**COVID-19 Antibody Therapeutics Tracker: A Global Database of Antibody Therapeutics for the Prevention and Treatment of COVID-19**

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**Statement of Significance**

Chinese Antibody Society, in collaboration with [The](https://www.antibodysociety.org/)[Antibody Society](https://www.antibodysociety.org/)**,** developedthe “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.

**Key words:**

SARS-CoV-2, COVID-19, neutralizing antibody, spike (S) protein, clinical trial, online database

**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 treatment of COVID-19. In March 2020, the  Chinese Antibody Society, in collaboration with [The](https://www.antibodysociety.org/) [Antibody Society](https://www.antibodysociety.org/), 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 ~150 programs and molecules included in the “Tracker” as of mid-July 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. The United States and China are the two leading countries in terms of the total number of COVID-19 antibody therapeutics in development.

**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 July 17, 2020, there are 13,888,874 confirmed cases and 592,719 deaths worldwide with 188 countries affected (<https://coronavirus.jhu.edu/map.html>). As the COVID-19 pandemic is emerging as the global healthcare crisis, scientists worldwide are actively developing prophylactic and therapeutic interventions.  Antibody therapeutics hold enormous promise for treatment of COVID-19 (3). To join the global endeavor against the pandemic with our expertise, Chinese Antibody Society, in collaboration with [The](https://www.antibodysociety.org/)[Antibody Society](https://www.antibodysociety.org/)**,** developedthe “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**](https://www.antibodysociety.org/)[**Antibody Society**](https://www.antibodysociety.org/) **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, full studies base 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 (JSON) 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 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 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 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.

1. **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) shows 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 **Figure 1A**, the “Tracker” is currently tracking 147 programs and molecules for COVID-19 interventions from discovery to clinical development. Among these, 85 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 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 IC50 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 treatment REGN-COV2 (REGN10933+REGN10987) (Table 2).

In another study, groups from Chinese Academy of Sciences in Beijing and Junshi Biosciences in Shanghai reported two human antibodies (CA1 and CB6) 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 IC50 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 1×105 50% tissue culture infectious dose (TCID50) 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 post infection (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 (TNF), 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 repurposing for the treatment of COVID-19 (12). As shown in **Figure 1A**, 59 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).

1. **Antibody formats**

As shown in **Figure 1B**, over 80% of these therapeutics are in conventional full-length IgG-based monoclonal antibody format, 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). Among the four most advanced antibody therapeutics that specifically target SARS-CoV-2 S protein, all are conventional human monoclonal antibodies (mAbs), with Regeneron's REGN-COV2 comprising a 2-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 D614G variant](https://c212.net/c/link/?t=0&l=en&o=2848754-1&h=1673238101&u=https%3A%2F%2Fwww.biorxiv.org%2Fcontent%2F10.1101%2F2020.07.04.187757v1&a=the+now+prevalent+D614G+variant) (15).

Five programs are 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. 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 IC50 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, VEGF/IL-6, CD16/SARS-CoV-2. Fusion protein and other formats, such as DARPin, mRNA-encoding mAb, radiotherapeutics, are also being tested for the treatment of COVID-19.

1. **Antibody development status**

Among the programs and molecules we are tracking, over 60% are in discovery and preclinical stages (**Figure 2A**), including the majority of those that specifically target the SARS-CoV-2 S protein via blocking viral entry. Five antibody candidates targeting the SARS-CoV-2 S protein have entered clinical studies, including REGN-COV2 (Regeneron, three clinical trials in Phase 1/2/3), LY-CoV555 (Eli Lilly/AbCellera, two clinical trials in Phase 1 and 2), JS016 (Eli Lilly/Junshi Biosciences, clinical trial in Phase 1), TY027 (Tychan, clinical trial in Phase 1) , and CT-P59 (Celltrion, clinical trial in Phase 1) (see detailed information in the “Tracker” and Table 2).

Lilly scientists developed LY-CoV555 (also called LY3819253) in just three months after AbCellera and the Vaccine Research Center at the National Institute of Allergy and Infectious Diseases at the National Institutes of Health identified it from the blood sample taken from one of the first U.S. 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. CT-P59 was developed by Celltrion and is being evaluated in Phase 1 clinical trial in healthy volunteers following positive pre-clinical results (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.

Most of the other COVID-19 antibody therapeutic candidates in clinical trials are repurposed drugs aimed at 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 (17). 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.

The United States and China are the two leading countries in developing COVID-19 antibody therapeutics, followed by Canada, Germany, South Korea, UK, and France (**Figure 2B**).

**Conclusion and Perspectives**

The COVID-19 pandemic is causing unprecedented worldwide impacts on healthcare, research and economies. To bring the pandemic under control, 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 (18,19), MERS-CoV (20), SARS-CoV-2 (21-24) 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 (25), S309(26), VHH-72 (27), and ADI55689/ADI56046 (28), 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.

