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Genomics-led insight into the coronavirus evolution, pathogenicity and management

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Abstract

Coronavirus disease 2019 (COVID-19) has so far been the most devastating pandemic ever faced by mankind. Caused by the highly transmissible severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), the disease is becoming deadly due to frequent emergence of variants. The virus belongs to the group, Betacoronaviruses, and shares more than 90% amino acid identity with SARS-CoV. The SARS-CoV-2 possess a single-stranded positive-sense RNA which is the largest known viral RNA genome consisting of 25,000-30,000 nucleotides with 14 ORFs. The 3'-region of the genome harbours four structural proteins, namely; the spike, nucleocapsid, envelope and the membrane proteins; the S protein plays the most important role during infection. Genomics-led studies are pre-requisites to understand the pathogenicity of any pathogen and for devising its management strategies. The availability of SARS-CoV-2 sequence data and suitable bioinformatics platforms have allowed researchers to identify potential therapeutic targets and to predict immune response for accelerating therapeutics and vaccine development. A plethora of such options are available that includes repurposing existing drugs, monoclonal antibodies, anti-inflammatory agents, *etc*. Moreover, different types of vaccines such as mRNA-based, viral vector, inactivated virus, *etc*., with different efficacy levels have been approved. However, their efficacy might get compromised with time, particularly due to frequent mutations in the viral genomes. Here, we provide a comprehensive insight into the genome structure, evolution, pathogenicity as well as the achieved success and limitations in management of this notorious virus.

1. Introduction

The recent outbreak of COVID-19, caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has been one of the major pandemics in the known human history (Yang *et al*., 2020). The coronavirus infection first broke out in Wuhan in Hubei, China in December 2019 and was declared as a Public Health Emergency of International Concern on 30th January, and later, as a pandemic on 11th March 2020; by the World Health Organization (WHO). As of September, 2021, there are more than 231 million confirmed cases of infection and nearly 5 million deaths worldwide due to SARS-CoV-2 (https://coronavirus.jhu.edu/map.html).

Although, the latest pandemic had been the most devastating, coronaviruses, in general, are not new as a threat to human health. To date, there are seven known human coronaviruses (HCoVs; HCoV–229E, OC43, NL63, HKU1, SARS-CoV, MERS-CoV, and SARS-CoV-2) that fall within the alpha- and betacoronavirus genera; and all of them had been reported to be involved in respiratory diseases (Gupta *et al*., 2020). The earlier known severe acute respiratory syndrome (SARS) coronavirus and middle east respiratory syndrome (MERS) virus, and SARS-CoV-2 belong to the same genus (betacoronavirus; Anderson *et al*., 2004). These viruses can infect vertebrates, including human, dogs, cats, mice, rats, swine, rabbits, cattle, horses, bats and cetaceans and birds (chickens, turkeys, and pheasants) (Smith, 2006). The first known case of SARS-CoV infection in human was the one that originated from Guangdong, China in November 2002-03 (Fouchier *et al*., 2003). Another major outbreak of coronavirus emerged in 2012 as MERS in the Middle East, sharing similar characteristics (Mackay and Arden, 2015; reviewed by Khan *et al*., 2020); it lead to a major global public health crisis (Peeri *et al*., 2020). Another virus related to SARS-CoV was discovered in horseshoe bats in 2013, named bat SARS-CoV (Ge *et al*., 2013). The exact source and natural reservoir of SARS-CoV-2 remains inexplicit, but findings suggest that the open wet markets in Wuhan, China, might have led to the transmission of the latest SARS-CoV-2 from animal hosts to humans (Morrens *et al*., 2020).

The SARS-CoV-2 can escalate dangerously, thereby opening the way for its global spread (Gupta *et al*., 2020). With the rise in its spread, SARS-CoV-2 has been frequently undergoing mutations, attributing to the emergence of several newer variants; for example, 501Y.V1 (B.1.1.7) in the UK and 501Y.V2 (B.1.351) in South Africa (Fontanet *et al*., 2021). Both alpha and beta variants had undergone mutation (N501Y) in the receptor-binding domain of the spike (S) protein, thereby contributing to an increased viral transmission. Two additional mutations (E484K and K417N) were observed in the S

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protein of the 501Y.V2 variant with capability of immune escape (Wimber *et al*., 2021). A new emerging lineage, P.1 (501Y.V3), was detected, including another set of mutations (N501Y, E484K and K417T) in Manaus, Brazil (Faria *et al*., 2021).

2. Coronavirus genome and evolution

2.1 SARS-CoV-2 genome structural organization and function

The SARS-CoV-2 has a single-stranded positive-sense RNA (+ssRNA) genome of SARS-CoV-2 is the largest known viral RNA genome consisting of 25,000-30,000 nucleotides. The genome contains a 5'-cap and a 3'-poly-A tail. The 52 untranslated region (UTR) is 265 nt long, while the 3'-UTR is 229 nt long. It has 14 ORFs from 5' to 3' direction (Finkel *et al*., 2021). ORF-1a/ab at the 5' end; the most fundamental region, encodes the non-structural proteins (Nsps). At the 3' end, the structural proteins: spike (S), envelope (E), membrane (M), and nucleocapsid (N) are prominent; they play significant roles in viral structure integrity, and in the case of the S protein, viral entry into the host. Along with them, several accessory proteins such as ORF-3b, 6, 7a/b, 8b, 9a/b and 10 are interspersed among them (Gupta *et al*., 2020) (Figure 1). The ORF-1a/ab gene is approx. 21,300 nt long and encodes replicase polyprotein 1a (pp1a) and polyprotein 1ab (pp1ab). A -1 frameshift between ORF1a and ORF1b produces the polypeptides pp1a and pp1ab (Finkel *et al*., 2021). Each of these polyproteins gets proteolytically cleaved into 16 putative Nsps (Nsp-1 to Nsp-16). The replication-transcription complex (RTC) is formed from these Nsps and is required for viral RNA replication and transcription (Knoops *et al*., 2008).

