

Perspectives on monoclonal antibody therapy as potential therapeutic intervention for Coronavirus disease-19 (COVID-19)

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Abstract

Last decade witnessed the outbreak of many life-threatening human pathogens including Nipah, Ebola, Chikungunya, Zika, Middle East respiratory syndrome coronavirus (MERS-CoV), Severe Acute respiratory syndrome coronavirus (SARS-CoV) and more recently novel coronavirus (2019-nCoV or SARS-CoV-2). The disease condition associated with novel coronavirus, referred to as Coronavirus disease (COVID-19). The emergence of novel coronavirus in 2019 in Wuhan, China marked the third highly pathogenic coronavirus infecting humans in the 21st century. The continuing emergence of coronaviruses at regular intervals poses a significant threat to human health and economy. Ironically, even after a decade of research on coronavirus, still there are no licensed vaccines or therapeutic agents to treat coronavirus infection which highlights an urgent need to develop effective vaccines or post-exposure prophylaxis to prevent future epidemics. Several clinical, genetic and epidemiological features of COVID-19 resemble SARS-CoV infection. Hence, the research advancements on SARS-CoV treatment might help scientific community in quick understanding of this virus pathogenesis and develop effective therapeutic/prophylactic agents to treat and prevent this infection. Monoclonal antibodies represent the major class of biotherapeutics for passive immunotherapy to fight against viral infection. The therapeutic potential of monoclonal antibodies has been well recognized in the treatment of many diseases. Here, we summarize the potential monoclonal antibody based therapeutic intervention for COVID-19 by considering the existing knowledge on the neutralizing monoclonal antibodies against similar coronaviruses SARS-CoV and MERS-CoV. Further research on COVID-19 pathogenesis could identify appropriate therapeutic targets to develop specific anti-virals against this newly emerging pathogen.

Key words: Coronavirus; Emerging threat; Monoclonal Antibody, Immunotherapy, Infectious diseases; Viruses; Zoonoses

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Introduction

In December 2019, cases of pneumonia of unknown cause were reported in Wuhan, Hubei Province, China which was later confirmed to be caused by novel coronavirus SARS-CoV-2. The clinical condition caused by novel coronavirus is referred to as COVID-19.¹⁻⁴ Coronaviruses (CoVs) are a large family of viruses that are phenotypically and genotypically diverse. CoVs are enveloped viruses containing single-stranded positive-sense RNA that belongs to *Coronaviridae* family of the *Orthocoronavirinae* subfamily which can cause illness in birds, mammals and humans. The viral genome is about 27-32 kb, which encodes for both structural and non-structural proteins.

The structural proteins such as membrane (M), envelope (E) protein, nucleocapsid (N) protein and spike protein (S) play a major role in virus entry and virus replication in the host cell.⁵⁻⁸ Two highly pathogenic coronaviruses of zoonotic origin such as SARS-CoV and MERS-CoV were identified earlier which causes widespread epidemics and fatality in many countries. SARS-CoV-2 is the third known highly pathogenic human coronavirus infection in the last two decades after MERS-CoV and SARS-CoV.³ Although it is believed to be originated from bats, the exact source of SARS-CoV-2, animal reservoir and enzootic patterns of transmission still remain uncertain.

The COVID-19 symptoms have reportedly ranged from mild to severe that can ultimately lead to death. The symptoms usually appear 2-14 days after viral exposure which includes fever, cough, shortness of breath and pneumonia. The severe cases showed respiratory, hepatic, gastrointestinal and neurological complications that can lead to mortality. The transmission of COVID-19 is reported to be human-to-human transmission *via.*, respiratory droplets or direct contact with the infected patients.^{1-3,6,9-13} The virus spreads to more than 20 countries within short period and nearly 73,000 infected cases of COVID-19 with a total of 1,870 deaths were reported as of February 18, 2020. The numbers of infected cases and death associated with COVID-19 is increasing daily. More number of infected cases has been reported in China, followed by Singapore, Hong Kong Thailand, Korea, Japan, Taiwan, Malaysia, Vietnam, Australia, Germany, USA, France, UAE, UK, Canada, Italy, Philippines, India, Spain, Finland, Sweden, Belgium, Nepal, Sri Lanka, Egypt, and Cambodia.¹³

Significant efforts have been made to develop therapeutic interventions against coronavirus infection. Major research has been focused on identifying anti-viral molecules targeting the spike protein as it mediates viral entry, and their potential in inducing host immune responses and eliciting protective antibody responses in infected individuals. In this review, we highlight the therapeutic potential of neutralizing antibodies that showed promising efficacy against SARS-CoV or MERS-CoV which might have the potential for the therapy and prophylaxis of SARS-CoV-2.

