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

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**Abstract**

Facing COVID-19 pandemic as a global healthcare crisis, scientists worldwide are collaborating to develop prophylactic and therapeutic interventions against COVID-19.  Antibody therapeutics hold enormous promise for treatment of COVID-19. Chinese Antibody Society, in collaboration with [The](https://www.antibodysociety.org/) [Antibody Society](https://www.antibodysociety.org/), has been developing the “COVID-19 Therapeutic Antibody Tracker” (“Tracker”) to track the global antibody-based COVID-19 programs in preclinical and clinical development. All the data were collected from the public domain and cross-verified by volunteers.

The tracker is integrated into Chinese Antibody Society’s website using WordPress system. The data is regularly updated and proofread. Exploratory data analysis and visualization has also been conducted to present the latest trends of COVID-19 antibody development. We categorized the data mainly by their targets, formats, status of development, developers and countries. Among the programs and molecules, more than 50% of the COVID-19 antibody candidates are targeting the SARS-COV-2 Spike protein (S protein) and in the antibody format. Most of these virus-specific therapeutic antibodies are in discovery or preclinical stage. USA and China are the two leading countries in developing COVID-19 antibody therapeutics. Most of the current COVID-19 antibody therapeutic candidates in clinical trials are repurposing drugs aimed at other targets other than the virus-specific protein.

**Statement of Significance**

Chinese Antibody Society, in collaboration with [The](https://www.antibodysociety.org/)[Antibody Society](https://www.antibodysociety.org/)**,** developedthe “COVID-19 Therapeutic Antibody Tracker” (“Tracker”) to provide a global database for scientists and the general public to track ongoing preclinical and clinical development of antibody-based therapeutics for prevention and treatment of COVID-19 during the pandemic in a timely manner.

**Introduction**

The recent outbreak of COVID-19 has emerged from a public health emergency to a major global pandemic. As the COVID-19 pandemic is the global healthcare crisis, scientists worldwide are collaborating to develop prophylactic and therapeutic interventions against COVID-19.  Antibody therapeutics hold enormous promise for treatment of COVID-19. 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 Therapeutic Antibody Tracker” (“Tracker”) to track the worldwide antibody-based COVID-19 therapeutics in preclinical and clinical development.

**Establishment of the “Tracker”**

**The data of the “Tracker” is being collected from resources of public domain by volunteers from [The](https://www.antibodysociety.org/) [Antibody Society](https://www.antibodysociety.org/) and the Chinese Antibody Societies. As the workflow shown in Figure 1, as a major approach, the data was collected and summarized from literatures, preprints, search engines, company websites, biotech newsfeed, social media, government databases, etc. In another way, when available, automatic process is being developed and integrated to retrieve data from online databases such as ClinicalTrials.gov by command-line tools. For example, to construct queries based the Application Programming Interface (API) tool of ClinicalTrials.gov, full studies base url [XY1] used as the base query and supplied with parameters including a search expression string containing search fields, values, and logical operators for search and filtering. To circumvent the limitation of an maximum of 100 returned results allowed per query, the total number of query hits and their rankings were first obtained, then a loop was constructed using the “min\_rnk” and “max\_rnk” parameters to iteratively send query for every 100 hits until all hits are exhausted. Two versions of such queries were built in Python to simultaneously retrieve hits in JavaScript Object Notation (JSON) format. Returned hits were then analyzed manually to ensure relevancy, and logged into an SQLite database indexed by NCTID (unique study ID). A direct connection between the database and the main script was achieved using the open-source library sqlite3 [XY2]. When updating the database, the NCTID of a specific hit can be compared against the list of existing NCTIDs in the database. If an entry does not yet exist in the database, it will be flagged for manual review and if relevant, entered into the database. If entry exists in the database, its clinical phase will be updated automatically. An example of our script with detailed explanation for usage can be found on Github repository [XY3] 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. We categorized the data as: target, format, status of development, developer and country, as well as references.

To build the “Tracker”, the data table containing filtered results was uploaded to the website of Chinese Antibody Society, which was build using WordPress system. 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 data analysis and visualization based on the key features of the collected antibody therapeutic information that is 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 in different countries.

A screenshot of a social media post

Description automatically generatedFigure 1.Process of building the COVID-19 Therapeutic Antibody Tracker

**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 information: including antibody targets, formats, and development status.

1. **Antibody targets**

Neutralizing antibodies are an important components in host immune responses to viral pathogens [1]. 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) [2, 3]. Therefore, the S protein, especially the receptor binding domain (RBD), is the primary target for neutralizing antibodies. As shown in **Figure 2A**, the “Tracker” is currently tracking 147 programs and molecules for COVID-19 interventions from discovery to clinical development. Among the programs and molecules, 83 are targeting the SARS-COV-2 S protein as antiviral interventions by blocking virus entry. Four antibody candidates targeting the SARS-COV-2 S protein have entered clinical stages, including REGN-COV2 [4], LY-CoV555, JS016 [5], and TY027 (see detail information in “Tracker”).

