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SARS-CoV-2 Neutralizing Antibodies for COVID-19 Prevention and Treatment

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SARS-CoV-2, COVID-19, neutralizing antibodies, antibody-dependent enhancement, escaping variants

Abstract

Prophylactic and therapeutic drugs are urgently needed to combat coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Over the past year, SARS-CoV-2 neutralizing antibodies have been developed for preventive or therapeutic uses. While neutralizing antibodies target the spike protein, their neutralization potency and breadth vary according to recognition epitopes. Several potent SARS-CoV-2 antibodies have shown degrees of success in preclinical or clinical trials, and the US Food and Drug Administration has issued emergency use authorization for two neutralizing antibody cocktails.

Nevertheless, antibody therapy for SARS-CoV-2 still faces potential challenges, including emerging viral variants of concern that have antibody-escape mutations and the potential for antibody-mediated enhancement of infection or inflammation. This review summarizes representative SARS-CoV-2 neutralizing antibodies that have been reported and discusses prospects and challenges for the development of the next generation of COVID-19 preventive or therapeutic antibodies.

INTRODUCTION

Neutralizing antibodies mitigate or completely block viral infections by targeting structural components of pathogens. Neutralizing antibodies can either be actively induced by vaccination or infection, or passively transferred into humans for prophylactic or therapeutic uses. Examples of neutralizing antibody–based drugs are the antibody cocktails ZMapp and Inmazeb to combat Ebola virus outbreaks (1). In addition, neutralizing antibody–based preventions/treatments for infection with respiratory syncytial virus (RSV), hepatitis B virus, rabies virus, and HIV are currently approved or in clinical trials (2). Since the beginning of the coronavirus disease 2019 (COVID-19) pandemic, numerous neutralizing antibodies targeting severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) have been developed and have shown promise in preclinical and clinical studies; the US Food and Drug Administration (FDA) has issued emergency use authorizations (EUAs) for several neutralizing antibodies as COVID-19 therapeutics. Despite the preliminary success of SARS-CoV-2 neutralizing antibody development, curing COVID-19 with therapeutic antibodies remains challenging due to the need to understand the optimal time of antibody administration, the potential for antibody-dependent enhancement (ADE) of infection, and the recent emergence of viral neutralizing antibody escape variants (3). In this review, we summarize current neutralizing antibody discovery efforts and review challenges for neutralizing antibody–based COVID-19 treatment and prevention.

CLASSIFICATION OF SARS-COV-2 NEUTRALIZING ANTIBODIES

SARS-CoV-2 is an enveloped virus consisting of structural proteins including spike (S), nucleocapsid, membrane, and envelope proteins. While all structural proteins are important for the viral life cycle, the S protein plays an essential role in interacting with the host cell surface receptor angiotensin-converting enzyme 2 (ACE2) and mediating viral entry (4). Therefore, potent neutralizing antibodies target the S protein and can interrupt viral entry steps to block infection. Knowledge of neutralization mechanisms, how and where neutralizing antibodies bind on the S protein, and how antibody binding affects S protein conformation is guiding the design of antibodies, drugs, and vaccines.

The SARS-CoV-2 S glycoprotein is composed of the S1 subunit, which contains the N-terminal domain [NTD; amino acids (aa) 16–309] and the receptor-binding domain (RBD; aa 319–541), and the transmembrane S2 subunit (aa 687–1273), which contains the fusion peptide (FP) and the heptad repeat 1 (HR1) and heptad repeat 2 (HR2) regions (**Figure 1**). On the surface of virions, SARS-CoV-2 S glycoprotein forms homotrimers, which mediate virus entry into host cells (5–8). During virus entry, the cellular protease transmembrane protease serine 2 (TMPRSS2) primes SARS-CoV-2 S, and the RBD engages the ACE2 receptor (6). These events result in the S protein trimers undergoing conformational changes that result in S1 shedding. After receptor engagement, the fusion peptide initiates membrane fusion, resulting in refolding of the HR1 and HR2 regions into a postfusion conformation, which triggers viral/cellular membrane fusion

