the cytokine storm in severe cases of COVID-19 (Chauhan et al., 2020). This strategy was recently tested during three weeks in ten patients treated with a combination of ruxolitinib, a JAK1/2 inhibitor, and eculizumab, an anti-C5a complement monoclonal antibody. The results showed improved lung function and decreased circulating D-dimer levels (Giudice et al., 2020). Interestingly, some studies have proposed that complement blockade might be of benefit in severe COVID-19; however, several risk factors for such infections were related following eculizumab administration (Diurno et al., 2020; Laurence et al., 2020). This medicine is still being investigated in clinical trials (NCT number: 04288713 and NCT number: 04346797) for the treatment of moderate to severe pneumonia related to COVID-19.

**Main vaccines against Sars-CoV-2 available**

CoronaVac is produced by the Chinese company Sinovac Biotech. The vaccine uses the inactivated Sars-CoV-2 virus in its formulation as well as other vaccines that are under development, such as BBIBP-CorV and BBV152 (Zang et al., 2021). The vaccine passed Phase III clinical trials in Brazil, Chile, Indonesia, the Philippines, and Turkey. CoronaVac does not need to be frozen, and both the vaccine and raw material for formulating the new doses could be transported and refrigerated at 2–8 °C, temperatures at which flu vaccines are kept (Sinovac Biotech).

Several results from CoronaVac’s Phase III demonstrate positive results regarding its effectiveness. A study in Chile found it 67% effective against symptoms, reduced hospitalizations by 85%, intensive care visits by 89%, and deaths by 80%. In Brazil, it showed 50.7% effectiveness at preventing symptomatic infections and 83.7% effective in preventing mild cases needing treatment. Effectiveness against symptomatic infections increased to 62.3% with an interval of 21 days or more between the doses (Mallapati, 2021). Final Phase III results from Turkey announced on 3 March 2021 showed an effectiveness of 83.5% (Riad et al., 2021). On January 22, 2021 the Brazil’s health regulatory agency (Anvisa) granted the first CoronaVac vaccine registration against COVID-19, for emergencial use in Brazil. The immunizer from the Sinovac/Butantan Laboratory had its safety, quality and effectiveness checked and attested by Anvisa’s technical team (https://vacinacovid.butantan.gov.br/).

The vaccine produced by the pharmaceutical company AstraZeneca in conjunction with the University of Oxford has become a wide option in the fight against SARS-CoV-2. It uses a chimpanzee common cold viral vector known as ChAdOx1, which expresses the gene that allows human cells to produce the SARS-CoV-2 spike protein (AstraZeneca). Between April 23 and Nov 4, 2020, 11 636 participants from UK and Brazil were included in the interim primary effectiveness analysis. In participants who received two standard doses, vaccine effectiveness was 62.1% and in participants who received a low dose followed by a standard dose, effectiveness was 90.6%. Overall vaccine effectiveness across both groups was 70.4% (Voysey et al., 2021).

On March 12, 2021 the Anvisa authorized the distribution of the AstraZeneca / Oxford vaccine in Brazil. The immunizer produced in Brazil within Fiocruz Institute had its safety, quality and effectiveness checked and attested by Anvisa’s technical team (Ministério da Saúde, 2021c).

Another vaccine against COVID-19 similar to AstraZeneca’s is produced by the pharmaceutical company Janssen. It is known as JNJ-78436735 or Ad26.COV2.S. The viral agent used as a vector is adenovirus 26. Initially, the Janssen vaccine was shown to induce antibodies against SARS-CoV-2 in 90% of people after the first dose. Just one dose of vaccine was 66% effective in preventing moderate to severe COVID-19 and 100% effective in preventing COVID-19–related hospitalization and death (Livingston et al., 2021).

The Pfizer/BioNTech Vaccine is a lipid nanoparticle-formulated, nucleoside-modified mRNA encoding the prefusion spike glycoprotein of SARS-CoV-2. This vaccine has been recommended to people 16 years of age and older, with a dose of 30 μg (0.3 mL) IM. The vaccination requires two shots given 21 or more days apart. Anti-SARS-CoV-2 antibodies persist for at least 119 days after the first vaccination and prevention of the SARS-COV-2 infection is 95% effective (Oliver et al., 2020; Meo et al., 2021). On December 11, 2020, the US Food and Drug Administration (FDA) authorized the emergency use of the Pfizer-BioNTech COVID-19 vaccine (FDA, 2020).

On February 23, 2021 the Anvisa granted the first registration of the Pfizer/BioNTech vaccine for widespread use in the Americas. The vaccine had its safety, quality and effectiveness checked and attested by Anvisa’s technical team of servers (Ministério da Saúde, 2021a).

The Russian Institute Gamaleya developed Sputnik V (Gam-COVID-Vac), an adenovirus-based candidate vaccine against COVID-19e The Sputnik V vaccine consists of two replication-defective recombinant adenoviruses: type 26 (rAd26-S) and type 5 (rAd5-S), both carrying the gene for the SARS-Cov-2 spike glycoprotein (Logunov et al., 2020). The results of phase I-II studies indicated good immunogenicity and safety, however, only 38 volunteers were enrolled for each of the two formulations (frozen and lyophilized) (Logunov et al., 2020). Recent interim results of a Sputnik V phase 3 trial in a large cohort indicated 91.6% effectiveness against COVID-19 and lack of adverse vaccination-related adverse effects (Logunov et al., 2021).

However, the development of the Sputnik V vaccine has been criticized for unusually haste, corner cutting, and an absence of transparency (Balakrishnan, 2020; Cohen, 2020; Bucci et al., 2021). Serious concerns regarding interim results from the phase III trial were also raised (Bucci et al., 2021). Data sharing is one of the cornerstones of research integrity, yet Logunov et al. (2021) stated that raw data will not be shared before the trial is completed. Among the concerns raised are: the full study protocol has not been made publicly available; the clinical and laboratory criteria used to determine...
suspected COVID-19 were not informed; the data, numerical, and statistical significance results reported showed major inconsistencies (Bucci et al., 2021).

On April 27, 2021 the Anvisa announced that the import of the Sputnik V vaccine was not approved for use in Brazil. According to the agency, after evaluation, flaws in the development and production of the immunizing agent would have been found (Ministério da Saúde, 2021b). The concerns are similar to those now reported in May 2021 by Bucci et al. (2021).

