

Coronaviruses and the Associated Potential Therapeutics for the Viral Infections

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Abstract

Coronaviruses (CoVs), named after the crown-like spikes on their surfaces, belong to the RNA virus family Coronaviridae. Coronaviruses are enveloped RNA viruses with a linear positive-sense single-stranded genome consisting of the open reading frames (ORFs), the 5'-methylated cap, and the 3'-poly (A) tail. The open reading frames encode structural proteins and nonstructural proteins that may be drug-targetable. Antiviral medications seek to target these key proteins via different mechanisms. There have been seven coronaviruses discovered that are capable of infecting human beings, three of which including *MERS-CoV*, *SARS-CoV* and *SARS-CoV-2*, originated in wild animals and evolved to develop rapid human-to-human transmission, resulting in severe respiratory diseases among other pathologies, even deaths. Particularly, the outbreak of the novel Wuhan coronavirus *SARS-CoV-2* has now rapidly spread across China and into many other countries. Sadly, there is no any effective vaccine or specific drug available. Many patients infected with *SARS-CoV-2* have succumbed. Thus, there is a burning need for the anti-coronavirus drug development. The antiviral prodrug, Remdesivir, developed by the company Gilead, is currently under clinical investigation in China.

Keywords: Coronavirus; Structural proteins; Non-structural proteins; Infection; Drug; Vaccine

Introduction

During December 2019, patients with pneumonia of unknown symptoms first appeared in Wuhan, China [1]. And later, the novel coronaviruses (CoVs) were diagnosed and isolated and called as 2019-nCoV (or COVID-19), with a new name *SARS-CoV-2* given by World Health Organization (WHO) on February 11 [2-6]. *SARS-CoV-2* spread in China rapidly with person-to-person transmission. Outside of China, patients with *SARS-CoV-2* have been diagnosed in 26 other countries such as Japan, South Korea, Singapore, United States, Canada and Europe. Infection with *SARS-CoV-2* can result in severe diseases and even death. As of February 14, 2020, there are 66577 patients diagnosed in China, with 1524 deaths, with the mortality rate approximated at 2.29%. Meanwhile, 525 cases and 2 deaths have been reported in other 26 countries. The *SARS-CoV-2* outbreak in China is currently catching global attention and is becoming a severe public health emergency.

Coronaviruses (CoVs) were first discovered in chickens in 1937 and first identified in human in 1965, and were named due to the crown-like spikes on the surface of these viruses. They belong to the RNA virus family Coronaviridae [7]. The Coronaviridae family has been divided into four genera named alpha (α) coronavirus, beta (β) coronavirus, gamma (γ) coronavirus and delta (δ) coronavirus, respectively [7,8]. There are seven coronaviruses discovered capable of infections in humans. The novel Wuhan coronavirus *SARS-CoV-2* is a type of beta coronavirus.

Scientists worldwide are fighting against coronaviruses and the severe health problems associated with it. Unfortunately, there is still no effective vaccine or coronavirus-targeted therapeutic drug available, though promising progress has been made in the study of coronaviruses. Remdesivir, an anti-viral drug developed by the company Gilead, was found for its therapeutic activity against coronavirus and other RNA viruses, and is expected to be a potential effective drug. It is currently used to treat CoV patients under clinical trials in China. In this review, we will discuss the progress in CoV research and the potential development of therapeutic drugs, especially, the updated situation of *SARS-CoV-2* and the possibility of the CoV-targeting drugs aimed on the CoV structural proteins.