Current challenges in developing neutralizing antibodies against SARS-CoV-2 include mutations in the spike protein (29). Mutations in the virus can lead to escape variants (30). Combination of multiple mechanisms and binding domains has been reported in MERS-CoV (31) and SARS-CoV (30) 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 for 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 (NTD) of the SARS-CoV-2 S protein. The 4A8 human antibody exhibits high neutralization potency against SARS-CoV-2 with the IC50 value of 0.607 μg/ml (4.047 nM) (32).

Antibodies that target the spike protein beyond 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 (33). 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 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 (34,35). 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 (36). Blocking the HSPGs on human cells by therapeutic antibodies has been proposed for treating COVID-19 and other virus infections (3,37).

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 (38-40). Most of the mutations found in the RBD of SARS-CoV-2 are of low frequency (40). 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 and future 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 coronavirus infections.

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**References**

1. Li, Q., Guan, X., Wu, P., Wang, X., Zhou, L., Tong, Y., Ren, R., Leung, K.S.M., Lau, E.H.Y., Wong, J.Y. *et al.* (2020) Early Transmission Dynamics in Wuhan, China, of Novel Coronavirus-Infected Pneumonia. *The New England journal of medicine*, **382**, 1199-1207.

2. Zhou, F., Yu, T., Du, R., Fan, G., Liu, Y., Liu, Z., Xiang, J., Wang, Y., Song, B., Gu, X. *et al.* (2020) Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet*, **395**, 1054-1062.

3. Ho, M. (2020) Perspectives on the development of neutralizing antibodies against SARS-CoV-2. *Antibody therapeutics*, **3**, 109-114.

4. Huser, V. and Cimino, J.J. (2013) Linking ClinicalTrials.gov and PubMed to track results of interventional human clinical trials. *PLoS ONE*, **8**, e68409.

5. Vaduganathan, M., Vardeny, O., Michel, T., McMurray, J.J.V., Pfeffer, M.A. and Solomon, S.D. (2020) Renin-Angiotensin-Aldosterone System Inhibitors in Patients with Covid-19. *The New England journal of medicine*, **382**, 1653-1659.

6. Wan, Y., Shang, J., Graham, R., Baric, R.S. and Li, F. (2020) Receptor Recognition by the Novel Coronavirus from Wuhan: an Analysis Based on Decade-Long Structural Studies of SARS Coronavirus. *J Virol*, **94**.

7. Wrapp, D., Wang, N., Corbett, K.S., Goldsmith, J.A., Hsieh, C.L., Abiona, O., Graham, B.S. and McLellan, J.S. (2020) Cryo-EM structure of the 2019-nCoV spike in the prefusion conformation. *Science*, **367**, 1260-1263.

8. Yan, R., Zhang, Y., Li, Y., Xia, L., Guo, Y. and Zhou, Q. (2020) Structural basis for the recognition of SARS-CoV-2 by full-length human ACE2. *Science*, **367**, 1444-1448.

9. Hansen, J., Baum, A., Pascal, K.E., Russo, V., Giordano, S., Wloga, E., Fulton, B.O., Yan, Y., Koon, K., Patel, K. *et al.* (2020) Studies in humanized mice and convalescent humans yield a SARS-CoV-2 antibody cocktail. eabd0827.

10. Baum, A., Fulton, B.O., Wloga, E., Copin, R., Pascal, K.E., Russo, V., Giordano, S., Lanza, K., Negron, N., Ni, M. *et al.* (2020) Antibody cocktail to SARS-CoV-2 spike protein prevents rapid mutational escape seen with individual antibodies. eabd0831.

11. Shi, R., Shan, C., Duan, X., Chen, Z., Liu, P., Song, J., Song, T., Bi, X., Han, C., Wu, L. *et al.* (2020) A human neutralizing antibody targets the receptor-binding site of SARS-CoV-2. *Nature*.

12. Atal, S. and Fatima, Z. (2020) IL-6 Inhibitors in the Treatment of Serious COVID-19: A Promising Therapy? *Pharmaceut Med*, 1-9.

13. Paul-Pletzer, K. (2006) Tocilizumab: blockade of interleukin-6 signaling pathway as a therapeutic strategy for inflammatory disorders. *Drugs of today (Barcelona, Spain : 1998)*, **42**, 559-576.

14. Luo, P., Liu, Y., Qiu, L., Liu, X., Liu, D. and Li, J. (2020) Tocilizumab treatment in COVID-19: A single center experience. *J Med Virol*, **92**, 814-818.

