Review article

COVID-19 antibody therapeutics tracker: a global online database of antibody therapeutics for the prevention and treatment of COVID-19

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Abstract

Facing the COVID-19 global healthcare crisis, scientists worldwide are collaborating to develop prophylactic and therapeutic interventions against the disease. Antibody therapeutics hold enormous promise for the treatment of COVID-19. In March 2020, the Chinese Antibody Society, in collaboration with The Antibody Society, initiated the "COVID-19 Antibody Therapeutics Tracker" ("Tracker") (https://chineseantibody.org/ covid-19-track/) program to track the antibody-based COVID-19 interventions in preclinical and clinical development globally. The data are collected from the public domain and verified by volunteers on an ongoing basis. Here, we present exploratory data analyses and visualization to demonstrate the latest trends of COVID-19 antibody development, based on data for over 150 research and development programs and molecules included in the "Tracker" as of 8 August 2020. We categorized the data mainly by their targets, formats, development status, developers and country of origin. Although details are limited in some cases, all of the anti-SARS-CoV-2 antibody candidates appear to target the viral spike protein (S protein), and most are full-length monoclonal antibodies. Most of the current COVID-19 antibody therapeutic candidates in clinical trials are repurposed drugs aimed at targets other than virus-specific proteins, while most of these virus-specific therapeutic antibodies are in discovery or preclinical studies. As of 8 August 2020, eight antibody candidates targeting the SARS-CoV-2 S protein have entered clinical studies, including LY-CoV555, REGN-COV2, JS016, TY027, CT-P59, BRII-196, BRII-198 and SCTA01. Ongoing clinical trials of SARS-CoV-2 neutralizing antibodies will help define the utility of these antibodies as a new class of therapeutics for treating COVID-19 and future coronavirus infections.

Statement of Significance: The Chinese Antibody Society, in collaboration with The Antibody Society, developed the "COVID-19 Antibody Therapeutics Tracker" to provide free and open access to a global database for tracking ongoing preclinical and clinical development of antibody-based therapeutics for prevention and treatment of COVID-19 during the pandemic in a timely manner.

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INTRODUCTION

The recent outbreak of COVID-19 has grown from a public health emergency to a major global pandemic. COVID-19 is caused by the coronavirus SARS-CoV-2 (1,2). As of 8 August 2020, there are 19 481 330 confirmed cases and 723 599 deaths worldwide with 188 countries affected (https://coronavirus.jhu.edu/map.html). As the COVID-19 pandemic is emerging as a global healthcare crisis, scientists worldwide are actively developing prophylactic and therapeutic interventions. Antibody therapeutics are being developed for the treatment of COVID-19 (3). To provide a service platform for the global endeavor against the pandemic with our expertise, the Chinese Antibody Society, in collaboration with The Antibody Society, developed the "COVID-19 Antibody Therapeutics Tracker" ("Tracker") (https://chineseantibody.org/covid-19-track/) to track the antibody-based COVID-19 therapeutics in preclinical and clinical development worldwide in a timely manner.

ESTABLISHMENT OF THE "TRACKER"

The data included in the "Tracker" are collected from resources in the public domain by volunteers from The Antibody Society and the Chinese Antibody Society on an ongoing basis. As shown in Table 1, as a first approach, the data are collected from a variety of sources, including published literature, preprints, company websites, biotech newsfeeds, social media, government databases and summarized. To reduce the amount of the manual work, when possible, an automatic process is being developed and integrated to retrieve data from online databases such as ClinicalTrials.gov by command-line tools (4). For example, to construct queries based on the Application Programming Interface (API) tool of ClinicalTrials.gov, query uniform resource locator (url) for all study records (i.e. "full studies url") was used as the base query and supplied with additional parameters, including a search expression string containing search fields, values and logical operators for search and filtering. Two versions of such queries were built and embedded in a Python script that iteratively sends requests for every 100 hits until all hits are exhausted. Returned hits from both queries, in JavaScript Object Notation format, were further processed by the Python script for manual inspection to ensure relevancy. Relevant entries were then logged into an SQLite database indexed by NCTID (unique study ID). When updating the database, the NCTID of a returned hit will be compared with that of existing entries in the database. If it does not exist in the database, it will be flagged for manual review and if relevant, it will be entered into the database. Otherwise, its clinical phase will be updated automatically. An example of our script with a detailed explanation for usage can be found in the Github repository (https://github.com/xinyu-dev/cas-covid-mab-tracker). Therapeutics programs based on non-antibody proteins with the similar mechanisms of actions as antibodies, such as recombinant ACE2 protein and Fc-fusion proteins, are also included. Unrelated information such as diagnostic antibodies, polyclonal plasma from convalescent patients and clinical trials without specific indications to COVID-19 patients in the experimental design,