Final considerations

Twenty months after the first Covid-19 notifications, more than 170 million individuals were infected worldwide with SARS-CoV-2, and around 3.5 million deaths occurred. Unlike the period of the last great pandemic that occurred at the beginning of the past century, the COVID-19 pandemic occurs at a time of significant scientific and technological advances in biomedical sciences, which, in theory, could be applied immediately in the control and treatment of patients. However, no drug or vaccine has yet been specifically approved for COVID-19. Therapeutic intervention approaches used successfully in other infectious agents need an in-depth investigation directed to the specific infection mechanism of the SARS-CoV-2 and the unique COVID-19 physiopathology. Among the available therapeutic approaches, such as vaccines, target inhibitors, and new drugs, the drug repurposing already approved by the FDA has been shown to be an efficient short-term alternative, mainly due to its low cost and prompt application to patients. This strategy considers the knowledge of the molecular basis of the disease. As a result of the global task force to control the COVID-19 pandemic, a new intervention was introduced by Garvin et al. (2020), who blamed the bradykinin storm for the most severe symptoms of COVID-19. The authors point out that many of the symptoms manifested by patients with COVID-19 are similar to other clinical conditions caused by the increase in bradykinin. The strategy would be pharmacologic intervention targeting the renin-angiotensin system to reduce bradykinin levels. In this sense, there exist at least ten approved drugs that might be used to control the severe symptoms of COVID-19.

The genetic variability of molecules that participate in the entry of SARS-CoV-2 into the host cells and, especially, of the numerous molecules involved in the immune responses should be considered for the development of effective therapeutic interventions. Because the frequencies of genetic variants influencing the response to drugs, as well as COVID-19 susceptibility and severity may differ widely among world populations, knowing their distribution is a critical element in seeking strategies to respond to the pandemic. Moreover, understanding the repertoire of viral epitopes that specific HLA allotypes can bind is of great importance for the development of vaccines that can provide protection for most individuals.

Computational modeling and simulations with toxicity analysis scenarios are needed to boost pharmacological interventions and drug repurposing, aiming at potential drugs to reduce viral load, viral clearance, and morbidity and mortality in clinical outcomes (Al-Kofahi et al., 2020). New therapeutic agents can be developed by analyzing theoretical structure-activity data in a three-dimensional approach, obtained by recent molecular modeling techniques. Choosing the right dose for a clinical trial requires considering the risk of toxicity and ensuring the best chance of successfully reaching therapeutic targets (Al-Kofahi et al., 2020; Dong et al., 2020). It is noteworthy that in vitro to in vivo extrapolations can underestimate or overestimate the real needs of medicines, but it is considered an initial advance.

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Conflict of Interest

The authors declare no conflict of interest.

Author Contributions

DLAF conceived and designed this manuscript, JPBX, FRFS, CP and RSB drafted the manuscript, and designed the figure and the table, AF, ALC, AIM, AMFA, AR, ABWB, CFM, CMC, DP, DR, DFG, DMF, DV, ERT, EC, EMFSR, EMP, FFT, FACC, GSAF, HV, IMC, JCO, JHSR, JLS, JELV, JCBDP, JMS, JSB, KBO, KE, LCL, LCFG, LEDF, LMY, MELC, MRC, MAA, MP, MAEW, MARC, MJSMG, MKA, NMK, QALN, RHH, RLG, RNS, MM, SFYO, VKQG, WRP and WCS drafted the manuscript and proofread the manuscript technically, MLPE, VV, CPS, LRC and WASI formulated and supervised the study. All authors read, revised and approved the final manuscript.

References

Ahn JY, Sohn Y, Lee SH, Cho Y, Hyun JH, Baek YJ, Jeong SJ, Kim JH, Ku NS, Yeom JS et al. (2020) Use of convalescent plasma therapy in two COVID-19 patients with acute respiratory distress syndrome in Korea. J Korean Med Sci 35:e149.

Alifano M, Alifano P, Forgez P and Iannelli A (2020) Renin-angiotensin system at the heart of COVID-19 pandemic. Biochimie 174:30-33.

Al-Kofahi M, Jacobson P, Boulware DR, Matas A, Kandaswamy R, Jaber MM, Rajasingham R, Young JAH and Nicol MR (2020) Finding the dose for hydroxychloroquine prophylaxis for COVID-19: The desperate search for effectiveness. Clin Pharmacol Ther 108:766-769.

Amadi B, Mwiya M, Musuku J, Watuka A, Sianongo S, Ayoob A and Kelly P (2002) Effect of nitazoxanide on morbidity and mortality in Zambian children with cryptosporidiosis: A randomised controlled trial. Lancet 360:1375-1380.

Amoroso A, Magistrini P, Vespasiano F, Bella A, Bellino S, Puoti F, Alizzi S, Vaisitti T, Boros S, Grossi PA et al. (2021) HLA and AB0 polymorphisms may influence SARS-CoV-2 infection and COVID-19 severity. Transplantation 105:193-200.

Anastassopoulou C, Gikarioti Z, Patrinos GP and Tsakris A (2020) Human genetic factors associated with susceptibility to SARS-CoV-2 infection and COVID-19 disease severity. Hum Genomics 14:40.
Arisan ED, Dart A, Grant GH, Arisan S, Cuhadaroglu S, Lange S and Uysal-Ozgener P (2020) The prediction of miRNAs in SARS-CoV-2 genomes: hsa-miR databases identify 7 key miRs linked to host responses and virus pathogenicity-related KEGG pathways significant for comorbidities. Viruses 12:614.

Asha K, Kumar P, Sanicas M, Meseko CA, Khanna M and Kumar B (2018) Advancements in nucleic acid based therapeutics against respiratory viral infections. J Clin Med 8:6.

Ashburn TT and Thor KB (2004) Drug repositioning: Identifying and developing new uses for existing drugs. Nat Rev Drug Discov 3:673-683.

Asselta R, Paraboschi EM, Mantovani A and Duga S (2020) ACE2 and TMPRSS2 variants and expression as candidates to sex and country differences in COVID-19 severity in Italy. Aging (Albany NY) 12:10087-10098.

Badawi A (2020) Hypercytokinemia and pathogen-host interaction in COVID-19. J Inflammm Res 13:255-261.

Báez-Santos YM, St John SE and Mesecar AD (2015) The SARS-coronavirus papain-like protease: Structure, function and inhibition by designed antiviral compounds. Antiviral Res 115:21-38.

Baig AM, Khaleeq A, Ali U and Syeda H (2020) Evidence of the COVID-19 virus targeting the CNS: Tissue distribution, host-virus interaction, and proposed neurotropic mechanisms. ACS Chem Neurosci 11:995-998.

Balakrishnan VS (2020) The arrival of Sputnik V. Lancet Infect Dis 20:1128.

Bao H, Gao F, Xie G and Liu Z (2015) Angiotensin-converting enzyme 2 inhibits apoptosis of pulmonary endothelial cells during acute lung injury through suppressing miR-4262. Cell Physiol Biochem 37:759-767.