RSV: respiratory syncytial virus

EUA: emergency use authorization

ADE: antibody-dependent enhancement

ACE2: angiotensin-converting enzyme 2

NTD: N-terminal domain

RBD: receptor-binding domain

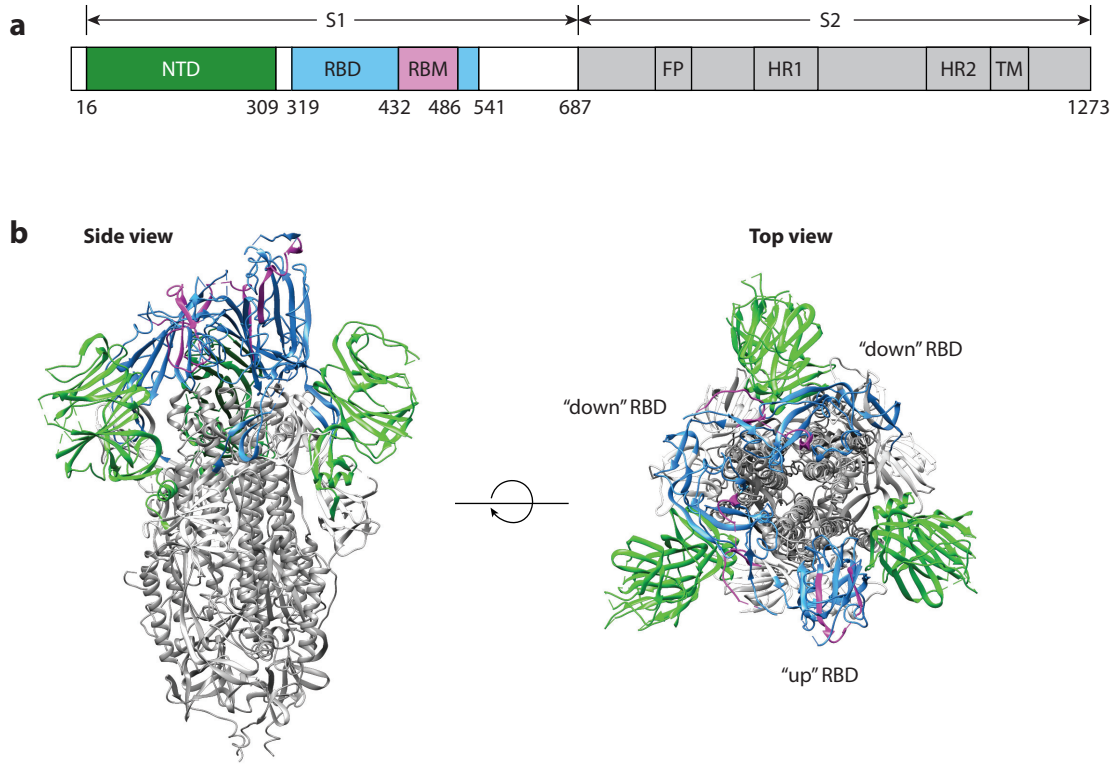

Figure 1

The SARS-CoV-2 spike (S) protein. (*a*) Schematic of SARS-CoV-2 S protein subdomains. Locations of these domains are indicated by amino acid residue numbers. (*b*) Prefusion structure of SARS-CoV-2 S protein. A stabilized SARS-CoV-2 S protein, 2P, with one "up" RBD (PDB ID: 6VSB) is shown. NTD (green), RBD (light blue), RBM (magenta), and S2 (gray) domains were colored corresponding to the schematic in panel a. Image of the prefusion S protein structure (PDB ID: 6VSB) (10) was created with UCSF Chimera (12). Abbreviations: NTD, N-terminal domain; RBD, receptor-binding domain; RBM, receptor-binding motif; FP, fusion peptide; HR1, heptad repeat 1; HR2, heptad repeat 2; PDB, Protein Data Bank; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; TM, transmembrane domain.

(9–11). Therefore, neutralizing antibodies targeting different subdomains on S protein could interrupt these entry steps and prevent SARS-CoV-2 infection. Thus far, neutralizing antibodies targeting RBD, NTD, and S2 have been reported for potential translation to human use.

RBD Antibodies

The RBD exhibits remarkable mobility relative to the rest of the S protein. Structures of S protein ectodomains and viral particles have revealed three distinct conformations, including all RBDs in the "down" (horizontal) state (3-RBD-down) and states with either one (1-RBD-up) or two (2-RBD-up) RBDs in the "up" (vertical) position. When an RBD engages with ACE2, the S protein trimers undergo conformational changes and become an unstable state with all three RBDs up (3-RBD-up) to optimally trigger viral entry (9–11). Dissection of neutralizing antibody specificities in SARS-CoV-2 convalescent sera indicates that approximately 90% of the neutralizing antibody response is directed to the RBD (13). RBD antibodies tend to have high neutralization potency; therefore, current SARS-CoV-2 neutralizing antibodies in clinical trial stages (**Table 1**) are predominantly RBD antibodies. Barnes and colleagues (14) classified RBD antibodies into four

Table 1 SARS-CoV-2 neutralizing antibodies approved or in clinical trials for therapeutic use (as of July 27, 2021)