were excluded. For quality evaluation, all the final data included in the "Tracker" were cross-verified manually by at least two independent volunteers. For presentation in the "Tracker," we categorized the following data: target, molecular format, development status, developer, country of origin and the supporting reference.

To build the "Tracker," the data table containing filtered results was uploaded to the website of the Chinese Antibody Society, which was build using WordPress. We used WPDatatable Plugin to integrate the data table from backend to front end of the webpage. On our "Tracker" website, the whole dataset was displayed as an interactive table and grouped by the categories we defined above. We also performed analysis and visualization based on the key features of the collected antibody therapeutic data that are most relevant to the scientific community and general public. These include the numbers of therapeutic targets, formats and program development status of the antibody therapeutics. In addition, we plotted the distribution of program development status by country to track the progress of COVID-19 antibody therapeutics programs globally.

DATA ANALYSIS

To further elaborate the function of the "Tracker," we performed data visualization and analysis based on the key features of the collected antibody therapeutic data, including antibody targets, formats and development status.

Antibody targets

Neutralizing antibodies are critical components in host immune responses to viral pathogens (3). As an enveloped single-strand RNA virus, SARS-CoV-2 enters into a human cell through its spike (S) protein binding to angiotensin-converting enzyme 2 (ACE2) (5,6). The structures of SARS-CoV-2 S protein trimer (7) and human ACE2 (8) show that the receptor-binding domain (RBD) on the SARS-CoV-2 S protein S1 subunit directly contacts with human ACE2 (8). Therefore, the S protein, in particularly the RBD or the S1 subunit, is the primary target for most neutralizing antibodies.

As shown in Fig. 1A, the "Tracker" is currently tracking 153 programs and molecules for COVID-19 interventions from discovery to regulatory agency authorization. Among these, 89 target the SARS-COV-2 S protein as antiviral interventions by blocking virus entry. Most of the anti-SARS-COV-2 antibodies were isolated from single memory B cells derived from convalescent patients or immunized transgenic animals.

Regeneron Pharmaceuticals Inc. (Regeneron) used both approaches to isolate antibodies that bind distinct and non-overlapping epitopes on the monomeric RBD of the spike protein with high affinity (K_D = 0.56 to 45.2 nM) (9). These antibodies have potent neutralization activities against pseudoviral particles or live virus with IC_{50} values of 1–10 pM (10). Using an in vitro assay, they found escape mutants were not generated following treatment with a cocktail composed of non-competing antibodies. Regeneron is developing two of their antibodies as the cocktail