Barbu MG, Condrat CE, Thompson DC, Bugnar OL, Cretoiu D, Baig AM, Khaleeq A, Ali U and Syeda H (2020) ACE2 involvement in signaling pathways during viral infection. Front Cell Dev Biol 8:143.

Bartoszewski R, Dabrowski M, Jakieła B, Matalon S, Harrod KS, Sanak M and Collawn JF (2020) SARS-CoV-2 may regulate cellular responses through depletion of specific host miRNAs. Am J Physiol Lung Cell Mol Physiol 319:L444-L455.

Becerra-Flores M and Cardozo T (2020) SARS-CoV-2 viral spike G614 mutation exhibits higher case fatality rate. Int J Clin Pract 74:e13525.

Behe KM, Beier J, Espererster A and Paul LD (2008) Antiinflammatory properties of ambroxol. Eur J Res Med 13:557-562.

Benetti E, Tita R, Spiga O, Cioffi A, Birolo G, Bruselles A, Doddato B, Becerra-Flores M and Cardozo T (2020) SARS-CoV-2 main protease Mpro for COVID-19 treatment: An in silico approach. Mem Inst Oswaldo Cruz 115:e2000179.

Bogardus FB (1919) Influenza pneumonia treated by blood Transfusion. South Med J 109:765-768.

Borba MGS, Val FFA, Sampaio VS, Alexandre MA, Melo GC, Brito M, Mourão MPG, Brito-Sousa JD, Baia-da-Silva D, Guerra MVF et al. (2020) Effect of high vs low doses of chloroquine diphosphate as adjunctive therapy for patients hospitalized with severe acute respiratory syndrome Coronavirus 2 (SARS-CoV-2) infection. JAMA Netw Open 3:e200857.

Bosch BJ, Martina BEE, Van Der Zee R, Lepault J, Hajjema BJ, Versluis C, Heck AJR, De Groot R, Osterhaus AD and Rottier PJM (2004) Severe acute respiratory syndrome Coronavirus (SARS-CoV) infection inhibition using spike protein heptad repeat-derived peptides. Proc Natl Acad Sci U S A 101:8455-8460.

Boulware DR, Pullen MF, Bangdiwala AS, Pastick KA, Lofgren SM, Okao EC, Skipper CP, Nascene AA, Nicol MR, Abassi M et al. (2020) A randomized trial of hydroxychloroquine as postexposure prophylaxis for Covid-19. N Engl J Med 383:517-525.

Brown BL and McCullough J (2020) Treatment for emerging viruses: Convalescent plasma and COVID-19. Transfus Apher Sci 59:102790.

Bruscella P, Bottini S, Baudesson C, Pawlotsky J-M, Feray C and Trabucchi M (2017) Viruses and miRNAs: More friends than foes. Front Microbiol 8:824.

Buemi E, Berkhof J, Gillibert A, Gopalakrishna G, Calogero RA, Butler LM, Andreev K, Naudet F and Vlassov V (2021) Data discrepancies and substandard reporting of interim data of Sputnik V phase 3 trial. Lancet 397:1881-1883.

Buonaguro L, Tagliamonte M, Tornesello ML and Buonaguro FM (2020) SARS-CoV-2 RNA polymerase as target for antiviral therapy. J Transl Med 18:185.

Calabrese C, Annunziata A, Coppola A, Pafundi PC, Guarino S, Di Spirito V, Maddaloni V, Pepe N and Fiorentino G (2021) ACE gene I/D polymorphism and acute pulmonary embolism in COVID19 pneumonia: A potential predisposing role. Front Med (Lausanne) 7:631148.

Caly L, Druce JD, Catton MG, Jans DA and Wagstaff KM (2020) The FDA-approved drug ivermectin inhibits the replication of SARS-CoV-2 in vitro. Antiviral Res 178:104787.

Cao B, Wang Y, Liu W, Wang J, Fan G, Ruan L, Song B, Cao Y, Li L, Feng Z, Wan S, Huang P, Sun X, Wen F, Huang X, Ning G and Wang W (2020) Comparative genetic analysis of the novel coronavirus (2019-nCoV/SARS-CoV-2) receptor ACE2 in different populations. Cell Discov 6:11.

Cento A, Fonseca AS, Ferreira SGDS, Azevedo MLV, Vaz de Paula CB, Nagashima S, Machadinho-Souza C, Miggiolaro AFGRS, Baena CP, de Noronha L et al. (2020) Deregulated miRNA expression is associated with endothelial dysfunction in post-mortem lung biopsies of COVID-19 patients. Am J Physiol Lung Cell Mol Physiol 320:L405–L414.

Chaccour C, Casellas A, Matteo AB-D, Pineda I, Fernandez-Montero A, Ruiz-Castillo P, Richardson M-A, Rodriguez-Mateos M, Jordán-Iborra C, Brew J et al. (2021) The effect of early treatment with ivermectin on viral load, symptoms and humoral response in patients with non-severe COVID-19: A pilot, double-blind, placebo-controlled, randomized clinical trial. EClinicalMedicine 32:100720.
Channappanavar R, Fett C, Mack M, Eyck PPT, Meyerholz DK and Perlman S (2017) Sex-based differences in susceptibility to severe acute respiratory syndrome coronavirus infection. J Immunol 198:4046-4053.

Chauhan AJ, Wiffen LJ and Brown TP (2020) COVID-19: A collision of complement, coagulation and inflammatory pathways. J Thromb Haemost 18:2110-2117.

Chen L, Xiong J, Bao L and Shi Y (2020) Convalescent plasma as a potential therapy for COVID-19. Lancer Infect Dis 20:398-400.

Chen L-J, Xu R, Yu H-M, Chang Q and Zhong J-C (2015) The ACE2/Apelin signaling, microRNAs, and hypertension. Int J Hypertens 2015:896861.

Chen Y, Liu Q and Guo D (2020) Emerging coronaviruses: Genome structure, replication, and pathogenesis. J Med Virol 92:418-423.

Chowdhury T, Roymahapatra G and Mandal SM (2020) In silico identification of a potent arsenic based approved drug dariparins against SARS-CoV-2: Inhibitor of RNA dependent RNA polymerase (RdRp) and essential proteases. Insect Disord Drug Targets 21:608-618.

Cohen J (2020) Russia’s claim of a successful COVID-19 vaccine doesn’t pass the ‘smell test,’ critics say. Science. DOI: 10.1126/science.abb6791.

Cornillez-Ty CT, Liao L, Yates JR, Kuhn P and Buchmeier MJ (2009) Evidence on the use of tocilizumab in COVID-19: A systematic review. Pulmonaryology 27:52-66.