Antibody name	Drug name	Targeting region	Institutions	Animal models for preclinical data	Clinical trial status	References
REGN-COV-2 (REGN10933 + REGN10987)	Casirivimab + imdevimab	SARS-CoV-2 RBD	Regeneron	Rhesus macaque; hamster	EUA; phase III (NCT04425629; NCT04452318)	25, 93, 94
LY-CoV555 + LY-CoV016 (LY3819253 + LY3832479)	Bamlanivimab + etesevimab	SARS-CoV-2 RBD	Eli Lilly	Rhesus macaque	EUA; phase III (NCT04497987; NCT04427501)	27, 95
VIR-7831 (GSK4182136)	Sotrovimab	SARS-CoV-2 RBD	Vir Biotechnology, GSK	Hamster	EUA; Phase III (NCT04545060; NCT04913675)	53, 58
AZD7442 (AZD8895 + AZD1061) or (COV2–2196 + COV2–2130)	Tixagevimab + cilgavimab	SARS-CoV-2 RBD	AstraZeneca, Vanderbilt University	Rhesus macaque; hACE2-transduced mouse	Phase III (NCT04625725; NCT04625972)	34, 35
CT-P59	Regdanvimab	SARS-CoV-2 RBD	Celltrion	NA	Phase III (NCT04602000)	96
SCTA01	NA	SARS-CoV-2 S protein	Sinocelltech	NA	Phase III (NCT04644185; NCT04683328)	NA
TY027	NA	SARS-CoV-2 S protein	Tychan	NA	Phase III (NCT04649515)	NA
DZIF-10c (BI 767551)	NA	SARS-CoV-2 S protein	Cologne University Hospital, University of Marburg, The German Center for Infection Research (DZIF), Boehringer Ingelheim	NA	Phase III (NCT04631705; NCT04631666)	97
STI-2020 (COVI-AMG)	NA	SARS-CoV-2 S protein	Sorrento	Hamster	Phase III (NCT04584697)	98
P2C-1F11 and P2B-2F6	BRII-196 and BRII-198	SARS-CoV-2 RBD	Tsinghua University, Brii Biosciences	NA	Phase III (NCT04501978)	31
ADM03820	NA	SARS-CoV-2 S protein	Ology Bioservices	NA	Phase I (NCT04592549)	NA
HFB30132A	NA	SARS-CoV-2 S protein	HiFiBiO Therapeutics	NA	Phase I (NCT04590430)	NA
JS016	NA	SARS-CoV-2 RBD	Institute of Microbiology, Chinese Academy of Sciences, Junshi Biosciences, Eli Lilly	NA	Phase I/II (NCT04441918; NCT04780321)	NA
ABBV-47D11	NA	SARS-CoV-2 RBD	AbbVie	NA	Phase I (NCT04644120)	99
HLX70	NA	SARS-CoV-2 RBD	Hengenix Biotech, Sanyou Biopharmaceuticals, Shanghai ZJ Bio-Tech	NA	Phase I (NCT04561076)	NA
STI-1499 (COVI-GUARD)	NA	SARS-CoV-2 S protein	Sorrento	Hamster	Phase I (NCT04584697)	98

Abbreviations: EUA, emergency use authorization; NA, not available; RBD, receptor-binding domain; S, spike; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

