Opinion Paper

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The molecular footprints of COVID-19

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Abstract: COVID-19 is the third spread of animal coronavirus over the past two decades, resulting in a major epidemic in humans after SARS and MERS. COVID-19 is responsible of the biggest biological earthquake in the world. In the global fight against COVID-19 some serious mistakes have been done like, the countries' misguided attempts to protect their economies, lack of international co-operation. These mistakes that the people had done in previous deadly outbreaks. The result has been a greater economic devastation and the collapse of national and international trust for all. In this constantly changing environment, if we have a better understanding of the host-virus interactions than we can be more prepared to the future deadly outbreaks. When encountered with a disease which the causative is unknown, the reaction time and the precautions that should be taken matters a great deal. In this review we aimed to reveal the molecular footprints of COVID-19 scientifically and to get an understanding of the pandemia. This review might be a highlight to the possible outbreaks.

Keywords: Covid-19; footprint; genome; pandemia; Sars Cov-2.

Coronaviruses and epidemiology

Coronaviruses are in the *Coronaviridae* family. They are enveloped viruses with a positive-sense single-stranded RNA genome and a nucleocapsid of helical symmetry. The genome size of coronaviruses ranges from approximately 26–32 kilobases, one of the largest among RNA viruses. They mostly cause respiratory tract and gastrointestinal tract infections in birds and mammals [1].

Up to date, seven coronavirus that infects humans, has been identified. CoV-229E, HCoV-OC43, HCoV-NL63 and HKU1 human coronaviruses (HCoV) have been accepted as the main causative agents of common cold [2]. In 2002 SARS-CoV, in 2012 MERS-CoV and in 2019 Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) three new HCoV has caused life threatening diseases in humans [3–5]. In addition to these HCoV, in 2018 new animal coronaviruses such as swine deltacoronavirus (PDCoV) and swine outbreak diarrhea virus (PEDV) caused major economic losses in China and the USA [6].

Starting from December 21, 2019, the increase in pneumonia cases with unknown causes in Wuhan caused local hospitals to worry. The samples of these pneumonia patients whom admitted to three hospitals in Wuhan were tested for 18 viruses and four bacteria, SARS-CoV and MERS-CoV using the Respi Finder Smart 22. All the samples were found negative for the tested common respiratory pathogens [7].

A brief history of emergence

The demographic data of the patients with unknown causes of pneumonia were examined. Only nine patients' data had been reached. Eight of these patients visited the Huanan seafood market prior to the onset of the disease, and although one patient did not visit the market, it was found out that he stayed in a hotel near the market between 23 and 27 December 2019. It was suspected that the Huanan seafood market in Wuhan could be the source to this unknown causative agent. However, the fact that a patient had never visited the market, despite staying at a hotel near the market before the onset of the disease, indicated possible droplet delivery or the patient was infected from a source, which is currently unknown [8].

Frankly, this infectious disease had the capacity to be a major problem public health issue as the Chinese spring festival was due, where hundreds of millions of people would attend. Therefore, on 30 December 2019, the local disease control center presented a report to the Chinese

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Center for Disease Control (CDC) about the disease, and two days later, the World Health Organization (WHO) was informed by the Chinese CDC about the cases of pneumonia of unknown etiology [9, 10]. On 31 December 2019 WHO president Tedros Adhanom Ghebreyesus announced that they named this pandemia as COVID-19. Expansion of coding to avoid stigmatizing a specific region, animal species or human; it was defined as "CO" for "corona", "VI" for "virus", "D" for "disease". On January 6, 2020, a level two emergency response was launched by the Chinese CDC [9].

Meanwhile, on January 3, 2020, the genome of a new coronavirus from the beta genus was identified. The scientists of the National Institute for Viral Disease Control and Prevention (IVDC) had sequenced the genome with the combination of Sanger, Illumina and nanopore sequencing, in bronchoalveolar lavage fluid (BALF) samples from a patient from Wuhan. The virus was named 2019-nCoV and the disease was called new coronavirus infected pneumonia (NCIP). The full genome sequence of several 2019-nCoVs on January 10, 2020, had been accessible on the www.gisaid.org organization (GISAID: Global Initiative on Sharing All Influenza Data) with access numbers EPI_ISL_402119, EPI_ISL_ 402020 and EPI_-ISL_402121 to all researchers for the understanding of the molecular properties of this emerging pathogen (Table 1), and all relevant information was also reported to the WHO. At the same time Chinese CDC had developed a few rapid and precise screening tests to prevent and control 2019-nCoV outbreak [11, 12].

