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REVIEW

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Therapeutic antibodies for COVID-19: is a new age of IgM, IgA and bispecific antibodies coming?

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ABSTRACT

Early humoral immune responses to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) are dominated by IgM and IgA antibodies, which greatly contribute to virus neutralization at mucosal sites. Given the essential roles of IgM and IgA in the control and elimination of SARS-CoV-2 infection, the mucosal immunity could be exploited for therapeutic and prophylactic purposes. However, almost all neutralizing antibodies that are authorized for emergency use and under clinical development are IgG antibodies, and no vaccine has been developed to boost mucosal immunity for SARS-CoV-2 infection. In addition to IgM and IgA, bispecific antibodies (bsAbs) combine specificities of two antibodies in one molecule, representing an important alternative to monoclonal antibody cocktails. Here, we summarize the latest advances in studies on IgM, IgA and bsAbs against SARS-CoV-2. The current challenges and future directions in vaccine design and antibody-based therapeutics are also discussed.

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Introduction

Coronavirus disease-2019 (COVID-19) is a global threat induced by a newly emerged virus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The rapid spread of COVID-19 not only prompts the development of effective vaccines at an unprecedented pace but also expedites the development of novel therapies, including therapeutic SARS-CoV-2-neutralizing antibodies and the reuse of existing antibodies approved for other indications.

Antibodies are a versatile and important component of the human immune system, of which the monoclonal antibody (mAb) represents a new frontier for the treatment of infectious diseases due to its specificity and potency. As predicted by William Haseltine, a biologist in Harvard, mAbs would be the first therapy specifically developed to target SARS-CoV-2.[1] To date, more than 10 mAbs have been granted Emergency Use Authorization (EUA) by the United States or approved by other countries to treat COVID-19, and over 70 mAbs are being evaluated in clinical trials in different therapeutic settings. These trials will be essential for the development of novel COVID-19 treatments in the very near future.

In patients with COVID-19, the severity of the disease correlates to high viral load in the respiratory tract, the primary site of SARS-CoV-2 infection and shedding.[2] Analysis of antibody responses has shown that SARS-CoV-2 induces specific antibodies mediated by three major immunoglobulin (Ig) isotypes, IgM, IgA, and IgG.[3,4] Among them, specific IgM and IgA are the early antibody responses that start and peak within 7 days, whereas specific IgG antibodies develop more than a week (10–18 days) after infection and persist for months (Figure 1a).[4–6] However, almost all neutralizing mAbs in clinical use are the IgG isotype. No IgM or IgA mAbs are currently marketed. Moreover, these IgG mAbs are mostly administered via intravenous (i.v.) infusion. The concentration of IgG antibodies is 200–500 times lower in the lungs than in serum, highlighting that i.v. administration could not induce effective mucosal immune responses.[7] What is worse, many potent IgG mAbs, including those with EUAs and some in clinical trials, do not neutralize the emerging SARS-CoV-2 variants of concern (VOCs).[8–11] Thus, there is an urgent need for the development of more potent antibody-based therapies against the virus.

Upon SARS-CoV-2 infection, viruses first affect the upper respiratory tract. Therefore, the mucous membrane is the first line of immune system defense. IgM and IgA are mucosal antibodies in the early stages of immune response against mucosal pathogens. IgM typically assembles into pentamers that contain 10 antigen-binding sites and the joining chain (J-chain) (Figure 1b). The J-chain of pentameric IgM enables its binding to the polymeric Ig receptor (pIgR) on cells, allowing the transcytosis of IgM from the circulation to the mucosal surfaces.[16] In contrast, IgA exists in monomeric form (mIgA) in serum but is present as dimers (dIgA) at mucosal surface, termed secretory IgA (sIgA), which contains two IgA molecules with a J-chain and a secretory component (SC) (Figure 1b). In respiratory and gastrointestinal tracts, IgM and sIgA serve as the main mediator of mucosal immunity. These features make the intranasal delivery of IgM or IgA neutralizing antibodies feasible for the treatment of COVID-

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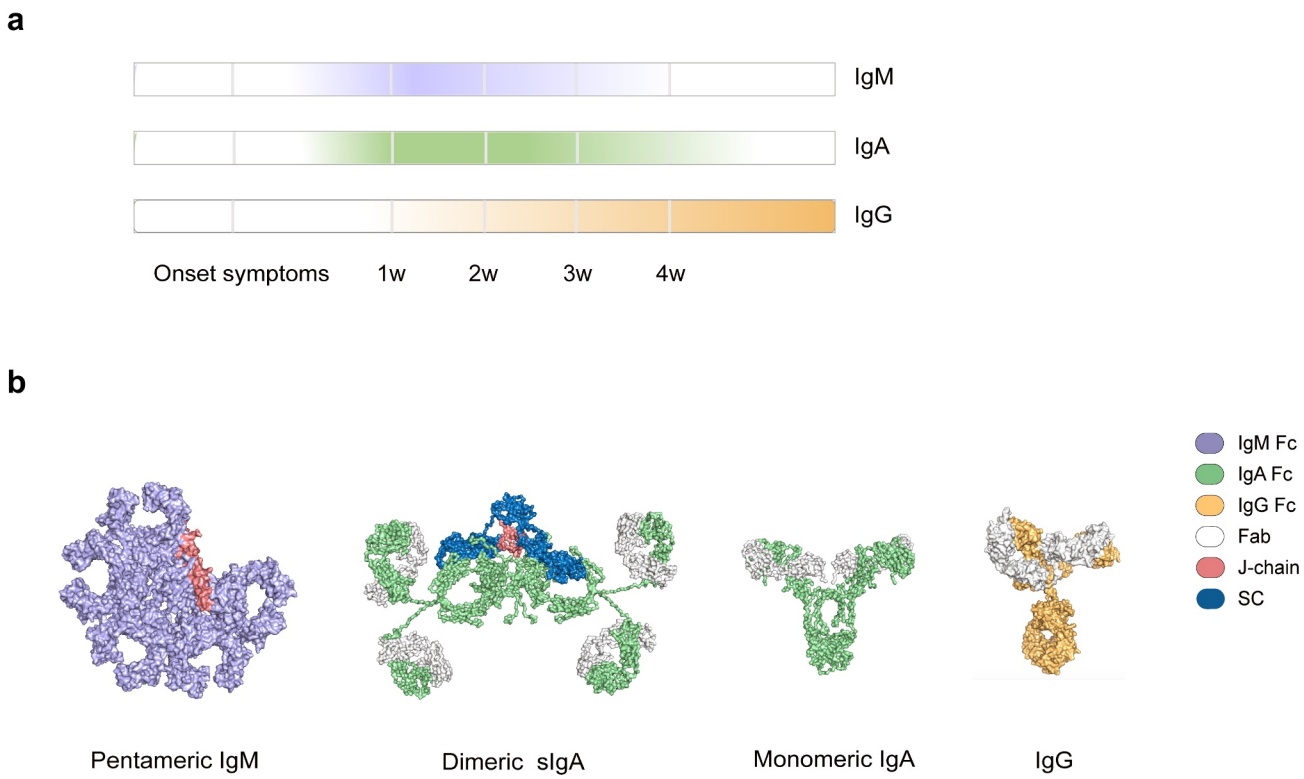