The Classification of Coronaviruses

Coronaviruses (CoVs) only infect with human beings and other vertebrates and are associated with multiple infectious diseases, particularly, by targeting the respiratory, digestive and nervous systems. Coronaviruses (CoVs) belong to the family of Coronaviridae and the subfamily of Orthocoronavirinae. They are divided into four genera named alpha (α) coronavirus, beta (β) coronavirus, gamma (γ) coronavirus and delta (δ) coronavirus, respectively [9,10]. Currently, there are seven coronaviruses (CoVs) discovered to be capable of infecting human beings. Four of which only cause the common cold, including *HCoV-229E* (discovered in 1966), *HCoV-NL63* (in 2004), *HCoV-OC43* (in 1967) and *HCoV-HKU1* (in 2005), with the first two being alpha (α) coronaviruses and the last two being beta (β) coronaviruses. The three other coronaviruses cause more severe respiratory disease processes. They originate in animals and eventually infect humans as they develop further. These viruses are the *MERS-CoV* (discovered in 2012), *SARS-CoV* (in 2002) and *SARS-CoV-2* (in

2019) [11]. All of the three belong to beta (β) coronaviruses [12,13]. As demonstrated, *SARS-CoV* originated from bats, and *MERS-CoV* was isolated from camel, but the original host of *SARS-CoV-2* is still not clear.

The Genomic Structure of Coronaviruses

Coronaviruses (*CoV*s) are the type of enveloped RNA viruses with a linear positive-sense single-strand. These coronaviruses have large RNA genomes with the length of 27-32 kb. They are very similar, with

a 5'-methylated cap, a 3'-poly (A) tail (Figure 1) capping the two ends of the remaining open reading frames (ORFs). The genes located in the open reading frame ORF1a express 11 nonstructural proteins (Nsps) from Nsp1 to Nsp11, with the genes of ORF1b expressing proteins from Nsp12 to Nsp16 [8,9,14]. The capping structure at the 5'-end of coronavirus mRNAs plays vital roles in RNA stability, translation initiation and evading host antiviral response [7,15-17]. And at the 3' end, four or five structural proteins such as Spike (S), envelope (E), membrane (M) and nucleocapsid (N) proteins are encoded by other ORFs (Figure 1) [12].