Therapeutic Intervention for COVID-19

Neither an effective vaccines nor anti-viral therapeutic agents have been approved to treat COVID-19 or any other human CoV infection till date. The current approach to coronavirus disease management focuses on supportive care. Rapid public health interventions with antibodies, anti-virals or novel vaccine strategies are highly essential to contain the virus and disease transmission. Passive antibody therapy can be considered as a way to limit COVID-19 epidemics. Passive immunization of antibody that can recognize epitopic regions in the foreign virus particle can reduce the virus replication and disease severity. Antibodies for passive immunotherapy can be isolated from the blood of the infected patients or it can be manufactured in the laboratory. Immunotherapy by transferring the convalescent sera to infected patients may be effective in humans in neutralizing the virus and prevent further infection. Based on the existing evidence and prior experience in treating other viral infections such as influenza, SARS, MERS and Ebola, the early administration of convalescent plasma or hyper-immune immunoglobulin from patients that contains significant antibody titers can likely reduce the viral load and disease mortality.¹⁴⁻¹⁹ However, the key challenges such as availability of sufficient donors, clinical condition, viral kinetics, and host interactions of SARS-CoV-2 needs to be elucidated before considering convalescent plasma as a therapeutic option. However, there is an urgent need to consider novel therapies for treating clinically advanced conditions in order to reduce mortality, virus spread and to mitigate the potential future outbreaks. Although researchers are in the process of developing specific preventive and therapeutic

intervention strategies including vaccines, monoclonal antibodies, peptides, interferon therapies and small-molecule drugs to combat SARS-CoV-2, it may require several months to test its efficacy *in vitro/in vivo* and also it largely depends on the results of the clinical trials. Even though this virus is newly identified, the clinical and genetic features showed similarity with SARS-CoV.³ Their similarities would make it easier to utilize the existing knowledge and adapt the available vaccines or therapeutic models developed against other coronaviruses to target the unique aspects of SARS-CoV-2.

Immunotherapy is regarded as an effective method for clinical treatment of infectious diseases. The use of monoclonal antibodies is a new era in infectious disease prevention which overcomes many drawbacks associated with serum therapy and intravenous immunoglobulins preparations in terms of specificity, purity, low risk of blood-borne pathogen contamination and safety. Monoclonal antibodies are versatile class of pharmaceuticals that have been successfully used by pharmaceutical industry which can provide an efficient therapeutic intervention with a highly specific treatment against particular disease.²⁰⁻²³ Many monoclonal antibodies against viruses are developed in recent years and some are in clinical pipeline.²⁴⁻²⁶

CoV infection starts with the interaction of receptor binding domain located in the S protein and target receptor on the host cell surface such as Angiotensin converting enzyme 2 (ACE2) for SARS-CoV and dipeptidyl peptidase-4 (DPP4) for MERS-CoV.²⁷ The effective treatment options against SARS-CoV-2 can either based on the use of broad-spectrum anti-viral drugs or by using specific therapeutic molecules that can directly interrupt any stages of the viral lifecycle or the receptor proteins located in the host cell surface to restrain the virus binding thereby blocking the virus attachment and entry. This can be achieved by using peptidic fusion inhibitors, anti-SARS-CoV-2 neutralizing monoclonal antibodies, anti-ACE2 monoclonal antibodies and protease inhibitors. The spike protein present on the viral membrane plays a vital role in virus entry and is the principal antigenic component responsible for inducing host immune response.²⁸ Hence, it has been considered as a key target to develop potential effective therapeutics against coronavirus infection. The receptor-binding motif located in the receptor-binding domain (RBD) of S1 sub-unit of spike protein interacts with the cell receptor and mediates the virus attachment with the host cells.²⁹ Similar to SARS-CoV, SARS-CoV-2 utilizes host receptor, angiotensin-converting enzyme 2 (ACE2) for its attachment and entry (**Figure 1**).³⁰⁻³² Hence the therapies for SARS-CoV can be extrapolated to use for SARS-CoV-2. The specific neutralizing monoclonal antibodies either against receptor-binding domain (RBD) in spike protein or specific antibody that binds to ACE2 could effectively block the virus entry (**Figure 2**). The structure of SARS-CoV-2, SARS-CoV and MERS-CoV spike protein and monoclonal antibody interaction sites are shown in **figures 3, 4, and 5**. The protein structure figures were generated by PyMOL. As both SARS-CoV and SARS-CoV-2 uses same host cell surface receptor, potential blocking agents or strategies tested to prevent SARS entry could be evaluated against SARS-CoV-2. Coughlin and Prabhakar, (2012) reported a series of human monoclonal antibodies targeting the RBD region of S protein