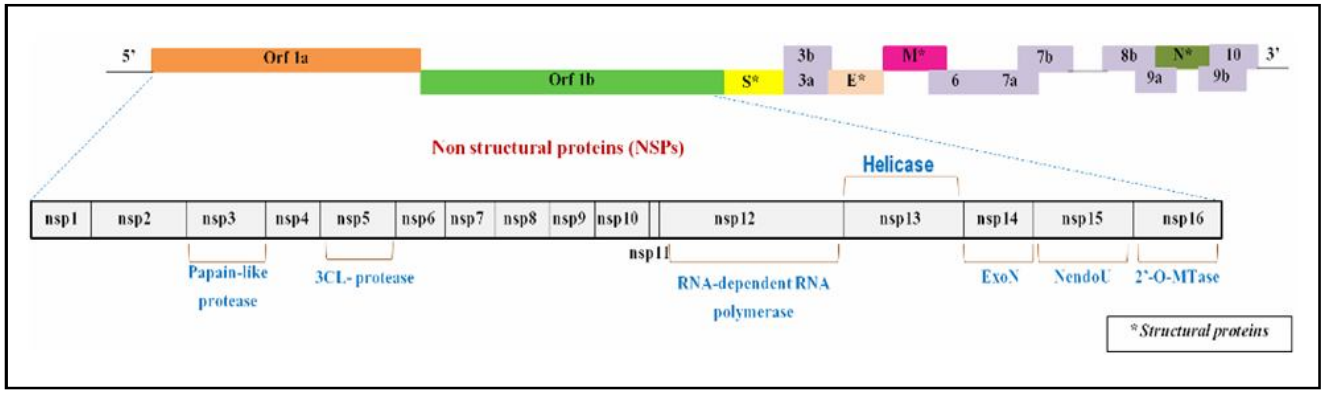

Figure 1: Genome organization of SARS-CoV-2. Different ORFs are shown in different colored boxes and the region harboring the NSPs is shown magnified (adapted from Gupta *et al*., 2020).

The S protein (200 kDa) binds to angiotensin-converting enzyme 2 (ACE2) receptors on the host cell surface, facilitating fusion and entry of SARS-CoV-2 into the host cell (Wan *et al*., 2020). The S protein is extensively N-linked glycosylated, and an N-terminal signal sequence allows it to enter the endoplasmic reticulum (ER). It has two subunits: S1 and S2. The S1-domain consists of the receptor-binding domain (RBD), which enables viral adherence to target cells. This subunit also regulates viral tissue tropism and the host range. The S2 subunit forms the stalk of the S protein and ensures viral entry by mediating the fusion of viral and cellular membranes (de Groot *et al*., 1987). The most prevalent structural protein in the viral membrane is M protein (25-30 kDa), which is important for virus assembly and is responsible for shaping the virions (Neuman *et al*., 2011). The S and N proteins regulate virion size *via* interacting with the M protein (Gupta *et al*., 2020). The M protein is a dimer that can take two distinct conformations to increase membrane curvature and facilitating its binding to nucleocapsids (Neuman *et al*., 2011). According to Fehr and Perlman (2015), the interaction between the S and M proteins is crucial for S protein recognition in the ER-Golgi intermediate compartment (ERGIC)/Golgi complex and new virion assembly. The transmembrane protein, E (approx. 8-12 kDa), is the smallest structural protein; it assists in viral assembly, budding, and release. This protein has an N-terminal ectodomain and a C-terminal endodomain with ion channel function (Armstrong *et al*., 1984). Recombinant CoVs lacking E protein have been demonstrated to have lower viral titers, slowed viral maturation, or to generate incompetent offspring, highlighting its relevance in virus synthesis and maturation. Because of its unique function, it was proposed that such recombinant CoVs lacking E protein could be useful in generation of live attenuated SARS-CoV vaccines (Ortego *et al*., 2002). The N protein (46 kDa) is involved in genome encapsidation, packaging of the viral genome into a ribonucleoprotein complex (nucleocapsid). It is CoV's sole protein that binds to the virus's genome. It is required for timely virus replication and transmission. It is gaining importance in pathogenicity as an interferon (IFN) inhibitor (Cui *et al*., 2015). It is considered as a significant antigen because of its abundance in the host during infection. Its high antigenicity had been used to develop SARS-CoV rapid-diagnosis kits (Chang *et al*., 2006).

2.2. Coronavirus diversity, evolution and divergence

Coronaviruses belong to order Nidovirales; subfamily, Coronavirin, and family, Coronaviridae. They are viruses of 80-120 nm in diameter (Cascella *et al*., 2020; Villas-Boas *et al*., 2020). This group of viruses infect a wide range of mammalian hosts, and and affect their respiratory system, liver, intestine, kidney, and central nervous system. The previously classified three subfamilies, group 1 (mammalian CoV), group 2 (mammalian CoV), and group 3 (avian CoV) (reviewed by Villas-Boas *et al*., 2020) have been renamed into alfacoronavirus (group 1), betacoronavirus (group 2) and gammacoronavirus (group 3) by International Committee for Viral Taxonomy. The recently classified fourth subfamily is delta coronavirus (group 4, birds and pigs CoV) (reviewed by Villas-Boas *et al*., 2020).