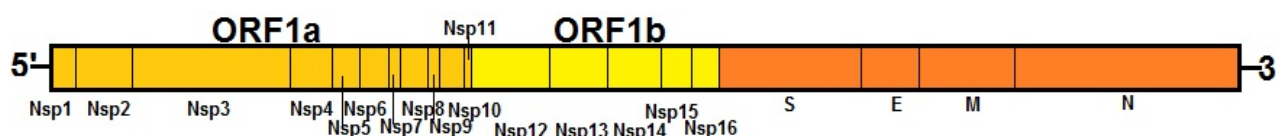


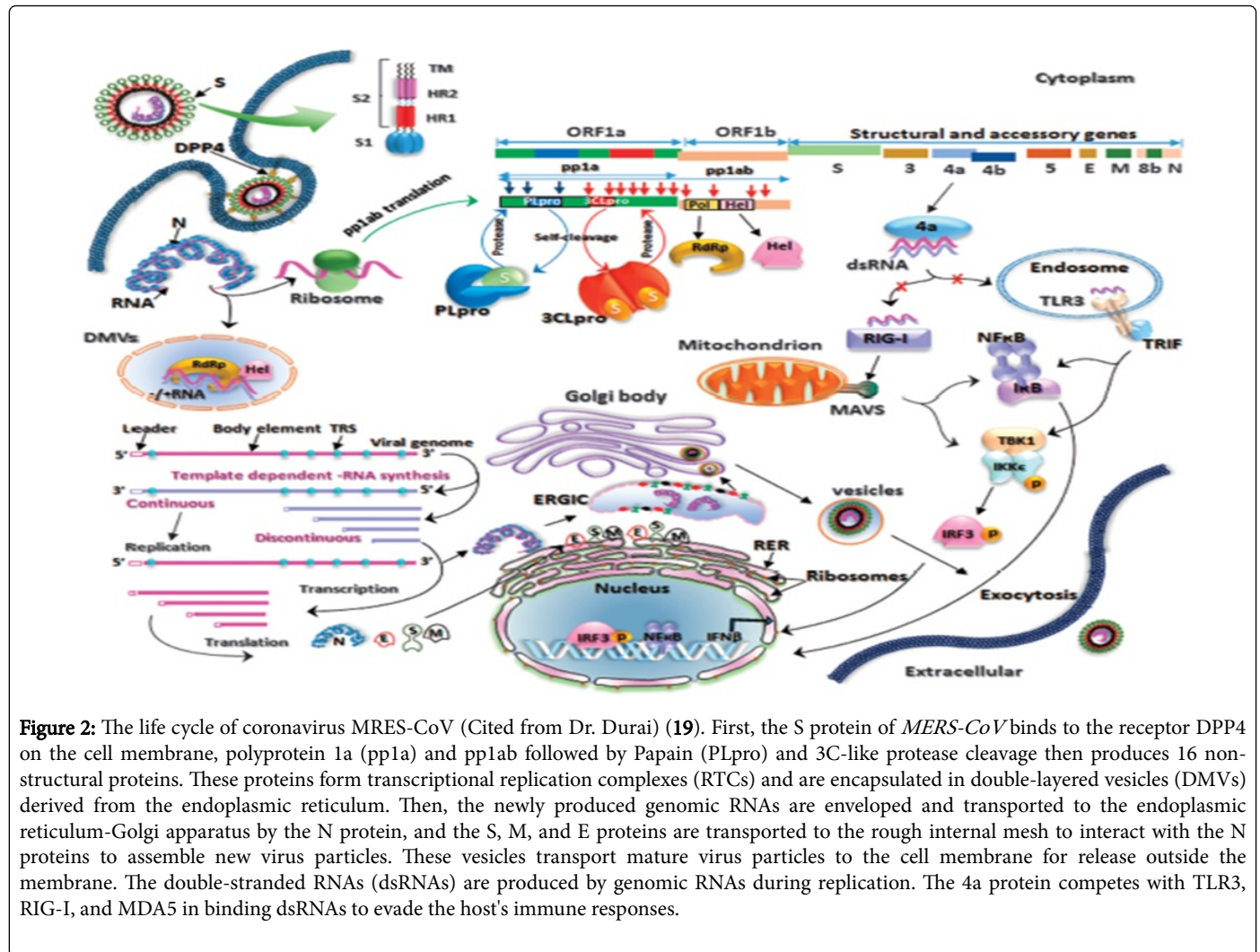
Figure 1: The genome structure of human coronaviruses consists of open reading frames to encode structural proteins and nonstructural proteins. There are 16 nonstructural proteins with different functions. Nsp3 and Nsp5 are a papain-like cysteine protease (PLpro) and 3C like serine protease (3CLpro), respectively. Nsp12 has RNA-dependent RNA polymerase (RdRp) activity, and Nsp13 is a helicase (Hel). Nsp14 and Nsp10/16 have the activities of N7 and 2'-O methyltransferase, respectively. The four structural proteins S, E, M and N are necessary for virus invasion and virion assembly.

The total 16 nonstructural proteins display their different functions. The proteins Nsp3 and Nsp5 are a papain-like cysteine protease (PLpro) and 3C like serine protease (3CLpro), respectively. Protein Nsp12 has RNA-dependent RNA polymerase (RdRp) activity, and Nsp13 is a helicase (Hel), with Nsp14 and Nsp10/Nsp16 having N7 and 2'-O methyltransferase, respectively. The structural proteins S, E, M and N are necessary for virion assembly and virus invasion [9,13]. The S proteins constitute spikes on the surface of the coronavirus and are critical for viruses to enter into the host cells. The E proteins play a critical role in virus assembly and are involved in the pathogenesis of the viruses. The M proteins have three trans-membrane domains that form virions and bind to the nucleocapsid N proteins. The N protein contains two domains that bind to the viral RNA genome through different mechanisms [9,12]. For instance, *SARS-CoV* has four genes to encode proteins S, E, M and N. *HCoV-HKU1* has five genes that express proteins S, E, M, N and HE, respectively. *SARS-CoV-2* shares over 96 percent of its RNA genome with other coronaviruses identified before [11,12].