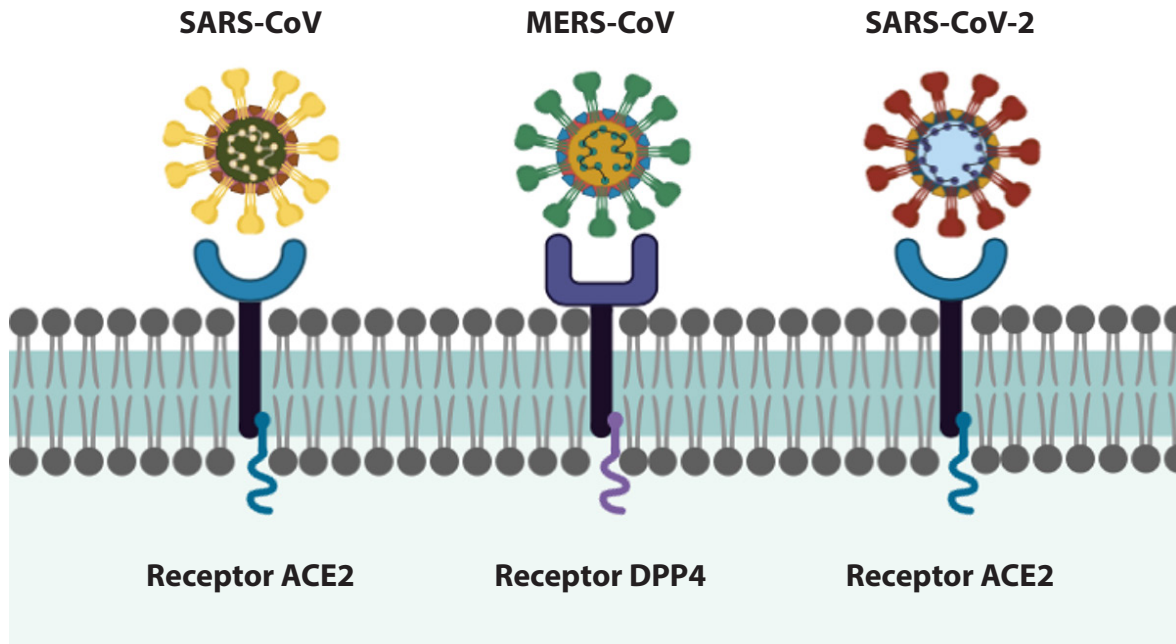


Figure 1. Graphical representation of SARS-CoV, MERS-CoV, SARS-CoV-2 and its cellular receptor.

The schematic representation shows the envelope spike proteins of SARS-CoV and MERS-CoV that binds to host receptor angiotensin-converting enzyme 2 (ACE2) and dipeptidyl peptidase 4 (DPP4), respectively. Similar like SARS-CoV, novel coronavirus SARS-CoV-2 uses ACE2 as its receptor for host entry. Binding between receptor binding domain in spike protein and the cellular receptor mediates membrane fusion and initiate the virus life cycle.

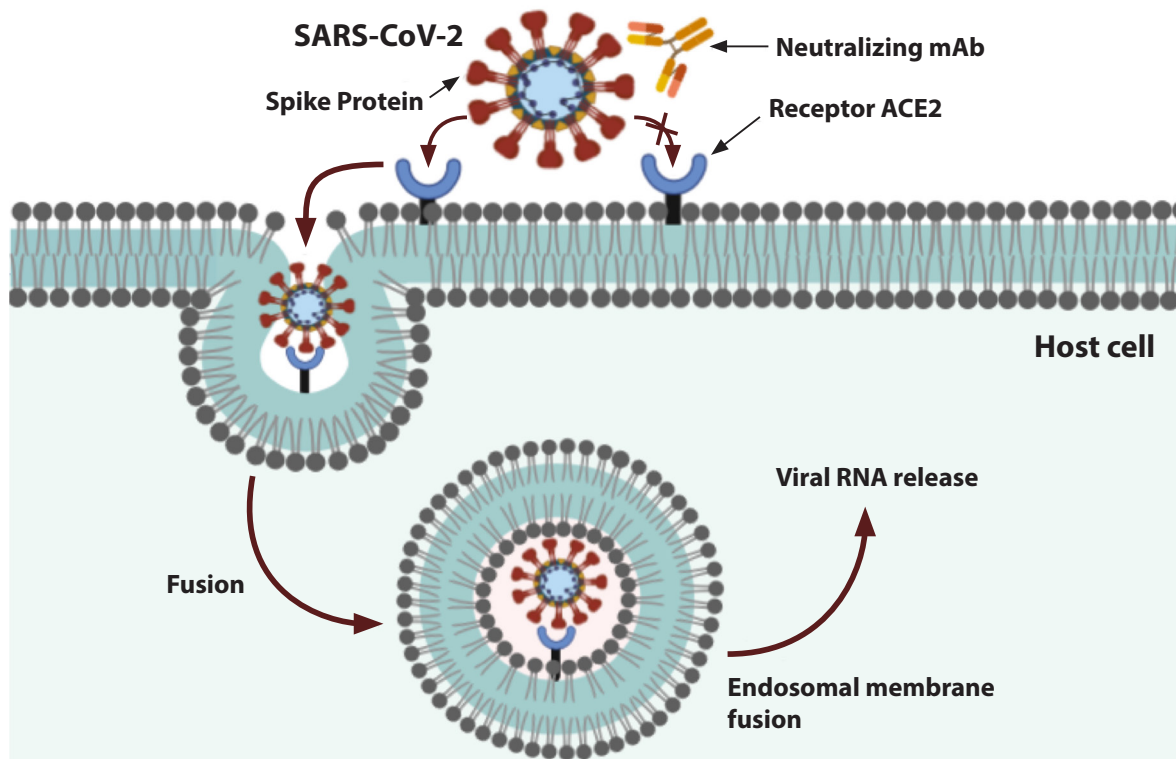


Figure 2. Schematic representation of SARS-CoV-2 neutralization mechanism.