With the increase in the number of cases in Wuhan, the city of Wuhan was closed on 23 January by local government [13] and as of January 28, 106 deaths in China and its provinces, more than 5,900 diagnoses had been confirmed and there were more than 9,000 suspected cases of 2019-nCoV infectious disease. On January 30, WHO declared this situation as "a public health emergency with international concern".

Table 1: Basic information for the first strain of 2019-nCoV.

Descriptors	Description
Code	CHPC 2020.00001, NPRC 2020.00001
Name in Chinese	新型冠状病毒武汉株01
Name in English	C-Tan-nCoV Wuhan strain
Taxonomy	Novel β genus coronavirus
Source of specimen	Clinical patients
Source of collection	Wuhan, Hubei province, China
Isolation date	Jan 6, 2020
Risk level	BSL-3
Contact Info	ivdcolm@ivdc.chinacdc.cn, chpc@chinacdc.cn

Note: CHPC refers to the Center for Human Pathogen Collection of China CDC, and NPRC refers to the National Pathogen Resource Center of China.

While several research groups in China were carrying out studies for the isolation, genome structure and similarities and differences with other coronaviruses, and treatment of this new virus, the first cases in Europe were reported from France on January 24, 2020 [14]. Both cases had a travel history to Wuhan, China.

As far as we know, these two cases are believed to be the first confirmed cases in France. In the first month of 2020, while China faced the outbreak of COVID-19, European countries were struggling with seasonal flu. Since COVID-19 and influenza-like illness (ILI) symptoms are similar. Therefore, retrospectively all the patients whom were admitted to the intensive care unit (ICU) with ILI symptoms, between 2 December 2019 and 16 January 2020 at Avicenne and Jean Verdier hospital near Paris, France, and had RT-PCR tests negative for known respiratory pathogens at admission. The medical records of these ICU patients were retrospectively analyzed and 14 of the samples were selected from the biobank and tested by RT-PCR for SARS-CoV-2.A sample from a 42-year-old man who was born in Algeria and lived in France for many years was determined as positive. This patient has made his last trip abroad to Algeria in August 2019. Clinical and radiological findings of this case, were similar to those of COVID-19 cases from China [14]. Retesting old samples had pushed back the timeline of the global epidemic in Europe about a month and identifying the first infected patient had been of great epidemiological importance, as it significantly changed our knowledge of SARS-CoV-2 and its spread from country to country.

On February 11, 2020, the Coronavirus Study Group (CSG) of the International Virus Taxonomy Committee evaluated the differences of this virus, and they temporarily called it 2019-nCoV. Based on phylogeny and taxonomy, CSG has accepted this virus as the brother of SARS-CoV and named it as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [15].

On 21 February 2020, 47 COVID-19 cases were reported to WHO from nine European countries [Belgium (1), Finland (1), France (12), Germany (16), Italy (3), Russia (2), Spain (2), Sweden (1) and England (9)]. It was determined that 11 out of 32 hospitals where travel information was available were infected in China (10 cases related to Hubei and one case related to Shandongil), while the remaining 21 cases were infected in Europe. It was determined that 14 of them had interacted with a group in Bavaria, Germany

and seven of them had an interaction with a group in Haute-Savoie in France [16].

Although most of the initial cases of SARS-CoV-2 had a history of contact with the Huanan Seafood market, it was quickly understood that the virus could be transmitted from person to person. In the first study, which included an analysis of 425 patients with COVID-19, it showed that the incubation period was between 3 and 7days. The average is 5.2 days (95% CI: 4.1 to 7.0) and the 95th percentile of the distribution was 12.5 days (95% CI: 9.2 to 18). According to this study, the basic reproduction number (R0) until January 4, 2020 was 2.2, i.e., a patient infecting 2.2 other people (7). In mathematical modeling using WHO data, this value may be around 3.58 [17]). In Italy (Southern Italy), which is one of the countries most affected by this outbreak, the R0 value was reported as 3.6 according to April data [18]. From time to time in some of the cities in Turkey R0 value has been 4.5–5, but general the R0 value has been announced as 1.56 [19].