Figure 1. Antibody responses to SARS-CoV-2 infection. (a) Antibody responses of IgM, IgA, and IgG upon SARS-CoV-2 infection.[6] w, week. (b) The structures of pentameric IgM (PDB code 6KXS),[12] dimeric sIgA (PDB code 3CHN),[13] monomeric IgA (PDB code 1 R70),[14] and IgG (PDB code 1HZH)[15] are shown, with the specific domains in different colors. Fab, antigen-binding fragment; J-chain, joining chain; SC, secretory component. **Different antibody responses upon SARS-CoV-2 infection, with structures of IgM pentamers, dimeric sIgA, monomeric IgA, and IgG.**

19. Meanwhile, these characteristics also raise questions as to whether SARS-CoV-2-induced IgM or IgA neutralizing antibodies exert more potent effects than IgG, and whether IgM or IgA neutralizing antibodies are superior to IgG in covering escape variants of SARS-CoV-2. If so, more data are needed to show how we can improve the current vaccines or develop novel immunization methods to boost early and mucosal immune response in COVID-19.

Given these considerations, we provide here an overview of IgM and IgA therapeutic antibodies for COVID-19, focusing on those that target SARS-CoV-2. In addition, we also summarize the anti-SARS-CoV-2 bispecific antibodies (bsAbs), which are an important alternative to monoclonal antibody cocktails.

SARS-CoV-2 and conventional IgG mAbs

SARS-CoV-2 is an enveloped RNA virus that causes COVID-19, and the spike glycoprotein (S protein) on its surface is a transmembrane homotrimer and the target of neutralizing antibodies (Figure 2a). The S protein has two functional subunits (S1 and S2), of which the S1 subunit facilitates viral attachment to the surface of host cells. The S1 subunit further includes the N-terminal domain (NTD) and receptor-binding domain (RBD), which represent the key targets for neutralizing mAbs and potential therapies (Figure 2b).[17] Since the outbreak of the pandemic, neutralizing IgG mAbs against RBD or NTD have been the focus of investigation and development efforts. Of interest, all mAbs authorized or in clinical trials target the RBD, which interacts with the angiotensin-converting enzyme 2 (ACE2) receptor (Figure 2a).[18] While most mAbs recognize different epitopes fully or partially overlapping with the ACE2-binding sites, some mAbs target sites close or distal to the ACE2-binding sites. Although none of the NTD-directed mAbs are under clinical testing, the NTD is an essential and promising target for neutralizing mAbs.[8,19–22] However, the neutralization mechanism of NTD-binding mAbs remains unclear. One possible mechanism is that the NTD-specific mAbs may neutralize SARS-CoV-2 by retraining the conformational changes of the S protein.[19] Another study suggested that the anti-NTD mAbs may inhibit SARS-CoV-2 infection at a post-attachment phase and block subsequent virus entry or fusion steps.[21]

Therapeutic IgG mAbs against SARS-CoV-2 and the existing antibodies against non-SARS-CoV-2 antigens in COVID-19 have been extensively discussed in several detailed reviews.[23–27] We thus do not focus on them here, but summarize all the therapeutic IgG antibodies for COVID-19 that we identified in Table 1, including their origin, development platform, target, features, and the current status of clinical trials. The targets are varied, and include SARS-CoV-2, cytokine and chemokine, and complement. Given the emergence of SARS-CoV-2 variants, we also summarize the neutralization of SARS-CoV-2 VOCs by the existing IgG antibodies with EUAs or in clinical development (Table 2). The summarized VOCs include B.1.1.7 (Alpha, first identified in the United Kingdom), B.1.351 (Beta, first identified in South Africa), P.1 (Gamma, first identified in Brazil), B.1.617.2 (Delta, first identified in India), B.1.617.1 (Kappa, first identified in India), and B.1.427/B.1.429 (Epsilon, first identified in USA), as well as two pseudoviruses containing multiple mutations. Although many