15. Yurkovetskiy, L., Pascal, K.E., Tompkins-Tinch, C., Nyalile, T., Wang, Y., Baum, A., Diehl, W.E., Dauphin, A., Carbone, C., Veinotte, K. *et al.* (2020) SARS-CoV-2 Spike protein variant D614G increases infectivity and retains sensitivity to antibodies that target the receptor binding domain. *bioRxiv*.

16. Liu, J., Zhang, S., Zhang, T., Xiao, H., Du, J., Zeng, S., Kong, Y., Liu, B., Li, X., Lin, J. *et al.* (2020) Isolation of a human monoclonal antibody specific for the receptor binding domain of SARS-CoV-2 using a competitive phage biopanning strategy. *Antibody therapeutics*, **3**, 95-100.

17. Bughani, U., Saha, A., Kuriakose, A., Nair, R., Sadashivarao, R.B., Venkataraman, R., Patel, S., Deshchougule, A.T., S, S.K., Montero, E. *et al.* (2017) T cell activation and differentiation is modulated by a CD6 domain 1 antibody Itolizumab. *PLoS ONE*, **12**, e0180088.

18. Drosten, C., Günther, S., Preiser, W., van der Werf, S., Brodt, H.R., Becker, S., Rabenau, H., Panning, M., Kolesnikova, L., Fouchier, R.A. *et al.* (2003) Identification of a novel coronavirus in patients with severe acute respiratory syndrome. *The New England journal of medicine*, **348**, 1967-1976.

19. Ksiazek, T.G., Erdman, D., Goldsmith, C.S., Zaki, S.R., Peret, T., Emery, S., Tong, S., Urbani, C., Comer, J.A., Lim, W. *et al.* (2003) A novel coronavirus associated with severe acute respiratory syndrome. *The New England journal of medicine*, **348**, 1953-1966.

20. Zaki, A.M., van Boheemen, S., Bestebroer, T.M., Osterhaus, A.D. and Fouchier, R.A. (2012) Isolation of a novel coronavirus from a man with pneumonia in Saudi Arabia. *The New England journal of medicine*, **367**, 1814-1820.

21. Huang, C., Wang, Y., Li, X., Ren, L., Zhao, J., Hu, Y., Zhang, L., Fan, G., Xu, J., Gu, X. *et al.* (2020) Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet*, **395**, 497-506.

22. Lu, R., Zhao, X., Li, J., Niu, P., Yang, B., Wu, H., Wang, W., Song, H., Huang, B., Zhu, N. *et al.* (2020) Genomic characterisation and epidemiology of 2019 novel coronavirus: implications for virus origins and receptor binding. *Lancet*, **395**, 565-574.

23. Zhou, H., Chen, X., Hu, T., Li, J., Song, H., Liu, Y., Wang, P., Liu, D., Yang, J., Holmes, E.C. *et al.* (2020) A Novel Bat Coronavirus Closely Related to SARS-CoV-2 Contains Natural Insertions at the S1/S2 Cleavage Site of the Spike Protein. *Current biology : CB*, **30**, 2196-2203.e2193.

24. Zhu, N., Zhang, D., Wang, W., Li, X., Yang, B., Song, J., Zhao, X., Huang, B., Shi, W., Lu, R. *et al.* (2020) A Novel Coronavirus from Patients with Pneumonia in China, 2019. *The New England journal of medicine*, **382**, 727-733.

25. Wang, C., Li, W., Drabek, D., Okba, N.M.A., van Haperen, R., Osterhaus, A., van Kuppeveld, F.J.M., Haagmans, B.L., Grosveld, F. and Bosch, B.J. (2020) A human monoclonal antibody blocking SARS-CoV-2 infection. *Nature communications*, **11**, 2251.

26. Pinto, D., Park, Y.-J., Beltramello, M., Walls, A.C., Tortorici, M.A., Bianchi, S., Jaconi, S., Culap, K., Zatta, F., De Marco, A. *et al.* (2020) Structural and functional analysis of a potent sarbecovirus neutralizing antibody. 2020.2004.2007.023903.

27. Wrapp, D., De Vlieger, D., Corbett, K.S., Torres, G.M., Wang, N., Van Breedam, W., Roose, K., van Schie, L., Team, V.-C.C.-R., Hoffmann, M. *et al.* (2020) Structural Basis for Potent Neutralization of Betacoronaviruses by Single-Domain Camelid Antibodies. *Cell*.

28. Wec, A.Z., Wrapp, D., Herbert, A.S., Maurer, D.P., Haslwanter, D., Sakharkar, M., Jangra, R.K., Dieterle, M.E., Lilov, A., Huang, D. *et al.* (2020) Broad neutralization of SARS-related viruses by human monoclonal antibodies. *Science (New York, N.Y*.