Table 1. Procedures of building the COVID-19 antibody therapeutics tracker

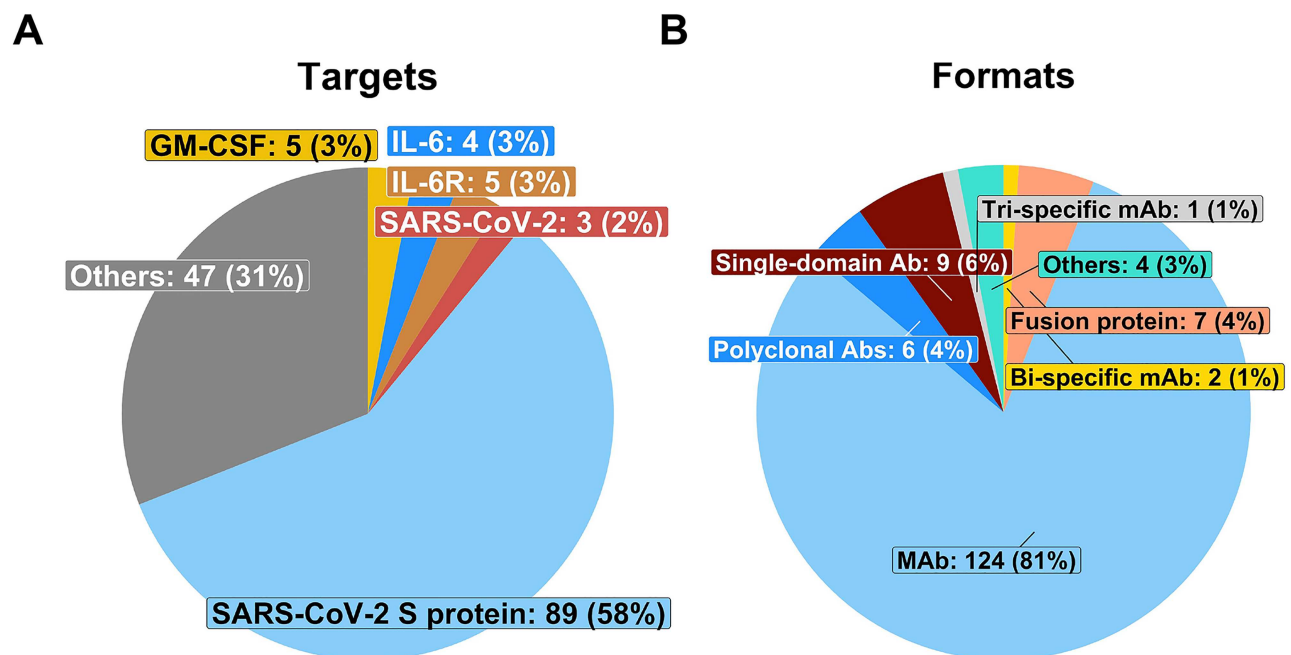| Step 1	Data Acquisition	Source: public domains Method: 1) Entries from search engines, company websites, biotech news feed, social media and government databases were collected. 2) When an API tool is available, such as in the case of ClinicalTrials.gov, Python scripts developed in-house were used for automatic querying and retrieval
Step 2	Filtering and validation	Filtering: entries describing preclinical or clinical development of diagnostic antibodies, polyclonal antibodies, convalescent plasma therapies, immune globulin intravenous therapies, small molecules and recombinant proteins other than immunoglobin (Ig), Ig fragments and Ig fusion proteins were removed from our collection. Studies and clinical trials without explicitly stating COVID-19 or SARS-CoV-2 as their indication or target were also eliminated. Filtering was performed manually unless an API tool was available, in which case, it was performed by the Python scripts mentioned above Validation: validation of each entries that we retained in our collection is performed manually, by inspecting and cross-validating using multiple sources if possible
Step 3	Data analysis	Data analysis was performed, and statistics on key aspects, such as drug targets, format and clinical status were generated using R and Python
Step 4	Data visualization	Interactive table and charts published on our website (chineseantibody.org) were generated using WPData Table, a commercial plug-in for WordPress. Static table and charts used for this publication were generated using R
Step 5	Update and Maintenance	New data are being collected, analyzed and published on our website on a weekly basis

Figure 1. Analysis of targets and formats of the therapeutics under development for COVID-19. (A) Targets of therapeutic antibodies under development for treating COVID-19. SARS-CoV-2 represents the targets that are SARS-CoV-2 virus specific but unspecified. Only the top five targets by amounts are shown, the rest were populated in "Others," such as IL-1, IL-12, IL-17, C5, C5a, PD-1, 4-1BB, P-selectin, etc. (B) The formats for therapeutics under development for treating COVID-19. MAb represents the conventional full-length IgG, including the chimeric Abs. Polyclonal Abs represents purified polyclonal Abs from immunized transgenic animals or transiently transfected cells, which originally derived from swine, transgenic cow, ostrich, avian and human. "Others" include one non-antibody recombinant protein (rhACE2), and DARPin, mRNA-encoding mAb and radiotherapeutic formats. The number of programs for each target and format are shown, followed by the proportion to the total number of all programs in paraphrase. Figure 1 is based on "Tracker" data as of 8 August 2020.

