Antibody therapies for the treatment of COVID-19

Zhiqiang Ku, Xiaohua Ye, Georgina To'a Salazar, Ningyan Zhang and Zhiqiang An*

Texas Therapeutics Institute, Brown Foundation Institute of Molecular Medicine,

McGovern Medical School, The University of Texas Health Science Center at Houston,

Houston, Texas 77030, USA

*Corresponding Author

Zhiqiang An

E-mail: Zhiqiang.An@uth.tmc.edu

Significance

Development of SARS-CoV-2 neutralizing antibodies with the desired efficacy and safety profile is a critical part of the toolbox of therapies for the treatment of COVID-19. We discuss in this review the current state of discovery and development of such antibodies.

Abstract

An outbreak of COVID-19, the disease caused by infection of the coronavirus SARS-CoV-2, that began in December 2019 in Wuhan, China has caused more than 2,990,559 confirmed human infections and 207,446 deaths as of April 27, 2020 (Coronavirus COVID-19 Global Cases by the Center for Systems Science and Engineering (CSSE) at Johns Hopkins University). Scientists are working quickly on multiple aspects of the pandemic. Genetic analyses are conducted to reveal the source and evolution of SARS-CoV-2, providing knowledge that can be used to contain it and to avoid future outbreaks. Epidemiological studies which incorporates lessons learned from outbreaks of previous related viral diseases can guide development of public health measures effective to contain the current and future outbreaks. Basic virology studies reveal viral structure and function. Pathology studies inform development of strategies to interfere with infection. COVID-19 prevention and treatment strategies are being developed in preclinical and clinical studies. Antibody-based therapy is one viable treatment option. Here, we discuss some of the most active areas of developing strategies to treat COVID-19, focusing on approaches to generate neutralizing antibodies against SARS-CoV-2 for prophylactic and therapeutic treatment of COVID-19.

A. The structures and functions of SARS-CoV-2 viral proteins

SARS-CoV-2, along with SARS-CoV and MERS-CoV, belongs to the *Betacoronavirus* genus in the Coronaviridae family (Figure 1A)[1, 2]. Bats are possible origins of SARS-CoV-2. SARS-CoV-2 is likely a result of natural selection either in an animal host before zoonotic transfer or in humans following zoonotic transfer [2, 3]. Similar to its family members SARS-CoV and MERS-CoV, SARS-CoV-2 has a large, positive-sense RNA genome, which encodes 4 structural proteins, 16 nonstructural proteins (nsp1-16), and some accessory

2

proteins (Figure 1B)[1, 2]. The structural proteins are spike (S), envelope (E), membrane (M), and nucleocapsid (N) proteins [4]. The spike protein comprises an N-terminal S1 subunit responsible for receptor binding and a C-terminal S2 subunit responsible for membrane fusion (Figure 1C) [5]. The S1 subunit is further divided into the N-terminal domain (NTD), the receptor-binding domain (RBD), subdomain 1 (SD1) and subdomain 2 (SD2). The S2 subunit is further divided into the fusion peptide (FP), the heptad repeat 1 (HR1) and heptad repeat 2 (HR2) (Figure 1C) [6]. Like SARS-CoV, SARS-CoV-2 enters cells through binding of the host cellular receptor angiotensin-converting enzyme 2 (ACE2) via its spike protein [2]. In contrast, MERS-CoV enters cells through binding of the host receptor dipeptidyl peptidase 4 (DPP4) via its spike protein [7]. These host receptors are indispensable for virus infection [2, 4]. Receptor binding triggers a conformational change of the spike protein to an activated state[8]. The activated spike is cleaved by a protease (TMPRSS2 for SARS-CoV and SARS-CoV-2) at the S1/S2 site, releasing the S1 subunit and exposing the FP on the S2 subunit [9]. The FP inserts into target cell membrane, HR1 and HR2 refold to form a postfusion conformation that drives viral membrane fusion with target cells (Figure 1D)[8, 10]. The cryo-EM structure of the SARS-CoV-2 spike in the prefusion conformation was recently published [11]. The interaction between SARS-CoV-2 spike RBD and the full-length human ACE2 has also been revealed by cryo-EM or crystallization[6, 12-14]. Similar to the spike protein of SARS-CoV, the SARS-CoV-2 spike protein also possesses extensive glycosylation, which may be important for virus binding to cells and facilitate immune evasion through epitope masking [15, 16]. The non-structural proteins encoded by coronaviruses are essential for virus replication inside cells [1]. For example, the RNA-dependent RNA polymerase (RdRp, also known as nsp12) is the key component of coronaviral replication and transcription machinery [1]. The cryo-EM structure

3

of RdRp in complex with cofactors nsp7 and nsp8 was recently published[17]. The rapid advance in the basic knowledge of SARS-CoV-2 paves the way for the discovery and development of vaccines and therapeutics for the prevention and treatment of COVID-19.