The SARS epidemic has made groups across the globe to study the exact time point of interspecies transfer of SARS-CoV from civets (Bovine CoVs, BCoVs) to humans (HCoV-OC43) (Vijgen *et al*.,

2006). Several novel coronaviruses in humans and animals have been discovered and their rate of evolution and time of divergence within the Coronaviridae family had been estimated using the BEAST program, gene sequences (ORF1ab, S, nucleocapsid), and datasets contributed by research groups (Vijgen *et al*., 2006; Pyrc *et al*., 2006; Vijaykrishna *et al*., 2007; Hon *et al*., 2008; Patrick *et al*., 2010). The S and nucleocapsid genes in porcine hemagglutinating encephalomyelitis virus (PHEV), BCoV, and HCoV-OC43 showed different evolutionary rates. There was 100 years difference between the time of divergence of PHEV lineage from that of HCoV-OC43 and BCoV lineage (Vijgen *et al*., 2006). Using the helicase gene sequence, the evolutionary history of coronaviruses was estimated to be of about 420 years (Vijaykrishna *et al*., 2007). By aligning a big dataset of SARS-Rh-BatCoV ORF1 sequences, the evolutionary time for human SARS-CoV was estimated to be in the year 1972 which was 31 years before the SARS epidemic, and civet SARS-CoV in 1995 and the most recent time point for both human and civet SARS-CoV was estimated to be in 2001 (Lau *et al*., 2010; Patrick *et al*., 2010).

The BCoV has been reported to be the closest to the human CoV (hCoV) (Vijgen *et al*., 2006). SARS-CoV-2 has 88% similarity with bat SARS-like CoV (bat-SL-CoVZC45 and bat-SL-CoVZXC21), 79% with SARS-CoV, and 50% with MERS-CoV. However, the S protein gene of SARS-CoV-2 has only 75% similarity with bat-SL-CoVZC45 and bat-SLCoVZXC21 (Lu *et al*., 2020). There is 76% sequence similarity between the Wuhan-Hu-1 and SARS-CoV S strain Tor2 (Jaimes *et al*., 2020).

Nucleotide sequence similarity studies have reported 99.98-100% identity among SARS-CoV-2, SARS-CoV and MERS-CoV, indicating that the virus has shifted to humans recently (Tizaoui *et al*., 2020). The sequences of SARS-CoV and SARS-CoV-2 are highly similar. The B and T cell epitopes for SARS-CoV-2 showed higher homology with SARS-CoV too (Grifoni *et al*., 2020). An insight into these potential regions is a step-forward move towards understanding the immune response of SARS-CoV-2 which would facilitate planning and designing of vaccines against coronavirus (Grifoni *et al*., 2020; Tizaoui *et al*., 2020).

3. Coronavirus pathogenicity

SARS-CoV-2 typically infects human alveolar type II cells and bronchial epithelial cells, where it attaches to the surface receptor ACE2 *via* the S glycoprotein on its surface (Qian *et al*., 2013; Zhou *et al*., 2020). Following this attachment, proteolytic cleavage occurs within the S2 subunit which is induced by the cell surface-associated transmembrane protease serine 2 (TMPRSS2), cathepsin, or another protease (Qian *et al*., 2013). The fusion of the virus with the host cell membrane is triggered by this conformation alteration in the S protein, ensuring viral entry through endocytosis (Romano *et al*., 2020). The virus then releases its genomic RNA into the cytosol/ cytoplasm of the host cell.

The coronaviruses affecting humans are mostly alpha-CoVs (HCoV-229E and HCoV-NL63) and beta-CoVs of strain A (HCoV-OC43 and HCoV-HKU1) (Villas-Boas *et al*., 2020) that cause varying degrees of severity in humans with respiratory and non-respiratory infections. These variants cause upper respiratory infection limited to self and cause common colds which are easily fought back by the human immune system without needing any medical attention (Villas-Boas *et al*., 2020). A person with weak immunity and elder age shows symptoms of lower respiratory tract infection along with common cold. The mortality rate in case of SARS-CoV infection is about 10% while that in case of MERS-CoV is about 35% (Cascella *et al*., 2020). The SARS-CoV-2 virus has a higher affinity to bind to the host than SARS-CoV due to the modification of its viral S protein, among other structural proteins which results in enhanced transmission (Zhou *et al*., 2020). The host response severity depends on an innate response to viral recognition which involves the expression of type-1 IFNs and pro-inflammatory cytokines (Prompetchara *et al*., 2020). Viral proliferation can lead to the large-scale recruitment of neutrophils and monocyte macrophages to the lungs. If the antiviral response is delayed or inhibited, it leads to a hyper-inflammatory environment (Prompetchara *et al*., 2020). Huang *et al*. (2020) found that levels of IL-1B, IL-1RA, IL-8, IL-10, IFN-gamma, IP10, MCP1, and MIP1s are higher in COVID-19 patients than in healthy adults.

The commonality between the epidemics that happened in 2002 and 2003 was the interspecies viral transmission; for example, from Chinese ferret-badger (*Melogale moschata*), masked palm civet (*Paguma larvata*), and raccoon dog (*Nyctereutes procyonoides*) to humans (Guan *et al*., 2003). SARS-CoV is believed to be a recombination between these CoVs when transfected to humans from animals. The seafood market in China might not be the main source of CoV (Perlman and Netland, 2009; Villas-Boas *et al*., 2020) as the investigations showed negative results when tested for the presence of SARS-CoV in masked palm civet in either domestic or wild type (Poon *et al*., 2009). A SARS-CoV like CoV has been found in Chinese horseshoe bat (*Rhinolophus* spp.) (Li *et al*., 2005; Lau *et al*., 2005; Villas-Boas *et al*., 2020) which were available in the animal market in China. The study suggests possible transmission of the CoV from this bats to animals like masked palm civets and then to humans (Perlman and Netland, 2009). Genetic variations in the SARS-CoV-2 and ACE2 receptor can affect the transmission, clinical manifestation, mortality, and efficacy of drugs and vaccines for COVID-19. The high transmissions and progressive disease of SARS-CoV-2 in a small but significant proportion of infected individuals might be contributed by some genetic factors. Large scale studies in populations of geographically diverse ancestry have demonstrated substantial genetic variation in viral protein-coding regions, with widely varying allele frequencies (Lek *et al*., 2016). The SARS-CoV-2 S protein binds ACE2, the host cell receptor, with a 10- to 20-fold greater affinity compared to SARS-CoV, and contains a polybasic furin cleavage site resulting from a unique insert to SARS-CoV-2 that could enhance infectivity compared to SARS-CoV-2 and MERS (Ayal *et al*., 2020). The conformational change in the S protein between the S1 and S2 domains favours the binding to the ACE2 receptor, and thus increases the probability of infection (Plante *et al*., 2021). The D614G mutation in the S protein was peculiar found in the most infectious form of SARS-CoV-2 (Callaway *et al*, 2021). SARS-CoV-2, being an RNA virus, is prone to mutations as they are copied inside their hosts, because enzymes that copy RNA are error-prone. Many mutations are neutral; however, a few mutations may benefit the virus leading to increased transmissibility, higher infectivity, and higher virulence resulting in severe disease, immune/vaccine escape, or any their combinations (Novelli *et al*., 2021). The failure of tests such as RT-PCR could be due to the mutations in a region of the genome targeted. Mutations in the RBD of the S protein allowed the virus to escape recognition by antibodies and were not detected for months. Different variants have been detected around the world with mutations in the S protein which appears to increase the transmissibility of SARS-CoV-2. These sequence changes has raised