Table 2. Summary of the eight SARS-CoV-2 S specific programs in clinical trials

Name	Target	Format	Status	Developer	Country	ClinicalTrials.gov Identifier
REGN-COV2 (REGN10933 + REGN10987)	SARS-CoV-2 S protein	mAb	Phase 1/2/3	Regeneron/NIAID	USA	NCT04425629 NCT04426695 NCT04452318
LY3819253 (LY-CoV555)	SARS-CoV-2 S protein	mAb	Phase 1/2	AbCellera/Eli Lilly	Canada/USA	NCT04427501
JS016	SARS-CoV-2 S protein	mAb	Phase 1	Junshi Biosciences/Institute of Microbiology, Chinese Academy of Sciences/Eli Lilly	China/USA	NCT04441918
TY027	SARS-CoV-2 S protein	mAb	Phase 1	Tychan	Singapore	NCT04429529
CT-P59	SARS-CoV-2 S protein	mAb	Phase 1	Celltrion	South Korea	Not available
BRII-196	SARS-CoV-2 S protein	mAb	Phase 1	Brii Bio/TSB Therapeutics/Tsinghua University/the 3rd People's Hospital of Shenzhen	China/USA	NCT04479631
BRII-198	SARS-CoV-2 S protein	mAb	Phase 1	Brii Bio/TSB Therapeutics/Tsinghua University/the 3rd People's Hospital of Shenzhen	China/USA	NCT04479644
SCTA01	SARS-CoV-2 S protein	mAb	Phase 1	Sinocelltech Ltd/Chinese Academy of Sciences	China	NCT04483375

treatment REGN-COV2 (REGN10933 + REGN10987) (Table 2).

In another study, groups from the Chinese Academy of Sciences in Beijing and Junshi Biosciences in Shanghai reported two human antibodies (CA1 and CB6) that have been isolated from a convalescent COVID-19 patient using single B cell sorting and cloning techniques (11). The human antibodies showed potent neutralization activity in vitro against SARS-CoV-2 with IC_{50} of 0.036 ± 0.007 μg/mL (0.24 ± 0.047 nM) for CB6 and 0.38 μg/mL (2.53 nM) for CA1. Structural analysis revealed that CB6 is an ACE2 blocker that recognizes an epitope overlapping with the ACE2-binding site on the RBD of the SARS-CoV-2 spike protein. The LALA mutation was introduced to the Fc portion of CB6 (CB6-LALA) to lower the risk of Fc-mediated acute lung injury in animals. CB6-LALA was shown to inhibit SARS-CoV-2 infection in rhesus monkeys in both prophylactic and treatment settings. In this study, rhesus monkeys (3 per treatment and control group) were challenged with 1×10^5 50% tissue culture infectious dose ($TCID_{50}$) SARS-CoV-2 via intratracheal incubation, and then either CB6-LALA (50 mg/kg) or an equal volume of phosphate-buffered saline was administered at days 1 and 3 postinfection (dpi) intraperitoneally. In the control group, viral loads reached peak levels on 4 dpi, then declined naturally.

In contrast, CB6-LALA treatment reduced virus titers immediately after administration. On 4 dpi, CB6-LALA reduced the viral titer by approximately 3 logs compared to that of the control group. In the prophylactic group, a single dose of CB6-LALA (50 mg/kg) before SARS-CoV-2 challenge significantly protected the animal from SARS-CoV-2 infection. Currently, CB6-LALA (also called JS016) has been developed for clinical testing (Table 2).