On 11 March, WHO declared COVID-19 as a pandemic disease, with 118,000 positive cases and 4,291 deaths in 114 countries [20] (Figure 1). In March, many countries, especially Italy, Spain and France, closed their borders and started implementing serious quarantine measures.

In Turkey, the first case was reported on March 11. Patient had a travel history to Europe. Immediately an effective struggle was started with COVID-19. All the schools, primary, secondary and high school and preschool and Universities were closed. Public activities were restricted. Sports competitions were postponed. Over the age 65 and under 20, people were kept at home. Flexible working hours were put in to action in the state and private sector. The flights to about 20 countries were blocked. And the studies to determine the "contact source" started by filiation groups.

As of May 22, 5,127,125 confirmed cases, 333,398, deaths and 1,964,622, recovered have been reported in 188 countries. For Turkey 154,500, 4,276, and 116,111 was reported respectively [21].

Origin and evolution of SARS-CoV-2

To identify the origin of the virus that caused the pandemic, its host(s), to determine its evolutionary development, and to understand the molecular mechanism of its transmission among species will make us able to prevent its spread and to develop the appropriate control measures if necessary.

The similarity of the 2019-nCoV genome sequence obtained from the first nine patients in China was 99.98% and the similarity in the amino acid sequence was 100%. However, the genome sequence of 2019-nCoV is 79% similar to the SARS-CoV genome and 50% similar to the MERS-CoV genome. The genome sequence of the bat-SL-CoVZC45 (accession number: MG772933) is 87.99 and 87.23% similar to the genome sequence of the bat-SL-CoVZC45 (accession number: MG772933) to the 2019-nCoV [22, 23]. Phylogenetic analysis of 2019-nCoV and the associated reference genomes show that betacoronaviruses form five sub-branches (Embevovirus, Merbecovirus, Nobecovirus, Hibecovirus and Sarbecovirus). Phylogenetic analysis of the samples in the Sarbecovirus group shows that this group is divided into three clades according to the distribution of variations in the genome. Genome sequences located in 2019-nCoV isolated from

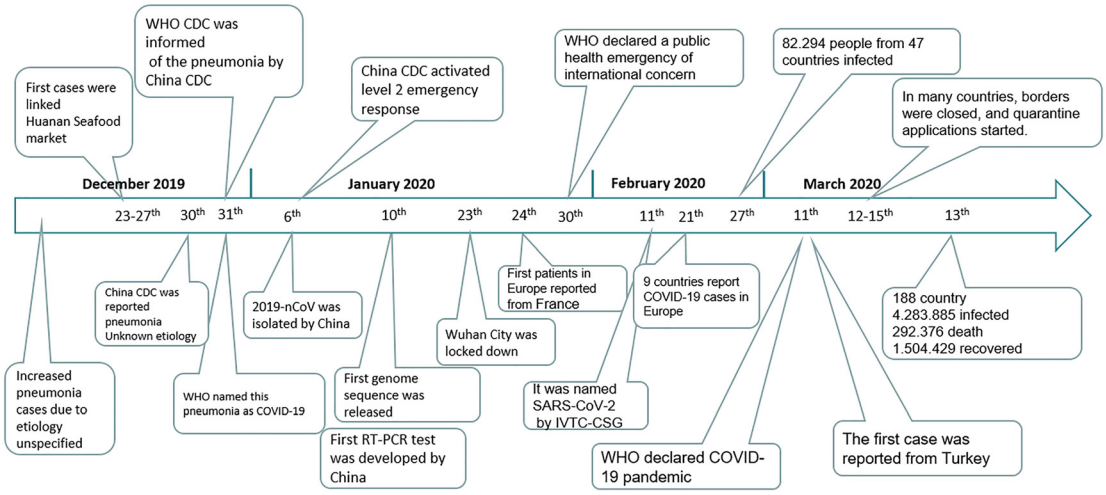

Figure 1: Significant developments in the onset of the SARS-CoV-2 outbreak.