concerns among vaccine researchers due to their location in or close to the RBD; thus affecting other neutralizing antibodies target, the N-terminal domain.

4. Fighting the coronavirus: Drug based and non-drug strategies

4.1 Bioinformatics for drug designing against SARS-CoV-2

The coronaviruses that can infect humans are expected to follow a pattern of evolution and widen their host range to animals. Getting deeper into the evolutionary history of the virus, tracing the virus across hosts and looking for similarity of other viruses to SARS-CoV-2 is a prerequisite to such investigations (Khadraoui, 2020; Hufsky *et al*., 2021).

The Microbiome Informatics Team Leader at EMBL-EBI adopted their online resource MGnify to bring different RNA fragments together to look for the presence of coronavirus in a sample The VIRify pipeline within this package had been adopted as a new virus identifier for coronavirus detection (Hufsky *et al*., 2021). Different bioinformatics centres including resources at EMBL-EBI have dedicated cells for coronavirus research for development of viral sequence databases. For example, the SARS-CoV-2 genome browser in Ensembl has SARS-CoV-2 reference genome, Rfam database for RNA families has COVID-19 sequence data for RNA annotation and secondary structure prediction, UniProt has resources for viral and human protein sequences pertinent to the disease, while the COVID-19 Data Portal in EMBL-EBI is dedicated to data submission and open access (Khadraoui, 2020). The portal has grown into a huge resource site with open access to nearly 0.2 million scientific publications on COVID-19 contributed by some 300 research centres from about 30 countries (Khadraoui, 2020; Hufsky *et al*., 2021). Some of the bioinformatics resources that are being extensively used for coronavirus genomics investigation and drug designing are presented in Figure 2.

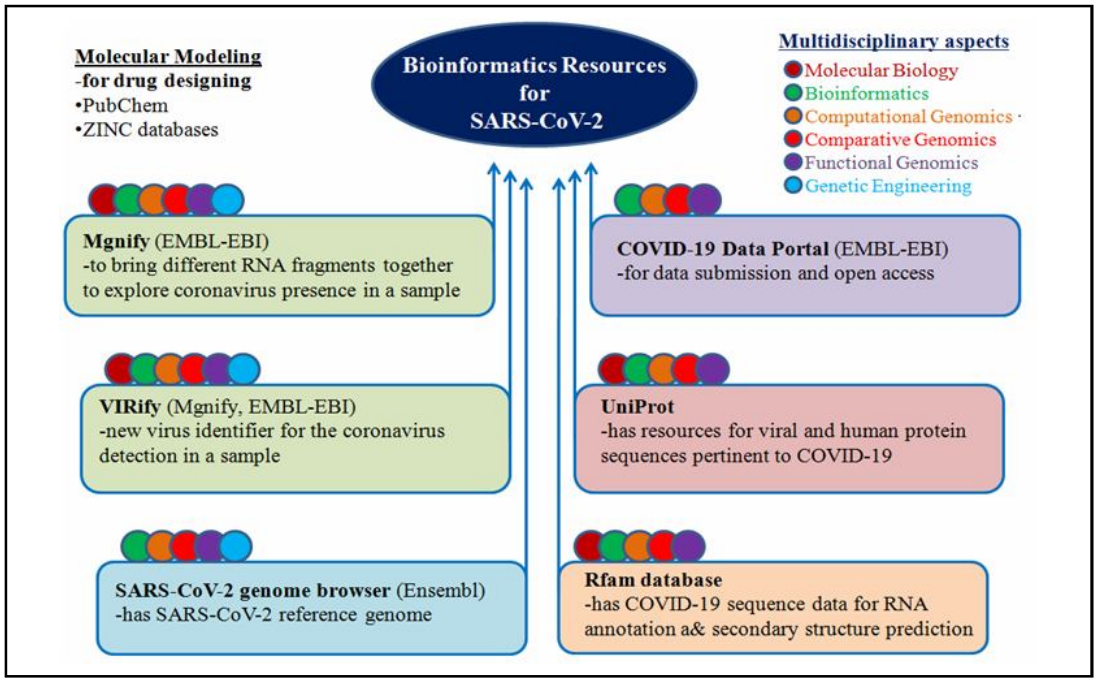

Figure 2: Application of bioinformatics in coronavirus genomics investigation and drug designing.