Cortegiani A, Ippolito M, Greco M, Granolle V, Protti A, Gregoretti C, Giarratano A, Eina S and Cecconi M (2021) Rational and evidence on the use of tocilizumab in COVID-19: A systematic review. Pulmonology 27:52-66.

Couillard B, Valle C, de Lamballerie X, Canard B, Seidah NG and Decroy E (2020) The spike glycoprotein of the new coronavirus 2019-nCoV contains a furin-like cleavage site absent in CoV of the same clade. Antiviral Res 176:104742.

Dai W, Zhang B, Jiang X-M, Su H, Li J, Zhao Y, Xie X, Jin Z, Peng J, Liu F et al. (2020) Structure-based design of antiviral drug candidates targeting the SARS-CoV-2 main protease. Science 368:1331-1335.

Damas ND, Fossat N and Scheel TKH (2019) Functional interplay between RNA viruses and non-coding RNA in mammals. Noncoding RNA 5:1.

Datta RK, Chinnapaiyan S and Unwalla H (2019) Aberrant microRNAomics in pulmonary complications: Implications in lung health and diseases. Mol Ther Nucleic Acids 18:413-431.

Eckerle LD, Becker MM, Halpin RA, Li K, Venter E, Lu X, Scherbakova S, Graham RL, Baric RS, Stockwell TB et al. (2010) Infidelity of SARS-CoV Nsp14-exonuclease mutant virus replication is revealed by complete genome sequencing. PLoS Pathog 6:e1000896.

Elbe S and Buckland-Merrett G (2017) Data, disease and diplomacy: GISAID’s innovative contribution to global health. Glob Chall 1:33-46.

Elfiky AA (2020) Anti-HCV, nucleotide inhibitors, repurposing against COVID-19. Life Sci 248:117477.

Ellinghaus D, Degenhardt F, Bujanda L, Buti M, Albillos A, Invernozi P, Fernandez J, Prati D, Baselli G, Assetta R et al. (2020) The ABO blood group locus and a chromosome 3 gene cluster associate with SARS-CoV-2 respiratory failure in an Italian-Spanish genome-wide association analysis. medRxiv. DOI: 10.1101/2020.05.31.20114991.

Fan BSO, Vargus-Pinilla P, Amorim CEG, Sortica VA and Bortolini MC (2020) ACE2 diversity in placental mammals reveals the evolutionary strategy of SARS-CoV-2. Genet Mol Biol 43:e20200104.

Fernández-Hernando C and Suárez Y (2018) MicroRNAs in endothelial cell homeostasis and vascular disease. Curr Opin Hematol 25:227-236.

Finglert-Medina A, Konrad S, Castronovo CQ, Lima CR, Silva FS, Ferreira AC, Mattos M, de Freitas CS, Soares VC, Dias SSG, Temerozo JR et al. (2020) Atazanavir, alone or in combination with ritonavir, inhibits SARS-CoV-2 replication and proinflammatory cytokine production. Antimicrob Agents Chemother 64:e00825-20.

Furgala-Wojas A, Kowalska M, Nowacyzk A, Fijałkowski Ł and Sałat J (2015) Plasticity and cross-talk of endothelial cell homeostasis and vascular disease. Curr Opin Hematol 22:85-97.

Garbers C, Hermans MM, Schaper F, Müller-Newen G, Grötzinger J, Rose-John S and Scheller J (2012) Plasticity and cross-talk of Interleukin 6-type cytokines. Cytokine Growth Factor Rev 23:85-97.

Garvin MR, Alvarez C, Miller JJ, Prates ET, Walker AM, Amos BK, Mast AE, Justice A, Aronow B and Jacobson D (2020) A mechanistic model and therapeutic interventions for COVID-19 involving a RAS-mediated Bradykinin storm. Elife 9:e59177.

Gentile D, Patamia V, Scala A, Sciortino MT, Piperno A and Rescifina A (2020) Putative inhibitors of SARS-CoV-2 main protease from a library of marine natural products: A virtual screening and molecular modeling study. Mar Drugs 18:225.
Ghafouri-Fard S, Noroozi R, Omran MD, Braniwicki W, Psipiech E, Sayad A, Pyke K, Labaj PP, Valsaee R, Taileri M et al. (2020) Angiotensin converting enzyme: A review on expression profile and its association with human disorders with special focus on SARS-CoV-2 infection. Vascul Pharmacol 130:106680.

Ghosh S, Firdous SM and Nath A (2020) siRNA could be a potential therapy for COVID-19. EXCLI J 19:528-531.

Gibson WT, Evans DM, An J and Jones SJM (2020) ACE 2 coding variants: A potential X-linked risk factor for COVID-19 disease. bioRxiv: 2020.04.05.026633.

Gildenhuys S (2020) Expanding our understanding of the role polyprotein conformation plays in the coronavirus life cycle. Biochem J 477:1479-1482.

Girardi E, López P and Pfeffer S (2018) On the importance of host microRNAs during viral infection. Front Genet 9:439.

Giudice V, Pagliano P, Vattrella A, Masullo A, Poto S, Polverino BM, Gammaldi R, Maglio A, Sellitto C, Vitale C et al. (2020) Combination of ruxolitinib and eculizumab for treatment of severe SARS-CoV-2-Related acute respiratory distress syndrome: A controlled study. Front Pharmacol 11:857.

Ghafouri-Fard S, Noroozi R, Omrani MD, Branicki W, Psipiech E, Sayad A, Pyke K, Labaj PP, Valsaee R, Taileri M et al. (2020) Angiotensin converting enzyme: A review on expression profile and its association with human disorders with special focus on SARS-CoV-2 infection. Vascul Pharmacol 130:106680.

Ghosh S, Firdous SM and Nath A (2020) siRNA could be a potential therapy for COVID-19. EXCLI J 19:528-531.

Gibson WT, Evans DM, An J and Jones SJM (2020) ACE 2 coding variants: A potential X-linked risk factor for COVID-19 disease. bioRxiv: 2020.04.05.026633.

Gildenhuys S (2020) Expanding our understanding of the role polyprotein conformation plays in the coronavirus life cycle. Biochem J 477:1479-1482.

Girardi E, López P and Pfeffer S (2018) On the importance of host microRNAs during viral infection. Front Genet 9:439.

Giudice V, Pagliano P, Vattrella A, Masullo A, Poto S, Polverino BM, Gammaldi R, Maglio A, Sellitto C, Vitale C et al. (2020) Combination of ruxolitinib and eculizumab for treatment of severe SARS-CoV-2-Related acute respiratory distress syndrome: A controlled study. Front Pharmacol 11:857.

Ghafouri-Fard S, Noroozi R, Omrani MD, Branicki W, Psipiech E, Sayad A, Pyke K, Labaj PP, Valsaee R, Taileri M et al. (2020) Angiotensin converting enzyme: A review on expression profile and its association with human disorders with special focus on SARS-CoV-2 infection. Vascul Pharmacol 130:106680.