The Infection of Coronaviruses and the Associated Health Problems

MERS-CoV (in 2012), *SARS-CoV* (in 2002) and *SARSCoV-2* (in 2019) are the three key coronaviruses that were originally from animals, eventually infected human and resulted in severe health problems while *HCoV-229E*, *HCoV-NL63*, *HCoV-OC43* and *HCoV-HKU1* are four common human coronaviruses and only cause the

common cold or other mild symptoms. The processes of coronavirus infection of cells are very complicated, but are similar. *MERS-CoV* infects its host's respiratory tract via interactions with the DPP4 receptor, activating a series of downstream immune responses [18], as shown with the process of *MERS-CoV*'s infection in the Figure 2 [19]. The RBD domain of S protein binds to the receptor DPP4 (also called CD26) on the cell membrane. Viruses enter inside cells and release RNA genomes in cytoplasm [20,21]. Viral RNAs bind to ribosomes where to translate viral proteins. The open reading frames of genomes ORF1a and ORF1b were translated into polyprotein 1a (pp1a) and pp1ab, respectively, followed by the cleavage of Papain (PLpro) and 3C-like protease, that produces 16 non-structural proteins. These proteins form transcriptional replication complexes (RTCs) and are encapsulated in double-layered vesicles (DMVs) derived from the endoplasmic reticulum. AU-rich sequences in genomic RNA are called transcriptional regulatory sequences (TRSs). These TRSs are recognized by RTC and transcribed to produce subgenomic RNAs of different lengths, otherwise replication results in a full-length genome. Then the genomic RNA is enveloped and transported to the endoplasmic reticulum-Golgi apparatus by the N protein. The S, M, and E proteins are transported to the rough internal mesh to interact with the N protein to assemble new virus particles. These vesicles then transport matured virus particles to the cell membrane for release outside the membrane. The protein 4a competes with TLR3, RIG-I, and MDA5 and binds double-stranded RNAs (dsRNAs) to evade the host's immune response [22,23].



SARS-CoV-2 has similar genomic characteristics to the *SARS-CoV* that allows it to adapt well to the human respiratory tract. This is primarily attributed to its contact with the angiotensin converting enzyme II (ACE2) via its receptor binding domain (RBD) [6]. Although it is worthy to note that *SARS-CoV-2* is more contagious, it is estimated to be less pathogenic than *SARS-CoV* [24]. Some research has already been performed in identifying difference between the two viruses. One initial finding is that *SARS-CoV-2* contains a furin-like cleavage site (RRAR) in its Spike (S) protein that is lacking in *SARS-CoVs* [25]. More studies will be needed to understand how the genomic and structural differences between members of the coronavirus family affect their virulence and pathogenicity.

The Transmission of Coronaviruses

Currently, only seven coronaviruses have been demonstrated for human-to-human transmission. Particularly, the transmission occurs among people via droplets or wastes from coughing, sneezing and other respiratory systems. And three of them, including *MERS-CoV*, *SARS-CoV* and *SARS-CoV-2* initially pass from animals to human. Current evidence shows that the initial primary transmission of *MERS-CoV* can be traced to dromedary camels, although bats are thought to be potential intermediate hosts as well [26]. Human-to-

human transmission of MERS has been well-documented but has also been shown to be inefficient [27]. With proper implementation of quarantine and infection control protocol, human-to-human transmission of MERS could be greatly curbed [27]. Studies in Saudi Arabia and South Korea has shown that the R0 for MERS to be less than 1 while the incubation period was observed to range from 4-10 days [28].

As previously mentioned, the initial outbreak of *SARS-CoV* in Southern China quickly spread to nearby Hong Kong, and then on to many other major cities of the world due to Hong Kong's status as a major travel hub [29]. Beijing, the Chinese capital, became one of the most severely affected megapolises. A rough count in 2004 estimated 66% of cases to have arisen from mainland China and another 22% in Hong Kong, with 4% in Taiwan [30]. The primary hosts of the *SARS-CoV* is believed to be traced to animals of a reservoir in Southern China, but the virus quickly spread through rapid human-human contact [31]. The *SARS-CoV* spread through multiple conduits, but the two major routes was transmission through droplets or via contact with infected surfaces [29]. Studies have shown that the *SARS-COV* could survive in human serum, sputum and feces for over 4 days and even in urine for 3 days while remaining active infectivity. Extermination of the viruses was achieved with >56°C heat and UV irradiation exposure of 90 minutes and 60 minutes, respectively [32].