Extensive molecular studies for comparison of SARS-CoV, MERS-CoV, and SARS-CoV-2 have been going on to understand the viral protein and human protein interaction, viral protein localization in the host cells, and any common weaknesses in all these three viruses (Khadraoui, 2020; Hufsky *et al*., 2021). Potential targets for drugs have been identified which were common to SARS-CoV, MERS-CoV, and SARS-CoV-2, and a selection of drugs has been identified for repurposing in COVID-19 treatment (Gordon *et al*., 2020). The discovery of bioactive compounds for cost-effective drug designing within a short period has been possible because of the molecular modelling which facilitated pre-selection in binding efficacy of the drug molecules to the target molecule of interest (Villas-Boas *et al*., 2020). Molecular modelling has supported structure-based planning for drugs in designing the target molecule against the virus. In the virtual process of finding the hits, the databases such as PubChem (https://pubchem.ncbi.nlm.nih.gov/) (Kim *et al*., 2019) and ZINC databases (https://zinc.docking.org/) (Irwin and Shoichet, 2005) provide the origin and molecular structure of the compounds for screening (Villas-Boas *et al*., 2020). More than 300 candidate inhibitors against SARS-CoV-2 main protease (Mpro) were identified using PubChem and ZINC databases by molecular docking to understand the target-ligand complex (Ortega *et al*., 2020), and found PubChem CID 444,745 with higher efficacy in inhibiting the enzyme (Villas-Boas *et al*., 2020).

Conserved structured elements have been shown to play critical functional roles in the life cycles of coronaviruses (Yang and Leibowitz, 2015). Through, direct interactions with host RNA-binding proteins and helicases, structural elements add a layer of complexity to the regulatory information that is encoded in the viral RNA. Highly conserved RNA structural elements have been identified in several

viral families, many of which have been functionally validated (Jaafar and Kieft, 2019). Some of these are stem-loops in the 5'-UTR of SARS-CoV-2 structural elements which are conserved across betacoronaviruses and are known to impact viral replication (Yang and Leibowitz, 2015). Rangan *et al.* (2020) identified 106 structurally conserved regions that would be suitable targets for unexplored antiviral agents. Moreover, they predicted at least 59 unstructured regions that are conserved within SARS-CoV-2. Programmed -1 ribosomal frameshifting (-1 RF) is an essential regulating mechanism of translation used by SARS-CoV to synthesize the key replicative proteins. The integrity of RNA pseudoknot stability and structure in the -1 RF site is important for efficient -1 RF. Thus, small molecules interacting with high affinity and selectivity with the RNA pseudoknot in the -1 RF site of SARS-CoV (SARS-pseudoknot) would disrupt -1 RF and be fatal to viral infectivity and production. Park *et al.* (2011) discovered 43 RNA pseudoknot-binding ligand that inhibit the -1 ribosomal frameshifting of SARS-coronavirus by structure-based virtual screening.

4.2 Generative approaches for drug designing

Variational autoencoder (VAE) is a generic model for enhancing the diversity of generated data. Autoencoders instruct molecules into a vector that captures properties such as bond order, element and functional group (Bjerrum and Sattarov, 2018). Chenthamarakshan *et al.* (2020) demonstrated a VAE that captures molecules in a latent space. Once captured, variations are made on the original molecule vectors based on desired properties; these can then be decoded back into novel molecules. To optimize the structures, quantitative estimate of druglikeness, synthetic accessibility, and LogP regressors were used to improve the latent space variations. In a different approach, many of the issues were solved with traditional generative models by developing a novel advanced deep Q-learning network with fragment-based drug design (Tang *et al.*, 2020). This allowed for the enhanced exploration of space by assembling SARS-CoV-2 molecules one fragment at a time rather than relying on latent space adjustments. After making connections and rewarding molecules with the most drug-like connections, a pharmacophore and descriptor filter was used to refine the set. Tang *et al.* (2020) demonstrated a robust method for designing novel, high-binding compounds refined to the structure of SARS-CoV-2 3CLPro. The names of few drugs and their mechanism of actions are mentioned in Table 1.

4.3 Artificial intelligence-based drug discovery

The scale and efficiency that artificial intelligence (AI) brings to drug discovery are especially relevant for treating the COVID-19 (Mei and Tan, 2021). Beck *et al.* (2020) published an application of their Deep Learning-based drug-target interaction model that predicted commercially available antiviral drugs that may target the SARS-CoV-2 related protease and helicase. In another study, 332 interactions had been identified between SARS-CoV-2 proteins and human host proteins including ACE2, Furin, TMPRSS2, NRP1, eEF1A, *etc.* (Gordon *et al.*, 2020). Zeng *et al.* (2020) proposed that the AOPEDF (arbitrary-order proximity embedded deep forest approach) algorithm can predict novel drug-target interactions. AI algorithms were used to identify baricitinib which is an approved Janus kinase (JAK)1/JAK2 inhibitor, for treating rheumatoid arthritis, to be effective at inhibiting SARS-CoV2 infection as well as reducing virus-induced inflammation (Stebbing *et al.*, 2020). *In silico* molecular modelling suggests that several FDA-approved anticancer drugs (Capmatinib, Pemigatinib, Selpercatinib, and Tucatinib) might be able to inhibit COVID-19 by docking on Mpro and S of SARS-CoV-2 (Parveen and Alnoman, 2021).

Table 1: Available drugs in use against SARS-CoV-2 and their mechanisms of action

Name	Trials			Approved/ not approved	Reference
	Clinical	*In vivo*	*In vitro*		
Apilimod	SARS-CoV-2	N	SARS-CoV-2	NA	Riva *et al.*, 2020
MDL-28170	N	N	SARS-CoV-2	NA	Riva *et al.*, 2020
ONO 5334	N	N	SARS-CoV-2	NA	Riva *et al.*, 2020
Imatinib	N	N	SARS-CoV-2	Yes	Han *et al.*, 2021
Mycophenolic acid	N	MERS-CoV	MERS-CoV, HBV, HCV, arboviruses (JEV, WNV, YFV, dengue virus and CHIKV)	Yes	Han *et al.*, 2021
Quinacrine Dihydrochloride	N	N	SARS-CoV-2	Yes	Han *et al.*, 2021