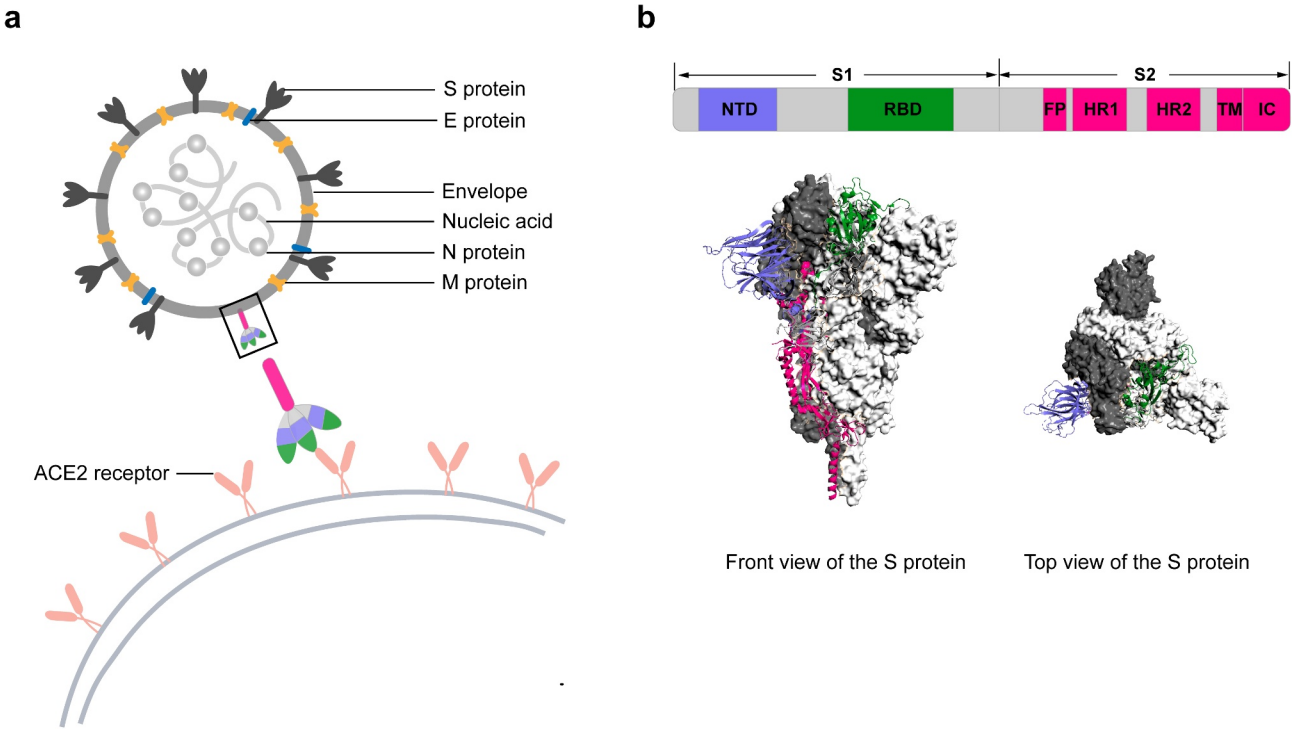

Figure 2. Schematic diagram of SARS-CoV-2 particle and the S protein. **SARS-CoV-2 particle, with different structural proteins, showing its interaction with ACE2 receptor on the host cells. More detailed structures of the S protein are shown.** (a) SARS-CoV-2 is an enveloped positive-sense single-stranded RNA (+ssRNA) virus. The spike glycoprotein (S protein) expressed on its surface mediates viral attachment to the host cells via the angiotensin-converting enzyme 2 (ACE2) receptor. Other major structural proteins of the SARS-CoV-2 particle include envelope (E) protein, membrane (M) protein, and nucleocapsid (N) protein. (b) SARS-CoV-2 S protein is divided into S1 and S2 subunits, of which, the S1 subunit includes the N-terminal domain (NTD, in tv-blue) and receptor-binding domain (RBD, in forest); the S2 subunit includes fusion peptide (FP), heptad region 1 and 2 (HR1, HR2), transmembrane domain (TM) and intracellular tail (IC) which are shown in hot pink. The structure of trimeric SARS-CoV-2 S protein (PDB code 6XR8)[131] is shown (lower), with two molecules on the surface illustrated with white and gray color, respectively, and the third molecule in cartoon indicated with different colors (NTD in tv-blue; RBD in forest, and the S2 in hot pink).

existing mAbs are resistant to the emerging SARS-CoV-2 VOCs, a global consortium study recently provided a detailed epitope landscape on the SARS-CoV-2 S protein and offered a framework for selecting antibody treatment.[115] The result of this effort not only helps us understand how viral variants might affect antibody-based therapeutics but also guides both treatment and prevention.

Therapeutic IgM antibodies against SARS-CoV-2

So far, specific IgM antibodies have been largely developed for SARS-CoV-2 serological testing. Thus, the investigation of therapeutic IgM antibodies against SARS-CoV-2 is very limited. In previous studies, reduced IgM levels have been observed in patients with severe pandemic influenza.[116] As a result, the treatment with IgM-enriched preparations has emerged. Indeed, the clinical trials that evaluate the passive immunotherapy with COVID-19 convalescent plasma (CCP) have rapidly grown owing to the absence of specific antiviral therapy. In CCP, specific antibodies (IgG/IgM/IgA) against SARS-CoV-2 are regarded as active components, since all isotypes display neutralizing activities.[117] However, numerous non-antibody proteins and chemical factors in CCP may drive detrimental outcomes in patients.[118] CCP therapy also raises a flurry of ethical questions.[119] As such, the quality, efficacy and safety of CCP against COVID-19 need to be further investigated and determined.

Instead of CCP, the preparation of polyvalent antibody for COVID-19 is another therapeutic choice. Trimodulin, a polyvalent antibody preparation derived from human plasma, contains IgM (~23%), IgA (~21%) and IgG (~56%).[120] In COVID-19 cell models, addition of trimodulin reduced inflammation and induced stronger immunomodulation compared to intravenous Ig preparation (IVIG).[121] Hence, trimodulin is currently being tested in a Phase 2 clinical trial for COVID-19 (NCT04576728) (Table 3). Nonetheless, the IgM component of trimodulin is of minor importance for Fc receptor (FcR)-mediated effector functions, so the beneficial immunomodulatory effects of trimodulin might be attributed to the IgA component, a neglected but critical part of SARS-CoV-2 infection[121] discussed in the following section.

In addition to the polyvalent antibody preparation, recombinant mAbs of IgG, IgM and IgA isotypes sharing the same antigen-binding fragment (Fab) against S protein were developed.[126] Remarkably, the neutralizing ability of IgM and IgA mAbs was dramatically higher than IgG mAbs, suggesting a strategy for developing effective therapies of IgM and IgA instead of IgG for COVID-19.[126] One explanation for the efficient neutralization conferred by IgM and IgA might be their capacity to bind multiple virions. Recently, an elegant work reported six engineered IgM antibodies that exhibit higher binding and neutralizing activities than their parental IgG1 antibodies. Among them, one IgM antibody (IgM-14), engineered from a previously isolated mAb (CoV2-14) by

Table 1. Overview of IgG antibodies evaluated as possible COVID-19 treatments.