COVID-19 invokes a hyperinflammatory state driven by multiple cells and mediators like interleukin (IL)-1, IL-6, IL-12, IL-17, IL-18, IL-22 and IL-33, tumor necrosis factor, granulocyte-macrophage colony-stimulating factor and complement (C5, C5a). Considering the proven role of cytokine dysregulation in causing this hyperinflammation, especially in the lungs, existing drugs targeting these mediators are being repurposed for the treatment of COVID-19 (12). As shown in Fig. 1A, 61 of the molecules included in the "Tracker" were developed to target the host immune system for other indications but were repurposed to treat COVID-19 by potentially alleviating COVID-19-related symptoms, such as cytokine storm and inflammation, instead of directly killing the viruses. For example, the IL-6 inhibitors levilimab, tocilizumab, sarilumab, olokizumab and siltuximab are being tested against COVID-19 (12–14).

Antibody formats

As shown in Fig. 1B, over 81% of these antibody therapeutics are in conventional full-length IgG-based monoclonal antibody format (but IgM/IgA, IgY-based therapeutics are also being developed), and the rest are in bi- or tri-specific antibody, single-domain antibody, polyclonal antibody, fusion protein or other formats (e.g. DARPin, mRNA-encoding mAb, radiotherapeutics, IgM/IgA). Among the eight antibody therapeutics in clinical trials that specifically target SARS-CoV-2 S protein, all are conventional human monoclonal antibodies (mAbs), with Regeneron's REGN-COV2 comprising a two-antibody cocktail. REGN-COV2's two antibodies bind non-competitively to the critical RBD of the virus's spike protein, which may diminish the ability of mutant viruses to escape treatment and protect against spike variants that have arisen in the human population (10). More recent research has also demonstrated protection coverage against the now prevalent spike protein D614G variant (15).

Five programs focus on the development of polyclonal antibodies that specifically target SARS-COV-2. For example, SAB-185 is generated by immunized transgenic cows using a proprietary DiversitAb platform, which was claimed to be more consistent and easier to scale up than convalescent plasma from recovered COVID-19 patients (https://www.sabbiotherapeutics.com/2020/04/24/behind-sabs-rapid-response-to-covid-19/). Nine programs are in single-domain antibody format, derived from phage display library, synthetic antibody library or immunization. rRBD-15 from the competitive biopanning of the synthetic antibody library competitively blocks the binding of RBD to ACE2 and inhibits SARS-CoV-2 pseudovirus infection with IC_{50} values of 12 nM (16). Two bi-specific and one tri-specific antibodies under development target both the virus and/or the host immune system, including SARS-CoV-2/NKp46 (https://www.globenewswire.com/news-release/2020/04/07/2012885/0/en/CYTOVIA-Therapeutics-and-MACROMOLTEK-to-Develop-Dual-Acting-Natural-Killer-Immunotherapy-Against-SARS-CoV2-COVID-19.html), VEGF/IL-6 (https://kodiak.com/press-releases/kodiak-sciences-announces-first-quarter-2020-financial-results-and-recent-business-highlights/) and CD16/SARS-CoV-2 (https://www.gtbiopharma.com/news-media/press-releases/detail/182/gt-biopharma-and-cytovance-biologics-announce-collaboration%7C%7CGT%20Biopharma). Fusion protein and other formats, such as DARPin, mRNA-encoding mAb, radiotherapeutics, are also being tested for the treatment of COVID-19.

Antibody development status

Among the programs and molecules we are tracking, over 60% are in discovery and preclinical stages (Fig. 2A), including the majority of those that specifically target the SARS-CoV-2 S protein via blocking viral entry. Eight antibody candidates targeting the SARS-CoV-2 S protein have entered clinical studies, including LY-CoV555 (Eli Lilly/AbCellera, two clinical trials in Phase 1 and 2), REGN-COV2 (Regeneron, three clinical trials in Phase 1/2/3), JS016 (Eli Lilly/Junshi Biosciences, clinical trial in Phase 1), TY027 (Tychan, clinical trial in Phase 1), CT-P59 (Celltrion, clinical trial in Phase 1), BRII-196 and BRII-198 (Brii Bio/TSB Therapeutics/Tsinghua University/the 3rd People's Hospital of Shenzhen, clinical trial in Phase 1) and SCTA01 (Sinocelltech Ltd/Chinese Academy of Sciences, clinical trial in Phase 1) (see detailed information in the "Tracker" and Table 2).