Wuhan and two bat species in Zhoushan (bat-SL-CoVZC45 'and bat-SL-CoVXC21) are located in clade 2. Viruses isolated from bats in South West China and human SARS-CoV viruses are located within clade 3. Genomes isolated from bats in Bulgaria and Kenya constitutes clade 1. In addition, phylogenetic analysis of 2019-n-CoV's RNA-dependent RNA polymerase (RdRp) gene shows that the new virus is different from SARS-CoV [7, 24].

Although this evidence suggests that SARS-CoV-2 evolved from bat virus, it may be an intermediate host between bats and humans. Lu et al. suggest four reasons for this speculation [7]: First, most bat species in Wuhan hibernate in late December; Second, bats are not sold in the Huanan Aquaculture market; Third, the sequence similarity between SARS-CoV-2 and bat-SL-CoVZC45 or bat-SL-CoVZXC21 is less than 90%; Fourth, bats are natural reservoir for both SARS-CoV and MERS-CoV. Hence, the virus can spread to humans *via* another intermediate host (masked palm musk cats for SARS-CoV, and dromedary camels for MERS-CoV).

On October 24, 2019, Tao et al. from China's Guangdong Wildlife Rescue Center detected a SARS-CoV-like CoV from the lung samples of two dead Malayan pangolins. There was pulmonary fibrosis, with a foamy fluid in the lungs of the pangolins [25]. In the samples which were obtained from Malayan pangolins Guangdong and Guangxi customs during an anti-smuggling operation, new coronaviruses representing SARS-CoV-2 were found [26].

Virus (pangolin-CoV) genomes isolated from these pangolins show a high similarity to batCoV-RaTG13 (90.55%) and SARS-CoV-2 (91.02%), but a much higher similarity between SARS-CoV-2 and batCoV-RaTG13(96.2%) was detected. Similarity ratios between Pangolin-CoV genome and other SARS-CoV genomes, bat-SL-CoVZXC21 (85.65%) and bat-SL-CoVZC45 (85.01%) were low. When all these results are evaluated together, it can be speculated that pangolin-CoV may be a common source of SARS-CoV-2 and RaTG13 [25].

The similarity between the SARS-CoV-2 and the amino acid sequence of the S protein of pangolin CoV in the receptor binding domain (RBD) is 97.4%, while the similarity between the SARS-CoV-2 and RaTG13 in the same region is 89.2%. Interestingly, pangolin coronavirus and SARS-CoV-2 share five critical identical amino acids of RBD of S protein, while bat-CoV-RaTG13 has only one [25].

These findings show that pangolin is a potential intermediate host. However, the role of bat and pangolin as a natural reservoir and intermediate host needs further investigation.

After the SARS-CoV epidemic basic research involving the transmission of bat and HCoV-like coronaviruses in cell culture and/or animal models has been going on for years in biosafety level 2 laboratories worldwide. Therefore, the possibility of SARS-CoV-2 spreading accidentally from the laboratory was a point that researchers drew attention to. In theory, it is possible that SARS-CoV-2 acquired mutation(s) in the RBD during adaptation to the transition in cell culture, as observed in SARS-CoV studies. However, the presence of regions with nearly identical RBDs in SARS-CoV-like coronaviruses in pangolins provides much stronger evidence that SARS-CoV-2 develops through recombination or mutation of the RBDs [27].

How could the virus spread so quickly?

Actually, the answer to this question is hidden in several different questions. Did the authorities try to suppress early warnings? Was there a lack of international cooperation in the fight against COVID-19? Did many countries have misguided attempts to protect their economies? Was WHO late for intervention? Although these questions have been widely discussed in the press and science community in the past few months, they have not been able to change the fact that the virus that threatens human health is spreading rapidly around the world. This epidemic has once again demonstrated that the local CDC and WHO need a more active action plan in which international cooperation is at the forefront by ignoring political interests in the fight against the pandemic. In today's world where we have almost reached the highest level in technology in the field of molecular biology and genetics, it is possible to control such outbreaks before the onset of the outbreak when pathogens of unknown origin are identified rapidly and if information is shared.