B. Repurposing drugs for the treatment of COVID-19

Discovery and development of drugs and vaccines against COVID-19 is in full swing in academic and biopharmaceutical company laboratories worldwide. Because of the urgency of finding treatments for the current pandemic, existing drugs developed for other viral diseases are being tested in the clinic for the treatment of COVID-19. Nucleoside analogues in the form of adenine or guanine derivatives target RdRp and block viral RNA synthesis in a broad spectrum of RNA viruses. Both approved nucleoside analogues, such as favipiravir and ribavirin, and experimental nucleoside analogues, such as remdesivir and galidesivir, may block SARS-CoV-2 RdRp and protect against COVID-19 [18] (Figure 1D). However, the coronavirus protein nsp14 has a unique exoribonuclease (ExoN) function, which provides the proofreading capability. This mechanism may affect the susceptibility of coronaviruses to nucleoside analogues [19]. Approved viral protease inhibitors, such as the HIV aspartic protease inhibitors lopinavir and ritonavir, have shown efficacy in a clinical trial [20]. It is hypothesized that lopinavir and ritonavir exhibit their efficacy by inhibiting the 3-chymotrypsin-like protease [20] (Figure 1D).

In addition to repurposing existing antiviral drugs, drugs used to modulate the host immune system for other disease indications are also being tested in the clinic for the treatment of COVID-19. The antimalarial and anti-inflammatory drugs hydroxychloroquine and chloroquine showed *in vitro* activity against SARS-CoV-2 [21]. Hydroxychloroquine and chloroquine may exhibit efficacy against COVID-19 by modulation of immune system and by affecting cell entry and replication of SARS-CoV-2 through pH modulation and

4

interfering post-translational modifications of viral proteins or receptors [22]. Adjunctive and supportive therapies such as azithromycin and tocilizumab are also being clinically tested for the treatment of COVID-19. Azithromycin is a macrolide antibacterial that may prevent bacterial superinfection on COVID-19 patients; macrolides may have immunomodulatory properties in pulmonary inflammatory disorders [23]. Tocilizumab is an interleukin-6 (IL-6) receptor-blocking antibody that inhibits IL-6-mediated signaling for the treatment of inflammatory diseases [24, 25]. The rationale for testing the efficacy of tocilizumab against COVID-19 is that IL-6 is a proinflammatory cytokine; cytokine release syndrome may be a component of severe disease in COVID-19 patients [26]. Discussed here are a few examples of a vast array of drugs and drug combinations being tested for the treatment of COVID-19. Although some clinical trials have produced promising results, no drugs have been definitively validated for COVID-19 treatment to date. Repurposing existing drugs and *de novo* discovery of new drugs for the treatment of COVID-19 is an active on-going effort worldwide.

C. Vaccines for COVID-19

An effective vaccine to prevent SARS-CoV-2 infection is urgently needed to control the global pandemic of COVID-19. Unfortunately, there are no currently approved human coronavirus vaccines. The spike protein is a vaccine target for coronavirus; studies on SARS-CoV and MERS-CoV demonstrated that antibodies targeting the spike protein, especially its receptor binding domain (RBD), efficiently neutralize virus infection[5, 27]. Although SARS-CoV-2 and SARS-CoV share high sequence identity and use the same receptor for cell entry, the sera of patients who recovered from SARS-CoV and SARS-CoV-2 showed limited cross neutralization[2, 28]. In a recent study, the SARS-CoV S murine polyclonal antibodies potently inhibited SARS CoV-2 S mediated entry into cells, indicating

5

that cross-neutralizing antibodies targeting conserved S epitopes can be elicited upon vaccination [29]. Multiple biopharmaceutical companies and academic institutions worldwide have announced SARS-CoV-2 vaccine programs. These programs target major strategies for vaccine development, which include production of live attenuated whole virion vaccines, inactivated whole virion vaccines, spike protein targeted nucleic acid vaccines, recombinant protein vaccines, and viral vector-based vaccines [30-32]. Currently, the most advanced SARS-CoV-2 vaccine candidates are in Phase I clinical trials.