Name		Subtype	Origin/Platform	Target	Features	Clinical trial (ID)	Ref.
SARS-CoV-2	Sotrovimab (VIR-7831)[a]	Human IgG1κ	S309, a natural antibody from a convalescent pt with SARS-CoV-1 infection	RBD	With the LS mutation of Fc to increase half-life; Approved in Australia, UK and EU	Phase 1/2/3 (NCT04913675, etc.)	28,29
	Casirivimab (REGN10933)[a]	Human IgG1κ	Immunized hulg mice and convalescent pts	RBD	EUA in USA when used as a cocktail drug named REGN-COV2; Approved in Japan, UK, EU and Australia	Phase 1/2/3 (NCT04425629, etc.)	30
	Imdevimab (REGN10987)[a]	Human IgG1λ					
	Bamlanivimab (LY-CoV555)[a]	Human IgG1	High-throughput microfluidic screening of B cells from a convalescent pt	RBD	EUA in USA as monotherapy revoked; EUA in USA when used in combination with etesevimab	Phase 1/2/3/4 (NCT04796402, etc.)	31
	Etesevimab (LY-CoV016)[a]	Human IgG1	-	RBD	EUA in USA when used in combination with bamlanivimab	Phase 2/3 (NCT04427501, etc.)	32
	AZD8895 (COV2-2196)[a] AZD1061 (COV2-2130)[a]	Human IgG1	B cells of convalescent pts	RBD	EUA in USA when used as a cocktail named AZD7442 (EVUSHELD^{TM})	Phase 1/3 (NCT04625725, etc.)	33
	BRII-196 (P2C-1F11) BRII-198 (P2B-1G5)	Human IgG1	B cells of infected pts	RBD	Approved in China when used in combination	Phase 2/3 (NCT04501978, etc.)	34,35
	Regdanvimab (CT-P59)	Human IgG	Phage display	RBD	Approved in S. Korea and EU	Phase 1/2/3 (NCT04602000, etc.)	36
	SCTA01 (H014) SCITA01C	Humanized IgG1	Immunized mice and phage display	RBD	-	Phase 1/2/3 (NCT04709328, etc.)	37
	C135-LS C144-LS	Human IgG1	B cells of convalescent pts	RBD	With the LS mutation of Fc to increase half-life; high potency when used in combination	Phase 1/2/3 (NCT04518410, etc.)	38,39
	MAD0004J08 (J08-MUT)	Human IgG1	B cells of convalescent pts	RBD	With engineered Fc to reduce ADE and increase half-life	Phase 1/2/3 (NCT04952805, etc.)	40,41
	ADM03820	Human IgG1	-	RBD	A cocktail consisting of two antibodies with non-competitive bindings	Phase 1/2/3 (NCT05142527, etc.)	42
	EpAbs (INM005)	Polyclonal F(ab)′$_2$ fragments of IgG	Hyperimmunized equine	RBD	-	Phase 2/3 (NCT04494984)	43,44
	XAV-19	Glyco-humanized polyclonal IgG	Immunized swine	RBD	-	Phase 2/3 (NCT04928430, etc.)	45
	ADG20	Human IgG	ADG-2	RBD	-	Phase 2/3 (NCT04805671)	27
	TY027	Human IgG	-	RBD	-	Phase 1/3 (NCT04649515, etc.)	46
	VIR-7832	Human IgG1κ	S309, a natural antibody from a convalescent pt with SARS-CoV-1 infection	RBD	Identical to VIR-7831 except for an additional GAALIE modification of Fc	Phase 1/2 (NCT04746183)	11
	STE90-C11	Human IgG1	Phage display	RBD	-	Phase 1/2 (NCT04674566)	47
	COR-101		STE90-C11 with FcγR-silenced Fc				
	BGB-DXP593	Human IgG	High-throughput single-cell sequencing of B cells from convalescent pts	-	-	Phase 1/2 (NCT04551898, etc.)	29
	MW33 (MW05/LALA)	Human IgG1κ	B cells of a convalescent pt	RBD	With the LALA mutation of Fc to eliminate ADE	Phase 1/2 (NCT04627584, etc.)	48,49
	COVI-AMG (STI-2020)	Human mAb	-	RBD	With engineered Fc to reduce ADE	Phase 1/2 (NCT04734860, etc.)	-
	REGN14256	-	-	-	-	Phase 1/2 (NCT05081388)	-
	LY-CoV1404 (bebtelovimab)	Human IgG1	B cells of a convalescent pt	RBD	-	Phase 2 (NCT04634409)	50
	ABBV-47D11 (47D11)	Human IgG1	Immunized hulg mice	RBD	-	Phase 1 (NCT04644120)	51
	ABBV-2B04 (2B04)	Humanized IgG1	Immunized mice				52

(*Continued*)

Table 1. (Continued).

Name	Subtype	Origin/Platform	Target	Features	Clinical trial (ID)	Ref.
HFB30132A (P4A1-2A)	Human IgG4	B cells of convalescent pts	RBD	With engineered Fc to reduce ADE and increase half-life	Phase 1 (NCT04590430)	53
SAB-185	Polyclonal IgG	Hyperimmunized Tc-bovines	S	-	Phase 1 (NCT04468958, etc.)	54
HLX70	Human mAb	-	RBD	-	Phase 1 (NCT04561076)	-
DXP604	Human IgG	High-throughput single-cell sequencing of B cells from convalescent pts	RBD	-	Phase 1 (NCT04669262)	-
LY-CoVMab (CA521^{FALA})	Human IgG4	Immunized mice	RBD	-	Phase 1 (NCT04973735)	55,56
JMB2002	Human IgG1	Phage-to-yeast display	RBD	-	Phase 1 (ChiCTR2100042150)	57
CT-P63	Human IgG	-	RBD	-	Phase 1 (NCT05017168)	-
CR3022	Human IgG1	Phage display	RBD	A SARS-CoV-1-specific mAb	-	58
rRBD-15	Human IgG1	Phage display	RBD	-	-	59
311mab-31B5 311mab-32D4	Human IgG1	B cells of convalescent pts	RBD	-	-	60
B38, H4	Human IgG1	B cells of infected pts	RBD	-	-	61
BD-368-2	Human IgG1	High-throughput single-cell RNA and VDJ sequencing of B cells from convalescent pts	RBD	-	-	62
CA1/CB6	Human IgG1	B cells of a convalescent pt	RBD	-	-	63
ADI-55951, etc.	Human IgG	B cells of a convalescent pt	RBD	-	-	64
COVA1-18, etc.	Human IgG1	B cells of convalescent pts	RBD	-	-	65
CC12.1, etc.	Human IgG	B cells of convalescent pts	RBD	-	-	66
4A8	Human IgG	B cells of convalescent pts	NTD	-	-	19
2–15, etc.	Human IgG1	B cells of infected pts	RBD/NTD/others	-	-	20
EY6A	Human IgG	B cells of a convalescent pt	RBD	-	-	67
S2E12 S2M11	Human IgG	B cells of convalescent pts	RBD	Form a strong cocktail of S2E12 and S2M11	-	68
ab1	Human IgG1	Phage display	RBD	-	-	69
CoV-06 CoV-14	Human IgG1	Phage display	RBD	Form a cocktail of CoV2-06 and CoV2-14	-	70
ADG-2	Human IgG	B cells of a convalescent pt with SARS-CoV-1 infection and yeast display	RBD	Broad spectrum against multiple CoV family members	-	71
COV2-2676 COV2-2489	Human IgG1	B cells of convalescent pts	NTD	-	-	21
BI 767551 (DZIF-10c)	Human IgG1	HbnC3t1p1_F4, a mAb from convalescent pts	RBD	With the C-terminal heavy chain lysine removed	-	72
9–105, etc.	Human IgG	B cells of convalescent pts	RBD/NTD	-	-	73
h11B11	Humanized IgG4	Mouse	ACE2	-	-	74
WRAIR-2125, etc.	Human IgG1	B cells of convalescent pts	RBD/NTD	Potent neutralizing activity against all major SARS-CoV-2 variants	-	75
910–30	Human IgG1	B cells of a convalescent pt	RBD	-	-	76
hSARS2-02 hSARS2-38	Chimeric IgG1	Mouse	RBD	-	-	77

(*Continued*)

Table 1. (Continued).