Ghosh S, Firdous SM and Nath A (2020) siRNA could be a potential therapy for COVID-19. EXCLI J 19:528-531.

Gibson WT, Evans DM, An J and Jones SJM (2020) ACE 2 coding variants: A potential X-linked risk factor for COVID-19 disease. bioRxiv: 2020.04.05.026633.

Gildenhuys S (2020) Expanding our understanding of the role polyprotein conformation plays in the coronavirus life cycle. Biochem J 477:1479-1482.

Girardi E, López P and Pfeffer S (2018) On the importance of host microRNAs during viral infection. Front Genet 9:439.

Giudice V, Pagliano P, Vattrella A, Masullo A, Poto S, Polverino BM, Gammaldi R, Maglio A, Sellitto C, Vitale C et al. (2020) Combination of ruxolitinib and eculizumab for treatment of severe SARS-CoV-2-Related acute respiratory distress syndrome: A controlled study. Front Pharmacol 11:857.

Ghafouri-Fard S, Noroozi R, Omrani MD, Branicki W, Psipiech E, Sayad A, Pyke K, Labaj PP, Valsaee R, Taileri M et al. (2020) Angiotensin converting enzyme: A review on expression profile and its association with human disorders with special focus on SARS-CoV-2 infection. Vascul Pharmacol 130:106680.

Ghosh S, Firdous SM and Nath A (2020) siRNA could be a potential therapy for COVID-19. EXCLI J 19:528-531.

Gibson WT, Evans DM, An J and Jones SJM (2020) ACE 2 coding variants: A potential X-linked risk factor for COVID-19 disease. bioRxiv: 2020.04.05.026633.

Gildenhuys S (2020) Expanding our understanding of the role polyprotein conformation plays in the coronavirus life cycle. Biochem J 477:1479-1482.

Girardi E, López P and Pfeffer S (2018) On the importance of host microRNAs during viral infection. Front Genet 9:439.
Laurence J, Mulvey JJ, Seshadri M, Racanelli A, Harp J, Schenck EJ, Zappetti D, Horn EM and Magro CM (2020) Anti-complement C5 therapy with eculizumab in three cases of critical COVID-19. Clin Immunol 219:108555.

Letko M, Marzi A and Munster V (2020) Functional assessment of cell entry and receptor usage for SARS-CoV-2 and other lineage B betacoronaviruses. Nat Microbiol 5:562-569.

Li F, Li W, Farzan M and Harrison SC (2005) Structure of SARS coronavirus spike receptor-binding domain complexed with its receptor. Science 309:1864-1868.

Li Q, Cao Z and Rahman P (2020) Genetic variability of human angiotensin-converting enzyme 2 (hACE2) among various ethnic populations. Mol Genet Genomic Med 8:e1344.

Li W, Moore MJ, Vasilieva N, Sui J, Wong SK, Berne MA, Somasundaran M, Sullivan JL, Luzuriaga K, Greenough TC et al. (2003) Angiotensin-converting enzyme 2 is a functional receptor for the SARS coronavirus. Nature 426:450-454.

Li W, Sui J, Huang I-C, Kuhn JH, Radashitzky SR, Marasco WA, Choe H and Farzan M (2007) The S proteins of human coronavirus NL63 and severe acute respiratory syndrome coronavirus bind overlapping regions of ACE2. Virology 367:367-374.

Li W, Zhang C, Sui J, Kuhn JH, Moore MJ, Luo S, Wong S-K, Huang I-C, Xu K, Vasilieva N et al. (2005) Receptor and viral determinants of SARS-coronavirus adaptation to human ACE2. EMBO J 24:1634-1643.

Li X, Zeng W, Li X, Chen H, Shi L, Li X, Xiang H, Cao Y, Chen H, Liu C et al. (2020) CT imaging changes of coronavirus disease 2019 (COVID-19): A multi-center study in Southwest China. J Transl Med 18:154.

Licastro D, Rajasekharan S, Dal Monego S, Segat L, D’Agaro P, Li X, Zeng W, Li X, Chen H, Shi L, Li X, Xiang H, Cao Y, Chen H, Liu C et al. (2020) CT imaging changes of coronavirus disease 2019 (COVID-19): A multi-center study in Southwest China. J Transl Med 18:154.

Licastro D, Rajasekharan S, Dal Monego S, Segat L, D’Agaro P, Li X, Zeng W, Li X, Chen H, Shi L, Li X, Xiang H, Cao Y, Chen H, Liu C et al. (2020) CT imaging changes of coronavirus disease 2019 (COVID-19): A multi-center study in Southwest China. J Transl Med 18:154.

Lippe G, Lavie CJ, Henry BM and Sanchis-Gomar F (2020) Do genetic polymorphisms in angiotensin converting enzyme 2 (ACE2) gene play a role in coronavirus disease 2019 (COVID-19)? Clin Chem Lab Med 58:1415-1422.

Livingston EH, Preeti NM and Creech CB (2021) The Johnson & Johnson vaccine for COVID-19. JAMA 325:1575.

Loczcechin A, Seron K, Barras A, Giovaneli E, Belouzard S, Chen Y-T, Metzler-Nolte N, Boukkerhour R, Dubusson J and Sznurieris S (2019) Functional carbon quantum dots as medical countermeasures to human Coronavirus. ACS Appl Mater Interfaces 11:42964-42974.

Logunov DY, Dolzhikova IV, Kublova OV, Tikhvatullin AI, Shcheblyakov DV, Dzhurailava AS, Groussova DM, Erokhova AS, Kovyrshina AV, Botikov AG et al. (2020) Safety and immunogenicity of an rAd26 and rAd5 vector-based heterologous prime-boost COVID-19 vaccine in two formulations: two open, non-randomised phase 1/2 studies based on clinical heterologous prime-boost COVID-19 vaccine in two formulations: two open, non-randomised phase 1/2 studies. Lancet 396:887-897.

Lopes RD, Macedo AVS, de Barros e Silva PGM, Moll-Bernardes RJ, Feldman A, D’Andrea G, Arruda S, de Souza AS, de Albuquerque DC, Lilian Mazza RT et al. (2020) Continuing versus suspending angiotensin-converting enzyme inhibitors and angiotensin receptor blockers: Impact on adverse outcomes in hospitalized patients with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) - The BRACE CORONA. Trial Am Heart J 13:49-59.

Lorente L, Martín MM, Franco A, Barrios Y, Cáceres JJ, Solé-Violán J, Perez A, Marcos Y, Ramos JA, Ramos-Gómez L et al. (2021) HLA genetic polymorphisms and prognosis of patients with COVID-19. Med Intensiva (Engl Ed) 45:96-103.