Another factor of the rapid spread of this outbreak is that the sensitivity of the developed diagnostic kits is not sufficient. For SARS2-CoV-2 detection human errors are also a problem, collection of the right specimen at the right amount and time is very important, these errors affect the tests' performance [28, 29]. From 205 COVID-19 positive patient 1,070 different sample was collected and tested with RT – PCR. It was shown that the positivity rates of RT – PCR differ according to the type of sample. BALF specimens showed the highest positive rates (14 of 15; 93%), followed by sputum (72 of 104; 72%), nasal swabs (5 of 8; 63%), fibro-bronchoscope brush biopsy (6 of 13; 46 %), pharyngeal swabs (126 of 398; 32%), feces (44 of 153; 29%), and blood (3 of 307; 1%). None of the 72 urine specimens were found positive. The mean cycle threshold values of all specimen types were more than 30 (<2.6 × 104 copies/mL)

except for nasal swabs with a mean cycle threshold value of 24.3 (1.4 × 106 copies/mL), indicating higher viral loads [30]. Many studies have shown that false negative results may have affected the spread of the disease [31, 32].

Antibody tests can help determine people who may be assumed to be immune. However, we currently do not have sufficient information about the accuracy of antibody tests. Data from a limited number of studies show that such tests may have fewer false negative results than RT – PCR tests, but more false positives [33–35].

Therefore, hundreds of thousands of COVID-19 patients worldwide may have been underdiagnosed! One of the most important prevention methods is to quarantine patients with 'negative' test results to limit the spread of the virus for the recommended time (about 14 days).

Genome structure of SARS-CoV-2

Coronaviruses have the largest genome (26.4–31.7 kb) of G + C content of 32–43% of all known RNA viruses. RNA-synthesized RNA synthesis in coronaviruses operates in two different ways: 1. genome replication, 2. transcription of a sgmRNA collection that delivers multiple copies of genomic RNA (gRNA) and encodes viral structural and accessory proteins. The genome of the SARS-CoV-2 contains 29,870 nucleotides and encodes 9,744 amino acids (NC_045512.2) [36].

The first ORF1ab which is the two-third of the 5′-proximal of the coronavirus genome, synthesizes two polypeptides with a frame shift: pp1a and pp1ab. These polypeptides are processed with virally encoded chymotrypsin-like protease (3CLpro, Mpro and one or two papain-like proteases) to form 16 non-structural (nsps) proteins that provide viral genome replication and subgenomic mRNA (sgmRNA) synthesis. The 3′end of the genome encodes structural and accessory proteins that vary in number between different coronaviruses (Figure 2). Spike (S), membrane (M), envelope (E) and nucleocapsid (N) proteins are synthesized from the four main structural genes in this region [36] (Figure 2).

The presence of the 5′ leader sequence has been shown to protect SARS-CoV mRNAs from endonucleolytic cleavage by nsp1-induced capping and provide a strategy for efficient deposition of viral mRNAs and viral proteins during infection. The transcription process is controlled by 6–7 nucleotide conserved transcription regulatory sequences (TRSs) located at the 3′end of the leader sequence and in front of each viral gene. Also, changing the frame-shifting efficacy in the ORF1ab region changes the proportion of replicase proteins that affect viral RNA synthesis and virus production. Thus, regulation of the two viral polymerase ratios encoded by ORF1a and ORF1b, plays a role in controlling different levels of sgmRNA during viral RNA synthesis [36].

Especially in the scientific community, there are different thoughts of SARS-CoV-2, such as like SARS-CoV this virus will mutate and lose its effectiveness, or because of mutations the treatments will be ineffective. Because of this, it is necessary to have knowledge about the viruse's genome structure, replication and translation andinformation of the occurring mutations.

Genetic variance analysis plays a crucial role in enhancing the knowledge about this new virus, which will globally enable to take measures to prevent a possible second outbreak. Thanks to the worldwide efforts of scientists and the consortium of the Global Initiative for Sharing All Influenza Data (GISAID), the full viral genome sequences were quickly made public and the number of full genomes uploaded to the GISAID database reached 27,373 as of May 17 [37].