The mean incubation period of SARS patient is estimated to be 6.4 days with a R0 of around 2.7 [29]. Radiological features of SARS patients shows “ground-glass” opacities that spread rapidly and peaks around days 8-10 after initial onset of the disease [33]. The source of the *SARS-CoV-2* outbreak has been successfully traced to the Huanan seafood market in Wuhan, China, where various type of animals were kept in close proximity to each other and to humans. The primary hosts for *SARS-CoV-2* are believed to be bats, but human-to-human transmission has quickly developed and is quite rapid, spreading through droplets or other types of close contact [24]. The average incubation period was calculated to be 5.2 days, although in some cases, up to two weeks was reported [34,35]. The WHO estimates of the reproduction number of *SARS-CoV-2* ranges from 1.4 to 2.5, but other calculations have posited it to be as high as 3.28 [36].

The Potential Treatments of Coronavirus Infections

Nowadays, there is no any anti-viral vaccine and drug being approved for the treatment of coronavirus infection. Patients infected with the four common coronaviruses (*HCoV-229E*, *HCoV-NL63*, *HCoV-OC43* and *HCoV-HKU1*) show mild symptoms such as cold and coughing. However, as for *MERS-CoV*, *SARS-CoV* and *SARS-CoV-2*, patients infected could have severe respiratory problems that can quickly deteriorate into multi-system organ failure and death. There is no effective drug or other treatment available. Currently, patients were mostly treated with supportive care through fluids and nutrition, thus helping their own immune systems to fight off the virus [1,34,37]. SARS patients were often treated with broad-spectrum

antibiotics to cover other causes of respiratory disease, before being committed to anti-virals. Ribavirin, for example, was such an anti-viral that was used en-masse in Hong Kong. Low-dose steroids were often given as well [38]. Remdesivir, an antiviral originally designed to treat Ebola, has shown to be effective towards *SARS-CoV-2 in-vitro* and is currently undergoing extensive medical trials in China [39]. There exists an urgent need to quickly develop anti-CoV vaccines or drugs.

The Development of Coronavirus Vaccines

There are different strategies to develop vaccines including live-attenuated, inactivated, subunits, viral vectors and DNA vaccines [40]. Several vaccines of *SARS-CoV* and *MERS-CoV* are under investigation (Table 1). Some vaccines targeting to *SARS-CoV* and *MERS-CoV* are currently in different stages of ongoing development, with many of them seeking to target the viral spike (S) protein [41]. As reported, the inactivated *SARS-CoV* vaccines and the DNA vaccines against S protein can induce strong responses to anti-S antibody and have been tested in Phase I clinical trials. These vaccines all show a potential toxicity such as eosinophilic or other immune-pathological diseases [40,42]. A key domain of the Spike protein that has been explored for the development of *SARS-CoV* vaccine is the receptor-binding domain (RBD) in the S1 subunit [43]. Kim et al. constructed two adenoviral recombinant vectors (Ad5) encoding the full-length S protein and the S1 extracellular domain of S protein of *MERS-CoV*, which can induce specific immune responses in mice. However the same responses have yet to be demonstrated in dromedary camels [43].

Vaccines	Target	Comments	References
Inactivated <i>SARS-CoV</i> vaccines	Full-length S protein	Induced strong antibody and tested in phase I trials; Induced eosinophilic diseases	[16,19-21,23]
Live, attenuated <i>SARS-CoV</i> vaccines	E protein	Attenuated E mutant vaccines induce protection in hamsters and mice; Immunocompromised patients have a risk of infection.	[65-68]
<i>SARS-CoV</i> DNA vaccines	Full-length S protein	Induce strong antibody and tested in phase I trials; Induce immunopathological diseases.	[16,21-24]
Viral vector vaccines of <i>MERS-CoV</i>	Full-length S protein or S1 extracellular domain of S protein	Induce neutralizing antibody immune responses; Cannot induce T cells responses.	[25,69]
Subunit vaccines of <i>SARS-CoV</i>	RBD of S protein	Induce neutralizing antibodies; May not neutralize <i>SARS-CoV</i> .	[70]
DNA vaccines of <i>MERS-CoV</i>	Consensus S protein	Induce protective responses in mice, macaques and camels.	[18]

Table 1: The *SARS-CoV* and *MERS-CoV* vaccines under development.