Lu R, Zhao X, Li J, Niu P, Yang B, Wu H, Wang W, Song H, Huang B, Zhu N et al. (2020) Genomic characterization and epidemiology of 2019 novel coronavirus: Implications for virus origins and receptor binding. Lancet 395:565-574.

Lukassen S, Chua RL, Trefzer T, Kuhn NC, Schneider MA, Mulvey T, Winter H, Meister M, Veith C, Boots AW et al. (2020) SARS-CoV-2 receptor ACE2 and TMPRSS2 are primarily expressed in bronchial transient secretory cells. EMBO J 39:e105114.

Luke TC, Kilbane EM, Jackson JL and Hoffman SL (2006) Meta-Analysis: Convalescent blood products for Spanish influenza pneumonia: A future H5N1 treatment? Ann Intern Med 145:599-609.

Mallapaty S (2021) China COVID vaccine reports mixed results - What does that mean for the pandemic? Nature. DOI: 10.1038/d41586-021-00094-z.

Malby S, Plank M, Tay HL, Collison A and Foster PS (2016) Targeting MicroRNA function in respiratory diseases: Mini-review. Front Physiol 7:21.

Marano G, Vaglio S, Pupella S, Faco G, Catalano L, Liubrumo GM and Grazzini G (2016) Convalescent plasma: New evidence for an old therapeutic tool? Blood Transfus 14:152-157.

Marchi R, Sugita B, Canta A, Fonseca AS, Bortoletto S, Fiorentin K, Ferreira S and Cavalli LR (2021) The role of microRNAs in modulating SARS-CoV-2 infection in humans: a systematic review. Infect Genet Evol 91:104832.

Matsuyama S, Nagata N, Shiraito K, Kawase M, Takeda M and Taguchi F (2010) Efficient activation of the severe acute respiratory syndrome coronavirus spike protein by the transmembrane protease TMPRSS2. J Virol 84:12658-12664.

Matsuyama S, Nao N, Shiraito K, Kawase M, Saito S, Takayama I, Nagatac N, Sekizuka T, Kato H, Kato F et al. (2020) Enhanced isolation of SARS-CoV-2 by TMPRSS2-expressing cells. Proc Natl Sci U S A 117:7001-7003.

McCoy J, Wambier CG, Vano-Galvan S, Shapiro J, Sinclair R, Ramos PM, Washenik K, Andrade M, Herrera S and Goren A (2020) Racial variations in COVID-19 deaths may be due to androgen receptor genetic variants associated with prostate cancer and androgenetic aloppecia. Are anti-androgens a potential treatment for COVID-19? J Cosmet Dermatol 19:1542-1543.

Mc Gonagle D, Sharif K, O’Regan A and Bridge wood C (2020) The role of cytokines including Interleukin-6 in COVID-19 induced pneumonia and macrophage activation syndrome-like disease. Autoimmun Rev 19:102537.

Mehta P, McAuley DF, Brown M, Sanchez E, Tattersall RS, Manson JJ and HLH Across Speciality Collaboration UK (2020) COVID-19: Consider cytokine storm syndromes and immunosuppression. Lancet 395:1033-1034.

Meng G, Surana NK, St Ge me JW and Waksman G (2006) Structure of the outer membrane translocator domain of the Haemophilus influenzae Hia trimeric autotransporter. EMBO J 25:2297-2304.

Meo SA, Bukhari IA, Akram J, Meo AS and Klonoff DC (2021) COVID-19 vaccines: Comparison of biological, pharmacological characteristics and adverse effects of Pfizer/BioNTech and Moderna Vaccines. Eur Rev Med Pharmacol Sci 25:1663-1669.

Mercuro NJ, Yen CF, Shim DJ, Maher TR, McCoy CM, Zimetbaum PJ and Gold HS (2020) Risk of QT interval prolongation associated with use of hydroxychloroquine with or without concomitant azithromycin among hospitalized patients testing positive for coronavirus disease 2019 (COVID-19). JAMA Cardiol 5:e201834.

Mishra R, Kumar A, Ingle H and Kumar H (2020) The interplay between viral-derived mirnas and host immunity during infection. Front Immunol 10:3079.

Mohammadpour S, Esfahani AT, Halaji M, Lak M and Ranjbar R (2021) An updated review of the association of host genetic factors with susceptibility and resistance to COVID-19. J Cell Physiol 236:49-54.

Murakami M, Kamimura D and Hirano T (2019) Pleiotropy and specificity: Insights from the Interleukin 6 family of cytokines. Immunity 50:812-831.
COVID-19: genetic and therapeutics

Nersisyan S, Shkurnikov M, Turchinovich A, Knayzev E and Tenevitsky A (2020) Integrative analysis of miRNA and mRNA sequence data reveals potential regulatory mechanisms of ACE2 and TMPRSS2. PLoS One 15:e0235987.

Nguyen A, David JK, Maden SK, Wood MA, Weeder BR, Nellore A and Thompson RF (2020) Human leukocyte antigen susceptibility map for SARS-CoV-2. J Virol 94:e00510-20.

Ni B, Shi X, Li Y, Gao W, Wang X and Wu Y (2005) Inhibition of replication and infection of severe acute respiratory syndrome-associated coronavirus with plasmid-mediated interference RNA. Antivir Ther 10:527-533.

Oliver SE, Gargano JW, Marin M, Wallace M, Curran KG, Chamberland M, McClung N, Campos-Outcalt D, Morgan RL, Mbaeyi S et al. (2020) The Advisory Committee on Immunization Practices’ Interim Recommendation for Use of Pfizer-BioNTech COVID-19 Vaccine - United States, December 2020. MMWR Morb Mortal Wkly Rep 69:1922-1924.

Olubiyi OO, Olagunju M, Keutmann M, Loschitz J and Strodel B (2020) High throughput virtual screening to discover inhibitors of the main protease of the Coronavirus SARS-CoV-2. Molecules 25:3193.

Ovchinnikova ES, Schmitter D, Vegter EL, ter Maaten JM, Valente MAE, Liu LCY, van der Harst P, Pinto YM, de Boer RA, Meyer S et al. (2015) Signature of circulating microRNAs in patients with acute heart failure. Eur J Heart Fail 18:414-423.

Ovsyannikova IG, Haralambieva IH, Crooke SN, Poland GA and Poland MJ (2020) Association of treatment with hydroxychloroquine or azithromycin with in-hospital mortality in patients with COVID-19 in New York State. JAMA 323:2493-2502.

Peck KM and Lauring AS (2018) Complexities of viral mutation rates. J Virol 92:e01031-01017.