Lilly scientists developed LY-CoV555 (also called LY3819253) in just 3 months after AbCellera and the Vaccine Research Center at the National Institute of Allergy and Infectious Diseases (NIAID) at the National Institutes of Health (NIH) isolated a B cell from a blood sample taken from one of the first US patients who recovered from COVID-19 (Table 2). In early June 2020, LY-CoV555 became the world's first SARS-CoV-2 specific antibody therapy to enter a clinical trial for the prevention and treatment of COVID-19 (Table 2). Regeneron initiated a late-stage clinical trial evaluating REGN-COV2 for the treatment and prevention of COVID-19 in late June 2020. This Phase 3 trial will evaluate REGN-COV2's ability to prevent infection among uninfected people who have had close exposure to a COVID-19 patient (such as the patient's housemate). REGN-COV2 has also moved into the Phase 2/3 portion of two adaptive Phase 1/2/3 trials testing the cocktail's ability to treat hospitalized and non-hospitalized (or "ambulatory") patients with COVID-19. JS016 is the first SARS-CoV-2 neutralizing antibody to enter clinical trials in China. Junshi and Eli Lilly are collaborating to co-develop JS016 globally, with Junshi leading clinical development in China and Lilly leading clinical development in the rest of the world (Table 2). The trial is a randomized, double-blind and placebo-controlled study to evaluate the tolerability, safety, pharmacokinetic and immunogenicity of JS016 in healthy subjects. TY027 was developed by Tychan in partnership with the whole-of-Singapore government engagement (Table 2). TY027 is being explored for the treatment of patients with COVID-19 to slow the progression of the disease and accelerate recovery, as well as for its potential to provide temporary protection against infection of SARS-CoV-2. Following positive preclinical results, CT-P59 was developed by Celltrion and is being evaluated in a Phase 1 clinical trial in healthy volunteers (Table 2). CT-P59 has been proven to be effective in neutralizing different kinds of coronavirus related strains, including the D614G variant strain of SARS-CoV-2. BRII-196 and BRII-198 were developed by Brii Bio, TSB Therapeutics, Tsinghua University and the 3rd People's Hospital of Shenzhen (17). BRII-196 can completely block viral entry and neutralize live SARS-CoV-2 infection in cell culture assays. It binds to a highly conserved epitope on the spike protein. BRII-198 binds to a different epitope on the spike protein and has additive to synergistic effect when combined with BRII-196. Both of them have the potential of becoming an effective therapy against the COVID-19 pandemic. SCTA01 was developed by Sinocelltech Ltd and Chinese Academy of Sciences. It is a humanized monoclonal antibody, efficiently neutralizes SARS-CoV-2 and SARS-CoV pseudoviruses as well as authentic SARS-CoV-2 at *nM* level by engaging the S RBD (18).

Most of the other COVID-19 antibody therapeutic candidates in clinical trials are repurposed drugs aimed at