For *MERS-CoV*, the vaccines were designed based on recombinant S protein or RBD domain of S protein [42,44,45]. In his work, Dr. Muthumani demonstrated that the DNA vaccine based on the recombinant S protein displayed its potent efficacy in mice, camels and rhesus macaques [45]. Currently, this vaccine is being investigated at phase I clinical trials. During SARS outbreak in 2003, the neutralized antibodies from the memory B cells of SARS survivors or their convalescent sera have been used to treat *SARS-CoV* patients. In 2012, similar strategies were used to treat *MERS-CoV* patients during the MERS outbreak [40,46-51].

Vaccines for *SARS-CoV-2* are currently under investigation but likely will not become widely available until this episode of the

outbreak has ended, much like the case for the *SARS-CoV* vaccine [52]. Before the vaccine is released, however, the risk of *SARS-CoV-2* infection for immune compromised persons, the elderly as well as healthcare workers will remain high in the affected regions. Special considerations should be discussed and put in place to further protect the health of these vulnerable groups.

The Development of CoV-Targeting Drugs

The drugs for targeting the coronavirus structural proteins

Human coronaviral genomes encode four or five structural proteins including envelope (E), membrane (M), nucleocapsid (N) and spike (S) [53-64]. These structural proteins are necessary for virion assembly and virus invasion and are the targets for drug development. Although there has yet to be any medication approved for specific CoV

treatment, scientists will continue their search for anti-CoV drugs. As shown in Table 2, the drug candidates targeting the structural proteins are under investigations. Coronavirus S protein is a 180-200 kDa membrane glycoprotein containing two subunits S1 and S2 that plays a significant role during virus infections [8,11-15]. All human coronaviruses enter into their target cells via the receptor-binding domain (RBD) of S protein [11]. Viral S proteins are thus the critical targets for drug development.