Petersen SF and Ho Y-C (2020) SARS-CoV-2: A storm is raging. J Clin Invest 130:2202-2205.

Pentini A, Hosseini MM and Akhavan-Niaki H (2021) First comprehensive computational analysis of functional consequences of TMPRSS2 SNPs in susceptibility to SARS-CoV-2 among different populations. J Biomol Struct Dyn 39:3576-3593.

Peng L, Liu K-Y, Xue F, Xiao Y-F, Tu P-A and Zhou C (2020) High throughput virtual screening to discover inhibitors of the main protease of the Coronavirus SARS-CoV-2. Molecules 25:3193.

Paria K, Paul D, Chowdhury T, Pyne S, Chakraborty R and Mandal AK and Thompson RF (2020) The role of host genetics in the immune response to SARS-CoV-2 and COVID-19 susceptibility and severity. Immuno Rev 296:205-219.

Paniri A, Hosseini MM and Akhavan-Niaki H (2021) First comprehensive computational analysis of functional consequences of TMPRSS2 SNPs in susceptibility to SARS-CoV-2 among different populations. J Biomol Struct Dyn 39:3576-3593.

Peck KM and Lauring AS (2018) Complexities of viral mutation rates. J Virol 92:e01031-01017.

Petersen SF and Ho Y-C (2020) SARS-CoV-2: A storm is raging. J Clin Invest 130:2202-2205.

Peng L, Liu K-Y, Xue F, Xue X, Peng X, Tu P-A and Zhou C (2020) Improved early recognition of coronavirus disease-2019 (COVID-19): Single-center data from a Shanghai Screening Hospital. Arch Intern Med 203:272-276.

Peng M, Watanabe S, Chan KWK, He Q, Zhao Y, Zhang Z, Lai X, Luo D, Vasudevan S G and Li G (2017) Luteolin restricts dengue virus replication through inhibition of the proprotein convertase furin. Antivir Res 143:176-185.

Pinto D, Park Y-J, Beltramello M, Walls AC, Tortorić MA, Bianchi S, Jaconi S, Culap K, Zatta F, De Marco A et al. (2020) Cross-neutralization of SARS-CoV-2 by a human monoclonal SARS-CoV antibody. Nature 583:290-295.

Preziosi PR, Maier MC, Woods BA and Charchar FJ (2020) A guide to the short, long and circular RNAs in hypertension and cardiovascular disease. Int J Mol Sci 21:3666.

Pushpamok S, Iorio F, Eyers PA, Escott KJ, Hopper S, Wells A, Doig MA, Guilliams T, Latimer J, McNamee C et al. (2020) Association of treatment with hydroxychloroquine or azithromycin with in-hospital mortality in patients with COVID-19 in New York State. JAMA 323:2493-2502.

Rapoport M, Ruggiero A, Squeglia F, Maga G and Berisio R (2020) Structural view of SARS-CoV-2 RNA replication machinery: RNA synthesis, proofreading and final capping. Cells 9:1267.

Rosa SGV and Santos WC (2020) Clinical trials on drug repositioning for COVID-19 treatment. Rev Panam Salud Publica 44:e40.

Rocco PRM, Silva PL, Cruz FF, Melo-Junior MAC, Tierno PFGMM, Moura MA, De Oliveira LFG, Lima CC, Dos Santos EA, Junior WF et al. (2021) Early use of nizatidine in mild Covid-19 disease: Randomised, placebo-controlled trial. Eur Respir J 14:2003725.

Romano M, Ruggiero A, Squeglia F, Maga G and Berisio R (2020) Structural view of SARS-CoV-2 RNA replication machinery: RNA synthesis, proofreading and final capping. Cells 9:1267.

Sah R, Rodriguez-Morales AJ, Jha R, Chu DKW, Gu H, Peiris M, Bastolla A, Lal BK, Ojha HC, Rabaan AA et al. (2020) Complete genome sequence of a 2019 novel Coronavirus (SARS-CoV-2) strain isolated in Nepal. Microbiol Resour Announc 9:e00169-20.

Saha I, Ghosh N, Maity D, Sharma N, Sarkar JP and Mitra K (2020) Genome-wide analysis of Indian SARS-CoV-2 genomes for the identification of genetic mutation and SNP. Infect Genet Evol 85:104457.

Salmena L, Poliseno L, Tay Y, Kats L and Pandolfi PP (2011) A ceRNA hypothesis: The Rosetta Stone of a hidden RNA language? Cell 146:353-358.

Sapoval N, Mahmoud M, Jochum MD, Liu Y, ElworthRAL, Wang Q, Albín D, Ogilvie HA, Lee MD, Villapal S et al. (2021) Hidden genomic diversity of SARS-CoV-2: Implications for qRT-PCR diagnostics and transmission. Genome Res 31:635-644.

Sarma A, Phukan H, Halder N and Madanan MG (2020) An in-silico approach to study the possible interactions of miRNA between human and SARS-CoV2. Comput Biol Chem 88:107352.

Schaper F and Rose-John S (2015) Interleukin-6 receptor antagonists in critically ill patients with Covid-19. N Engl J Med 384:1491-1502.

Rad SAH and McLellan AD (2020) Implications of SARS-CoV-2 mutations for genomic RNA structure and host microRNA targeting. Int J Mol Sci 21:4807.

RECOVERY Collaborative Group (2021) Dexamethasone in hospitalized patients with Covid-19 - Preliminary report. N Engl J Med 384:693-704.
Figueiredo et al.

Soufi GJ and Iravani S (2021) Potential inhibitors of SARS-CoV-2: A preliminary report from Iran. Infect Genet Evol 84:104384.

Toriello L, Kerr E, Cowled C, Bean AGD, Stewart CR, Dearnley M and Farr RJ (2020) MicroRNA biomarkers for infectious diseases: From basic research to biosensing. Front Microbiol 11:1197.

Trobaugh DW and Khalimova WB (2017) MicroRNA regulation of RNA replication and pathogenesis. Trends Mol Med 23:80-93.

From basic research to biosensing. Front Microbiol 11:1197.

Towle D, Martin A, Bartels S, Ewens W, Bao Y, et al. (2020) Safety and efficacy of the ChAdOx1 nCoV-19 vaccine against SARS-CoV-2: an interim analysis of four randomised controlled trials in Brazil, South Africa, and the UK. Lancet 397:99-111.

Toutou AL and Baric RS (2012) SARS coronavirus pathogenesis: Host innate immune responses and viral antagonism of interferon. Curr Opin Virol 2:264-275.

U S A 117:11727-11734.

Uludag H, Parent K, Aebiabadi HM and Haddadi A (2020) Prospects for RNAi therapy of COVID-19. Front Med Biol 8:916.