According to the data obtained from the GISAID database, three main SARS-CoV-2 clades are defined. Clade G (those carrying the D614G variant in the Spike protein), Clade V (those carrying the G251V variant in the ORF3a nsp3 protein) and Clade S (those carrying the ORF8-L84S variant). As more complete sequences are obtained, it will help identify specific geographic distributions of virus variants [37].

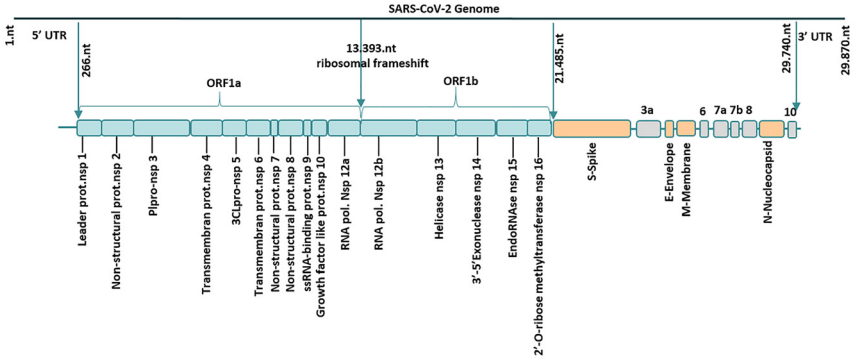

Figure 2: SARS-CoV-2 genome, structural and non-structural protein domains.

Mercatelli D et al. has done a comparative analysis of the 10.014 SARS-CoV-2 genomic sequences which they have obtained from GISAID, April 20, 2020, they identified a total of 67,364 variations compared to the NC_045512.2 Wuhan reference genome. While 130 samples, mostly of Asian origin, are the same as the reference genome, 9,884 samples have shown to have at least one mutation [38].

Overall, the least mutated samples (on average, less than 3/sample) originated from Asian samples (909 total), while a higher mutation rate (5/sample) was observed on all other continents. On a country basis, the lowest deviation from the reference is seen in Asian countries such as China, Singapore and Japan, where the virus originated.

The most common mutation in Gclade is the D614G mutation in Spike protein. Along with this mutation, there is a silent mutation (F106F) in nsp6 protein, P314L in nsp12b, and a mutation at position 241 in the 5′UTR region. All four of these mutations are common in Europe, Africa, America and Oceania. In the 5′UTR region, 241.nt mutations appear slightly less frequently than the other three variations in the G-clade group, due to less coverage of the 5 ′UTR and 3′ UTR regions during sequencing.

In some genomes of the G clade which is characterized by the D614G mutation, in the nucleocapsid gene (N) a mutation that has occurred consecutively, converting triple GGG into AAC and causing the two amino acids (RG203KR) of the N protein to change has been observed. This mutation was observed to occur almost always (99.7%) with the D614G mutation and forms a G-subclade of the SARS-CoV-2 population that overflows this trinucleotide nucleocapsid mutation.

In V clade, the most common mutation is the G251V mutation in the ORF3a gene. This mutation is usually (>95%) seen in the genomic C14805T position as a silent mutation and the L37F mutation in the nsp6 protein. Clade V appears to be common in sequences from Europe. There is also a separate V-subclade that was seen with P585S and I559V mutations in the nsp2 protein.

The most common mutation in S clade is the L84S mutation in ORF8. This mutation is common in genomes sequenced in Asia and America. The L84S mutation is often accompanied by a silent mutation of the C8782T in the nsp4 region and less frequent variations are detected in other nsp13 and nsp14 regions.

As a result, all European countries share very similar profiles of the virus, but in Asia, due to the prevalence of the nsp6: L37F in Japan, ORF8: L84S and nsp4: S76S in China, and ORF3a: G251V mutation in Hong Kong, a distinct difference is observed between these countries [38].