Interaction of spike protein and the cellular receptor is required for membrane fusion and entry into the target cell. The monoclonal antibodies targeting spike protein of SARS-CoV-2 could potentially inhibit the virus binding to its cellular receptor thereby preventing its entry into the cell.

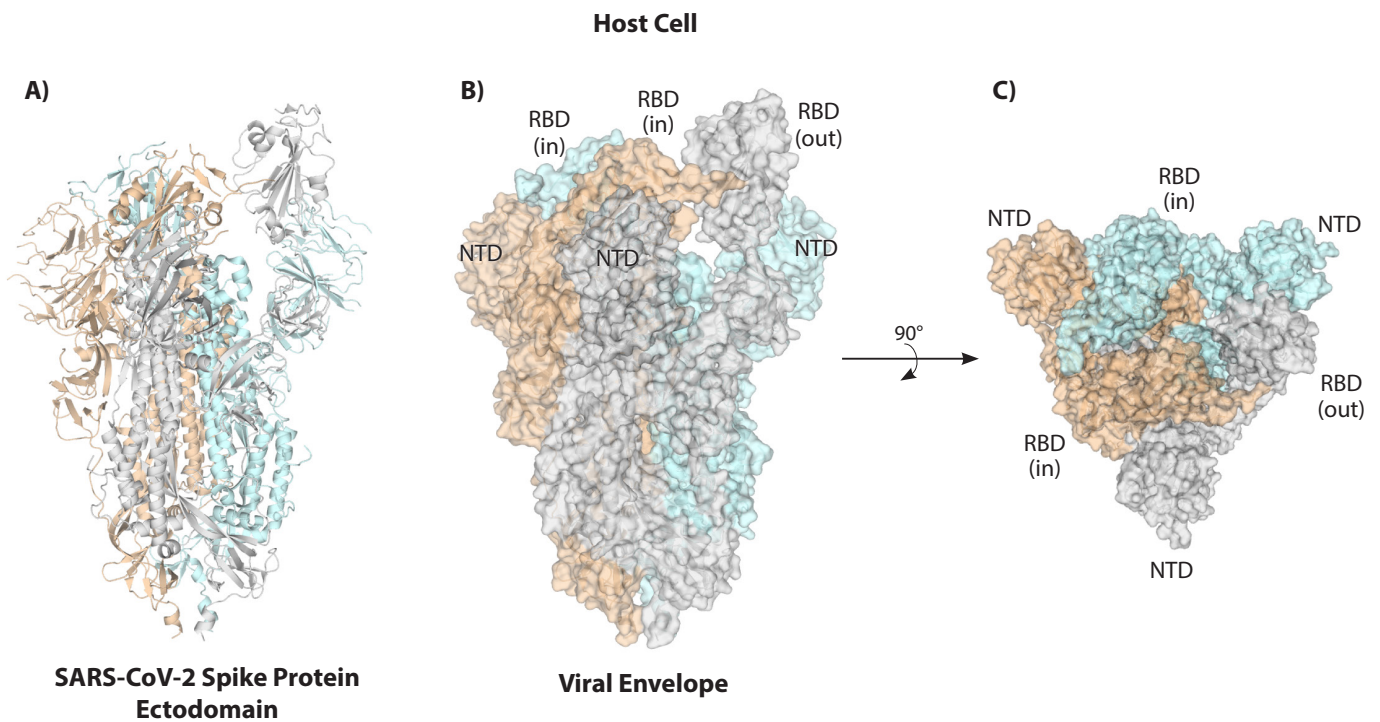


Figure 3. Structure of SARS-CoV-2 spike protein ectodomain (PDB ID 6VSB)⁷¹.

A) Ribbon diagram of the trimeric spike protein.

B) Surface representation (side view) of the trimeric spike protein.

C) The surface facing the host cell consists of the N-terminal domain (NTD) and the receptor binding domain (RBD). The RBD can be in either the in or out conformation. The out conformation is proposed to interact with the host receptor ACE2.