Vegter EL, Ovchinnikova ES, van Veldhuisen DJ, Jaarsma T, et al. (2020) Mechanisms and enzymes involved in SARS coronavirus genome expression. J Gen Virol 84:2305-2315.

Walls AC, Park Y-J, Tortorici MA, Wall A, McGuire AT and Veesler D (2020) Structure, function, and antigenicity of the SARS-CoV-2 spike glycoprotein. Cell 181:281-292.

Warren RL and Birrell I (2021) HLA predictions from the bronchoalveolar lavage fluid and blood samples of eight COVID-19 patients at the pandemic onset. Bioinformatics 36:5271-5273.

Wrapp D, Wang N, Corbett KS, Goldsmith JA, Hsieh C-L, Abiona O, Graham BS and McElhaney JS (2020) Cryo-EM structure of the 2019-nCoV spike in the prefusion conformation. Science 367:1260-1263.

Wu C-J, Huang H-W, Liu C-Y, Hong C-F and Chan Y-L (2005) Ribavirin shows antiviral activity against SARS-CoV-2 and downregulates the activity of TMPRSS2 and the expression of ACE2 in vitro. Can J Physiol Pharm 93:863-869.

Xiao Y, Kang L, Ma W, Shi L, Zhang L, Zhou Z, Yang J. (2018) Coronavirus S and related rehospitalizations. Clin Res Cardiol 106:598-609.

Xue Z, Xiao Y, Li Q, Pan Y, Sun J, et al. (2020) Potential inhibitors of SARS-CoV-2: Recent advances. J Drug Target 29:349-364.

Yoon JK, Park J, Park J, Kang S, Park S, et al. (2020) Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia. J Thromb Haemost 18:844-847.

Yuan L, Chen J, Sun W, Wu Y, Xiao W, Liu S, Chen E et al. (2020) Hydroxychloroquine in patients with mainly mild to moderate coronavirus disease 2019: Open label, randomised controlled trial. BMJ 369:m1849.

Yue Y, Wang X, Li H, Zhao Z, et al. (2020) The establishment of reference sequence for SARS-CoV-2 infection in human. J Med Virol 92:667-674.

Zhang J, Wan Y, Luo C, Ye G, Geng Q, Auerbach A and Li F (2020) Cell entry mechanisms of SARS-CoV-2. Proc Natl Acad Sci U S A 117:11727-11734.

Zou J, Li M, Yoder M, et al. (2020) Structure, function, and antigenicity of the SARS-CoV-2 RBD protein as a viral attachment inhibitor and vaccine. Cell 181:293-303.
COVID-19: genetic and therapeutics

Wu R, Wang L, Kuo H-CD, Shannar A, Peter R, Chou PJ, Li S, Hudilkar R, Liu X, Liu Z et al. (2020) An update on current therapeutic drugs treating COVID-19. Curr Pharmaceut Rep 6:56-70.

Wu Y, Li C, Xia S, Tian X, Kong Y, Wang Z, Gu C, Zhang R, Tu C, Xie Y et al. (2020) Identification of human single-domain antibodies against SARS-CoV-2. Cell Host Microbe 27:891-898.

Xia S, Zhu Y, Liu M, Lan Q, Xu W, Wu Y, Ying T, Liu S, Shi Z, Jiang S et al. (2020) Fusion mechanism of 2019-nCoV and fusion inhibitors targeting HR1 domain in spike protein. Cell Mol Immunol 17:765-767.

Xiao D, Li X, Su X, Mu D and Qu Y (2021) Could SARS-CoV-2-induced lung injury be attenuated by vitamin D? Int J Infect Dis 102:196-202.

Xiu S, Dick A, Ju H, Mirzaie S, Abdi F, Cocklin S, Zhan P and Liu X (2020) Inhibitors of SARS-CoV-2 entry: and future opportunities. J Med Chem 63:12236-12274.

Xu X, Han M, Li T, Sun W, Wang D, Fu B, Zhou Y, Zheng X, Yang Y, Li X et al. (2020) Effective treatment of severe COVID-19 patients with tocilizumab. Proc Natl Acad Sci U S A 117:10970-10975.

Yamamoto M, Kiso M, Sakai-Tagaya Y, Iwatsuki-Horimoto K, Imai M, Takeda M, Kinoshita N, Ohnagari N, Gohda J, Semba K et al. (2020) The anticoagulant farnesol potently inhibits SARS-CoV-2 protein-mediated fusion in a cell fusion assay system and viral infection in vitro in a cell-type-dependent manner. Viruses 12:629.

Yamamoto N, Ariumi Y, Nishida N, Yamamoto R, Bauer G, Gojobori T, Shimotohno K and Mizokami M (2020) SARS-CoV-2 infections and COVID-19 mortalities strongly correlate with ACE1 I/D genotype. Gene 758:144944.

Yan R, Zhang Y, Li Y, Xia L, Guo Y and Zhou Q (2020) Structural basis for the recognition of SARS-CoV-2 by full-length human ACE2. Science 367:1444-1448.

Yang H, Xie W, Xue X, Yang K, Ma J, Liang W, Zhao Q, Zhou Z, Pei D, Ziebuhr J et al. (2005) Design of wide-spectrum inhibitors of the Virus that Causes COVID-19, https://www.cdc.gov/coronavirus/2019-ncov/transmission/variant.html (accessed 23 April 2021).

FDA Briefing Document (2020) Pfizer-BioNTech COVID-19 vaccine. U.S. Food and Drug Administration; 53, https://www.fda.gov/media/144245/download (accessed 26 April 2021).

Internet Resources

Centers for Disease Control and Prevention (2021) About Variants of the Virus that Causes COVID-19, https://www.cdc.gov/coronavirus/2019-ncov/transmission/variant.html (accessed 23 April 2021).

Ministério da Saúde (2021a) O primeiro registro definitivo concedido para uma vacina no Brasil e nas Américas, https://www.gov.br/anvisa/pt-br/assuntos/noticias-anvisa/2021/informes-de-popolacao-brasileira (accessed 26 April 2021).

Ministério da Saúde (2021b) Anvisa não aprova importação da vacina Sputnik V, https://www.gov.br/anvisa/pt-br/assuntos/noticias-anvisa/2021/anvisa-nao-aprova-importacao-da-vacina-sputnik-v (accessed 27 April 2021).

Ministério da Saúde (2021c) Anvisa aprova registro da vacina da Fiocruz/AstraZeneca e de medicamento contra o coronavírus, https://www.gov.br/anvisa/pt-br/assuntos/noticias-anvisa/2021/anvisa-aprova-registro-da-vacina-da-fiocruz-astrazeneca-e-de-medicamento-contra-o-covid19 (accessed 27 April 2021).

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