Name		Subtype	Origin/Platform	Target	Features	Clinical trial (ID)	Ref.
	2–36	Human IgG1	B cells of infected pts	RBD	Cross-reactivity against SARS-CoV-1, SARS-CoV-2, and all current SARS-CoV-2 variants	-	20,78
	58G6, etc.	Human IgG	B cells of convalescent pts	RBD	-	-	79
	MW06	Human IgG1	B cells of a convalescent pt	RBD	Cross-reactivity against SARS-CoV-1 and SARS-CoV -2; form a cocktail with MW05 against SARS-CoV -2	-	80
	1H1, etc.	Rabbit IgG	Immunized rabbit	RBD	-	-	81
	ZRC3308-A7 ZRC3308-B10	Humanized IgG1	-	RBD	Form a cocktail named ZRC-3308	-	82
	IMM-BCP-01	-	-	S	A cocktail consisting of three antibodies with non-overlapping bindings	-	-
Cytokine and chemokine	Tocilizumab[a]	Humanized IgG1κ	Mouse	IL-6 R	EUA in USA	Phase 2/3/4 (NCT04317092, etc.)	83
	Levilimab	Human IgG1	-	IL-6 R	Approved in Russia	Phase 3 (NCT04397562)	84
	Olokizumab	Humanized IgG4κ	Rat	IL-6	-	Phase 2/3 (NCT04380519, etc.)	85
	Siltuximab	Chimeric IgGκ	Mouse	IL-6	-	Phase 2/3 (NCT04322188, etc.)	86
	Clazakizumab	Humanized IgG1	Rabbit	IL-6	-	Phase 2/3 (NCT04381052, etc.)	87
	Sarilumab	Human IgG1	-	IL-6Rα	-	Phase 1/2/3/4 (NCT04357808, etc.)	88
	MEDI3506	Human IgG1	-	IL-33	-	Phase 2 (EudraCT2020-001736-95)	89
	Secukinumab (AIN457)	Human IgG1κ	-	IL-17A	-	Phase 2/3 (NCT04403243, etc.)	90
	Ixekizumab	Humanized IgG4κ	Mus musculus	IL-17A	-	Phase 3 (NCT04724629)	91
	Canakinumab (ACZ885)	Human IgG1κ	-	IL-1β	-	Phase 2/3 (NCT04362813, etc.)	92
	F-652	IL-22:IgG2-Fc fusion protein	-	IL-22	-	Phase 2 (NCT04498377)	-
	Risankizumab	Humanized IgG1	Mouse	IL-23A	-	Phase 2 (NCT04583956)	93
	Gimsilumab	Human IgG1	-	GM-CSF	-	Phase 2 (NCT04351243)	94
	TJ003234	Humanized IgG1	-	GM-CSF	-	Phase 2/3 (NCT04341116)	94
	Mavrilimumab	Human IgG4λ2	Phage display	GM-CSF-Rα	-	Phase 2/3 (NCT04397497, etc.)	95
	Lenzilumab	Human IgG1κ	-	GM-CSF	-	Phase 2/3 (NCT04351152, etc.)	96
	Otilimab	Human IgG1	-	GM-CSF	-	Phase 2 (NCT04376684)	-
	Axatilimab (SNDX-6352)	Humanized IgG4	-	CSF-1R	-	Phase 2 (NCT04415073)	-
	Infliximab	Chimeric IgG1κ	Mouse	TNF-α	-	Phase 2 (NCT04425538, etc.)	97
	Adalimumab	Human IgG1κ	-	TNF-α	-	Phase 3 (NCT04705844)	-
	Bevacizumab	Humanized IgG1	Mouse	VEGF-A	-	Phase 2/3 (NCT04275414, etc.)	98
	Emapalumab	Human IgG1	-	IFN-γ	-	Phase 2/3 (NCT04324021)	99
	Leronlimab (PRO 140)	Humanized IgG4κ	Mouse	CCR5	-	Phase 2/3 (NCT04343651, etc.)	100
Complement	Ravulizumab	Humanized IgG2	Mus musculus	C5	-	Phase 3/4 (NCT04570397, etc.)	101
	Eculizumab	Humanized IgG2/4κ	Mouse	C5	-	Phase 2/3 (NCT04288713, etc.)	102
	Vilobelimab (IFX-1)	Chimeric IgG4	-	C5a	-	Phase 2/3 (NCT04333420)	103
	Avdoralimab	Human IgG1	-	C5aR1	With Fc silent	Phase 2 (NCT04371367, etc.)	104

(*Continued*)

Table 1. (Continued).

Name		Subtype	Origin/Platform	Target	Features	Clinical trial (ID)	Ref.
	NGM621	Humanized IgG1	-	C3	-	Phase 1/2 (NCT04582318)	-
Others	Itolizumab	Humanized IgG1κ	Mouse	CD6	Approved in India	Phase 2 (NCT04475588)	[105]
	Meplazumab	Humanized IgG2	-	CD147	-	Phase 1/2/3 (NCT04275245, etc.)	[106]
	CPI-006	Humanized IgG1	-	CD73	With FcγR deficient	Phase 1/3 (NCT04464395, etc.)	[107]
	Atibuclimab (IC14)	Chimeric IgG4κ	-	CD14	-	Phase 2 (NCT04391309, etc.)	-
	Monalizumab	Humanized IgG4κ	-	NKG2A	A checkpoint inhibitor	Phase 2 (NCT04333914)	[108]
	Nivolumab	Human IgG4	-	PD-1	-	Phase 2 (NCT04343144)	[109]
	Tilvestamab (BGB149)	Humanized IgG1κ	-	AXL	A candidate receptor for SARS-CoV-2	-	[110]
	Crizanlizumab	Humanized IgG2κ	-	SELP	-	Phase 2 (NCT04435184)	[111]
	Garadacimab (CSL312)	Humanized IgG4/λ	-	Factor XIIa	-	Phase 2 (NCT04409509)	-
	Glenzocimab	Humanized Fab	-	Platelet glycoprotein VI	-	Phase 2 (NCT04659109)	-
	hzVSF-v13	Humanized IgG4	Mouse	Vimentin	-	Phase 2 (NCT04676971, etc.)	[112]
	Lanadelumab	Human IgG1κ	-	Plasma kallikrein	-	Phase 1/2/3 (NCT04422509, etc.)	[113]
	Omalizumab	Humanized IgG1κ	Mouse	IgE	-	Phase 2 (NCT04720612)	[114]

ADE, antibody-dependent enhancement; CCR5, C-C chemokine receptor type 5; EU, European Union; EUA, Emergency Use Authorization; FcγR, Fc receptor γ chain; hulg, humanized immunoglobulin; mAb, monoclonal antibody; NTD, N-terminal domain; pt(s), patient(s); RBD, SARS-CoV-2 receptor-binding domain; S. Korea, South Korea; Ref., reference(s); Tc, transchromosomic; UK, United Kingdom.
[a]EUA, emergency use authorization.

Table 2. Neutralization of SARS-CoV-2 variants by the IgG antibodies with EUA or in clinical development.