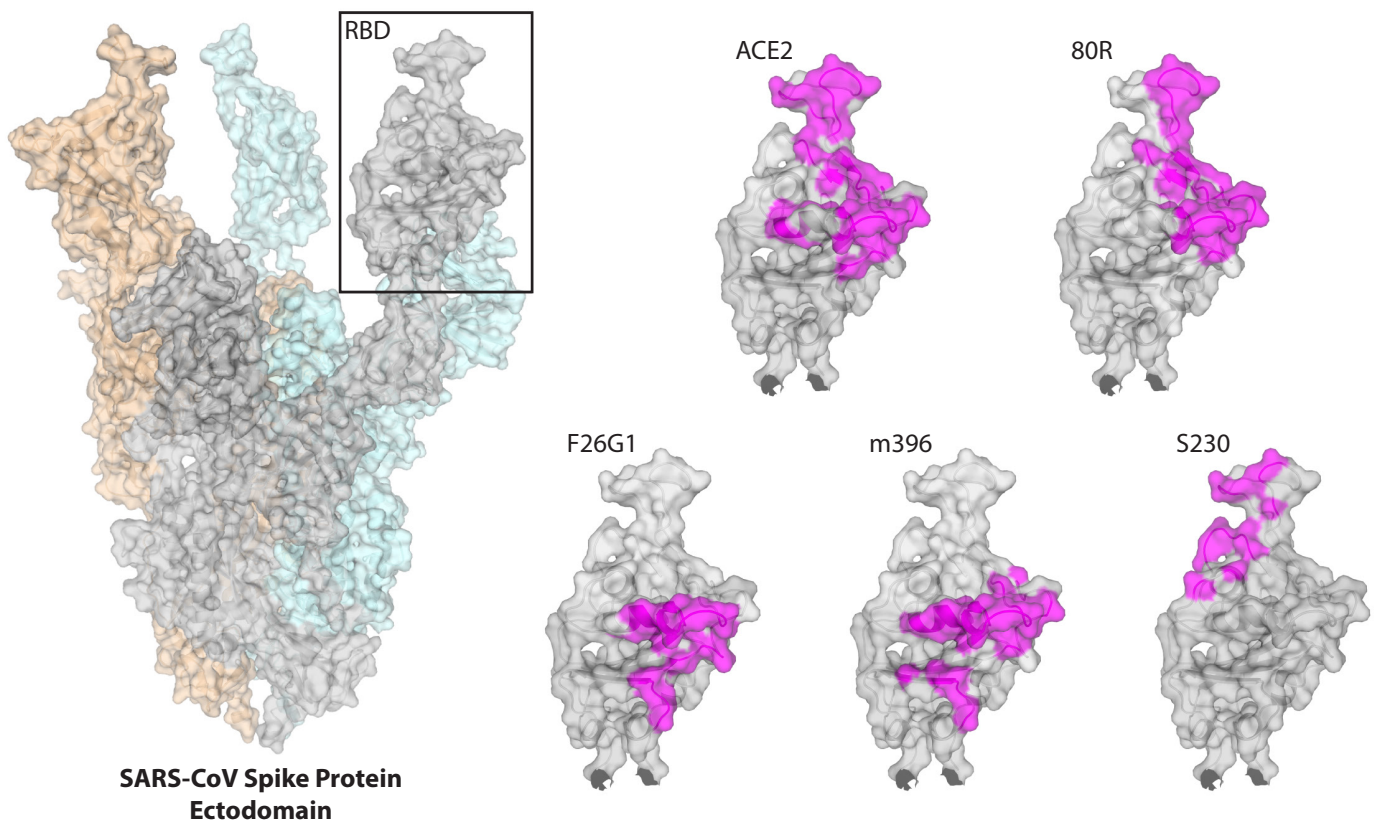


Figure 4. Structure of the trimeric SARS-CoV spike protein ectodomain in the RBD out conformation (PDB ID 6NB7)⁵¹.

The binding surface of the ACE2 receptor (PDB ID 6CS2)⁷² and the following antibodies are shown in magenta: 80R (PDB ID 2GHW)⁷³, F26G1 (PDB ID 3BGF)⁷⁴, m396 (PDB ID 2DD8)⁷⁵, and S230 (PDB ID 6NB7)⁵¹.