4.4 Use of antivirals and immunity against COVID-19

To tackle the increasing number of COVID-19 cases, use of antivirals has been adopted as the primary means. Antivirals are chosen based on their high potency and a high therapeutic index, *i.e.*, their effectiveness against the virus. Moreover, the antivirals should be non-toxic to the host. They must also have a high barrier to resistance as well as a universal ability to target a population of viral variants (Chan, 2020). Among the two types of antivirals (direct-acting antivirals, DAAs and host-targeting antivirals, HTAs), DAA drugs were used as complement vaccines against some SARS-CoV-2 variants, especially, in synergistic combinations (Chan, 2020; Pelly and Liotta, 2021). Such kinds of therapeutic agents are used to suppress disease progress in actively infected patients, also they can be used prophylactically to minimize new infections ratio. In 2020, several therapies including Remdesivir, Casirivimab/Imdevimab, Baricitinib/Remdesivir, Bamlanivimab, and convalescent plasma therapy were granted Emergency Use Authorization by the FDA. Many laboratories are attempting to develop DAAs that could suppress viral replication in COVID-19 positive patients (Pelly and Liotta, 2021).

Some of the DAAs used in COVID-19 are:

(i) Protease inhibitors like Lopinavir, Ritonavir, Darunavir, Danoprevir, and the experimental drug ASC-09.

(ii) Broad-spectrum antivirals include commonly used Umifenovir, which is largely licensed in China and Russia for influenza (Poveda *et al*., 2014).

(iii) RdRP inhibitor includes Favipiravir which is an oral antiviral.

(iv) Nucleosidase and neuraminidase inhibitors like Oseltamivir, Ribavirin and Azvudine.

(v) Polymerase Acidic Endonuclease Inhibitors like Baloxavir Marboxil.

The HTAs complement the DAAs, but are superior in several aspects. In the replication of several types of viruses, specific host proteins play crucial roles. Some types of HTAs are likely to be effective against the newly emerging viruses as they might leverage the same host protein for replication (Mei and Tan, 2021). The key step of the life cycle of SARS-CoV-2 is entering into host cells; therefore, blocking this step is critical for preventing the infection. Two mucosa-specific proteases, TMPRSS2 and TMPRSS4, catalyze the cleavage of SARS-CoV-2 S and trigger virus entry into host cells (Zang *et al*., 2020). Pegylated interferon alfa-2a and -2b alone and in combination with other antiviral agents, approved for treating hepatitis B virus and hepatitis C virus infection could be used to stimulate innate antiviral responses in COVID-19 patients. One research showed that type I and type III IFN have potential inhibitory effects on SARS-CoV-2 *in vitro* (Felgenhauer *et al*., 2020). Understanding the RNA virus and its interactions with host proteins could improve therapeutic interventions for COVID-19. Recently, Sun *et al*. (2021) reported the generation of *in vivo* structure maps and models of the SARS-CoV-2 RNA genome. They determined the SARS-CoV-2 genome structure in infected human cells and from refolded RNAs that enabled prediction of host proteins binding to viral RNA using a deep-learning tool, and identification of FDA-approved drugs for repurposing to reduce SARS-CoV-2 infection in cells.

Lately, there have been considerable interest and research in preventing the coronavirus infection by increasing general immunity, and several traditional herbs are being explored. The roles of medicinal and aromatic plants (Mehrotra, 2020), sesame and flaxseeds (Ahmad and Ghosh, 2020) and spices (Palai *et al*., 2020) as immunity boosters and potential prophylactic measures against COVID-19 have been elaborately reviewed recently.

4.5 Vaccine-based strategies to combat COVID-19

Development of a therapeutic antibody response in the host is the prerequisite for successful vaccine production. The process of vaccine development includes preclinical animal trials, phase I to III trials and studies on its ability to stimulate antibodies in human and finally, large scale production. Several vaccine projects have been successful in preclinical, phase I and phase II trials using recombinant DNA, mRNA, S protein subunits, virus like particles, viral vectors, and live attenuated viruses. According to WHO, as on January 5th, 2021, there are 63 candidate vaccines in human clinical trials and more than 172 candidates in preclinical stage worldwide against SARS-CoV-2. Among the evaluated vaccines, 13 candidates have entered phase III clinical trials. In less than a year, different types of vaccines against SARS-CoV-2 infection were made and approved with different efficacies; they are BioNTech/Pfizer (95%), Moderna (94.1%), Gamaleya (Sputnik V) (91.6%), Bharat Biotech, 2021 (Covaxin) (81%), *etc*. (Novelli *et al*., 2021). Some approaches, being followed for the development of an effective and safe vaccine against COVID-19, include the followings.

4.5.1 Live attenuated vaccines

Live attenuated vaccines (LAV) targeting several others viruses had been successful and are currently in clinical development for SARS-CoV-2. Attenuation is achieved by inducing mutation into the viral protein. It can generate T cell and B cell response, however is generally not suitable for immunocompromised individual. For example, Indian Immunological Limited is currently working together with Griffith University to develop a vaccine using codon deoptimization as a strategy against SARS-CoV-2. Such a candidate provides a long-lasting immunity against SARS-CoV-2 following a single shot (Ng *et al*., 2020). Del-NS1-SARS-CoV2 is an influenza based vaccine which is attenuated by deletion of a virulent element of the non-structural 1 gene. It is more immunogenic than the wild type virus and can be given as nasal spray (Kaur *et al*., 2020). An attenuated influenza virus was also modified to encode the RBD of SARS-CoV-2 S protein (Krause *et al*., 2020).