D. Convalescent plasma therapy

Convalescent plasma (CP) from patients who recovered from a viral disease is a therapeutic tool used when no approved specific antiviral agents are available. During outbreaks of SARS-CoV, MERS-CoV, influenza A (including H7N9, H1N1, and H5N1), and Ebola, CP treatment of infected patients showed beneficial effects including relief of clinical symptoms and reduced mortality [33-38]. CP transfusion is being tested to rescue patients with severe COVID-19. In one trial, single doses of 200 ml CP with a >1:640 neutralizing antibody titer were administered to 10 patients with severe COVID-19 at a median time of 16.5 days from onset of illness[39]. In patients who received CP transfusion, clinical symptoms (including fever, cough, shortness of breath, and chest pain) disappeared or largely improved. Viral RNA disappeared and there was a reduction of pulmonary lesions and reduced patient death compared to a matched historic control group [39]. Importantly, no adverse events were reported among patients receiving CP transfusion. The safety profile and potential therapeutic effect of CP transfusion among patients with severe COVID-19 are also supported by other reports with fewer patients [40, 41]. Notably, in addition to CP transfusion, all patients received standard care, including antiviral therapy. This limits the use of these preliminary studies for the assessment of CP

6

transfusion as a COVID-19 therapy. Before this COVID-19 therapy can be widely used alone or in combination with other treatment(s), it must be fully assessed in a randomized controlled clinical trial in a larger patient cohort. A minimum effective neutralizing antibody titer and optimal treatment time point needs to be established for CP therapy. Although CP is readily accessible during the pandemic, major challenges remain for large-scale application of CP treatment. These challenges include the limited availability of CP in large quantities and donor dependent variability in antibody specificities and titers. The US FDA has approved the use of plasma from recovered patients to treat patients who are critically ill with COVID-19, provided that doctors get approval [42]. The ongoing COVID-19 pandemic provides an unprecedented opportunity to perform clinical studies of CP treatment against a viral agent. If large-scale randomized clinical trials can demonstrate the efficacy and safety of CP, its therapeutic use among patients with severe disease and prophylactic use in high-risk populations could change the course of this ongoing pandemic.

E. SARS-CoV-2 neutralizing antibodies for the treatment of COVID-19

Neutralizing antibodies are an important component in host immune responses to viral pathogens. Neutralizing monoclonal antibodies have been developed as therapies for the treatment of viral infections including RSV, Influenza, Ebola, HIV, HCMV and Rabies [43]. The process for the discovery and development of viral neutralizing antibody therapies are well-established [43]. Scientists around the world have initiated programs to develop SARS-CoV-2 neutralizing antibodies. Currently, all published SARS-CoV-2 neutralizing antibodies are at early preclinical stages. We discuss here the current state of design and development of such antibodies.

1. *Viral targets for development of neutralizing antibodies against SARS-CoV-2 infection*

The spike protein of SARS-CoV-2 plays an essential role in virus entry into host cells and is a primary target of neutralizing antibodies [5, 9] (Figures 1C,D). Due to the functionality and high immunogenicity of the coronavirus S1 subunit, most neutralizing antibodies characterized for coronaviruses to date target S1, in particular the S1-RBD [44-46]. Two MERS-CoV neutralizing mAbs, G2 and 7D10, target the S1-NTD region and function by blocking spike protein interaction with the host receptor DPP4 [47, 48]. Compared to the S1 subunit, the coronavirus S2 subunit is more conserved and bears epitopes that could potentially be targeted by broadly neutralizing antibodies[10, 49]. Generation of antibodies with broad neutralizing activity against different coronaviruses, or at least SARS-related coronaviruses, would be of great value for confronting future waves of coronavirus-related disease. However, broadly neutralizing antibodies against different human coronaviruses are very rare, probably related to the sequence variance of spike protein and cryptic nature of the highly conserved epitopes [28, 50]. The S2 conformation is highly dynamic during membrane fusion, presenting a major challenge in preparing antigens for discovery of antibodies against this protein [10]. Antigen stabilizing strategies used in discovery of antibodies against HIV and RSV proteins may be explored in the design of stable coronavirus S2 proteins[51-53].

