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# Neutralizing antibodies targeting SARS-CoV-2 spike protein

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## ABSTRACT

SARS-CoV-2 causing the worldwide pandemic has changed people's life in multiple aspects dramatically since it's first identified in Wuhan, China at the end of 2019. While the numbers of infected patients and death toll keep vigorous increasing, curbing the progression of the pandemic is an urgent goal. Efforts have been made to search for prophylactic and therapeutic approaches including neutralizing antibodies development. By reviewing dozens of studies on anti-spike antibodies identification, we concluded that (1) promising therapeutic antibodies are being fished out by various approaches, such as screening of single B cells of convalescent patients, recombinant antibody library and B cells of immunized animals; (2) the epitopes are mainly RBD, but also some non-RBD domains, without the requisite of overlapping with ACE2 binding sites; (3) Neutralizing antibodies are convergent to a few germline genes, including IGHV3-30, IGHV3-53, IGHV3-66, with varying levels of somatic mutations. This review summarizes the progress in neutralizing antibodies development and the germline enrichment of effective antibodies, which will shed light on COVID-19 treatment and vaccine design.

## 1. Overview of SARS-CoV-2

The pandemic outbreak of COVID-19 starting from the end of 2019, have led to a global disaster with over 71 million people confirmed infected and more than 1.6 million death around the world (<https://covid19.who.int/>), which does not seem to end in a short time yet. This unprecedented severe pandemic is caused by a beta coronavirus, highly conserved with the virus causing epidemic SARS in 2003, and now is designated as SARS-CoV-2 by WHO.

Same as SARS-CoV, SARS-CoV-2 utilizes the receptor angiotensin-converting enzymes 2 (ACE2) on host cells as the entry fusion receptor by its viral spike (Hoffmann et al., 2020; Zhou et al., 2020), while there are some different receptors for other coronavirus, like DPP4 for MERS-CoV (Hulswit et al., 2016). The receptor binding domain (RBD) on viral spike is required for the interaction with ACE2 which was well elaborated by delicate structure resolved (Yan et al., 2020; Wrapp et al., 2020; Tai et al., 2019). The viral spike (S) is a homo-trimer glycoprotein, with 1 monomer in "up" conformation for the binding of ACE2 and the other 2 in "down" conformation. Each S protein monomer consists of cleaved S1 subunit and S2 subunit (Fig. 1A). Entry of the virus into host cell is a finely regulated process, typically consists of three steps: (i) the RBD in S1 subunit make direct contact with the host cell receptor, ACE2 (Lan et al., 2020) (Fig. 1B). (ii) S1 will be shed after binding to ACE2. Then the fusion peptide (FP) located in S2 subunit initiates membrane fusion

by inserting into cell membrane, allowing heptad repeat 1 (HR1) and heptad repeat 2 (HR2) of S2 to refold and form a post-fusion conformation and drives membrane fusion of the viral and target cell (White et al., 2008). Although some reports demonstrated cleavage of S protein prior to binding to ACE2 is essential for the infection of SARS-CoV, it seems not necessary for SARS-CoV-2 but still influential to the cell entry efficiency (Hoffmann et al., 2020; Shang et al., 2020; Bestle et al., 2020). (iii) Deliver the viral genetic material inside the cell for replication and reproduction of new virus particles (Millet and Whittaker, 2018).

Different approaches that hold back the above three steps could be effective drug development strategies. Neutralizing monoclonal antibodies are supposed to block the binding of virus to ACE2 on host cells (step 1). S protein of virus, especially the binding domain RBD could be the key drug target (Renn et al., 2020). Agents designed for prevention in the membrane fusion step includes the pan-coronavirus fusion inhibitor EK1 and its derivate EK1C4. These peptides target the HR1 domain and effectively inhibit the infection of SARS-CoV-2 authentic virus, as well as several other human coronaviruses (Xia et al., 2020). Inhibitors such as mAbs or EK1 mentioned above targeting the first two steps could have good prophylaxis and treatment usage (Xia et al., 2019; Baum et al., 2020). In the third step, other targets like 3C protease, RNA-dependent RNA polymerase (RdRp) are vital for antiviral drugs development, especially suitable for small molecules inhibitor but not ideal for therapeutic antibodies which generally only target extracellular or

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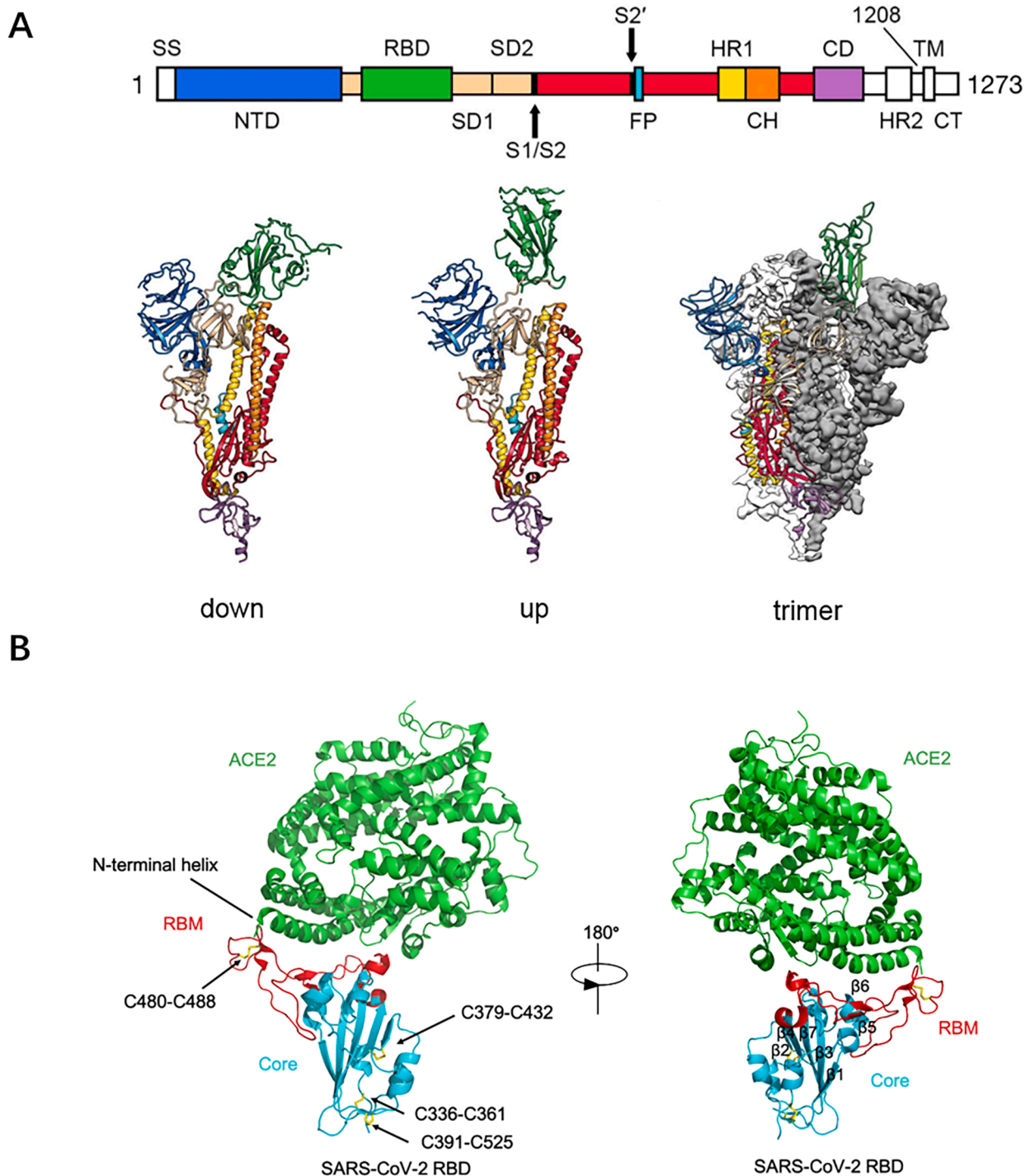
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membrane components. Remdesivir, the only one authorized drug targeting SARS-CoV-2, is an inhibitor of viral RdRp initially developed against Hepatitis C virus and then Ebola and Marburg virus. Now it was shown to relieve SARS-CoV-2 patients' symptoms (Wang et al., 2020; Sanders et al., 2019) and approved for treatment of COVID-19 in USA, Europe and Japan.