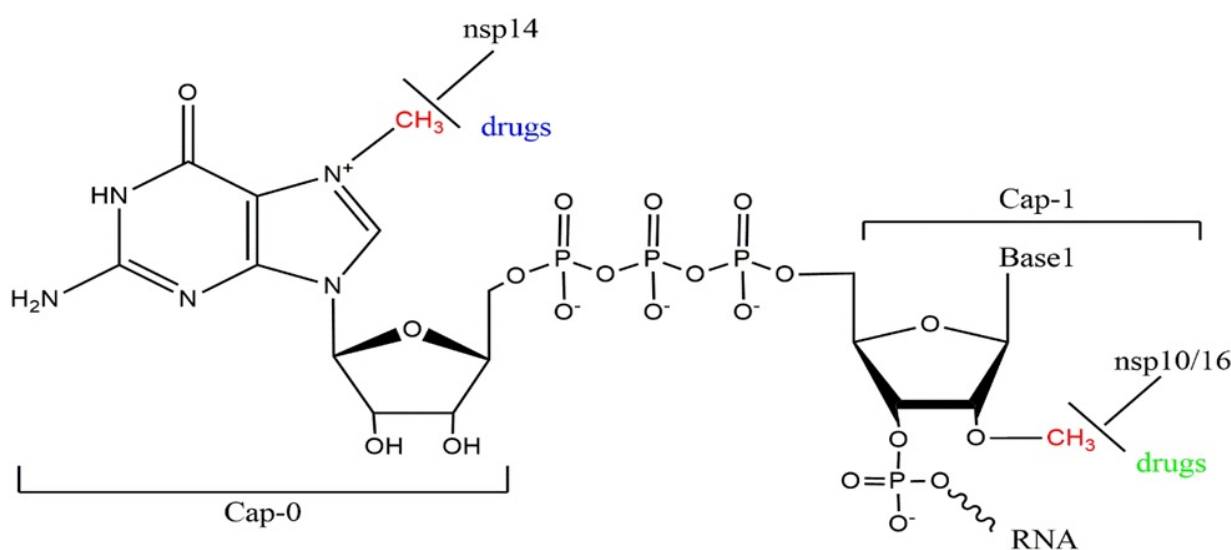


Figure 3: The process of coronavirus RNA capping and methylation. Coronaviruses use a conventional mechanism to cap and methylate their own RNAs (84). First, the coronavirus Nsp13 (TPase) removes the 5'-phosphate group of the nascent coronavirus mRNA. Then, a guanylyltransferase (GTase), dubbed capping enzyme, catalyses the attachment of GMP to the 5'-diphosphate coronavirus mRNA. Nsp14 of coronavirus (N7-MTase) methylates the cap onto the N7-guanine, releasing S-adenosyl-homocysteine (AdoHcy or SAH). Finally, Nsp10/16 of coronavirus (2'-O-MTase) further intervenes to yield a cap-1 structure.

Targeted structural proteins	Examples	Comments	References
RBD of S protein	m336, m337, m338 and Mersmab1 mAbs for <i>MERS-CoV</i>	High specific binding affinity, but narrow spectrum.	[27,65]
S2 subunit of S protein	HR2P	Inhibit fusion of S protein with DPP4, but narrow spectrum	[28-30]
S protein	Griffithsin	Specifically bind to S protein, broad spectrum	[31-33]
S, E, M, N	siRNA	Interfere with the expression of <i>SARS-CoV</i> S and E, M. Reduce RNA-binding affinity of N, but narrow spectrum.	[37, 66-69]

Table 2: The development of drugs targeting for structural proteins in development.

Aiming at *MERS-CoV*, Dr. Ying et al. developed serial monoclonal antibodies (mAbs) such as m336, m337 and m338. These mAbs specially target the receptor binding domain (RBD) of *MERS-CoV* S protein and compete with DPP4 for binding to RBD. Especially, the mAb m336 showed its extremely high binding affinity at pM level [54]. Dr. Mori et al identified a novel anti-HIV protein Griffithsin (GRFT) from a red alga from New Zealand [55]. Its anti-viral mechanism was believed to specifically bind to oligosaccharides on HIV gp120. Thus,

GRFT might have a broad-spectrum anti-viral activity. Indeed, GRFT was identified not only to inhibit viruses HIV, HCV and JEV, but also to block various coronaviruses including *HCoV-229E*, *HCoV-OC43*, *SARS-CoV* and *HCoV-NL63* [56,57]. However, GRFT cannot significantly inhibit the binding interactions of S proteins with its relevant receptors. Small interfering RNA (siRNA), a short double-stranded RNA, also displayed their effects on coronaviruses with the degradation of the target mRNA by complementary base pairing [58].

These siRNAs can be used to silence the crucial genes of coronaviruses and further inhibit the replication of these viruses [59-61]. Peptides can block viruses to interact with the host cells. HR2P, a specific peptide derived from S2 subunit of *MERS-CoV* S protein, was found to effectively inhibit *MERS-CoV* fusion and thus block *MERS-CoV* Infection [62-64].

The drugs for targeting the coronavirus nonstructural proteins

The genes located in the open reading frames ORF1a and ORF1b express 16 nonstructural proteins from Nsp1 to Nsp16 [9]. These

nonstructural proteins involved in various viral functions [65,66]. Such proteins, most likely Nsp7 and Nsp16, can direct the synthesis and the process of these coronavirus RNAs. For instance, Nsp3 can induce membrane disordering and regulate proliferation, Nsp3 and Nsp4 together affect viral membrane-paring. Nsp3, Nsp4 and Nsp6 can work together to induce double-membrane vesicles. Nsp14 and Nsp16 regulate mRNA capping, with Nsp12 for RNA-dependent RNA polymerase and Nsp13 for helicase (Figure 3) [10,66,67]. Thus, targeting these nonstructural proteins may provide potential opportunities for anti-coronavirus drug development (Table 3).