4.5.2 Inactivated vaccines

Inactivated vaccines (IVs) are produced by inactivating the virus molecule with heat, radiations (UV light) or chemicals which result in the production of a safe vaccine, especially for immuno compromised persons. These vaccines induce weaker immune responses than LAVs and need several booster doses. However, their production is time consuming, as the virus needs to be cultured in the lab and then inactivated (Xia *et al*., 2020). CoronaVac is an IV candidate, developed by the China's vaccine manufacturer, Sinovac Biotech. CoronaVac is made with beta-propiolactone as an inactivating agent and formulated with aluminium hydroxide as an adjuvant (Lim *et al*., 2020). Inactivated SARS-CoV-2 viruses possess the RBD within S protein as an immune inducer which is a popular immune inducer (Xia *et al*., 2020). With the safety and immunogenicity results from phase I and II clinical trials, this vaccine has achieved an efficacy of 50.7% in phase II and also received Conditional Marketing Authorization (CMA) in China (SinoVac, 2021). Another example of an inactivated vaccine is Beijing Bio-Institute of Biological Products Coronavirus Vaccine (BBIBP-CorV) produced by Sinopharm in China. It exhibited satisfactory results in early trials and had entered phase III trials (Xia *et al*., 2021). It had achieved an efficacy of 79.3% and received CMA in China. Covaxin developed by Bharat Biotech, Indian Council of Medical Research and National Institute of Virology, is India's first inactivated vaccine against COVID-19. The vaccine produces robust immune responses. Recently, Bharat Biotech has announced the phase III results of Covaxin that showed 81% interim efficacy in preventing COVID-19 in persons without prior infection after second dose.

4.5.3 Nucleic acid (DNA and mRNA based) vaccines

Nucleic acid vaccines introduce genetic instructions in the form of DNA or mRNA encoding disease-specific antigens to host cells and generate immunogens by utilizing the protein making machinery of the same. *In situ* synthesis of these foreign immunogens in the host cells elicits both antibody production and T cell induction providing protection against COVID-19 (Zhu *et al*., 2020). DNA vaccines use

plasmid DNA containing mammalian expression promoter and transgene encoding protein antigen, such as S protein of COVID-19 vaccines. No DNA vaccine has yet been approved against SARS-CoV-2, but 11 candidates are in clinical trials (Tebas *et al*., 2021). Inovio Pharmaceuticals, US, collaborating with Beijing Advaccine Biotechnology, University of Pennsylvania, University of Texas, Twist Biosciences and Lavalle University have developed the INO-4800 DNA vaccine (Chen *et al*., 2020). It was designed to optimize the S protein sequence of SARS-CoV-2 virus. The presence of humoral and T cell response in the preclinical trials demonstrates that INO-4800 can produce an effective immune response.

The mRNA-based vaccines induce the strongest immune response by mimicking a natural infection. US based Moderna and National Institute of Allergy and Infectious Diseases Vaccine Research Centre have developed mRNA-1273, a lipid nanoparticle encapsulated SARS-CoV-2 vaccine (Moderna, 2020). The encapsulated mRNA-1273 travels to the immune cells (lymph nodes) and instructs them to make copies of the S protein on their surface as if SARS-CoV-2 infects them and on the other side, immune cells discover the S proteins and prepare themselves for future response against SARS-CoV-2 virus (Saini *et al*., 2020). Another mRNA based vaccine candidate is BNT162b2, developed by Pfizer, in collaboration with German-based BioNTech and Shanghai-based Fosun Pharma. This vaccine had also been developed to instruct immune cells to make several copies of the full-length SARS-CoV-2 S protein.

4.5.4 Protein subunit vaccines

By using viral S protein, Clova Biopharmaceuticals, China, in collaboration with GlaxoSmithKline, UK, have developed SARS-CoV-2 S protein trimer candidate (Alvi *et al*., 2020). The full-length S protein, present in the Trimer-Tag Technology, elicited an immune response ultimately preventing the entry of viral particles through host ACE2 receptor. US-based Generex and Epivax have identified SARS-CoV-2 amino acid peptides and would utilize the li-Key peptide technology for the synthesis of COVID-19 vaccine (Perez *et al*., 2010).

4.5.5 Viral vector vaccines

The viral vector vaccines use non-pathogenic viral vectors to deliver antigen-coding DNA fragment to host cells for expression of antigen. These vaccines provide prolonged and enhanced protein expression and therefore, have better prophylactic use. Such vaccines can trigger the cytotoxic T-cells, leading to removal of infected cells (Shirley *et al*., 2020). Viral vectors are grouped under two categories: replicating viral vectors and non-replicating viral vector. These vectors are safe, genetically stable and do not integrate into host genome. The University of Oxford, UK, and Astra Zeneca had developed AZD1222 (ChAdOx1 nCoV-19) which is a SARS-CoV-2 vaccine candidate that used a chimpanzee adenovirus as a vector (ChAdOx1) modified to induce the S protein from SARS-CoV-2 (Kyriakidis *et al*., 2021). It was one of the first vaccine candidates to begin clinical trials and the only one using a debilitated chimpanzee adenovirus platform.

4.5.6 Virus like particle vaccines

The only vaccine candidate against COVID-19 employing this strategy was designed by the Quebec-based Medicago (coVLP) that aims to combine the efficacy of attenuated vaccines with the safety usually displayed by subunit vaccines. The approach used by Medicago uses virus-transfected *Nicotiana benthamiana* plant to express the prefusion trimeric subunit form of the S protein and assemble it on the surface of virus-like particles which are harvested and used (Kyriakidis *et al*., 2021).

4.6 Other non-drug strategies against COVID-19

4.6.1 Therapeutic antibodies

Several monoclonal antibodies against SARS-CoV-2 isolated from infected patients in recovery and convalescent periods can recognize RBD, N terminal domain, and S2 domain of S protein. Ju *et al.* (2020) isolated three potent antibodies P2C-1F11, P2C1A3, and P2B-2F6, which compete with ACE2 for binding to SARS-CoV-2 RBD without cross-reacting with plasma from SARS-CoV and MERS-CoV patients. P2C-1F11 displays the most potent neutralizing activity *in vitro* and *in vivo* among them. Chi *et al.* (2020) isolated a monoclonal antibody, 4A8, from a convalescent patient that neutralized both authentic SARS-CoV-2 and SARS-CoV-2 pseudovirus. A neutralizing antibody cocktail REGN-COV-2 reduced viral load and enhanced immune responses (NCT04425629) (Weinreich *et al*., 2021). Several antibodies targeting SARS-CoV-2 S protein are still undergoing trials for COVID-19 treatment; further research in ongoing (Yang *et al*., 2020).