A

Development Status

B

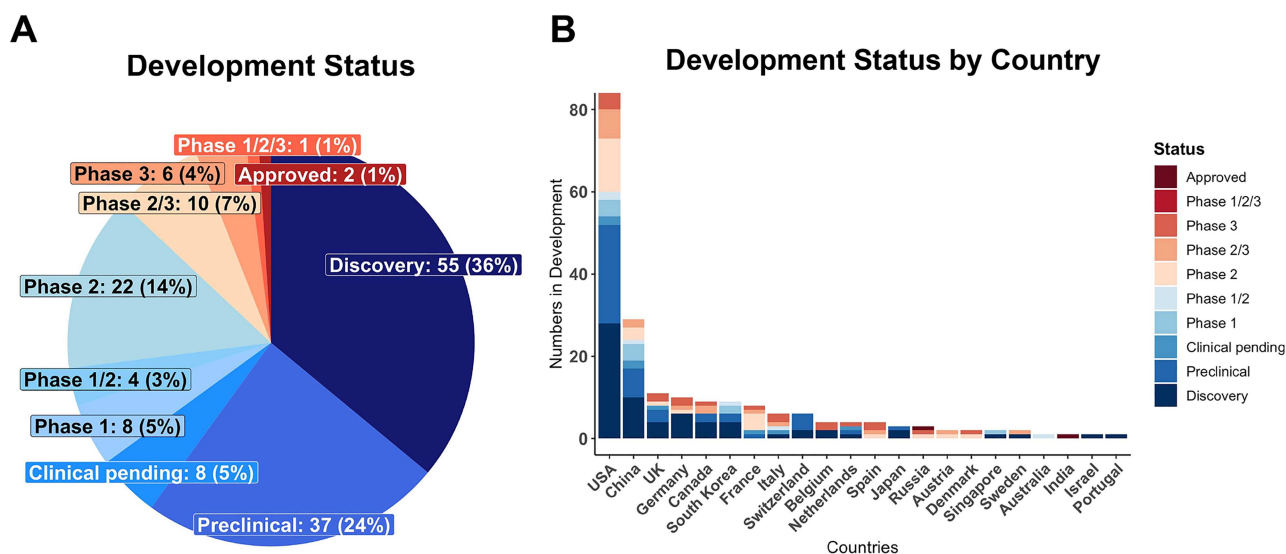### Development Status by Country

Figure 2. Development status of COVID-19 therapeutic antibodies. (A) Distribution of program development status for COVID-19 therapeutic antibodies in development globally. The status is categorized into discovery, preclinical, clinical pending, Phase 1, Phase1/2, Phase 1/2/3, Phase 2, Phase 2/3, Phase 3 and approved. Studies are categorized into discovery (in screening stage without any timeline given for the start of clinical testing) and preclinical (clinical testing planned) based on an estimate of how soon clinical testing may be started. (B) Stacked bar chart showing the status of antibody therapeutics development by country. The status of clinical trials is color-coded from dark blue (the earliest phase) to dark red (the latest phase). For therapeutic candidates being developed across multiple countries, each participating country has been counted separately in this chart. Figure 2 is based on "Tracker" data as of 8 August 2020.

host targets, rather than the viral S protein. Two antibody therapeutics that were repurposed as COVID-19 treatments have already reached the market. Levilimab (Ilsira), which was developed by BIOCAD to target IL-6 receptor, was registered in Russia for the inhibition of cytokine storm caused by coronavirus infection in early June 2020. The restricted emergency use of itolizumab (Alzumab) for the treatment of cytokine release syndrome in COVID-19 patients with moderate to severe acute respiratory distress syndrome was granted in India in July 2020. Developed by Biocon, itolizumab targets CD6 (19). The anti-IL6 receptor antibody, tocilizumab (Actemra), is being evaluated in multiple Phase 3 clinical trials to assess the safety and efficacy of intravenous plus standard of care in hospitalized adult patients with severe COVID-19 pneumonia.

Based on the number of research and development programs, the USA and China are the top two countries in developing COVID-19 antibody therapeutics, followed by Canada, Germany, South Korea, UK and France (Fig. 2B).

CONCLUSION AND PERSPECTIVES

The COVID-19 pandemic is causing unprecedented worldwide impacts on healthcare, research and economies. To bring the pandemic under control, the development of effective treatments is urgently needed. To help address the emergent information needs, our "Tracker" provides a useful reference for researchers and the public to track current progress of drugs developed for COVID-19.

SARS-CoV (20,21), MERS-CoV (22), SARS-CoV-2 (23–26) have caused major outbreaks and substantial disruption due to the lack of human immunity and facile transmission of the virus. It has been proposed that a

so-called "universal" target or strategy for inhibiting both SARS-CoV and SARS-CoV-2 or even all coronaviruses should be identified to allow treatment of not only the current COVID-19 pandemic but also future SARS-related coronavirus infections (3). In proof-of-concept studies, neutralizing antibodies, such as 47D11 (27), S309 (28), VHH-72 (29) and ADI55689/ADI56046 (30), against highly conserved region of RBD or the S1 subunit of the SARS-CoV-2 spike protein have also been shown to possess neutralizing activities against SARS-CoV. With an exception of VHH-72, these mAbs are fully human IgG molecules, which is a format suitable for therapeutic development, but more potent cross-neutralizing antibodies might be needed for clinical studies. Although it is challenging to develop "universal" antibodies targeting coronaviruses, efforts are currently being made to isolate broad and potent neutralizing antibodies against multiple coronaviruses, including SARS-CoV-2 (https://www.fiercebiotech.com/biotech/adagio-debuts-50m-to-fight-covid-19-and-next-pandemic).