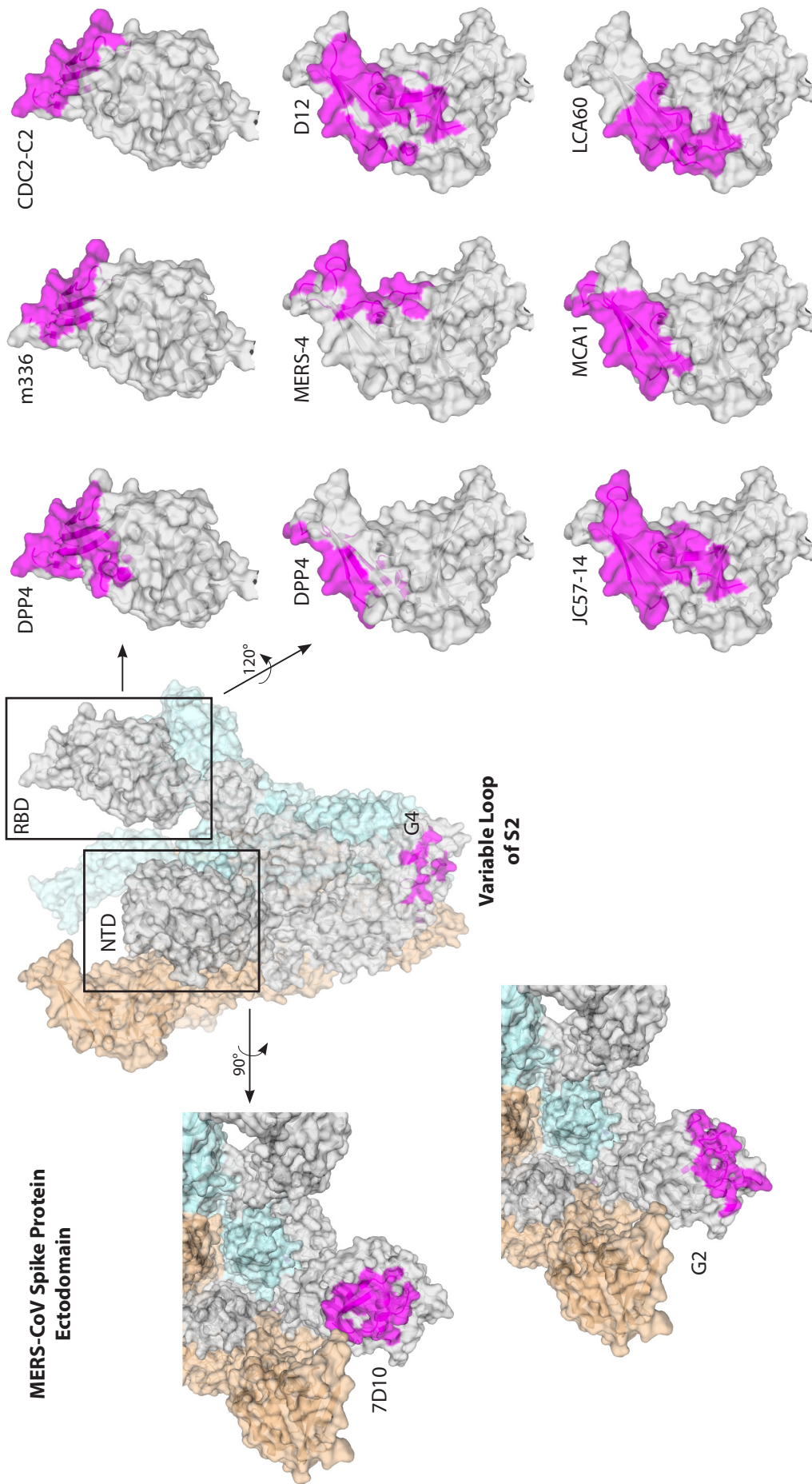


Figure 5. Structure of the trimeric MERS-CoV spike protein ectodomain in the RBD out conformation (PDB ID 5X59)⁷⁶.

The DPP4 binding surface (magenta, PDB ID 4KR0)⁷⁷ in the RBD is shown in two orientations (120° apart) for ease of comparison with the antibody binding surfaces. Three regions in which targeting antibodies have been reported are the RBD, NTD, and the variable loop of the S2 connector domain. All the interaction surfaces are shown in magenta. RBD: m336 (PDB ID 4XAK)⁷⁸, CDC2-C2 (PDB ID 6C6Z)⁶⁴, MERS-4 (PDB ID 5YY5)⁵⁵, D12 (PDB ID 4ZPT)⁶², JC57-14 (PDB ID 6C6Y)⁶⁴, MCA-1 (PDB ID 5GMQ)⁶⁷, and LCA60 (PDB ID 6NB4)⁵¹. NTD: 7D10 (PDB ID 6J11)⁶⁹ and G2 (PDB ID 6PXH)⁷⁰. Variable loop of the S2 connector domain: G4 (PDB ID 5W9J)⁶³.

of SARS-CoV.³³ The monoclonal antibodies targeting spike protein in SARS-CoV and MERS-CoV showed promising results *in vitro* and *in vivo* that could be potentially effective against SARS-CoV-2 are listed in the **table 1 and 2**.