4.6.2 Interferon (IFN) therapy

IFNs are natural antiviral molecules and immune modulating agents that inhibit viral replication and induce both innate and adaptive immune responses. Recombinant IFN-alpha was effective in treating SARS-patients in earlier trials (Loutfy *et al*., 2003). Earlier, in a set of trials, administering Type I IFN, Alfacon, along with a corticosteroid, resolved 50% of lung abnormalities and reduced impaired oxygen saturation associated with various respiratory diseases (Seesuay *et al*., 2018). For elongated use, the intravenous immunoglobulin could be a safe immunomodulator in patients of all age groups. It inhibits cytokine production and increases generation of anti-inflammatory mediators (Gilardin *et al*., 2015). For effective control of SARS, thymosin alpha-1 (Ta-1) had been reported to be a potential immune booster (Kumar *et al*., 2013). Therefore, these two alternatives had been considered promising against SARS-CoV-2 infection as well.

4.6.3 RNA-interference mediated gene silencing

Several gene silencing approaches targeting key proteins of coronaviruses had shown promises to inhibit replication of SARS-CoV in Vero E6 cell line of African green monkey kidney (Lundstorm, 2020). In another RNAi therapeutics effort against SARS-CoV, kidney FRhK4 cells of foetal rhesus monkey were transfected with siRNA before or after viral infection; prophylactic inhibition up to 90% lasting for at least 72 hours was observed. Besides, a combination of siRNAs targeting different regions of the viral genome provided better inhibition of the target virus (Zheng *et al*., 2004). Moreover, siRNA-mediated knock down of actin-binding protein, ezrin, also provided protection against SARS infection in the entry stage (Millet *et al*., 2015).

4.6.4 Convalescent plasma therapy

Convalescent plasma therapy is a way of artificially inducing passive immunity by transferring blood plasma from patients who have had a disease to new patients. This can provide the recipient immunity towards the disease because of the antibodies present in the blood plasma. Convalescent plasmatherapy had increased the titres of neutralizing antibodies resulting in the disappearance of SARS-CoV-

2 RNA, thus proving to be effective in reducing the disease time-course finally leading to recovery (Rajendran *et al*., 2020). Hung *et al.* (2011) reported comparatively less death risk in patients treated with convalescent plasma during the H1N1-virus pandemic in 2009, proving it to be an effective therapy against coronaviruses as well. It was observed that in the acute phase of infection, the antibodies can limit coronavirus reproduction helping in rapid recovery of the patients (Ni *et al*., 2020).

4.6.5 Oxygen therapy

Hypoxemia is a condition where oxygen concentration in arterial blood comes below the normal range of 85 to 100 mm Hg. It is defined by the British Thoracic Society as PaO_2< 60 mm Hg or SaO_2 < 90% (Al-Shaqsi and Brockway, 2013). Oxygen therapy used for treatment of hypoxemia and can aid in the relief of respiratory symptoms caused by COVID-19. Hypoxemic patients should receive oxygen therapy immediately and maintain a blood oxygen saturation level (SaO_2) of at least 90% (in pregnant women, between 92 and 95%) (Li *et al*., 2020). The Ministry of Health recommends oxygen therapy in patients with SARS and breathing difficulties, hypoxemia or shock (Pereira *et al*., 2020).

4.6.6 Mesenchymal stem cells

Mesenchymal stem cells (MSCs) are multipotent cells that are easily accessible and culturally expandable with genomic stability. MSCs are therapeutic cells that can be used in immunological disease due to their regenerative and anti-inflammatory capabilities (Fan *et al*., 2019). Al-Khawaga and Abdelalim (2020) conducted a systematic review of studies on acute lung injury and acute respiratory distress syndrome (ARDS), explaining the therapeutic role of MSCs. They argued that MSCs could be used to treat COVID-19 and that it may reduce the progression of severe cases.

4.6.7 Passive immunotherapy

The technique of intravenous immunoglobulin (IgIV) therapy consists of extracting antibodies from the blood of donors, already immunized, to be injected into another person's veins (Hughes *et al*., 2014). In 1950s, this monoclonal antibody-based method was introduced as a replacement therapy for patients with congenital antibody deficiency (Boros *et al*., 2005). Monoclonal antibodies directed to the S protein in SARS-CoV and MERS-CoV had shown promising results *in vitro* and *in vivo*, and could be effective against SARS-CoV-2 (Shanmugaraj *et al*., 2020). However, no monoclonal antibodies have been successfully marketed due to the large scale production of monoclonal antibodies being laborious, costly and time consuming.

5. Conclusion

While a complete understanding of the gene functions and evolution of coronaviruses is essential for handling the recent outbursts of SARS-CoV-2, knowledge of its pathogenicity and zoonotic transmission is crucial to prevent its future outbreaks. Though, considerable insights in these aspects have been obtained, still, the understandings are incomplete. That is why the present strategies are not full-proof in prevention or treatment of COVID-19. Several preventive and therapeutic options are available and more are under evaluation. The preventive alternatives include various types of vaccines and therapeutic alternatives include new as well as repurposed drugs. Some minor candidates such as micronutrients and phytochemicals have also gained importance as prophylactic applications against COVID-19 (Bellik *et al*., 2020). Meanwhile, considering recurring infection-waves, mainly due to frequent emergence of newer virus strains, several nations are considering options of coexistence. Of late, there is an overwhelming increase in research on this virus, where the latest technologies have been playing pivotal roles. The current emphasis on genomics-led research in coronavirus infection as well as in drug discovery, design and repurposing, would certainly prove to be highly fruitful and productive in future.

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Conflicts of interest

The authors declare no conflicts of interest relevant to this article.

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