Targeted nonstructural proteins	Examples	Comments	References
Nsp3	E64, Ub-vinylsulfone inhibitor	Specially inhibit DUBs domain of <i>SARS-CoV</i> and <i>HCoV-NL63</i> PLP2, but not inhibit <i>MERS-CoV</i>	[41,42]
Nsp5	3f, 3g and 3m	Inhibit NA and 3CLpro, broad spectrum.	[44]
Nsp12	ATA	Binds the catalytic sites of <i>SARS-CoV</i> 's Nsp12	[45]
Nsp14	PF35468, PA48202 and PA48523	Specially inhibit Nsp14 of <i>SARS-CoV</i> , not N7MTase	[58]
Nsp10/16	TP29	Inhibit <i>SARS-CoV</i> , <i>MERS-CoV</i> , IBV, TGEV, FCoV, MHV Nsp10/16. broad spectrum.	[7]

Table 3: The strategies to develop drugs via targeting nonstructural proteins.

The nonstructural protein Nsp3 is a papain-like protease that processes polyprotein 1a to release Nsp1, Nsp2 and Nsp3 [68-70]. E64, a cysteine protease inhibitor, can inhibit the Nsp3s of *SARS-CoV* and *HCoV-NL63*, but not those of *MERS-CoV* [71]. PLP2 domains of *SARS-CoV* and *HCoV-NL63* exhibit activity of deubiquitinating enzyme (DUB). Ubiquitin-Vinyl Sulfone (Ub-vinylsulfone, Ub-VS) displayed its potent and specific inhibitory activity against deubiquitinating enzymes (DUBs) [72]. Nsp5 is a 3C-like protease that is vital for coronavirus replication. Thus, it is an attractive target for the development of anti-coronaviral therapeutics [73]. Dr. Kumar et al. [74] reported the pyranones 3f, 3g and 3m could inhibit both neuraminidases (NA) and 3CL protease. All coronavirus Nsp12 proteins have the RNA-dependent RNA polymerase (RdRp) activities responsible for RNA replication [75]. Dr. Yap et al. reported that aurintricarboxylic acid (ATA) that can polymerize and block the interactions of proteins and nucleic acids could inhibit the RdRp activity of *SARS-CoV* Nsp12 by binding to its catalytic sites [75]. Dr. Sun et al. reported the three natural and microbial product extracts PF35468, PA48202 and PA48523 could inhibit Nsp14 of *SARS-CoV* [76]. Dr. Ke and his team demonstrated that the two peptides K12 and K29 derived from Nsp10 could inhibit the activity of *SARS-CoV*'s nsp16 in a dose-dependent manner, and block the MTase activity of the Nsp10/Nsp16 complex [77]. Another peptide, TP29, inhibited Nsp10 and Nsp16 of six viruses including *SARS-CoV*, *MERS-CoV*, IBV, TGEV, FCoV and MHV [7].

Outlook and Challenges

Up to now, a large number of antiviral compounds or prodrugs have been reportedly applied to treat coronaviruses, with some currently under clinical investigation. Meanwhile, there are also many herbal medicines that are being used to treat *SARS-CoV-2* patients during the current outbreak in China. However, unfortunately, there has yet to be

any formally approved drug made commercially available [78-81]. And another challenge is that, coronaviruses are one of the most multitudinous and rapidly mutated viruses. The novel viruses emerge frequently at unpredictable times. So in the long term, the development of novel, broad-spectrum antiviral drugs may become the ultimate dream for responding to new threats of circulating and emerging *CoV* infections [82,83].

What is promising is that Remdesivir (GS-5734), an antiviral nucleotide analog, is currently in clinical trials. Remdesivir can significantly target Nsp12 proteins of both *SARS-CoV* and *MERS-CoV*, providing an option for the treatment of the novel coronavirus *SARS-CoV-2*. Although Remdesivir is not yet approved for the market, Gilead and the Chinese Health Bureau have reached an urgent agreement to support and accelerate the phase III clinical trials for Remdesivir to treat the Chinese patients infected with *SARS-CoV-2* during the current outbreak. Such a novel anti-coronavirus drug is needed not just in China, but all over the world as Covid-19 continues to spread.

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