For effective disease prevention, the combination of different monoclonal antibodies that recognizes different epitopes on the viral surface could be assessed to neutralize wide range of isolates including escape mutants and best candidates could be

Table 1. Neutralizing monoclonal antibodies targeting SARS-CoV and their mechanism of action

Monoclonal antibody	Mechanism of action	References
80R	<ul style="list-style-type: none"> Binding to the conformational epitope (amino acid residues 426-492) on S1 fragment of SARS-CoV. Blocking the interaction of S1 subunit protein with cellular receptor ACE2 using 6 complementary determining region (CDR) <i>in vitro</i> and <i>in vivo</i> (Mouse). 	11,20,41,42
CR3014	<ul style="list-style-type: none"> Binding to the amino acid residues 318-510 and amino acid residue 565 with high affinity on S1 fragment of SARS-CoV. Blocking the interaction of S1 subunit protein with cellular receptor ACE2 <i>in vitro</i> and <i>in vivo</i> (Ferret). 	43-45
CR3022	<ul style="list-style-type: none"> Binding to the amino acid residues 318-510 on S1 fragment of SARS-CoV. Blocking the interaction of S1 subunit protein (RBD) with cellular receptor ACE2 <i>in vitro</i>. 	44
F26G18	<ul style="list-style-type: none"> Binding to the linear epitope (amino acid residues 460-476) on S1 fragment of SARS-CoV. Blocking the interaction of S1 subunit protein (RBD) with cellular receptor ACE2 <i>in vitro</i>. 	42
F26G19	<ul style="list-style-type: none"> Binding to the conformational epitope (amino acid residues 359-362, 391-392, 424-427, and 486-492) on S1 fragment of SARS-CoV. Blocking the interaction of S1 subunit protein (RBD) with cellular receptor ACE2 <i>in vitro</i>. 	42
m396	<ul style="list-style-type: none"> Binding to the conformational epitope (amino acid residues 482-491) on S1 fragment of SARS-CoV. Blocking the interaction of S subunit protein using CDR loops H1, H2, H3, and L3 with cellular receptor ACE2 <i>in vitro</i>. 	42,46
1A9	<ul style="list-style-type: none"> Binding to the Heptad repeat (HR) loops including heptad repeat 1 (HR1) and heptad repeat 1 (HR2) domain on S2 fragment of SARS-CoV. Blocking the interaction of S2 subunit protein (amino acid residues 1111-1130) with cellular receptor <i>in vitro</i>. 	47,48
201	<ul style="list-style-type: none"> Binding to the amino acid residues 490-510 on S1 fragment of SARS-CoV. Blocking the interaction of S1 subunit protein with cellular receptor ACE2 <i>in vitro</i> and <i>in vivo</i> (Mouse Syrian Hamster). 	33,49
68	<ul style="list-style-type: none"> Binding to the amino acid residues 130-150 of SARS-CoV <i>in vitro</i> and <i>in vivo</i> (Mouse) 	33,49
4D4	<ul style="list-style-type: none"> Binding to the amino acid residues 12-261 of SARS-CoV and N-terminal of RBD Inhibiting the post-interaction in the viral penetration <i>in vitro</i>. 	33,50
S230	<ul style="list-style-type: none"> Binding to epitopes partially overlapping with receptor binding motifs on B domain of SARS-CoV. Blocking the interaction of S1 subunit protein with cellular receptor ACE2 <i>in vitro</i> 	51

Table 2. Neutralizing monoclonal antibodies targeting MERS-CoV and their mechanism of action

Monoclonal antibody	Mechanism of action	References
MERS-4	<ul style="list-style-type: none"> Binding to the C-terminal segment of the $\beta 5$-$\beta 6$, $\beta 6$-$\beta 7$ and $\beta 7$-$\beta 8$ loops on the receptor-binding subdomain in RBD of MERS-CoV with no overlap DPP4 binding surface. Blocking the interaction of S1 subunit protein with cellular receptor DPP4 <i>in vitro</i> by inducing $\beta 5$-$\beta 6$ shallow groove on the RBD. 	52-55
MERS-27	<ul style="list-style-type: none"> Binding to the C-terminal segment of the $\beta 6$-$\beta 7$ loop and $\beta 7$ strand on RBD of MERS-CoV and overlap with the DPP4 binding surface. Blocking the interaction of S1 subunit protein with cellular receptor DPP4 <i>in vitro</i>. 	52-57
4C2	<ul style="list-style-type: none"> Binding to the C-terminal segment of the $\beta 6$-$\beta 7$ loop and $\beta 7$ strand on RBD of MERS-CoV and overlap with the DPP4 binding surface. Blocking the interaction of S1 subunit protein with cellular receptor DPP4 <i>in vitro</i> and <i>in vivo</i> (Mouse). 	52,53,56,58
m336	<ul style="list-style-type: none"> Binding to the C-terminal segment of the $\beta 5$-$\beta 8$ strands, $\beta 5$-$\beta 6$ loop and $\beta 6$-$\beta 7$ loop in RBD of MERS-CoV and overlap with the DPP4 binding surface. Blocking the interaction of S1 subunit protein with cellular receptor DPP4 by mimicking the interaction between RBD and DPP4 in the similar binding angle <i>in vitro</i> and <i>in vivo</i> (Mouse and rabbit). 	52,53,56,59-61
G4	<ul style="list-style-type: none"> Binding to the glycosylated surface on the S2 subunit protein <i>in vitro</i>. 	52,62,63
D12	<ul style="list-style-type: none"> Binding to the C-terminal segment of the $\beta 6$-$\beta 7$ loop and $\beta 7$ strand on RBD of MERS-CoV and overlap with the DPP4 binding surface. Blocking the interaction of S1 subunit protein with cellular receptor DPP4 <i>in vitro</i>. 	52,56,63,64