Name	B.1.1.7	B1.1.7Δ8[a]	B.1.351	B.1.351Δ9[b]	P.1	B.1.617.2	B.1.617.1	B.1.427/ B.1.429	Ref.
Sotrovimab	–		–		–	–	–	–	9,11
Casirivimab	–	–	+++	++	++		–	–	8–10
Imdevimab	–	–	+	–	–		–	+	8–10
Casirivimab+Imdevimab	–	–	+	–	–		–		8–10
Bamlanivimab	–	–	+++	+++				+++	8,9
Etesevimab	–	+	+++	+++				+	8,9
Bamlanivimab+Etesevimab	–	+	+++	+++					8
BRII-196	–	–	–	–					8
BRII-198	–	–	+	+					8
BRII-196+BRII-198	–	–	–	–					8
VIR-7832	+		–		–	–	–		11
ABBV-47D11	+		+		+		++		10
ABBV-2B04	–		+++		+++		+++		10
AZD8895	–	–	+	+	–		–		8,10
AZD1061	–	–	–	–	–		–		8,10
AZD8895+AZD1061	–	–	+	–	–		–		8,10

Neutralization activities of mAb are ranked based on the fold changes (FC) of the 50% inhibitory concentration (IC_{50}) titers relative to the wild-type viruses, or the 50% effective concentration (EC_{50}). The FC(IC_{50})>1,000 or EC_{50} > 10,000 ng/ml is presented as '+++', indicating completely resistance of the mAb to the VOCs; the FC of 50< FC(IC_{50})≤1,000 or 1,000< EC_{50} ≤ 10,000 ng/ml is presented as '++', indicating partially resistance; the FC of 3< FC(IC_{50})≤50 or 200< EC_{50} ≤ 1,000 ng/ml is presented as '+', indicating little resistance; the FC(IC_{50})≤3 or EC_{50} ≤ 200 ng/ml is presented as '–', indicating non-resistance; the blank cell indicates data not available. Ref., reference(s).

[a]B1.1.7Δ8, pseudoviruses containing eight mutations of the B1.1.7 variant including ΔH69/ΔV70, Δ144, N501Y, A570D, P681H, T716I, S982A and D1118H.

[b]B.1.351Δ9, pseudoviruses containing nine mutations of the B.1.351 variant including L18F, D80A, D215G, Δ242-Δ244, R246I, K417N, E484K, N501Y and A701V.

Table 3. Overview of IgM and IgA antibodies against SARS-CoV-2.

Name		Type	Origin/platform	Target	Features	Clinical trial (ID)	Ref.
SARS-CoV-2	Trimodulin	Polyvalent IgM/ IgA/IgG composition	-	-	Composition of IgM (~23%), IgA (~21%) and IgG (~56%)	Phase 2 (NCT04576728)	121
	IgM-14 (IGM-6268)	Human IgM	CR3022 and five IgG1 mAbs (CoV2-06, CoV2-09, CoV2-12, CoV2-14, and CoV2-16)	RBD	An intranasal-delivered candidate with a broad coverage of SARS-CoV-2 variants	Phase 1 (NCT05160402, NCT05184218)	70,122
	dIgA	Human IgA	B cells of convalescent pts	RBD	Neutralization potency: dIgA>IgG>mIgA	-	123
	dIgA	Human IgA1	Two IgG1 mAbs: B38 and H4	RBD	Neutralization potency: dIgA>mIgA>IgG1	-	124
	mAb362	Human IgA1	Immunized huIg mice	RBD	Neutralization potency: sIgA>dIgA>mIgA>IgG	-	125

dIgA, dimeric IgA; huIg, humanized immunoglobulin; mAbs, monoclonal antibodies; mIgA, monomeric IgA; pts, patients; RBD, receptor-binding domain; Ref., reference(s); sIgA, secretory IgA.

phage display,[70] showed over 230-fold potency in neutralizing SARS-CoV-2 compared to its corresponding IgG version (IgG-14) (Table 3). Strikingly, IgM-14 was more potent than IgG-14 in neutralizing SARS-CoV-2 VOCs, including Alpha, Beta and Gamma variants, as well as 21 other RBD mutants, indicating that IgM-14 is superior to IgG-14 in covering viral escape mutations. In mice, IgM-14 not only conferred potent therapeutic protection against different variants but also displayed desirable pharmacokinetics and safety profiles when administered intranasally.[122] Therefore, two Phase 1 clinical trials of IgM-14 (also known as IGM-6268) were started very recently in healthy volunteers and patients with mild-to-moderate COVID-19.

Therapeutic IgA antibodies against SARS-CoV-2

Mucosal immune system is by far the largest component of the entire human immune system. Most viruses invade via mucosal sites (e.g., respiratory tracts) where sIgA plays an important role. For years, sIgA has been described as the predominant antibody and the first barrier against pathogens at mucosal sites. Importantly, IgA has been shown to exert neutralizing activities on multiple viruses, such as human immunodeficiency virus (HIV),[127] and influenza virus.[128] In addition, IgA also contributes to virus neutralization to a greater extent than IgG in COVID-19, and the neutralizing IgA remains detectable in saliva for a longer time,[129] suggesting a critical role of IgA during the early phase of SARS-CoV-2 infection.

It should be noted that the circulating IgA, even in polymeric form, cannot have the same protective effect as mucosal sIgA to limit infections. Indeed, dIgA derived from COVID-19 convalescent donors is more potent than mIgA and the corresponding IgG against the same target,[123] suggesting that dIgA is a more potent neutralizer than IgG. The same holds true in another *in vitro* setting (Table 3).[124] Nevertheless, more studies are urgently required to assess the safety and therapeutic effects of IgA-enriched products in preventing SARS-CoV-2 infection.

In 2020, the first human IgA mAb against SARS-CoV-2, named mAb362, was developed.[125] In particular, mAb362 showed cross-reactivity against the RBD of both SARS-CoV-1 and SARS-CoV-2, and competitively blocked ACE2 receptor binding. Notably, mAb362 as mIgA, dIgA and sIgA showed significantly enhanced potency in neutralizing SARS-CoV-2 pseudovirus compared to the IgG isotype. The most potent mAb362 sIgA also neutralized authentic SARS-CoV-2, whereas the IgG isotype did not, indicating effective mucosal immunity of sIgA antibodies against SARS-CoV-2 (Table 3). Interestingly, in patients with Selective IgA Deficiency (SID), the lack of neutralizing anti-SARS-CoV-2 IgA and sIgA antibodies represents a possible cause of COVID-19 severity, vaccine failure and prolonged viral shedding,[130] emphasizing the importance of IgA antibodies in mucosal immune responses upon SARS-CoV-2 infection.