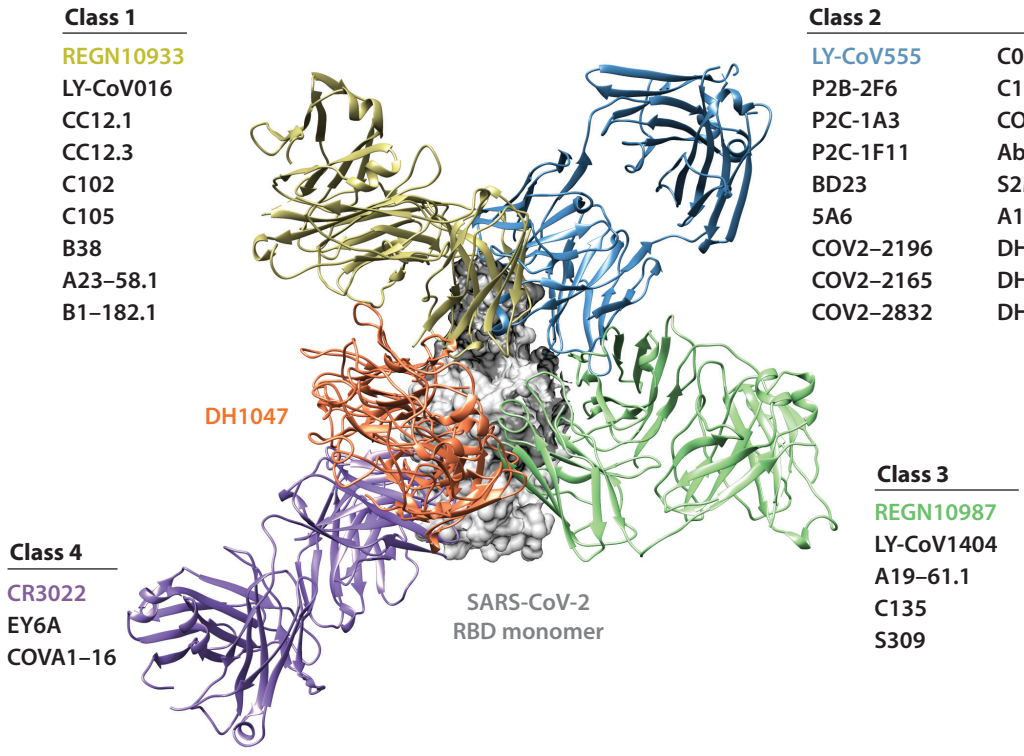

Figure 2

Classification of RBD-specific antibodies by structure. The RBD is shown as a surface in gray with the RBM colored black. Representative RBD-directed antibodies from each class are shown as ribbons for REGN10933 [*gold*; Class 1; PDB ID: 6XDG (25)], LY-CoV555 [*blue*; Class 2; PDB ID: 7KMG (26)], REGN10987 [*green*; Class 3; PDB ID: 6XDG (25)], and CR3022 [*purple*; Class 3; PDB ID: 6W41 (41)], with the cross-neutralizing RBD antibody DH1047 [*orange*; PDB ID: 7LD1 (15)] structure overlaid. Additional representative SARS-CoV-2 antibodies are listed. Abbreviations: PDB, Protein Data Bank; RBD, receptor-binding domain; RBM, receptor-binding motif; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2. Figure adapted with permission from Reference 14.

groups based on structure (**Figure 2**): Class 1 comprises ACE2-blocking neutralizing antibodies encoded by the immunoglobulin heavy chain variable region 3–53 gene (*IGHV3–53*), which bind only to up RBDs; Class 2 comprises ACE2-blocking neutralizing antibodies that bind to both up and down RBDs and can contact adjacent RBDs; Class 3 comprises ACE2-blocking neutralizing antibodies that bind outside the ACE2 site and recognize both up and down RBDs; Class 4 comprises neutralizing antibodies that bind outside the ACE2 site and bind only to up RBDs. Based on their capacity of cross-neutralizing other beta-coronaviruses, RBD antibodies can also be classified into non-cross-neutralizing antibodies and cross-neutralizing antibodies (15–19).

RBM: receptor-binding motif

RBD neutralizing antibodies without cross-reactivity. Generally, RBD antibodies that do not bind to conserved epitopes have poor cross-reactivity to other coronaviruses (CoVs). One of these regions in RBDs is the receptor-binding motif (RBM, aa 437–508; **Figure 1**), which is also known as the ACE2-binding site (6, 20, 21). Antibodies targeting or overlapping with the RBM directly compete with ACE2 and thus block ACE2/RBD binding (22). Antibodies of this class exhibit the most potent neutralization against SARS-CoV-2 (14, 22).

Fab: fragment antigen-binding

IGHV3–53 is the most frequently used IGHV gene among the RBM-targeting antibodies (14, 23). All IGHV3–53 RBD antibodies share similar structural properties and thus belong to Class 1 of the structural classification (**Figure 2**) (14); they recognize only up RBDs, have short complementarity-determining region 3 of antibody heavy chains (CDRH3) loops (<15 aa), and do not bind adjacent RBDs (14, 23, 24). A few highly potent IGHV3–53 RBD neutralizing antibodies have been isolated, including antibody REGN10933 from Regeneron (25), LY-CoV016 from Lilly (27), and other neutralizing antibodies: CC12.1, CC12.3 (23, 28), C102, C105 (14), B38 (29), A23–58.1, and B1–182.1 (30). IGHV3–53 antibodies display lower somatic mutation rates (23, 24), suggesting that V_H3–53 antibody contacts are encoded by germline amino acids requiring little affinity maturation upon exposure to SARS-CoV-2.