Although few drug specific to SARS-CoV-2 is approved to the market, amount of pharmaceutical studies for COVID-19 exploded in this area

due to the global concern of the coronavirus. Vaccine maybe the most promising reagent to be quickly developed to the market to deal with the situation effectively now, which is mainly for the epidemic prevention and control. However, vaccines are not 100% protective, due to the decline of vaccination by some people or unsuccessful immunization by which people will not always develop appropriate antibodies after inoculation (Cohen, 2020). Fundamental foundation of vaccine is the response ability of human adaptive immune system to the pathogens,



**Fig. 1.** Schematic of spike structure and relevance to ACE2 binding. This figure is adapted from Wrapp et al. (2020) and Lan et al. (2020). (A) Schematic of spike structure of SARS-CoV-2 colored by domain and side views of spike of SARS-CoV-2. SS: signal sequence, S2': S2' protease cleavage site, FP: fusion peptide, HR1: heptad repeat 1, CH: central helix, CD: connector domain, HR2: heptad repeat 2, TM, transmembrane domain, CT: cytoplasmic tail. Arrows denote protease cleavage sites. (B) Overall structure of the SARS-CoV-2 RBD bound to ACE2. ACE2 - green; RBD core - cyan; RBM - red; disulfide bonds - sticks and indicated by arrows. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

essentially neutralizing antibodies induced by pathogenic antigens. On the other hand, therapeutic antibody can be developed in parallel, mainly for individual protection and treatment of infected patients. Therefore, therapeutic antibodies have some unique advantages as a passive immune therapy approach.

In this mini review, we focus on the development of therapeutic monoclonal Abs (mAb), especially targeting the spike protein of SARS-CoV-2 in COVID-19. This could contribute to the understanding of COVID-19 pathology, host immunity to coronavirus, prevention and control strategy, vaccine development, and drug development.

## 2. Potential Ab drugs derived from convalescent patients and germline distribution

When coronavirus including SARS-CoV-2 infection happens, the body's adaptive immune system can learn to recognize new, invading pathogens. Serving as an important component of adaptive immunity, B cells generate antibodies that can block the virus from infecting cells, as well as mark the virus for destruction, and these humoral antibodies last for more than 2 weeks for future protection (Callaway, 2020; Ma et al., 2020). Thus making recombinant neutralizing antibodies isolated from SARS-CoV-2 convalescent patients to be the most rapid and readily manufacturable immune intervention for either prevent or treat COVID-19 disease (Sempowski et al., 2020).

At early outbreak of the pandemic, owing to the inspiration of treatment of SARS, MERS with convalescent serum, serotherapy was encouraged for the treatment on continuous deteriorated, severe SARS-CoV-2 patients, in the lack of medicine specific to COVID-19 (Chen et al., 2020). In March, the first reported study includes a trial of 5 critically ill patients transfused with high titer SARS-CoV-2 neutralizing antibody (IgG) containing plasma, and all patients exhibited improvement in clinical status, thus got the proof of concept for therapeutic antibody targeting SARS-CoV-2 (Shen et al., 2020). In another study recruiting a cohort of 10 severe SARS-CoV-2 patients, inactivated convalescent plasma infusion shows safety and good tolerance, as well as improvement of clinical symptoms within a week post-infusion (Duan et al., 2020). However, these convalescent sera based therapies are not suitable for quality controllable, homogeneous, consistent, and production scalable therapeutic agents for widespread use. Besides that, the standard convalescent plasma (CP) therapy needs random controlled trails to determine the optimal timing and indication for CP therapy (Duan et al., 2020). Recombinant neutralizing monoclonal antibodies (mAbs) either isolated from convalescent patient's memory B cells or screening from a humanized antibody library are appropriate potential drugs for general use.

Due to the homology between spike protein of SARS-CoV and SARS-CoV-2, protection ability of antibodies induced by one was analyzed on the other for identification of broad neutralizing antibodies (Wec et al., 2020). On February, Ying's group in Fudan University reported that among several antibodies found in 2006 from a convalescent SARS patient, one antibody, CR3022 could efficiently bind to SARS-CoV-2 spike and be a potential therapeutic agent for COVID-19 (Tian et al., 2019). Later, scientists from Vir Biotechnology company in Switzerland reported several mAbs identified from a 2003 SARS survivor's memory B cells, among which mAb S309 potentially neutralizes authentic SARS-CoV-2 with an  $IC_{50}$  of 79 ng/ml. S309 recognizes a highly reserved glycan-containing epitope in S-RBD but does not compete with receptor attachment, could be further use in combination with other antibodies for prophylaxis and therapy of SARS-CoV-2 infection (Pinto et al., 2020).