2. Methods for isolating SARS-CoV-2 neutralizing antibodies

To target the whole spike protein or domain proteins, several well-established methods have been used for isolating SARS-CoV-2 monoclonal antibodies (Table 1). Xiong *et al.* isolated several neutralizing antibodies from mice immunized with SARS-CoV-2 RBD using the hybridoma technology [54]. Wu *et al.* identified high-affinity human single-domain antibodies targeting five types of neutralizing or non-neutralizing epitopes on SARS-CoV-2 RBD through panning a phage-displayed single-domain antibody library [55]. Ju *et al.*

8

characterized 206 RBD-specific mAbs isolated from single B cells of eight SARS-CoV-2 infected patients [56]. Once a panel of monoclonal antibodies is generated, biochemical assays, such as ELISA binding, cell-based binding, affinity measurement, and epitope mapping and binning, are commonly used to characterize the antibodies (Table 1). Lead antibody candidates are then evaluated for their neutralization activities in *in vitro* cell based assays and in *in vivo* animal models.

To reduce the time from that required for *de novo* discovery of SARS-CoV-2 neutralizing antibodies, researchers have assessed available SARS-CoV antibodies for cross-neutralization of SARS-CoV-2, given the ~76% sequence identities in their spike proteins [56, 57]. For example, a SARS-CoV mAb (47D11) generated from a hybridoma of humanized mice neutralized SARS-CoV with an IC_{50} of 0.19 µg/ml and cross neutralized SARS-CoV-2 with an IC_{50} of 0.57 µg/ml. Although the 47D11 mAb binds to the RBD of both viruses, it could not block RBD binding to ACE2, suggesting presence of a broadly neutralizing epitope that is not directly involved in receptor binding[57]. Another SARS-CoV mAb, CR3022, binds to the RBD of both SARS-CoV-2 and SARS-CoV, but only neutralizes SARS-CoV [50]. A structural study indicates that CR3022 recognizes a highly conserved cryptic epitope on RBD that is distinct from the receptor-binding site[50].

3. *In vitro assays for screening and selection of SARS-CoV-2 neutralizing antibodies*

Antibodies that bind to the spike protein with high affinity can be first tested for their ability to block spike interaction with ACE2 or directly tested in cell based viral neutralization assays *in vitro*. Two *in vitro* assay systems are commonly used to evaluate the neutralization activity of antibodies against coronavirus [56]. One is based on live virus infection of the Vero E6 cell line; it is the gold standard of *in vitro* neutralization assay.

9

Briefly, after infection by SARS-CoV-2, the cells can display cytopathic effects (CPE), which can be visually observed or form viral plaques that can be detected by immunofluorescent staining [56]. However, this assay system is restricted, as it needs to be performed in Biosafety Level-3 (BSL-3) facilities. The other *in vitro* assay system commonly used to assess antibodies against coronavirus is based on a pseudovirus. The pseudovirus bears the spike of SARS-CoV2 in the lentiviral/retroviral backbones and has reporter genes such as GFP or luciferase. Expression of the reporter genes is used to indicate infection[54, 56]. This method is much less restricted by the need of BSL-3 facilities, and can be high throughput. However, the conformation and number of the spike proteins on the pseudovirus may be different from those on the authentic virus. Often, researchers use the pseudovirus assay for initial high throughput screenings of lead antibodies followed by the live virus assay to further validate the lead candidates.

4. ***In vivo models for testing SARS-CoV-2 neutralizing antibodies***

Monkey and mouse models have been reported for testing SARS-CoV-2-neutralizing antibodies [58-60]. In the monkey study, researchers found that rhesus macaques infected with SARS-CoV-2 through the intratracheal route had mild illness, and their lungs showed signs of pneumonia similar to those in humans with COVID-19 [58]. After 3 or 6 days of infection, the virus could be isolated from bronchus, lung tissues, and oropharyngeal swabs. However, no monkey developed severe symptoms during the study[58]. In a study using a mouse model, transgenic mice with human ACE2 expression, but not wild-type mice, were found to be susceptible to SARS-CoV-2 infection [59]. Mice inoculated with SARS-CoV-2 through the intranasal route had a 5~10% loss of body weight and histopathology in the lung, such as interstitial pneumonia, and infiltration of immune cells. No mice died during the study [59]. To establish a model that can mimic more severe human

10

infections, different animal models and other experimental factors must be considered and tested.