Unlike IGHV3–53 antibodies, other RBM antibodies, such as those in Class 2 of the structural classification (**Figure 2**) (14), recognize both up and down RBDs, have long CDRH3 loops (>15 aa), and mostly bind adjacent RBDs in a single S trimer, which could provide extra binding avidity effects (14). We have isolated RBD neutralizing antibodies DH1041, DH1042, and DH1043, which belong to this subgroup (15). Cryo–electron microscopy structures of fragment antigen-binding (Fab) binding to stabilized spike S-2P trimer (11) showed that all S-2P trimers stoichiometrically bound to Fabs, with DH1041 and DH1043 binding to both up and down RBDs in an S-2P trimer. The primary epitopes of DH1041 and DH1043 were centered on the RBM (15). Similarly, several potent RBD neutralizing antibodies developed thus far belong to this group, including P2B–2F6, P2C–1A3, P2C–1F11 (31, 32), BD23 (33), COV2–2196, COV2–2165, COV2–2832 (34, 35), C002 and C104 antibodies (14), COVA2–39 (22), Ab2–4 (36), LY-CoV555 (27), A19–46.1 (30), 5A6 (37), and S2M11 (38). These antibodies recognize both up and down RBDs; thus, they not only directly block ACE2 binding but also bridge between adjacent down RBDs to lock the S protein into a prefusion conformation, thereby inhibiting S from opening up to engage ACE2.

In addition to these RBM-targeting RBD antibodies, some SARS-CoV-2 neutralizing antibodies recognize RBD epitopes that do not overlap with the ACE2-binding footprint. These non-RBM-targeting RBD antibodies belong to Class 3 or 4 of the structural classification (**Figure 2**) (14). Depending on the approaching angles and binding sites on the S protein, some of these antibodies target epitopes that are distal to the RBM subdomain yet still block ACE2 binding, while others do not block it. For instance, REGN10987 (25), LY-CoV1404 (39), S2A4 (13), A19–61.1 (30), and C110 (14) exhibit potent neutralization and ACE2-blocking capacity due to steric clashes between antibody and ACE2 on S protein. In contrast, other non-RBM-targeting RBD antibodies showed no competition with ACE2 binding to S protein, such as non-ACE2-blocking antibodies DH1044 (15) and C135 (14).

Cross-neutralizing RBD antibodies. Cross-neutralizing antibodies that are broadly protective against human and animal group 2B or 2C beta-coronaviruses are urgently needed not only for therapeutic use but also for guiding vaccine design. In **Table 2**, we summarize several cross-neutralizing human antibodies against SARS-CoV-2-related CoVs. The first cross-reactive antibody reported, CR3022, is a weakly neutralizing antibody against SARS-CoV but does not neutralize SARS-CoV-2 (40, 41). Other SARS-CoV and SARS-CoV-2 cross-neutralizing antibodies, namely S309 (16), CV2–75 (42), COVA1–16 (43), and S2×259 (44), target epitopes distinct from the ACE2-binding site. S309 does not compete with ACE2 binding to S, while COVA1–16, CV2–75, and S2×259 block ACE2. Structural analysis suggests that these cross-neutralizing antibodies belong to Group 2, 3, or 4 of the structure classes (**Figure 2**) (14), and their epitopes are highly conserved within human and animal sarbecoviruses.

Table 2 Cross-neutralizing SARS-CoV-2 receptor-binding domain antibodies as potential pan-coronavirus therapeutics

Antibody name	Origin	Institution	In vitro cross-neutralization	In vivo cross-protection	Animal models for preclinical data	References
DH1047	SARS-CoV convalescent human	Duke Human Vaccine Institute	SARS-CoV-2 and variants SARS-CoV WIV1-CoV SHC014-CoV	SARS-CoV-2 SARS-CoV-2 Beta variant SARS-CoV WIV1-CoV SHC014-CoV	Rhesus macaque Mouse	15, 45
ADG-2	SARS-CoV convalescent human; affinity maturation	Adimab	SARS-CoV-2 and variants SARS-CoV WIV1-CoV SHC014-CoV	SARS-CoV-2 SARS-CoV	Mouse	19
S309	SARS-CoV convalescent human	Vir Biotechnology	SARS-CoV-2 and variants SARS-CoV	NA	NA	16
CV2–75	SARS-CoV convalescent human	Fred Hutchinson Cancer Research Center	SARS-CoV-2 and variants SARS-CoV	SARS-CoV-2	Mouse	42
COVA1–16	SARS-CoV-2 convalescent human	Scripps	SARS-CoV-2 and variants SARS-CoV	NA	NA	43
S2×259	SARS-CoV-2 convalescent human	Vir Biotechnology	SARS-CoV-2 and variants RaTG13-CoV SARS-CoV WIV1-CoV WIV16-CoV SHC014-CoV	SARS-CoV-2 Beta variant	Hamster	44

Abbreviations: NA, not available; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

Our group reported an RBD-directed cross-neutralizing antibody, DH1047, isolated from memory B cells of a recovered SARS-CoV individual (15, 45). DH1047 shows cross-reactivity with the S proteins of SARS-CoV, bat SHC014-CoV, RaTG13-CoV, and pangolin GX-P4L-CoV; it blocks ACE2/S binding and neutralizes SARS-CoV, SARS-CoV-2, WIV1-CoV, and SHC014-CoV (15, 45) but does not cross-block DH1041 types of SARS-CoV-2-specific neutralizing antibodies. Structural studies have revealed an epitope located outside the N-terminus of the RBM and distinct from the target epitopes of the non-cross-neutralizing antibody classes described above (**Figure 2**). Importantly, DH1047 protects mice from SARS-CoV, SARS-CoV-2, WIV1-CoV, and SHC014-CoV infection (45).