To get potential therapeutic antibodies, many efforts were made to isolate monoclonal antibodies from B cell pools of COVID-19 survivors, and then validate the inhibition effect one by one. At the end of April, scientists from Chongqing, China reported 2 human mAbs from SARS-CoV-2 recovered patients, the two antibodies effectively block the binding of RBD to human ACE2, and potentially inhibit pseudovirus infection with  $IC_{50}$  of 0.03–0.04  $\mu$ g/mL (Chen et al., 2020). Notably,

they found that all the 26 recovered patients have generated anti-RBD antibodies, however, there are only 3 out of 26 patients showed effective blockade of SARS-CoV-2 RBD binding to hACE2. Later, a joint research in China utilized recombinant RBD of SARS-CoV-2 S proteins as bait to sort specific memory B cells from peripheral blood mononuclear cells (PBMCs) of a COVID-19 convalescent patient and identified two potent neutralizing antibodies CA1 and CB6 ( $0.036 \pm 0.007$   $\mu$ g/mL for real virus infection in VERO cells). CB6 was also shown to inhibit authentic SARS-CoV-2 infection in rhesus monkey model. Further structure study reveals that CB6 competes with ACE2 for binding epitope on RBD, and shows 100 times higher binding affinity than ACE2 (Shi et al., 2020). By using similar method, another joint study got two ACE2 competing monoclonal antibodies B38 and H4 ( $IC_{50} = 1.967$   $\mu$ g/mL, 3.684  $\mu$ g/mL, B38 + H4, 0.3  $\mu$ g/mL, to real virus, respectively) from one convalescent patient, these two mAbs can reduce virus titers in infected lungs of a mouse model; since the two mAbs have different binding epitopes on RBD, they exhibit synergetic neutralizing ability and largely decrease the rate of immune escape in therapy (Wu et al., 2020). Emilie et al. identified 45 monoclonal antibodies by using spike protein as bait from a COVID-19 infected subject 21 days after the onset of disease, and found that these antibodies underwent minimal somatic mutation with limited clonal expansion. They also addressed that the majority of antibodies against the viral spike generated during the first week of infection are non-neutralizing and targets epitopes outside the RBD, while two antibodies disrupt the SARS-CoV-2 S&ACE2 interaction and potentially neutralize the virus without undergoing extensive maturation (Seydoux et al., 2020).

Later, more studies using similar strategy isolated anti-spike RBD antibodies from more than one convalescent patients. By isolating single B cells from eight patients who recovered from mild to severe symptoms, Ju et al. reported 206 antibodies specifically binding to SARS-CoV-2's RBD, antibody germline analysis indicates that each patient appears to have unique repertoire distribution patterns when response to SARS-CoV-2 infection, they also found that competition with ACE2 rather than binding affinity seems better predicts antibody's neutralizing potency. Three antibodies from patient #2 neutralize live SARS-CoV-2 potentially with  $IC_{50}$  from 0.03 to 0.41  $\mu$ g/mL, further crystal structural study revealed that the antibodies sterically inhibit the ACE2 receptor binding to CoV-2's RBD (Ju et al., 2020). Andreano et al. from Italy found 17 neutralizing antibodies from 7 COVID-19 patients (Andreano et al., 2020). Wan, Xing et al. from China isolated 8 antibodies which can be used as paired antibodies to potentially block infection of authentic virus with  $IC_{50}$  of 0.45 nM (Wan et al., 2020).

To race up process of neutralizing antibodies identification, single B cell sorting combined with high-throughput single cell RNA and VDJ sequencing technique was adopted to fish out antibodies from convalescent patients by Sunney Xie's team. The technique could not only analyze VDJ sequences enrichment situation but also help link the antibodies to specific B cell types from a heterogeneous population, they identified 8,558 antigen-binding clones and found the most potent one, BD-368-2 shows high therapeutic and prophylactic efficacy in SARS-CoV-2-infected mice (Cao et al., 2020). Rapid antibody discovery platform coupled single-B-cell antibody gene sequencing with high-throughput IgG isolation and screening assays was also established by Seth et al. from USA, they used different subdomains of SARS-CoV-2 S protein as antigen for antibody isolation. Most neutralizing mAbs identified are found to be RBD targeted, and more intriguing, the antigen-specific B cells were from the patients who are 50 days after onset, rather than 35/36 days, indicating the additional maturation of the memory B cell response occurred later in the additional 2 weeks of convalescence (Zost et al., 2020). Seth et al. further reported that passive transfer of the potent neutralizing RBD-targeting antibodies COV2-2196 or COV2-2130 (with  $IC_{50}$  of 15, 107 ng/mL to authentic virus, and 0.7, 1.6 ng/mL to pseudovirus, respectively) alone or in combination protected mice from SARS-CoV-2 virus infection, and each of the antibody shows protection in rhesus macaques (Zost et al., 2020). In addition to

adopting the single-cell sequencing technique, researchers from the Scripps Institute rapidly completed antibodies selection and validation in two weeks by combining high-throughput antibody generation pipeline with a rapid antibody characterization assay. Briefly, they sorted 3,160 spike binding memory B cells from a cohort of convalescent people and constructed an expression pool for selection, the antibodies activity were tested based on both live replicating and pseudovirus neutralization assays established in parallel. This rapid process made them discover multiple highly potent neutralizing antibodies (pseudovirus inhibition IC<sub>50</sub>: as low as 1 ng/mL) capable of providing protection against high-dose live virus challenge in Syrian hamsters (Rogers et al., 2020). It is noteworthy that they reported that the production of SARS-CoV-2 pseudotype virus by truncation of 18/28 residues containing an ER-Golgi retrieval signal sequence in the cytosolic tail of spike protein to facilitate the virus shedding from the cells.