Therapeutic bsAbs against SARS-CoV-2

Combining multiple IgG mAbs has been known to have a synergistic effect on neutralizing SARS-CoV-2 by targeting different epitopes of the RBD. For example, the combination of casirivimab and imdevimab has been granted EUA to treat mild-to-moderate symptoms of COVID-19 in high-risk patients. However, effects similar to those of mAb combinations can be achieved by a single bsAb, which have two distinct specificities and may have reduced time-consuming and expensive development (Figure 3a), as well as increased potency due to enhanced functional affinity. Use of bsAb may also decrease the likelihood of viral escape.[135,136]

The first bsAb against SARS-CoV-2 was constructed by linking non-neutralizing binders to neutralizing binders in a bispecific scaffold.[132] Specifically, the authors first identified Fabs that bind to the RBD but do not block ACE2 binding by phage display, and then they assembled them into a knob-in-hole (KIH) bispecific IgG scaffold with human-derived variable heavy (VH) binders that block ACE2, resulting in a VH/Fab bsAb (Figure 3b). Remarkably, these bsAbs showed 20- to 25-fold more potency in neutralizing pseudotyped and authentic SARS-CoV-2 than the mono-specific bivalent VH-Fc or IgG alone or even as a cocktail. The study was an attempt to target multiple epitopes, both neutralizing and non-neutralizing, within a single therapeutic molecule, providing a promising and rapid engineering strategy to improve the potency of SARS-CoV-2 antibodies.

Soon afterward, another study reported a human bispecific IgG1-like molecule CoV-X2 in a CrossMAb format (Figure 3c) on the basis of two neutralizing mAbs (C121 and C135) derived from convalescent COVID-19 patients.[38] CoV-X2 could simultaneously bind two non-overlapping RBD epitopes,

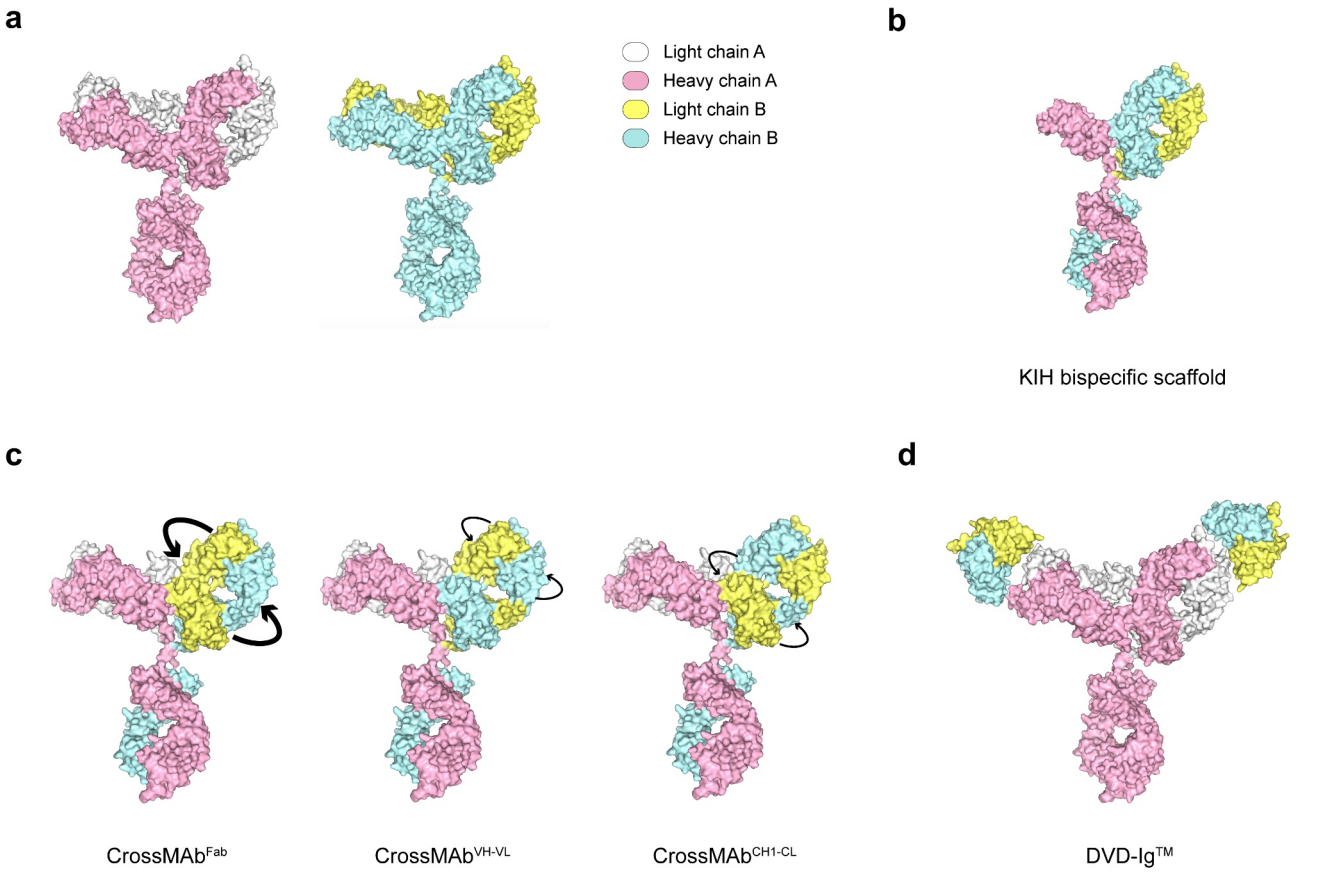

Figure 3. Structural models of bsAb formats used in SARS-CoV-2 infection.**Generation of bsAbs models, with different formats used in SARS-CoV-2 infection.** (a) Two IgG antibodies A and B (PDB code 1HZH)[15] are used to generate the structural models of bsAbs in different formats, including the knob-in-hole (KIH) bispecific scaffold, the CrossMAb format, and the DVD-Ig™ format, followed by manual adjustment. (b) The variable heavy (VH)-Fc from antibody A (knob) and the Fab-Fc from antibody B (hole) are assembled into a KIH bispecific IgG molecule.[132] (c) Two different heavy and two different light chains are assembled into a CrossMAb bispecific molecule, which involves creating hybrid molecules by crossing over the two domains making the Fab (left), or just swapping the variable domain (middle) or the first constant domain (right).[133] (d) The DVD-Ig™ molecule is a dual-specific tetravalent IgG-like molecule that contains two variable regions in each arm, an inner domain of antibody A and an outer domain of antibody B.[134]

and showed a broader coverage of SARS-CoV-2 variants, including the escape mutants generated by the parental mAbs; in a mouse model, CoV-X2 also protected mice from disease and suppressed viral escape.[135]

Very recently, Cho et al. reported five ultrapotent DVD-Ig bsAbs (Figure 3d) by combining non-overlapping specificities.[136] Of all the bsAbs that could neutralize authentic SARS-CoV-2, one bsAb, CV1206_521_GS, neutralized SARS-CoV-2 with more than 100-fold higher potency than a cocktail of its constituent antibodies. Further analysis revealed that CV1206_521_GS crosslinked NTD and RBD in adjacent S proteins, a mode of action that is unavailable to conventional mAbs even when used in combination. In addition, two other bsAbs showed the ability to neutralize SARS-CoV-2 VOCs, including Alpha, Beta, Gamma and Delta variants, at near wild-type potency. More importantly, one potent bsAb was effective against SARS-CoV-2 carrying a key variant mutation of E484K in the hamster model.[136] This finding provided a novel design of bsAb by targeting different epitopes to improve the potency in neutralizing SARS-CoV-2 variants.