The Walker group at Adimab isolated antibodies ADI-56046 and ADI-55689 (17), as well as an affinity-matured antibody, ADG-2 (19); these antibodies all also cross-neutralize SARS-CoV, SARS-CoV-2, and WIV1. Further structural analyses have suggested that the ADI-55689, ADI-56046, and ADG-2 footprints overlap somewhat with the ACE2-binding site (17, 19) and that the ADG-2 epitope overlaps with the DH1047 epitope (45). Like DH1047, these cross-neutralizing antibodies also bind S protein through an angle of approach that is relatively horizontal to the viral surface (17), suggesting that both highly conserved recognition motifs and horizontal approach angles are essential for cross-neutralizing activity (15, 18, 19).

NTD Antibodies

Neutralizing antibodies also can target the NTD of the S protein and generally do not block ACE2 engagement; rather, they lock the S protein and prevent conformational changes from pre- to postfusion state (46). Chi et al. reported the first SARS-CoV-2 NTD neutralizing antibody 4A8, which exhibited potent neutralizing activity with an IC50 of 0.39 μg/mL against authentic SARS-CoV-2 virus (51). Suryadevara et al. reported NTD antibodies COV2–2676 and COV2–2489, which neutralize SARS-CoV-2 by inhibiting a postattachment step and protect mice from SARS-CoV-2 challenge (47). Our group isolated five potent NTD neutralizing antibodies with epitopes similar to 4A8, COV2–2676 and COV2–2489. Our five NTD-directed neutralizing antibodies bound to 3-RBD-down or 1-RBD-up S proteins, with the constant domain of the Fab directed upward away from the virus membrane. These five neutralizing antibodies neutralized live SARS-CoV-2 virus at IC50s ranging from 0.09 to 0.61 μg/mL, and one of the most potent antibodies, DH1050.1, protected 4 out of 5 cynomolgus macaques from SARS-CoV-2 challenge (15). We also identified a non-neutralizing NTD antibody, DH1052, that could reduce virus replication and lung inflammation in mice and monkeys (15), possibly through non-neutralizing fragment crystallizable (Fc) region–mediated antibody effector functions (48). Indeed, recent studies demonstrated that Fc effector functions are required for human antibody-mediated therapeutic protection (49, 50). The roles of non-neutralizing RBD and NTD antibodies in protection from or treatment of SARS-CoV-2 infection, however, require further investigation.

NTD antibodies share structural and genetic features. Neutralizing NTD antibodies DH1050.1, DH1050.2, DH1049, and 4A8 are all derived from the V_H1–24 gene segment (15, 51). That these NTD neutralizing antibodies utilize the same V_H gene and bind to S protein with similar approaches suggests that they may belong to an NTD antibody class (52). Moreover, a structural study by McCallum et al. identified an antigenic supersite recognized by all available NTD-specific neutralizing antibodies (53). A potent NTD antibody in this study, S2X333, inhibited cell-to-cell fusion, activated effector functions, and protected hamsters from SARS-CoV-2 challenge (53). However, the NTD region is highly variant across different CoVs and thus unlikely to be the target for cross-neutralizing antibodies. Nevertheless, NTD neutralizing antibodies could be potentially combined with RBD antibodies for more potent antibody cocktails.

S2 Antibodies

The S2 subunit is critical for viral/cellular membrane fusion. As the most conserved S protein subunit, S2 has 63–98% sequence similarity in pairwise comparisons across the seven human CoVs (54) and therefore is a potential target for pan-CoV neutralizing antibodies and vaccines. However, due to the limited neutralizing potency of S2 antibodies isolated so far (15, 42, 54), and with no in vivo protection data reported to date, whether S2-directed antibodies can protect against infection is yet to be determined.