Nearly all the neutralizing antibodies isolated from convalescent patients bind to RBD of spike protein. However, researchers in AMMS, China, isolated a potent neutralizing antibody 4A8 that targeting the N-terminal domain on spike, structure of which was determined by cryo-EM and mechanism of conformational restraining was also proposed by the authors (Chi et al., 2020). In accordance with this finding, Philip et al. from Netherlands isolated monoclonal antibodies from 3 convalescent COVID-19 patients, they reported these antibodies had low levels of somatic hypermutation and showed a strong enrichment in VH1-69, VH3-30-3 and VH1-24. Two antibodies, 1-18 and 2-15 showed extremely high potency with the IC<sub>50</sub> of neutralizing virus infection at about 8 ng/mL. EM study reveals that antibody 2-15 has a stoichiometry of 3:1 to each S protein trimer, rather than 1:1, and binds S protein monomer in both “up” and “down” conformations, that maybe partially explains the extreme high potency. Another neutralizing antibody, 1-21 binds non-RBD region of the S protein and does not block ACE2. The authors proposed that its binding out of RBD could interfere the conformational change induced by ACE2 so that it disrupts the subsequent steps required by virus entry (Brouwer et al., 2020). Later in July, Lihong et al. from USA reported 19 potent neutralizing antibodies targeting multiple epitopes, nearly half of these mAbs binding to NTD. By picking out 5 of 40 patients' plasma samples with highest neutralizing abilities for single B cells sorting, they got the potent mAbs with 50% virus-inhibitory concentration of 0.7–9 ng/mL (Wang et al., 2020). Besides, Xiaoniu et al. of Biotheus Inc. developed a biparatopic protein by combining the spike NTD-targeting mAb 89C9 with ACE2 ectodomain for passive immune therapy. The engineered molecule shows potent inhibition to both S-pseudovirus and authentic virus, while the IC<sub>50</sub> to pseudotyped virus is below 100 pM, about 100-fold more potent than ACE2-Fc itself. The special class of hybrid antibody-receptor design may offer the potential to treat COVID-19 (Miao et al., 2020). Interestingly, researchers from Regeneron Pharmaceuticals screened fully human antibodies from 3 SARS-CoV-2 convalescent patients and their humanized mice model, and identified pairs of highly-potent individual antibodies that simultaneously bind the RBD of spike protein. The so called therapeutic antibody cocktail REGN-COV-2 (REGN10987 + REGN10933) is promising to decrease the potentials for virus escape. They also showed that the predominant lineage of humanized mice antibodies utilized VH3-53, while the human-derived antibodies adopted VH3-66 and VH2-70 germlines (Hansen et al., 2020). At the beginning of August, the efficacy of the cocktail REGN-COV-2 was evaluated in both rhesus macaques and golden hamsters. The team reported REGN-COV-2 greatly protects animals from infection by reducing virus load in lower and upper airway and decreases virus induced pathological sequelae when administered prophylactically or therapeutically (Baum et al., 2020). Researchers from USA enrolled 149 convalescent patients, most plasma samples collected do not contain high levels of neutralizing activity, however rare but recurring RBD-specific antibodies with potent antiviral activity were identified in all individuals tested (Robbiani et al., 2020). They identified three potent antibodies from 5 patients whose plasma shows strongest neutralizing abilities, the antibodies

show IC<sub>50</sub> to authentic virus less than 5 ng/mL. In March, policies and public health efforts have not addressed the gendered impacts of disease outbreaks, so the response to coronavirus disease 2019 (COVID-19) appears no different. Due to the socioeconomic status of females and their front-line interaction with communities, scientists call on governments and global health institutions to consider the sex and gender effects of the COVID-19 outbreak (Wenham et al., 2020). The above study clearly provided important information when considering the immune response and outcome from SARS-CoV-2 infection.

It is worth noting that, Christoph et al. analyzed the longitudinal and dynamic antibody response of SARS-CoV-2 infection from 12 recovered patients from 8 to 69 days after diagnosis, and demonstrate that SARS-CoV-2 neutralizing antibodies are readily generated from a diverse pool of precursors, with low levels of somatic mutations (Kreer et al., 2020). By comparing the antibodies germlines from convalescent patients and healthy donors, they found that IGHV3-30 was overrepresented in recovered patients, and the IGHV3-30 facilitated kappa over lambda chains (Fig. 3A). Moreover, they found that 11 of the 28 neutralizing antibodies demonstrated germline identities of 99%–100%, with no correlation detected between neutralizing activity and the level of somatic mutation, and the somatic hypermutation frequency is independent of the time of B cell isolation. What surprises researchers is that potential SARS-CoV-2 binding and neutralizing antibodies precursor sequences were found in some healthy donors, indicating low level somatic mutations are needed for neutralization ability. Consistently, by solving 8 structures of distinct COVID-19 human neutralizing antibodies & spike trimer/RBD complexes, Christopher et al. inferred minor contributions of antibody somatic hypermutations to epitope contacts (Barnes et al., 2020). In contrast to the antibodies from convalescent patient, in our lab, three potent SARS-CoV-2 neutralizing antibodies were screened from a combinatorial naïve library established 20 years ago. Furthermore, a high level of somatic hypermutation (up to 15 amino acids per molecule) was found for all three antibodies, many of which are involved in specific interactions revealed by crystal structures with SARS-CoV-2 spike RBD (Qiang et al., 2020).

### 3. Pharmaceutical antibodies developed by other methods

Although antibodies from infected people are naturally “human-derived” with expected less immunogenicity, which is an important factor in therapeutic antibody development, they are not always induced by a “correct” epitope on virus so as not to have the potential neutralizing efficacy or the ability to avoid virus escape by mutation. Therefore, besides discovery of neutralizing antibodies from infected population, some other efforts were also made, such as isolating antibodies from immunized animals or selection of antibodies from libraries *in vitro*, against rationally designed antigens, usually peptides of critical epitopes in the S-RBD of SARS-CoV-2. Sometimes competitive selection strategies were also employed to facilitate the finding of desired antibodies.

#### 3.1. Immunization of animals or library panning

Immunization of mice produces mouse-derived antibodies which need subsequent humanization. However, humanized mice produce antibodies already with human antibody germline region sequences. A cooperative work led by Frank Grosveld and Berend-Jan Bosch discovered a SARS-CoV and SARS-CoV-2 cross-active antibody, 47D11 through immunization of H/L variable region humanized mice H2L2, reformatting to human Fc later (Wang et al., 2020). In order to get cross-active antibodies, the immunization strategy is sequential immunization with ectodomain of S protein of different coronavirus: HCoV-OC43, SARS-CoV, MERS-CoV and a second round again (but without that of SARS-CoV-2). After ELISA screening, antibody clone 47D11 shows cross-neutralizing ability to both SARS-CoV and SARS-CoV-2 with K<sub>D</sub> value of 0.745 nM and 10.8 nM respectively. Apart from mouse immunization,

other animals were used, too. Pan et al. have developed an antibody by immunization of horse with S-RBD of SARS-CoV-2. Then F(ab')<sub>2</sub> fragment was harvested by removal of equine Fc instead of fusion to human Fc. *In vivo* results in mouse and horse showed inhibitory effects on SARS-CoV-2 with EC<sub>50</sub> at 0.07 µg/mL and EC<sub>80</sub> at 0.18 µg/mL (Pan et al., 2020).

Considering that antibodies derived from different approaches like animal immunization or convalescent patients may possess distinct targeting mechanisms, combination of them could achieve synergistic effect. A study from University of Maryland School of Medicine supported by Regeneron Pharmaceuticals, Inc. reported the cocktail of a pair of antibodies, one from immunized genetically-humanized mice, and the other from a human survivor (Hansen et al., 2020). Antibodies targeting viral spike from B cells derived from mice and human were collected and screened via binding and pseudotyped virus neutralization assay and finally validated by pseudotyped and authentic SARS-CoV-2 virus infection. After that, cross-competition binding assay was utilized to get a pair of most potent antibodies, REGN10933 and REGN10987. This combination simultaneously bind different epitopes on S-RBD without competition, proposed to provide ideal partners which could decrease the likelihood of virus escape mutants (Baum et al., 2020).