Current challenges in developing neutralizing antibodies against SARS-CoV-2 include mutations in the spike protein (31). Mutations in the virus can lead to escape variants (32). Combination of multiple mechanisms and binding domains has been reported in MERS-CoV (33) and SARS-CoV (32) antibody development. A combination (cocktail) of two antibodies that recognize different non-competing epitopes of the RBD or the spike protein of SARS-CoV-2 has been developed for clinical trials to treat COVID-19 (10). Since each of the non-competing neutralizing antibodies targeting the RBD of the spike protein has potent activity against the SARS-CoV-2 virus, combination of these antibodies does not show superior neutralizing activities in culture. Nevertheless, the major advantage of the cocktail strategy

is the ability to prevent epitope escape. More cocktail therapies that involve multiple targets or multiple steps of viral infection via different mechanisms would be worthwhile testing in the future.

While the RBD is the primary target for the development of neutralizing antibodies against SARS-CoV-2, non-RBD regions should be pursued as well. An antibody (4A8) has been isolated from convalescent COVID-19 patients shows the binding on the N-terminal domain of the SARS-CoV-2 S protein. The 4A8 human antibody exhibits high neutralization potency against SARS-CoV-2 with the IC_{50} value of 0.607 μg/mL (4.047 nM) (34).

Antibodies that target the spike protein other than the S1 subunit have rarely been reported so far. The S2 subunit, in particular heptad repeat (HR) loops including HR1 and HR2 domains, required for membrane fusion has been suggested as another potentially important target (3). The 1A9 antibody is a monoclonal antibody that binds the HR2 domain on the S2 subunit of SARS-CoV (35). Since the S2 subunit is highly conserved, it would be interesting to explore whether such antibodies have broad neutralizing activities against both SARS-CoV and SARS-CoV-2. A broad inhibitor targeting the HR region might be useful for the treatment of infection by current and future SARS-related coronavirus. Such a concept has been demonstrated in studies of peptide-based pan-coronavirus fusion inhibitors (36,37). A cocktail therapy that combines both ACE2 (S1) blockers and S2 inhibitors in two distinct functional domains of the spike protein would be worthwhile developing and testing. Host cell targets such as heparan sulfate proteoglycans (HSPGs) may provide the initial sites for virus attachment and entry (38). Blocking the HSPGs on human cells by therapeutic antibodies has been proposed for treating COVID-19 and other virus infections (3,39).

The D614G mutation on the SARS-CoV-2 spike protein has been recently identified for its role in increasing infectivity (15). Structural models predict that D614G would disrupt contacts between the S1 and S2 domains of the spike protein and cause significant shifts in conformation. It should be useful to closely monitor and analyze the mutations of SARS-CoV-2 as it spreads worldwide so neutralizing antibodies effective for multiple strains of the virus can be developed (31,40–41). Most of the mutations found in the RBD of SARS-CoV-2 are of low frequency (31). The D614G mutation outside the RBD, however, raises the question of whether this mutation in the spike protein may compromise the effectiveness of neutralizing antibodies for treating COVID-19 since the variant spreads globally and may enhance infectivity of the SARS-CoV-2. Four of Regeneron's human monoclonal antibodies (9) targeting the RBD of the SARS-CoV-2 spike protein have been evaluated for their ability to neutralize mutants (15). All human antibodies tested show similar neutralization potency against both D614 and D614G variants, indicating the D614G mutation might not affect the activities of ACE2 blocking antibodies that targeting the RBD of the viral spike protein. Overall, ongoing clinical trials of SARS-CoV-2 neutralizing antibodies will help define the utility of these antibodies as a new class of therapeutics for treating COVID-19 and future coronavirus infections.

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