Table 2. (Continued)

Monoclonal antibody	Mechanism of action	References
JC57-14	<ul style="list-style-type: none"> • Binding to the C-terminal segment of the $\beta 6$-$\beta 7$ loop and $\beta 7$ strand on RBD of MERS-CoV and overlap with the DPP4 binding surface. • Blocking the interaction of S1 subunit protein with cellular receptor DPP4 <i>in vitro</i>. 	52,56,64
MERS-GD27	<ul style="list-style-type: none"> • Binding to the C-terminal segment of the $\beta 5$-$\beta 8$ strands, $\beta 5$-$\beta 6$ loop and $\beta 6$-$\beta 7$ loop in RBD of MERS-CoV. • Blocking the interaction of S1 subunit protein with cellular receptor DPP4 by mimicking the interaction between RBD and DPP4 in the same binding angle <i>in vitro</i> and <i>in vivo</i> (Mice). 	52,65
MERS-GD33	<ul style="list-style-type: none"> • Binding to the C-terminal segment of the $\beta 5$-$\beta 8$ strands, $\beta 5$-$\beta 6$ loop and $\beta 6$-$\beta 7$ loop in RBD of MERS-CoV. • Blocking the interaction of S1 subunit protein with cellular receptor DPP4 mimicking the interaction between RBD and DPP4 in the same binding angle <i>in vitro</i>. 	52,66
LCA60	<ul style="list-style-type: none"> • Binding to the C-terminal segment of the $\beta 8$ strand, $\beta 6$-$\beta 9$ loop, and $\beta 6$-$\beta 8$ loop on RBD of MERS-CoV. • Blocking the interaction of S1 subunit protein with cellular receptor DPP4 <i>in vitro</i>. 	51
MCA1	<ul style="list-style-type: none"> • Binding to RBD with 6 complementarity-determining regions • Blocking the interaction of S1 subunit protein with cellular receptor DPP4 <i>in vitro</i> and <i>in vivo</i> (Mouse). 	67,68
CDC2-C2	<ul style="list-style-type: none"> • Blocking the interaction of S1 subunit protein with cellular receptor DPP4 <i>in vitro</i> and <i>in vivo</i> (Mouse). 	64
7D10	<ul style="list-style-type: none"> • Binding to N-terminal domain of S protein of MERS-CoV • Blocking the interaction of S1 subunit protein with cellular receptor DPP4 <i>in vitro</i> and <i>in vivo</i> (Mouse). 	69
G2	<ul style="list-style-type: none"> • Binding to N-terminal domain of S protein of MERS-CoV • Blocking the interaction of S1 subunit protein with cellular receptor DPP4 <i>in vitro</i>. 	69,70

used for passive immunotherapy. Monoclonal antibody cocktail may exhibit more potent anti-virus activity that could increase the effectiveness of the treatment and prevent the viral escape.³⁴⁻³⁶ Although, several monoclonal antibodies showed promising result in neutralizing SARS-CoV and MERS-CoV infection, the large-scale production of monoclonal antibodies is labor intensive, expensive and time consuming which outweighs the monoclonal antibody clinical application especially monoclonal antibodies against emerging pathogen. The recent advancement in the therapeutic protein production platforms could make the monoclonal antibody production at lower production costs and affordable. The sequences of monoclonal antibodies that are effective against SARS-CoV could be cloned and expressed in suitable expression system such as mammalian, yeast or plant and recombinant monoclonal antibodies could be tested against SARS-CoV-2. Plant expression system could be considered for the rapid production of monoclonal antibodies in a short time with the affordable cost which is one of the major advantages to be considered especially during epidemic situation.³⁷⁻⁴⁰

Concluding Remarks

The need to treat the emerging novel coronavirus that causes global impact throws spotlight on developing monoclonal antibody-based passive immunotherapy to provide a quick response. Even though there is a major progress towards the development of monoclonal antibody therapy for coronavirus infection, no monoclonal antibodies have yet been successfully marketed. The increasing understanding on MERS-CoV and SARS-CoV in recent years might galvanize the research community to make significant progress in the COVID-2019 therapeutic design in an accelerated time by utilizing the existing anti-viral regimen that showed promising results against

MERS and SARS. Further detailed understanding of the virus pathogenesis might increase the opportunities for the realistic design of therapeutics specific to novel coronavirus.

Author Contributions

All authors have made a considerable, direct and intellectual contribution to the work, and approved it for publication.

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Conflict of Interest

The authors declare that no conflict of interest.

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