To screen antibody library *in vitro* is an alternative approach to get the therapeutic antibodies with mature germline. It could not only save the hybridoma steps but also provide a platform for a variety of selection strategies to realize different purposes. Mouse immunization with SARS-CoV RBD followed by phage panning with SARS-CoV-2 RBD as antigen against the enriched antibody library from the former immunized mouse was used to select antibodies with cross-reactivity by Lv et al. (2020). This is a combination of animal immunization and antibody library screening as well as S-RBD of two SARS viruses. Finally, one potent antibody, H014 was selected with the neutralizing capacity for both SARS-CoV and SARS-CoV-2 pseudotyped virus and authentic SARS-CoV-2 virus in hACE2 mouse model with IC<sub>50</sub> of nanomolar level. Structure of the spike trimer in complex with the Fab resolved by Cryo-EM characterization unveiled that the antibody only binds the RBD in open conformation.

For human antibody library screening, many efforts have been done mainly on naïve or so-called pre-pandemic antibody libraries, among which S-RBD is most widely used as the biopanning antigen due to its key role in the interaction with ACE2 (Zeng et al., 2020; Bertoglio et al., 2020; Wang et al., 2020). Antibody library in various types such as single chain (scFv) antibody library, single domain antibody library, Fab antibody library, etc. were employed for selection (Qiang et al., 2020; Wang et al., 2020) when competition screen with ACE2 was a common selection strategy adopted (Zeng et al., 2020).

Bertoglio et al. reported SARS-CoV-2 neutralizing antibodies selected from a library constructed from healthy people. They emphasized the “pre-pandemic” concept that universal libraries from healthy donors offer the advantage of quick acquirement of candidates free from the limitation of patients’ material accesses (Bertoglio et al., 2020). Liu et al. screened single chain (scFv) antibody library as well as single domain antibody library (named domain antibody in the paper) by 4 rounds of site-directed phage panning against RBD of SARS-CoV-2 (Liu et al.,). Finally, they got 1 antibody (4A3) and 3 single domain antibodies (4A12, 4D5, and 4A10) with high affinity and potential of neutralizing to both pseudotyped virus and authentic virus infection. All of them have the affinity of nanomolar level. Zeng et al. screened blocking antibodies against S-RBD using a competitive panning strategy. Inhibition of SARS-CoV-2 pseudovirus infection is at IC<sub>50</sub> values of 12 nM (Zeng et al., 2020).

Wang et al. acquired a panel of potential SARS-CoV-2 neutralizing antibodies screened from a combinatorial Fab phage display library. The antigen used for screen is S-RBD and a mechanism-based screening strategy that contains a well-designed competition ELISA was adopted (Wang et al., 2020). Among the selected neutralizing Fabs, the most

attracting one is a monovalent Fab clone 5A6 which could bind both “up” or “down” conformations of S protein via different binding sites in the antibody revealed by the structural analysis. Since one spike protein complex is a trimer comprised of both “up” and “down” monomers and a full-length IgG is a dimer of monovalent Fab, one IgG could bind to two RBDs while a second IgG binds to the remaining RBD as well as an RBD of another spike trimer. This property makes each spike trimer accommodate 1.5 full-length IgG thus two spike proteins could be bridged by an IgG molecule. This explains the extraordinarily high avidity and neutralizing capacity of 5A6. Moreover, the authors also showed a method to deal with virus escaping by combination of two mutation-insensitive antibodies, 5A6 and 3D11.

### 3.2. Single-domain antibody screening

Antibody from some animals like camelid or shark is comprised of heavy chains only which contains only one variable domain (VHH) followed by a CH2-CH3 fragment. Single-domain antibodies also called nanobodies are kinds of engineered proteins based on the variable region of heavy chain-only antibodies, usually from llamas. Single-domain antibodies are much smaller to get to some regions where access of big molecule antibody is limited. Generally they are more likely to fit a site well with high affinity. Single-domain antibodies from a llama were reported to be developed by immunization with pre-fusion-stabilized coronavirus spikes (Wrapp et al., 2020). Crystal structures of the complex of the single-domain antibodies and antigen were determined to find two distinct epitopes and a conserved mechanism of neutralization. Bivalent form of the single-domain antibodies showed some cross-reactivity of neutralization on SARS-CoV and SARS-CoV-2 pseudotyped viruses. In another cases, S1-Fc and S-RBD of SARS-CoV-2 were taken as antigen for immunization to get an alpaca derived single-domain antibody (Hanke et al., 2020). The structure of this antibody-RBD epitope complex was resolved by cryo-EM at 2.9 Å resolution which revealed that the nanobody directly blocks the binding sterically.

Single-domain antibodies could also be screened from constructed VHH libraries besides animal immunization, too. Research group in Peking Union Medical College discovered a panel of single-domain antibodies by phage panning of VHH library against S-RBD. The best K<sub>D</sub> of these single-domain antibodies is sub-nanomolar. It showed neutralization effect on both pseudotyped and authentic SARS-CoV-2 virus infection (Robbiani et al., 2020). Huo et al. produced two closely related single-domain antibodies using a naïve llama VHH library and PCR-based maturation, H11-D4 and H11-H4, both of which target the same epitope (Huo et al., 2020). Walter et al. constructed 3 synthesized nanobody libraries named sybody, displayed on phages and ribosomes and screened against S-RBD of SARS-CoV-2. Finally 5 sybodies were got to inhibit the binding of S-RBD with human ACE2 (Walter et al., 2020).

The VHH format library from animals could also be “human-derived” by methods similar to antibody humanization. Human germline region could be the framework for grafting sequences to get VHH libraries of human origin. Wu et al. constructed a humanized VHH library by grafting naïve CDRs into framework regions of human IGHV alleles. Through phage panning *in vitro*, they obtained single-domain antibodies showing affinities of sub-nanomolar and a certain ability to neutralize pseudotyped virus (Long et al., 2020). Ab Studio Inc. also reported several single-domain antibodies from two humanized llamas’ antibody libraries. Afterwards, the single-domain antibodies were selected and improved by *in silico* approach and finally fused to Fc. Furthermore, they combined distinct VHHs pairwise to get bi-specific antibodies among which one showed synergistic blocking with K<sub>D</sub> of 0.25 nM and IC<sub>95</sub> of 12.2 nM (Anderson et al., 2020).

By the end of Nov. 2020, there are many candidates proceeding to the human clinical trials, with 7 already in phase 3. The first is Ly-CoV555 from AbCellera partnered with Eli Lilly, which began in March. Also Lilly with Junshi agreed to co-develop an antibody, JS016 for treatment of COVID-19. This is the antibody reported isolated from

convalescent patient (Shi et al., 2020) which now also enters phase 1 clinical study. Another promising ones are from Vir Biotechnology Inc.'s partnership with GlaxoSmithKline plc and Regeneron Pharmaceuticals Inc. Many others are also getting promising results in the trials, detailed in Table 1 below.