5. *ADE consideration and Fc engineering*

Antibody-dependent enhancement (ADE) is the phenomenon of non-neutralizing or sub-neutralizing antibodies facilitating virus infection, leading to more severe disease. The most widely known example is dengue ADE, which has various mechanisms [61, 62]. In one mechanism, certain immune cells, which don't express the receptor for virus entry but have the Fcγ receptors (FcγR) on surface, can be infected by dengue virus through the FcγR mediated virus entry pathway [62]. Although it is unknown whether ADE happens in SARS-CoV-2 infection and COVID-19 disease, several ADE mechanisms have been described in other human coronaviruses, including the closely related SARS-CoV[63-66]. In one mechanism, passive transfer of anti-spike IgGs, which were elicited by vaccine immunization, failed to prevent infection and enhanced lung pathology in a monkey model of SARS-CoV infection [64]. The antibodies exaggerated disease by modulating the monocyte and macrophage function in an FcγR dependent manner [64]. In another mechanism revealed by two studies, the neutralizing mAb S230 for SARS-CoV and Mersmab1 for MERS-CoV, triggered membrane fusion via receptor mimicry when they bound to the RBD of the spike [66, 67]. The presence of Mersmab1 enhanced the entry of MERS-CoV pseudovirus into macrophages and into FcγRII-expressing non-susceptible HEK293T cells [67]. Notably, the SARS-CoV-2 serum has a substantial cross-reactivity to the spike from SARS-CoV and MERS-CoV, while the cross-neutralization activity is very limited [56]. One possible explanation is that most antibodies target domains that are outside of the RBD and have few neutralizing epitopes [56]. These studies suggest that ADE might occur in SARS-CoV-2 infections. Therefore, clinical application of convalescent plasma

therapy, design and development of vaccines and therapeutic antibodies for COVID-19 should take the risk of ADE into consideration.

Perspective

The unprecedented impact of the current COVID-19 pandemic on the human race calls for unprecedented response from all aspects of society to combat the disease. To address the immediate need for therapies, repurposing existing drugs and strategies is a logical first step. This includes testing antivirals, drugs used to modulate the host immune system, and CP transfusion as therapies for COVID-19. It is likely that SARS-CoV-2 will stay with us as a seasonal infection [68]. Development of effective vaccines is the best weapon to confront COVID-19 if SARS-CoV-2 circulates as a seasonal virus or another coronavirus emerges as a serious threat in the future.

One challenge for developing COVID-19 therapies is the complexity of pathology and immunology associated with SARS-CoV-2 infection and its comorbidities. The vast majority of deaths have occurred in patients with underlying conditions [69]. Considerations for designing clinical trials for SARS-CoV-2 therapies include optimization of dose and dosing frequency, disease stage at which to administer therapy, and combination with other therapies. For SARS-CoV-2 infection, virus shedding happens before onset of clinical symptoms and the viral dynamics in infected patients are still yet to be fully determined [70]; treatment should be administered early enough to avoid severe symptoms. This timing of therapy can be achieved with a rapid, point of care diagnostic test.

Well-established antibody technologies enable laboratories in academia and drug development companies to isolate SARS-CoV-2 neutralizing antibodies in months or even weeks. However, development of SARS-CoV-2 neutralizing antibody therapies with the desired efficacy for human use is a complex process with many challenges. To best

12

choose epitopes, antibody formats, and antibody combinations, we must determine how

fast SARS-CoV-2 can generate escape mutants and which epitopes are more vulnerable

to neutralizing antibodies. Another important consideration is the engineering of Fc region

of the neutralizing antibodies to avoid the potential antibody-dependent enhancement

(ADE). Despite the challenges, development of neutralizing antibodies is a critical part of

the toolbox of therapies for the treatment of COVID-19.

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Conflict of interest statement

The authors declare no potential conflicts of interest.