SARS-COV-2 THERAPEUTIC ANTIBODIES

Thus far, the FDA has issued EUAs to two antibody cocktail pairs and one antibody monotherapy for the treatment of mild to moderate COVID-19 (**https://www.fda.gov/**). The first is Lilly antibody bamlanivimab (also known as LY-CoV555 or LY3819253; **Figure 2**) in combination with etesevimab (also known as LY-CoV016 or LY3832479). In a phase II clinical trial, this combination significantly decreased SARS-CoV-2 log viral load in early moderately severe infection. In a phase III clinical trial, the bamlanivimab + etesevimab cocktail was tested in 1,035 participants who were at high risk for progressing to severe COVID-19 and/or hospitalization. Compared to the placebo group ($n = 517$), the bamlanivimab + etesevimab group ($n = 518$) had a greater and more rapid virus level decline; it also had a 5% absolute reduction and a 70% relative reduction in COVID-19-related hospitalizations or death. There were no deaths in the bamlanivimab + etesevimab arm and 10 deaths in the placebo arm (55). The trial evaluating bamlanivimab + etesevimab in preventing COVID-19 is ongoing as of July 1, 2021 (NCT04497987).

The other authorized antibody cocktail, the Regeneron casirivimab + imdevimab (also known as REGN10933 +REGN10987; **Figure 2**) combination, reduced COVID-19-related hospitalization or emergency room visits within 28 days after treatment when compared to placebo. Lower viral RNA levels were detected in the nasopharyngeal swab of the antibody group compared to the placebo group (56). In addition, the casirivimab + imdevimab cocktail is still being studied in the phase III open-label RECOVERY trial of hospitalized patients in the United Kingdom (NCT04381936), two phase II/III clinical trials of COVID-19 treatments in hospitalized and outpatient ambulatory patients (NCT04425629, NCT04426695), and a phase III trial for preventing COVID-19 in household contacts of infected individuals (NCT04452318).

The GSK/Vir antibody sotrovimab, also known as VIR-7831 or GSK4182136, is derived from S309 with optimized variable and constant regions (57). A phase III clinical trial has demonstrated an 85% reduction in hospitalization or death in patients receiving sotrovimab as monotherapy compared to placebo (58). Therefore, it has been recently issued an EUA for treating mild to moderate COVID-19.

CHALLENGES FOR COVID-19 NEUTRALIZING ANTIBODY DEVELOPMENT

Viral Escape Mutations

Emergent and rapidly spreading SARS-CoV-2 variants (see **Table 3**) have multiple mutations in the S protein and are of concern due to their potential to escape current neutralizing antibodies as well as vaccine-induced antibodies. The first variant, D614G (59), was discovered in January 2020 and soon became the most prevalent form globally. D614G is unlikely to be an escape mutation as it has an open RBD conformation and is more susceptible to antibody neutralization (60). However, several variants with enhanced transmissibility (61), virulence (62), and potential neutralizing antibody escape capacity (63, 64) have emerged, including B.1.1.7 (Alpha), B.1.351 (Beta), B.1.1.248 (Gamma), B.1.1617.1 (Kappa) and B1.1617.2 (Delta), etc. (3). Of these, the Delta

Table 3 SARS-CoV-2 variants recognized by World Health Organization (WHO) as variants of concern (VOC) or variants of interest (VOI) as of July 27, 2021

VOC or VOI	WHO label	Pango lineage	Location of first outbreak
VOC	Alpha	B.1.1.7	United Kingdom
VOC	Beta	B.1.351	South Africa
VOC	Gamma	B.1.1.248 (P.1)	Brazil
VOC	Delta	B.1.617.2	India
VOI	Kappa	B.1.617.1	India
VOI	Eta	B.1.525	Multiple countries
VOI	Iota	B.1.526	New York, USA
VOI	Lambda	C.37	Peru

SARS-CoV-2 variant that originated in India is the most highly transmissible variant and is rapidly spreading globally.

Neutralization data have been reported by several independent groups for testing current neutralizing antibodies against multiple variants. The potency of most antibodies developed to date is largely unaffected by the Alpha variant mutations, although the Alpha variant showed significant resistance to non-RBM-targeting neutralizing antibodies B38, COVA2–15, and S309, as well as NTD-targeting antibodies, 4A8 and COV2–2489 (63, 65, 66). The Beta variant is more of concern; the neutralization activity of the Lilly antibody bamlanivimab (30, 66) is completely ablated. Consequently, the EUA of bamlanivimab monotherapy was recently revoked by the FDA. The AstraZeneca monoclonal antibody (mAb) cilgavimab (COV2–2196), Brii mAb Brii-198 (P2B-2F6), and the Regeneron mAb casirivimab all exhibited more than six-fold reduction in neutralization potency against the Beta variant (18, 65, 66, 67). Nevertheless, RBD neutralizing antibodies sotrovimab (VIR-7831) (57), DH1047 (45), A19–61.1 (30), S2×259 (44), and SARS2–38 (68) potently neutralized multiple variants including Alpha and Beta. In addition, DH1047, S2×259, and SARS2–38 protected mice or hamsters from Beta variant challenge (44, 45, 68) (**Table 2**). The newly emerging Delta variant was also resistant to the Lilly antibody bamlanivimab (69, 70), while no dramatic reduction of Delta variant neutralization was observed for etesivimab, casirivimab, imdevimab, tixagevimab, cilgavimab, etc. (69).