Combining the genomic details and epidemiological information and clinical features of COVID-19 patients, other studies can be extremely useful to identify strategies and treatments that can help reduce the burden of this disease. An important effect of mapping mutations is for the development of antiviral treatments that target specific areas. For example, if a vaccine is developed against the SARS-CoV-2 spike region, it may not effective in the European strains, because of the D614G mutation in the G clade that is found in the European strains.

Currently, there is no specific treatment for COVID-19. Given the high transmission rate of this virus between humans, it is important to determine the basis of its replication, structure, and pathogenicity to find a specific treatment or prevention. The spike protein is the main target for the vaccine developments as there is a high genetic similarity in the *Coronaviridae* family, the vaccine studies on going or had done in previous years for any virus in this family will also be useful for the COVID-19. The spike protein is longer in COVID-19, differences in the length of this protein are likely to play an important role in the pathogenesis of this virus. In a study to identify specific molecular details of the virus the interaction between SARS-CoV-2 proteins and human proteins involved in various complexes and biological processes have been systematically mapped this will help achieve therapeutic goals. With AP-MS analysis, 332 highly reliable protein interactions between SARS-CoV-2 proteins and human proteins were detected and the correlation between each viral protein and repeated experiments was observed as R = 0.46–0.72 [39]). Corona virus proteins and host protein interactions are given in Table 2 [39, 40].

To disrupt SARS-CoV-2- human protein-protein interactions, ligands from the IUPHAR / BPS Pharmacology Guidelines (2020-3-12) and ChEMBL25 database have been searched and candidate molecules, approved drugs, new research (INDs, “clinical”) or preclinical candidates have been selected. Of the 332 protein-protein targets, for 63 were targeted and 69 drug/IND/preclinical molecule candidates which could modulate and disrupt protein interaction was detected.

With an immunofluorescence-based test and qRT-PCR test the inhibition of SARS-CoV-2 infection in the Vero E6 cell line and related genes were monitored. Out of 69 candidate molecules 47 of them were potent candidates for Sigma R1/R2 receptors and mRNA translation.

The strong efficacy of translation inhibitors on viral infectivity (in the range of 10–100 nM) made these molecules attractive as candidate antivirals and also highlighted this route as an intervention point [39]. Although the mechanism of action of drugs targeting the Sigma1 and Sigma2 receptors has not been fully defined yet, it is

Table 2: Possible protein–protein interaction between host and coronavirus proteins.

Host cell proteins or pathways	Coronavirus proteins
DNA replication proteins	nsp1
Epigenetic and gene expression regulator proteins	nsp5, nsp8, nsp13, and E protein.
Proteins in vesicular traffic	nsp2, nsp6, nsp7, nsp10, nsp13, nsp15, Orf3a, E, M, Orf8.
Proteins in lipid modification pathway	Spike protein
Proteins in RNA processing and regulation	nsp8, N protein, ubiquitin ligases Orf10
Proteins in signal transmission	nsp8, nsp13, N protein
Nuclear transport pathway	nsp9, nsp15, Orf6
Cytoskeleton proteins	nsp1, nsp13
Mitochondrial proteins	nsp4, nsp8
Extracellular matrix proteins	nsp9
Native immune signal proteins (TBK1 and TBKP1)	nsp13
Innate antiviral immune signal proteins (TRIM59 and MIB1)	Orf3a, nsp9

thought that their activity as both anti- and pro-viral agents may have potential.

There are a number of major challenges in the clinical development of new anti-CoV drugs both virological and patient-related. First of all, CoVs are one of the most diverse and rapidly mutated virus groups, and new CoVs occur repeatedly at unpredictable times. Therefore, most anti-CoV drugs targeting the replication mechanism of an existing CoV may not be effective against another new CoV. This is especially true for viral enzyme inhibitors, mAbs and antiviral peptides that target the Spike protein and agents that target the host cell receptor.

The development of safe and effective anti-CoV drugs, clinical trials *in vitro* and/or animal models can only be achieved through the establishment of a well-organized, multidisciplinary, discreet international network of collaborators, clinicians, virologists and drug developers. The solution for the whole world is to work together. In fact, we cannot be protected unless any biological epidemic is globally addressed. We are all on the same ship.

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