#### 4. Recombinant ACE2 protein as therapeutic agent targeting S protein

Inspired by the advantage and success of neutralizing IgG antibodies, scientists also did some engineering to ACE2 to get ACE2-Fc fusion for neutralizing application. The host receptor for the viral spike is ACE2, which binds S protein with a high affinity. It is not surprising that administration of exogenous ACE2 may effectively compete with native ACE2 on cell surface to block the subsequent fusion steps. Monteil et al. demonstrated *in vitro* that human recombinant soluble ACE2 (*hrsACE2*) could inhibit growth of authentic SARS-CoV-2 in Vero cells as well as in engineered human blood vessel organoids and human kidney organoids (Monteil et al., 2020). A mutational landscape analysis of human ACE2 was performed by means of deep mutagenesis selection strategy against a mutational library in order to understand the interaction between host receptor and viral S as well as to engineer a decoy ACE2 with high affinity for competing native ACE2 binding of S (Chan et al., 2020). Finally, the authors revealed the critical sites for virus binding and got a soluble ACE2 mutants named sACE2.v2.4 with significantly increased affinity as a candidate for the treatment of COVID-19.

Meanwhile, Lei et al. presented a *hACE2* ectodomain as well as a *hACE2* mutant ectodomain with low catalytic activity in order not to

disturb the natural physiological process. It is fused with Fc of IgG1 with high affinity to S-RBD of SARS-CoV-2, and the ability to neutralize SARS-CoV-2 pseudotyped virus *in vitro* (Lei et al., 2020). However on the other hand, recombinant ACE2 proteins in different forms retaining the original enzymatic activity sometimes could provide benefits such as reduced vasoconstriction and increased healthy blood flow to infected lung tissue of patients with advanced COVID-19 disease. A clinical trial of soluble ACE2 with enzymatic activity for the treatment of SARS by GSK is at phase II stage (NCT01597635) (Khan et al., 2017).

Sorrento Therapeutics, Inc. designed a bi-specific fusion protein, ACE-MAB with two functional arms. One arm (Ab) is a fully human antibody that targets the spike protein of SARS-CoV-2 with high affinity. The other arm (TR) is a truncated ACE2 protein that binds to a different epitope of the spike protein. The ACE-MAB fusion protein could also block the binding of S-RBD with CD147 to mitigate lung inflammation and cytokine storm.

#### 5. Summary and discussion

In summary, hundreds of thousands of SARS-CoV-2 neutralizing mAbs have been successfully isolated from convalescent patients, immunized animals or phage-displayed human antibody libraries established in pre-pandemic period.

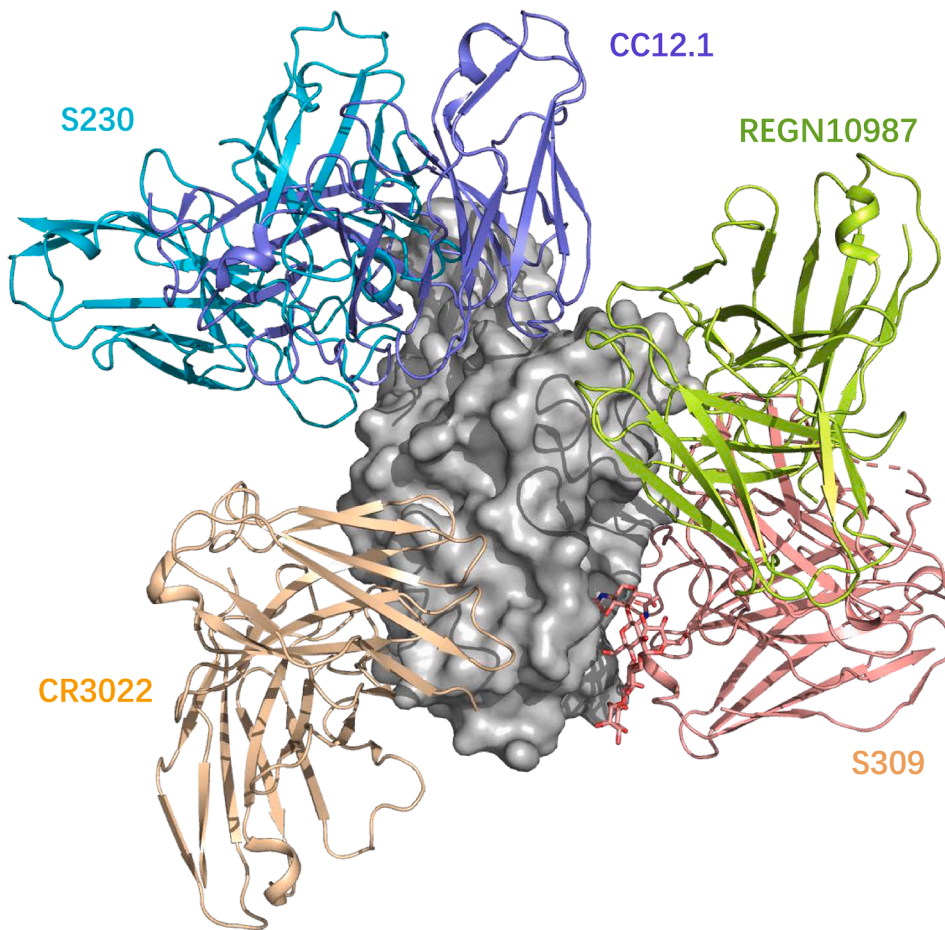
Structural studies looked into the epitope of these effective antibodies derived from different IGHV germline genes revealed that majority of the antibodies binds to RBD of spike protein (Fig. 2), while some of antibodies were found targeting non-RBD regions in S1 subunit, such as NTD of spike (Chi et al., 2020), meanwhile none of the antibodies