Although antibody cocktails that target different regions of the S protein are still the main format for the treatment of SARS-CoV-2, the newly explored bsAbs can exert potent effects via distinct mechanisms of action that cannot be achieved by conventional mAbs. The details of the design and format of the above bsAbs are summarized in Table 4.

Challenges and future perspectives

The COVID-19 pandemic has caused unprecedented health and economic crises worldwide. Historically, it has also triggered unprecedented efforts to develop vaccines and efficacious treatments for the disease. Although several COVID-19 vaccines are being used, all of them are administered intramuscularly or subcutaneously, which might not always induce an effective mucosal immune response.[137–139] So far, no vaccine to boost mucosal immunity has been developed for SARS-CoV-2 infection. Therefore, the current challenge in vaccine design is to induce long-lasting systemic and mucosal protection against all SARS-CoV-2 variants, and the same is true for antibody-based therapies. In this case, intranasal administration of selected high-affinity polyreactive IgM or sIgA might be a promising approach for COVID-19.

Traditionally, IgM antibodies have proven difficult to express and purify due to their large size and complexity. Thanks to advances in manufacturing, engineered IgM antibodies such as IgM-14[33] can be produced with good quality, and it will be administered by intranasal and intraoral spray in clinical trials. In fact, several engineered IgM antibodies are being investigated in oncology clinical trials, and more than half of these IgM target antigens that are poorly immunogenic, which makes it difficult to generate IgG mAbs.[16] However, multivalent antibodies, like IgM, might have an off-target effects, resulting in low affinity, less specificity and unexpected toxicities. Nonetheless, the use of IgM is anticipated as an essential approach to defend against complex pathogen infections, especially viruses that are difficult to target.

In addition to IgM, specific IgA response has been considered for vaccine design since the 1960s. The rotavirus vaccine is recognized as a model system for the therapeutic potential of intestinal IgA in digestive viral infections.[140] Another example is the oral poliovirus vaccine, which induces strong specific IgA responses to neutralize distinct serotypes.[141] Apart from an oral route, nasal administration is another strategy to induce sIgA in respiratory tracts. For example, intranasal administration of influenza vaccines induces strong IgA responses in nasal mucus, which correlate with vaccine efficacy.[142,143] A very recent study also reported a single intranasal dose of SARS-CoV-2 vaccine candidate that induces potent IgA responses in hamsters.[144] Although vaccine-induced IgA responses have been largely considered, the development of neutralizing IgA antibodies in preventing viral infections is very limited compared to IgG mAbs. It is noteworthy that IgA antibodies have been reported to have anti-inflammatory roles by inhibiting complement activation mediated by IgM or IgG. In this case, intranasal immunization should be an effective means to generate sIgA responses in respiratory tracts where SARS-CoV-2 could be eliminated without inducing dysregulated inflammatory consequences.

Last, but not least, exploration of novel engineered bsAbs may offer great potential as a versatile alternative to conventional mAbs. In addition, single-domain antibodies (sdAbs) derived from variable heavy homodimer (VHH) domains of antibodies in camels or llamas will become a trend for the next-generation of antibody-based therapeutics in the future. sdAbs are typically a peptide consisting of only heavy chains that retain the full antigen-binding capacity as conventional

Table 4. Overview of bsAbs against SARS-CoV-2.

Name		Type	Origin/platform	Target	Features	Ref.
SARS-CoV-2	Bis1, etc.	Bispecific VH/Fab IgG	Phage display	RBD	Combination of non-neutralizing binders with neutralizing binders in a KIH bispecific scaffold	[132]
	CoV-X2	Bispecific IgG1	C121 and C135, two mAbs from B cells of convalescent pts	RBD	Combination of the variable regions of C121 and C135 in a CrossMAb format	[38,135]
	CV1206_521_GS, etc.	Bispecific IgG1	Plasmablasts and B cells of convalescent pts	RBD or RBD +NTD	Combination of the variable regions of two mAbs with a GS or EL linker in a DVD-Ig™ format	[136]

Fab, antigen-binding fragment; KIH, knob-in-hole; mAbs, monoclonal antibodies; NTD, N-terminal domain; pts, patients; RBD, receptor-binding domain; Ref., reference(s); VH, variable heavy.

antibodies.[145] The small size (~15 kDa) of sdAbs allows them to reach antigens that conventional mAbs cannot.[146] Other benefits of sdAbs include flexible formatting, rapid and low-cost development, high production efficiency, and easy administration via nebulized inhalation.[146,147] Although the small size of sdAbs leads to a rapid renal clearance, strategies to extend their half-life, such as conjugation to the Fc domain of a conventional antibody, have been used.[146] Humanized sdAbs targeting the RBD exhibit potent neutralization activity against both pseudotyped and authentic SARS-CoV-2, and fusion of the human IgG1 Fc to sdAbs further improves their neutralization activity by up to 10 times.[148] Reformatting sdAbs into multivalent constructs[149] or a bispecific format[150] makes them more potent to broadly neutralize SARS-CoV-2 variants. In this regard, sdAb represents a promising therapeutic agent for passive immunization against SARS-CoV-2.

In summary, a comprehensive understanding of all immune processes involved in SARS-CoV-2 infection will be required to fully control the pandemic. Future vaccine development should aim at inducing rapid and mucosal immune responses via different routes of administration, including but not limited to intranasal delivery, which may achieve desirable results beyond those with conventional vaccine administrations. In terms of antibody-based therapeutics, efforts should be made to develop IgM and IgA antibodies, as well as engineered bsAbs or cross-isotype molecules[151] against SARS-CoV-2.

Abbreviations

ACE2, angiotensin-converting enzyme 2; bsAb(s), bispecific antibody(ies); CCP, COVID-19 convalescent plasma; CDR, complementarity-determining region; CH, constant heavy; CL, constant light; COVID-19, coronavirus disease 2019; dIgA, dimeric IgA; EUA, Emergency Use Authorization; Fab(s), antigen-binding fragment(s); FcR, Fc receptor; HIV, human immunodeficiency virusIg, immunoglobulin; i.v., intravenous; IVIG, intravenous Ig preparation; J-chain, joining chain; KIH, knob-in-holem; Ab, monoclonal antibody; mIgA, monomeric IgA; NTD, N-terminal domain; PDB, protein data bank; pIgR, polymeric Ig receptor; RBD, receptor-binding domain; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SC, secretory componentsd; Abs, single-domain antibodies; SID, Selective IgA Deficiency; sIgA, secretory IgAS protein, spike glycoprotein; VH, variable heavy; VHH, variable heavy homodimer; VL, variable light; VOCs, variants of concern

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Contributions

JZ and HZ wrote the paper and made the figures and tables. HZ and LS designed the review and made corrections.

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