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 alpha (TNFα), GM-CSF, complement (C5, C5a), etc. Considering the proven role of cytokine dysregulation in causing this hyperinflammation in the lungs, drugs targeting these mediators are being repurposing for the treatment of COVID-19 [6]. As shown in **Figure 2A**, sixty of the programs and molecules were developed to target the host immune system for other indications and now repurposed to treat COVID-19, by potentially alleviating COVID-19-related symptoms such as cytokine storm and inflammation instead of direct killing of the viruses. Drugs like the IL-6 inhibitors levilimab, tocilizumab, sarilumab and siltuximab are being tested against COVID-19 [6-8].

A close up of a map

Description automatically generatedF**igure 2**. Analysis of targets and formats of the therapeutics under development for COVID-19. (A) Distribution of therapeutic targets of therapeutic antibodies under development for COVID-19. (B). Distribution of the formats for therapeutics under development for Covid-19. The number of programs for each target and format are shown, followed by the proportion to the total number of all programs in paraphrase. Only the top five targets and formats by amounts are shown, the rest were populated in “Others”.

1. **Antibody formats**

In terms of the antibody formats, as shown in **Figure 2B**, over 80% of these therapeutics are in conventional antibody format, and the rest are in bi- or tri-specific antibody, single-domain antibody, polyclonal antibodies, fusion protein, and other (e.g. DARPin, mRNA-encoding mAb, radiotherapeutics) formats. Among the four most advanced antibody therapeutics that specifically targeting SARS-COV-2 S protein, three of them (LY-CoV555, JS016 and TY027) are in monoclonal antibody format, and the last one (Regeneron's REGN-COV2) is in double antibody cocktail. REGN-COV2's two antibodies bind non-competitively to the critical receptor binding domain of the virus's spike protein, which diminishes the ability of mutant viruses to escape treatment and protects against spike variants that have arisen in the human population [4]. More recent research 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" \t "_blank) [9].

Four programs are in polyclonal antibody format that specifically targets SARS-COV-2. The SAB-185 is generated by immunized transgenic cow using 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 potently inhibits SARS-CoV-2 pseudovirus infection with IC50 values of 12 nM. (ref: PMCID: PMC7197610) Two bi-specific and one tri-specific antibodies under developing are targeting 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 3A**), including the majority of the ones that specifically target the SARS-COV-2 virus S protein via blocking the virus entry. Four antibody candidates targeting the SARS-COV-2 S protein have entered clinical stages, including REGN-COV2 (Renegeron, three clinical trials in Phase 1/2/3), LY-CoV555 (Eli Lilly/AbCellela, two clinical trials in Phase 1 and 2), JS016 (Eli Lilly/Junshi, clinical trial in Phase 1), and TY027 (Tychan, clinical trial in Phase 1) (see detail information in “Tracker”).

Regeneron initiated the late-stage clinical trials evaluating REGN-COV2 for the treatment and prevention of COVID-19. A 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. LY-CoV555, is the world's first SARS-COV-2 specific antibody therapies went into clinical trial for the prevention and treatment of COVID-19. Lilly scientists rapidly developed the antibody in just three months after AbCellera and the Vaccine Research Center at the National Institute of Allergy and Infectious Diseases (NIAID) identified it from a blood sample taken from one of the first U.S. patients who recovered from 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. The trial is a randomized, double-blind and placebo-controlled study to evaluate the tolerability, safety and pharmacokinetic and immunogenicity of JS016 in healthy subjects. TY027 was developed by Tychan in partnership with the whole-of-Singapore government engagement. 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 with SARS-CoV-2.

Other than these four programs, most of COVID-19 antibody therapeutic candidates in clinical trials are repurposing drugs aimed at other targets rather than the S protein. Levilimab, which was develop by BIOCAD to targets IL-6R, has been registered in Russia for the inhibition of cytokine storm caused by coronavirus infection. The FDA has approved a phase III clinical trial to assess the safety and efficacy of intravenous tocilizumab (Actemra) plus standard of care in hospitalized adult patients with severe COVID-19 pneumonia.

USA and China are the two leading countries in developing COVID-19 antibody therapeutics, followed by Canada, Germany, South Korea, UK, and France (**Figure 3B**).

A screenshot of a cell phone

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**Figure 3**. 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 I, phase I/II, phase I/II/III, phase II, phase II/III, phase III and approved. (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.

**Conclusion and Perspectives**

While we are developing the “Tracker” and writing this review, the COVID-19 pandemic is evolving globally and resulting in unprecedented impacts on the worldwide healthcare, research and economy. COVID-19 requires urgent development of effective treatment. To help addressing the emergent needs, the “Tracker” provides a useful reference for researchers and public society to track current progress of drug development for COVID-19.

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