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Figure legend

Figure1. SARS-CoV-2 structures, life cycle and inhibition strategies of virus replication. (A) The virus particle structure of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The spherical particle of SARS-CoV-2 consists of four structural proteins, including the spike proteins (S), the membrane protein (M), the envelope protein (E) and the nucleocapsid (N). The S, M, and E proteins are incorporated in the virus membrane, and the N protein is inside the particle and associated with virus genomic RNA. (**B**) The single-stranded positive-sense RNA genome of SARS-CoV-2. The ORF1a, or the ORF1a and ORF1b together, encodes the large polyproteins pp1a and pp1ab. The two polyproteins are further cleaved into 16 non-structural proteins (nsp1-nsp16). The papain-like protease (PLpro), the 3C-like protease (3CLpro), the RNA-dependent RNA polymerase (RdRp), and the exonuclease (ExoN) are indicated. In addition to the non-structural and structural proteins, the genome of SARS-CoV-2 also encodes six accessory proteins. (**C**) The structure of spike protein. The spike protein is a trimer and each monomer comprises an N-terminal S1 subunit and a C-terminal S2 subunit. The S1 subunit is further divided into the N-terminal domain (NTD), the receptor-binding domain (RBD), subdomain 1 (SD1), and subdomain 2 (SD2). The S2 subunit is further divided into the fusion peptide (FP), the heptad repeat 1 (HR1) and heptad repeat 2 (HR2). During virus entry, S1 is responsible for receptor binding, and S2 is responsible for membrane fusion. Figure 1B-C were not drawn proportional to their genome sizes. (**D**) The life cycle of SARS-CoV-2 and inhibition of virus replication with different strategies. Upon binding to the cellular receptor angiotensin-converting enzyme 2 (ACE2), the spike protein is activated by protease cleavage, such as TMPRSS2. After membrane fusion, the genomic RNA is released into the cytoplasm. The ORF1a and ORF1ab are translated into pp1a and pp1ab, which are cleaved by PLpro and 3CLpro to produce non-structural proteins. Several nsps, including nsp7-10, nsp12, and nsp14, form the replication-transcription machinery to produce genomic and subgenomic RNAs. After the translation of structural proteins, the virion is assembled at the ER-Golgi intermediate compartment (ERGIC) and encapsidate the N protein and genomic RNA. The mature virion is released outside of cells by transportation through the vesicles. Virus replication at the steps of entry, proteolysis, and genome replication can be inhibited as indicated.
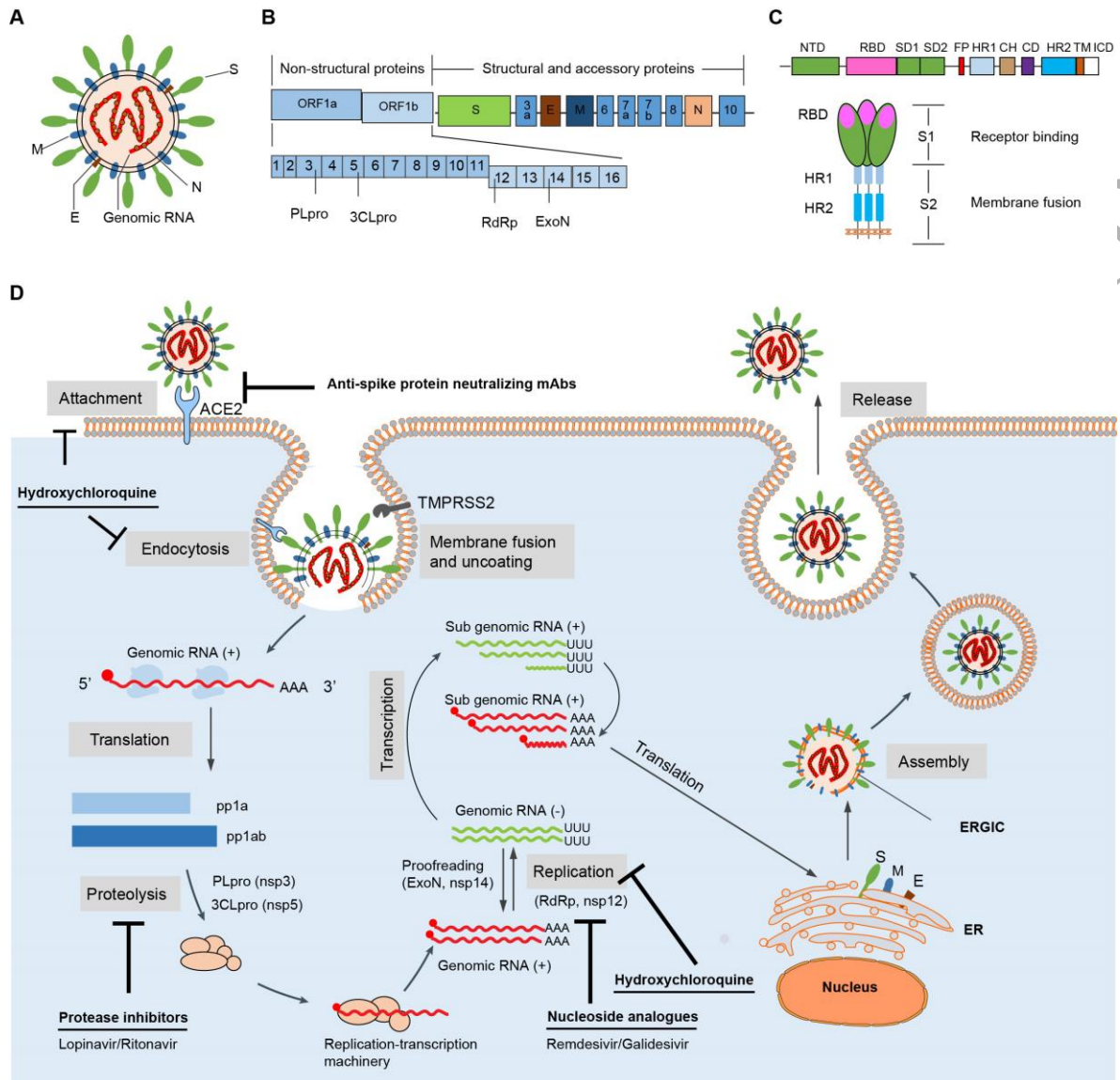
19