**Table 1**  
mAbs against SARS-CoV-2 in clinical studies <sup>a</sup>.

Sponsors	Drug code	Status	Trial ID	Est. start	Est. primary completion
Junshi/Eli Lilly	JS016 LY3832479 LY-CoV016	Phase 2	NCT04441918; NCT04441931; NCT04427501	6/5/2020; 6/19/2020;	Dec 2020; 10/2/2020;
Tychan Pte.	TY027	Phase 1	NCT04429529	6/9/2020	Oct 2020
Brii Biosciences	BRII-196	Phase 1	NCT04479631	7/12/2020	Mar 2021
Brii Biosciences	BRII-198	Phase 1	NCT04479644	7/13/2020	Mar 2021
Sinocelltech	SCTA01	Phase 1	NCT04483375	7/24/2020	Nov 2020
Sorrento Therapeutics	COVI-GUARD (STI-1499)	Phase 1	NCT04454398	9/17/2020	Feb 2021
Mabwell Bioscience	MW33	Phase 1	NCT04533048	8/7/2020	Dec 2020
HiFiBio Therapeutics	HFB30132A	Phase 1	NCT04590430	Oct 2020	July 2021
Ology Bioservices	ADM03820	Phase 1 pending	NCT04592549	11/16/2020	Aug 2021
Hengenix Biotech	HLX70	Phase 1 pending	NCT04561076	12/9/2020	Sep 2021
U. Cologne/Boehringer Ingelheim	DZIF-10c	Phase 1/2 pending	NCT04631705; NCT04631666	11/23/2020; 11/23/2020	6/30/2021; 6/30/2021
Sorrento Therapeutics	COVI-AMG (STI-2020)	Phase 1/2 pending	NCT04584697	Dec 2020	April 2021
Beigene	BGB DXP593	Phase 1 Phase 2 pending	NCT04532294; NCT04551898	8/31/2020; 10/30/2020	10/15/2020; 2/28/2021
AstraZeneca	AZD7442 (AZD8895 + AZD1061)	Phase 1 Phase 3 pending	NCT04507256; NCT04625725; NCT04625972	8/17/2020; 11/17/ 2020; 11/16/2020	Sep 2021; 7/31/2021; 6/16/2021
Celltrion	CT-P59	Phase 1 Phase 2/3	NCT04525079; NCT04593641; NCT04602000	7/18/2020; 9/4/2020; 9/25/2020	Nov 2020; 12/23/2020; Dec 2020
Vir Biotechnol/ GlaxoSmithKline	VIR-7831/GSK4182136	Phase 2/3	NCT04545060	8/27/2020	Jan 2021
AbCellera/Eli Lilly	LY-CoV555 (LY3819253) LY-CoV555 + LY-CoV016 (LY3832479)	EUA <sup>b</sup>	NCT04411628 (Phase 1) NCT04427501 (Phase 2) NCT04497987 (Phase 3) NCT04501978 (Phase 3) NCT04518410 (Phase 2/ 3)	5/28/2020 6/13/2020 8/2/2020 8/4/2020 Aug 2020	8/23/2020; 9/15/2020; 3/8/2021; July 2021; Nov 2020
Regeneron	REGN-COV2 REGN10933 + REGN10987	EUA <sup>b</sup>	NCT04425629 (Phase 1/ 2) NCT04426695 (Phase 1/ 2) NCT04452318 (Phase 3)	6/16/2020 6/10/2020 7/13/2020	12/19/2020; 1/25/2021; 6/15/ 2021

a. [antibodysociety.org/covid-19-biologics-tracker/](https://antibodysociety.org/covid-19-biologics-tracker/).

b. Emergency Use Authorization granted by US FDA.



**Fig. 2.** Variety of epitopes of antibody CR3022, S309, REGN10987, CC12.1 and S230 on spike RBD. Superimposition of RBD with five antibodies belong to different germ lines was shown, RBD is displayed in surface representation and antibodies are shown in ribbons. The structure used for superimposition of CR3022 (wheat color, IGHV5-51) and S309 (red color, IGHV3-30) glycan is shown in sticks. Both REGN10987 (limon color, PDB 6XDG) and S230 (cyan color, PDB 6NB7) are antibodies of IGHV3-30 germline, and binds to different motif of RBD. Another antibody CC12.1 (slate color, PDB 6XC2) of germline IGHV3-53 binds to similar epitope with that of S230.

targeting S2 subunit shows neutralizing potency (Ravichandran et al., 2020). The multiple uncovered epitopes, especially these conserved sites, like the glycan-containing epitope of S309 provide important information for SARS-CoV-2 spike protein based vaccine design or broad human coronavirus neutralizing agent development (Pinto et al., 2020).

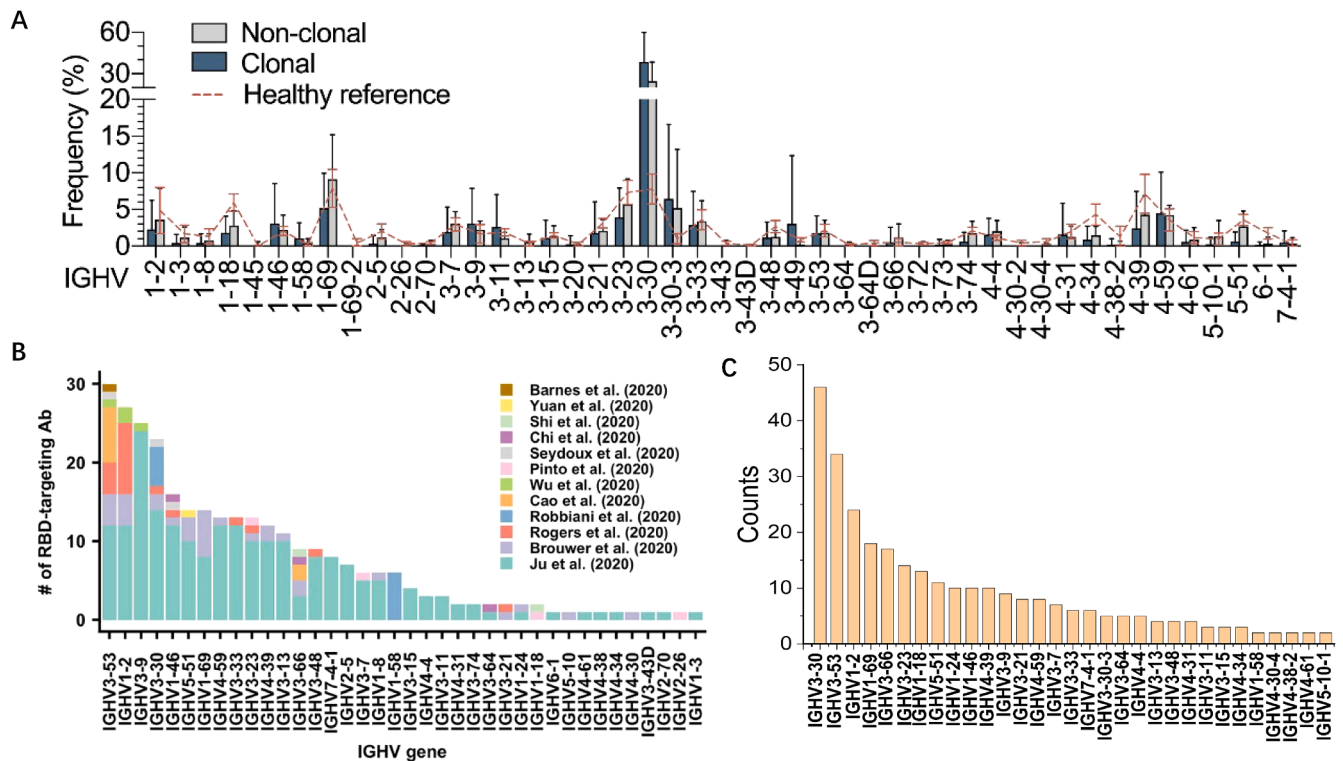
Of note, potentially neutralizing antibodies always show high-affinity to RBD, indicating a positive correlation between neutralization ability and binding affinity (Kreer et al., 2020). It was also reported that highly potent neutralizing antibodies recognize specific viral epitopes and block viral entry into host cells, whereas poorly neutralizing antibodies or antibodies with low affinity can promote entry and spread of virus upon secondary infection, resulting in increased viral burden and more severe disease progression through antibody-dependent enhancement (ADE) (Renn et al., 2020; Halstead, 2007; Diamond and Pierson, 2015). ADE can occur through two distinct mechanisms during viral infections, one is ADE via enhanced infection mediated by FcγRIIIa expressed on monocytes and macrophages, and the other is ADE via enhanced immune activation, which is caused by excessive Fc-mediated effector functions and immune complex formation (Lee et al., 2020). ADE should be avoided in the development of therapeutic antibodies targeting spike. The low-affinity antibodies or poorly neutralizing antibodies which might be produced after vaccine injection should also be considered during vaccine design. Other efforts to diminish ADE is to introduce LALA mutation in the Fc part of IgG1 (Renn et al., 2020) or adopt the IgG4 format (Qiang et al., 2020) for neutralizing antibodies development. Nanobodies or antibodies in Fab format with no Fc part have the natural advantage of avoiding ADE.