Several mAb cocktails have been developed to overcome possible emergence of escape and resistance during antibody therapy. Indeed, despite the reduced neutralization potency of casirivimab against both the Alpha and Beta variants (65, 69, 71–73), the casirivimab + imdevimab combination retained potent neutralization against all the variants tested (73). In addition, the Regeneron (bamlanivimab + etesevimab), AstraZeneca (cilgavimab + tixagevimab) and Vir/GSK (S309 + S2E12) antibody cocktails all retain unchanged and potent neutralization against all of the variants tested in vitro and in vivo (73), although S309 alone weakly neutralized the Alpha variant (65, 73). Therefore, for COVID-19 therapy, it is important to have cocktails composed of multiple antibodies targeting distinct epitopes to avoid viral escape. In addition, other S protein mutations have been identified in vitro that can escape from neutralizing antibodies and/or serum antibodies (74–76). Thus, current antibody therapies must be monitored in real time as escape mutations emerge during viral evolution.

Potential Infection Enhancement

ADE of virus infection and disease has been observed in dengue virus and other highly pathogenic CoVs, including SARS-CoV and MERS-CoV (Middle East respiratory syndrome coronavirus) (77–86). Conventional ADE of virus infection is mediated by Fc gamma receptor (FcγR) (87).

Antibodies with an ADE phenotype bind to a virus particle with the Fab domain and also bind FcγR-bearing cells with their Fc domain, thus enabling the virus to bypass specific receptor engagement and gain entry into the host cell via FcγR activity. In addition, vaccine-associated enhanced disease (VAED) has occurred in RSV vaccine recipients, which may be associated with unfavorable, nonprotective antibodies induced by vaccination (87). While in vitro ADE is usually defined as more viral entry/replication in target cell lines, in vivo ADE or VAED could show increased viral load and/or more severe immune cell recruitment and inflammatory responses, which could initiate tissue damage. Therefore, the risk of inducing potential enhancement of COVID-19 disease by SARS-CoV-2 neutralizing antibody treatment has been a general concern for antibody therapy as well as vaccine development.

Studies reported by our group (15) and others (88, 89) identified RBD-directed neutralizing antibodies that mediate conventional ADE of SARS-CoV-2. Despite these in vitro ADE effects, infusion of in vitro infection-enhancing antibodies in mice and cynomolgus macaques did not induce any in vivo enhancement of viral replication or disease, but rather potent protection against SARS-CoV-2 infection (15). In contrast to results with the conventional ADE antibodies, FcγR-independent SARS-CoV-2 infection enhancement has been reported for NTD antibodies in ACE2-positive, FcγR-negative cells (15, 90). Structural analysis data suggested that these in vitro infection-enhancing NTD antibodies bound to S with their Fab constant domains directed toward the virus membrane (15), and mutational analysis revealed a unique binding epitope for the infection-enhancing NTD antibodies (90). Nevertheless, in general, no infection enhancement was observed in mice or cynomolgus macaques after infusion of an in vitro infection-enhancing NTD antibody DH1052 (15). In these studies, one monkey had enhanced lung pathology compared to controls with increased cytokines in bronchoalveolar fluid (16). However, increasing the dose of antibody DH1052 did not result in additional monkeys with increased lung pathology, suggesting antibody-mediated effects were not the cause of lung pathology in this animal (16). In the Pfizer/BioNTech and Moderna mRNA COVID-19 vaccine efficacy trials, all but one of the severe cases of COVID-19 were in the placebo groups; therefore, in these two trials, no vaccine-induced enhanced infection was seen (91, 92). Finally, no safety issues have been seen in clinical trials of administration of convalescent serum in humans (16). Thus, as yet, no reproducible in vivo data support the occurrence of antibody-mediated SARS-CoV-2 infection enhancement. Nonetheless, it will be important to continue to monitor for safety ongoing COVID-19 antibody treatment and clinical trials.

CONCLUSION

Although two SARS-CoV-2 neutralizing antibody pairs have been authorized, development of the next generation of therapeutic antibodies for COVID-19 patients remains a priority, due to the emergence of SARS-CoV-2 variants of concern. Cross-neutralizing antibodies to combat SARS-CoV-2 neutralization escape variants and other CoVs are needed, since new zoonotic coronaviruses will likely emerge and cause new human CoV outbreaks in the future.

DISCLOSURE STATEMENT

D.L., P.A., G.D.S., K.O.S., and B.F.H. have patent applications for antibodies from Duke described in this review.

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