29. Korber, B., Fischer, W., Gnanakaran, S., Yoon, H., Theiler, J., Abfalterer, W., Foley, B., Giorgi, E., Bhattacharya, T., Parker, M. *et al.* (2020) Spike mutation pipeline reveals the emergence of a more transmissible form of SARS-CoV-2. 2020.2004.2029.069054.

30. ter Meulen, J., van den Brink, E.N., Poon, L.L., Marissen, W.E., Leung, C.S., Cox, F., Cheung, C.Y., Bakker, A.Q., Bogaards, J.A., van Deventer, E. *et al.* (2006) Human monoclonal antibody combination against SARS coronavirus: synergy and coverage of escape mutants. *PLoS medicine*, **3**, e237.

31. Widjaja, I., Wang, C., van Haperen, R., Gutiérrez-Álvarez, J., van Dieren, B., Okba, N.M.A., Raj, V.S., Li, W., Fernandez-Delgado, R., Grosveld, F. *et al.* (2019) Towards a solution to MERS: protective human monoclonal antibodies targeting different domains and functions of the MERS-coronavirus spike glycoprotein. *Emerging Microbes & Infections*, **8**, 516-530.

32. Chi, X., Yan, R., Zhang, J., Zhang, G., Zhang, Y., Hao, M., Zhang, Z., Fan, P., Dong, Y., Yang, Y. *et al.* (2020) A potent neutralizing human antibody reveals the N-terminal domain of the Spike protein of SARS-CoV-2 as a site of vulnerability. 2020.2005.2008.083964.

33. Lip, K.M., Shen, S., Yang, X., Keng, C.T., Zhang, A., Oh, H.L., Li, Z.H., Hwang, L.A., Chou, C.F., Fielding, B.C. *et al.* (2006) Monoclonal antibodies targeting the HR2 domain and the region immediately upstream of the HR2 of the S protein neutralize in vitro infection of severe acute respiratory syndrome coronavirus. *J Virol*, **80**, 941-950.

34. Xia, S., Liu, M., Wang, C., Xu, W., Lan, Q., Feng, S., Qi, F., Bao, L., Du, L., Liu, S. *et al.* (2020) Inhibition of SARS-CoV-2 (previously 2019-nCoV) infection by a highly potent pan-coronavirus fusion inhibitor targeting its spike protein that harbors a high capacity to mediate membrane fusion. *Cell Res*, **30**, 343-355.

35. Xia, S., Yan, L., Xu, W., Agrawal, A.S., Algaissi, A., Tseng, C.K., Wang, Q., Du, L., Tan, W., Wilson, I.A. *et al.* (2019) A pan-coronavirus fusion inhibitor targeting the HR1 domain of human coronavirus spike. *Sci Adv*, **5**, eaav4580.

36. Lang, J., Yang, N., Deng, J., Liu, K., Yang, P., Zhang, G. and Jiang, C. (2011) Inhibition of SARS pseudovirus cell entry by lactoferrin binding to heparan sulfate proteoglycans. *PLoS One*, **6**, e23710.

37. Geoghegan, E.M., Pastrana, D.V., Schowalter, R.M., Ray, U., Gao, W., Ho, M., Pauly, G.T., Sigano, D.M., Kaynor, C., Cahir-McFarland, E. *et al.* (2017) Infectious Entry and Neutralization of Pathogenic JC Polyomaviruses. *Cell reports*, **21**, 1169-1179.

38. Forster, P., Forster, L., Renfrew, C. and Forster, M. (2020) Phylogenetic network analysis of SARS-CoV-2 genomes. **117**, 9241-9243.

39. Yao, H., Lu, X., Chen, Q., Xu, K., Chen, Y., Cheng, L., Liu, F., Wu, Z., Wu, H., Jin, C. *et al.* (2020) Patient-derived mutations impact pathogenicity of SARS-CoV-2. 2020.2004.2014.20060160.

40. Korber, B., Fischer, W., Gnanakaran, S.G., Yoon, H., Theiler, J., Abfalterer, W., Foley, B., Giorgi, E.E., Bhattacharya, T., Parker, M.D. *et al.* (2020) Spike mutation pipeline reveals the emergence of a more transmissible form of SARS-CoV-2. 2020.2004.2029.069054.

**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 Application Programming Interface (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 & Validation** | **Filtering**: Entries describing preclinical or clinical development of diagnostic antibodies, polyclonal antibodies, convalescent plasma therapies, immune globulin intravenous (IGIV) 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 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 generate using WPData Table, a commercial plug-in for WordPress. Static table and charts used for this publication were generated using R. |
| **Step 5** | **Update & Maintenance** | New data are being collected, analyzed, and published on our website on a weekly basis. |

**Table 2. Summary of the Five 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 |

A close up of a map

Description automatically generated

**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 July 17, 2020.

A screenshot of a map

Description automatically generated

**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 July 17, 2020.