A

S
M
E Genomic RNA
N

B

Non-structural proteins | Structural and accessory proteins

ORF1a ORF1b S 3a E M 6 7a 7b 8 N 10

1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16

PLpro 3CLpro RdRp ExoN

C

NTD RBD SD1 SD2 FP HR1 CH CD HR2 TM ICD

RBD } S1 Receptor binding

HR1
HR2 } S2 Membrane fusion

D

Attachment Anti-spike protein neutralizing mAbs Release

ACE2

Hydroxychloroquine

Endocytosis TMPRSS2 Membrane fusion and uncoating

Genomic RNA (+) Sub genomic RNA (+) UUU UUU UUU

5' AAA 3' Sub genomic RNA (+) AAA AAA AAA

Transcription Translation

Translation Assembly

pp1a ERGIC

pp1ab Genomic RNA (-) UUU UUU

Proofreading (ExoN, nsp14) Replication (RdRp, nsp12) S M E

Proteolysis PLpro (nsp3) 3CLpro (nsp5) ER

AAA AAA Nucleus

Protease inhibitors Genomic RNA (+)

Lopinavir/Ritonavir Replication-transcription machinery **Nucleoside analogues**

Remdesivir/Galidesivir

Table 1. Strategies for the discovery and development of SARS-CoV-2 neutralizing antibodies.

Target	The spike protein of SARS-CoV-2		
Antibody discovery — mAb sources	**B cell from patient** • Memory B cell • Plasma B ell	**Antibody library** • Phage library • Yeast library • Ribosome library • Others	**Animal immunization** • Mice (wild type or humanized) • Rabbit • Monkey • Lamma • Others
Antibody discovery — mAb binding characteristics	• ELISA binding • Affinity measurement • Cell based binding • Epitope binning /mapping • Others		
Antibody discovery — Functional assays	• Blocking of spike (or RBD) binding to ACE2 • Blocking of spike-mediated membrane fusion • Pseudovirus based neutralization assay • Live virus based neutralization assay • Others		
Antibody discovery — Animal models	• Human ACE2 transgenic mice • Rhesus monkey • Ferrets • Cats • Others		
Antibody development — Design of lead antibody	• Antibody humanization (if necessary) • Affinity maturation (if necessary) • Antibody format (single mAb, mAb cocktail or bi-specific) • Consideration of Fc-mediated effector function • Consideration of ADE • Others		
Antibody development — Preclinical development	• Antibody CMC (Chemistry, Manufacture and Control) • PK / PD models • Toxicity profile • Others		

Clinical studies	• Clinical safety
	• Monotherapy
	• Combination therapy
	   Antibodies targeting different epitopes
	   Antibody + anti-viral small molecules
	   Antibody + immune modulatory drugs (e.g. anti-IL6)
	• Cohort selection
	   Patients with severe or mild symptoms
	   Prophylaxis for high-risk people (e.g. front-line medical workers)		

mAb: monoclonal antibody; ELISA: enzyme-linked immunosorbent assay; ACE2: angiotensin-converting enzyme 2; Fc: crystallizable fragment; ADE: antibody-dependent enhancement; PK: Pharmacokinetics; PD: pharmacodynamics; IL-6: Interleukine 6.