Looking into the germ lines of the SARS-CoV-2 neutralizing antibodies could reveal the immunological repertoire responding to the emergency situation where time is short as occurs. In 2011, Professor

Richard A. Lerner wrote in a review that “the VH1-69 germline gene may have evolved as an ‘emergency’ response element of the immunological repertoire against the influenza virus”, where he proposed the concept of S.O.S. component describing these first responders inside the immunological repertoire under emergency situations. The discovery of the so called S.O.S. antibody repertoire may have significance for the design of novel vaccines (Lerner, 2011). We wondered whether there is also a S.O.S. antibody repertoire after SARS-CoV-2 infection. After reviewing the literatures, we concluded that the IGHV3-30 is probably the S.O.S. component (Kreer et al., 2020), meanwhile, other germ lines including IGHV3-53, IGHV1-2, IGHV3-66, IGHV1-69 are among the top five antibody repertoires that produce the neutralizing antibodies (Fig. 3).

As we reviewed in the above part, Christoph and colleagues analyzed the longitudinal response of SARS-CoV-2-infected people by recruiting 12 COVID-19 patients from 8 to 69 days after diagnosis, and compared the IGHV spectrum of COVID-19 patients with 48 healthy individuals, found that the IGHV3-30 was markedly overrepresented and clone expanded in COVID-19 convalescent patients (Fig. 3A) (Kreer et al., 2020), thus we speculate that the IGHV3-30 germline is the S.O.S. component for SARS-CoV-2 infection. Although there are other reports summarized the germ lines of 294 SAR-CoV-2 neutralizing antibodies targeting RBD from 12 published papers, it shows IGHV3-53, IGHV1-2, IGHV3-9, IGHV3-30, IGHV1-46 are the top five germ lines of neutralizing antibodies, 3-30 is the fourth one (Yuan et al., 2020) (Figure 3B). However, over 200 Abs were from one literature of Ju et al. which might introduce a bias conclusion for the results. Hence, we analyzed the germline distribution of ~300 SARS-CoV-2 antibodies derived from 23 papers from the CoV-AbDab Database sponsored by University of Oxford due to June 20, 2020 (the website is <http://opig.stats.ox.ac.uk/webapps/covabdab/#collapseOne>). As shown in Fig. 3C, the





**Fig. 3.** IGHV germline distribution of SARS-CoV-2 spike-targeting antibodies. (A) Christoph (Kreer et al., 2020) reported the frequencies of VH gene segments of clonal and non-clonal sequences from all 12 COVID-19 patients, NGS reference data from 48 healthy individuals (collected before the outbreak of SARS-CoV-2) are depicted in red line. Bar and line plots show as mean  $\pm$  SD. (B) IGHV distribution of 294-RBD targeting antibodies from 12 literatures, analyzed by Yuan et al. (2020). (C) IGHV distribution of about 300 SARS-CoV-2 binding antibodies reported in the public database (<http://opig.stats.ox.ac.uk/webapps/covabdb/#collapseOne>) were analyzed, the data was due to June 20/2020. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

histogram represents the frequencies of SARS-CoV-2 binding antibodies of each germline, and the top 5 germlines are: IGHV 3–30, IGHV3-53, IGHV 1–2, IGHV1-69 and IGHV3-66, while the IGHV3-30 is the most enriched germline, consistent with the report of Christoph. More than one paper mentioned that limited somatic mutation occurs in these neutralization antibodies, indicating the change of a few amino acids (3–4) is enough to endow the neutralization ability, which is also reasonable for the antibody maturation in B cell during the acute process of virus infection.

As we described in this mini-review, a fruitful antibody development pipeline are under process driven by a close collaboration between academia and industry. Some of the neutralizing antibodies show quite promising result *in vitro*, *in vivo* and also in clinical trials, with seven of the antibodies (combination) are now in clinical trials. It is hopeful that we human being will succeed in combatting the SARS-CoV-2 pandemic by using these antibodies and vaccines. Additionally, since vaccines are rarely 100% effective and many people may decline a vaccine or skip immunization for other reasons, while vaccine trails need longer time for the person to develop appropriate antibodies (Cohen, 2020), therapeutic antibodies have some unique advantages compared to vaccines. Recombinant mAbs are (i) suitable for all the people in need, regardless of the immunological response rate induced by vaccines; (ii) The efficacy of neutralizing antibodies have been validated before administering and there is no extra antibodies that binds to NP protein or non-neutralizing antibodies; (iii) High binding affinity and potency decrease the concerns about ADE effect due to low affinity. In conclusion, therapeutic antibodies which can neutralize the SARS-CoV-2 is an unreplaceable approach for curbing and vanishing the SARS-CoV-2 spread.

### CRedit authorship contribution statement

**Shi Xiaojie:** Writing - original draft, Conceptualization. **Li Yu:** Writing - original draft. **Yan lei:** Visualization, Software. **Yang Guang:** Supervision. **Qiang Min:** Writing - original draft, Conceptualization.

### Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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