Tracking Therapeutic Antibody Development in a Pandemic

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The COVID-19 pandemic has generated a significant and rapid response from scientists who aim to develop drugs and vaccines in the academic, government, and industrial sectors. Such interventions are essential to containing SARS-CoV-2, the coronavirus that causes the COVID-19 disease. To inform and educate the public about global efforts to develop targeted therapies such as monoclonal antibodies (MAbs), The Antibody Society (TAS) and the Chinese Antibody Society (CAS) have designed and implemented a freely available online database called the COVID-19 Antibody Therapeutics Tracker (**1**).

Janice Reichert (executive director of TAS and founding editor in chief of the Informa Taylor & Francis journal *mAbs*) recalls the moment when she realized the enormity of charting the therapeutic antibody industry's response to the COVID-19 pandemic: "I've tracked trends in the development of antibody therapeutics for over 20 years. The first paper that I wrote on the topic was published in 2001. So tracking COVID-19 interventions was an obvious interest for me. There was just so much information. Every day new press releases were issued, and numerous papers appeared on preprint websites."

Reflecting on early efforts to compile data, Reichert observes, "I captured information in spreadsheets and organized it in a way that made sense to me, but it soon became clear that I needed assistance. After a few weeks of helping with data collection, the CAS team had the brilliant idea of turning that process into a searchable, online database." This novel collaboration between two nonprofit organizations has yielded an important tool for studying antibody therapeutics in development for COVID-19.

TAS and CAS share the goals of facilitating global communication and collaboration for discovery, development, manufacture, and commercialization of antibody-based therapeutics. Although unaffiliated, the two organizations have worked together in the past. Now the COVID-19 pandemic is driving a deeper collaboration based on the shared objective of supporting researchers in the field of therapeutic antibodies with up-to-date and accurate information during a rapidly evolving global emergency. With a large amount of COVID-19 data being published by scientists based in China, it made perfect sense to leverage both organizations' teams to provide the most complete information and holistic data set.

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"No one had created a searchable database that was specific to antibodies for COVID-19, so there was a clear need," Reichert explains. "The team at the Chinese Antibody Society designed a nice display with graphical representations of the data. Researchers around the world now are using the COVID-19 Antibody Therapeutics Tracker. To my knowledge, it remains the only coronavirus intervention tracker of its kind dedicated to therapeutic antibodies."

Filling an Urgent Need

Antibody and antiviral drugs could be lifesaving treatments for COVID-19. Although they might provide protection against the disease for only two to four weeks, that can be critical for patients with severe COVID-19 symptoms, and unlike a vaccine, such therapies don't come with the logistical challenge of needing to dose billions of healthy individuals around the world. Costs for treating only those patients who require antibody drugs could exceed US$1 billion, but that is likely to be a fraction of the cost associated with vaccinating 60–70% of the global population, which could exceed $10 billion and take years to roll out.

Many groups are investigating therapeutic antibody technologies to address the international medical emergency. Xiao Xiao (CAS member and senior scientist in biologics discovery at Merck) described the importance of the COVID-19 Antibody Therapeutics Tracker: "It allows researchers from both academia and industry to understand, based on data that are available within the public domain, the landscape of the number of antibody programs and the major discoveries in the fields of prophylactic or therapeutic antibodies as they progress into human trials." Weihan Liu (CAS executive committee member/

A Wealth of Resources

The Antibody Society and Chinese Antibody Society's COVID-19 Antibody Therapeutics Tracker captures trends in antibody discovery, development, and manufacture. In addition to a comprehensive database, the website features visualizations that assess antibody research by target, format, clinical status, and development status by country.

As of August 2020, the tracker had identified

- 152 programs in discovery and development for 46 targets
- 89 projects targeting S protein
- 49 antibody therapeutics in clinical trials (with 8 targeting S protein)
- 55 and 36 programs in discovery and preclinical stages, respectively
- 221 companies and institutions developing antibody therapeutics, representing 23 countries.

For updated information on clinical studies, please visit https://www.antibodysociety.org/covid-19-biologics-tracker and https://chineseantibody.org/covid-19-track.

vice president and doctoral candidate in cancer biology at the University of Chicago) says that the tracker was viewed more than 55,000 times in the first three weeks after it posted online in early June 2020. The numbers continue to increase rapidly, with several thousand researchers from the United States, China, and elsewhere in the world accessing the tracker every day.

Moving at the Speed of Data

Cong Yao (CAS executive committee member and patent counsel at Seattle Genetics) observes that "the selection of the information that we present is a unique view of the antibody pipeline for COVID-19 based on the knowledge of the experts from TAS and the CAS." The team brings its combined antibody expertise to analyze and screen the data, ensuring the quality of information contained within the database.

Lui reports, "The biggest challenge still is choosing what data to present. This space is moving fast, and we need to update the tracker each day. So we're thinking of using new technologies such as web crawlers and computational pipelines that will take data from the web automatically." That enables researchers simply to check data rather than gather and enter them manually. Liu adds, "Our colleague Xin Yu (CAS member and scientist at bluebird bio) has been leading this initiative, and hopefully our website will become much more automated." The team plans to expand tracking to other types of therapeutics soon.

A key challenge, Reichert notes, is that "we rely on what companies choose to put in the public domain, and often that is minimal. Ideally, we would have one entry per antibody candidate, but sometimes that hasn't been possible because of the limits to the raw data that we're working with. We've left some fields out of the tracker, but as more information becomes available over time, we may be able to make the database even more sophisticated and informative."

Tracker users are helping to minimize gaps and errors. Liu says, "For example, we initially included Biocad's Ilsira (levilimab) molecule at phase 3 clinical trials, but then the company contacted us saying that it already had registered the product in Russia. So we quickly updated our information."

Over time, the database could provide fascinating insights into antibody drug development, including preclinical success rates, something that Reichert says has been impossible to do in the past. "Will 50% make it into the clinic? 10%? 5%? How many companies actually will follow through because there is such a strong driving force for making progress? We might expect that in this situation you would have the highest possible preclinical to clinical transition, which would set an upper limit for that number."

Initial Insights

What can we learn from data already in the COVID-19 Antibody Therapeutics Tracker? During the TAS webinar "Antibodies to Watch in a Pandemic" (**2**), Reichert described her initial findings. She discovered that of the ~130 antibody-based COVID-19 interventions in commercial development, around one-third were "repurposed" antibody biologics that were intended to treat the symptoms of a COVID-19 infections, whereas two-thirds targeted SARS-CoV-2 itself.

Of those antibodies used to treat symptoms such as acute respiratory distress syndrome, important targets include interleukin-6, granulocyte-macrophage colony-stimulating factor, and the complement protein C5 as well as receptors for all these proteins. Currently, many antibody drugs are in late phases of development, with 16 in phase 3 clinical trials. Some already have been approved for other indications, including tocilizumab, sarilumab, siltuximab, emapalumab, canakinumab, and ravulizumab. Tocilizumab is a particularly promising candidate, having already been granted approval for treatment of "cytokine storms."

Thus far, levilimab is the only antibody registered for the treatment of patients with severe COVID-19 symptoms. It is a human MAb that targets membrane-bound and soluble forms of IL-6R. According to its producer, Biocad, clinical trial results showed that it significantly reduced COVID-19–related mortality. This MAb was registered on 5 June 2020 by the Government of the Russian Federation.

Approximately 88% of the anti–SARS-CoV-2 biologics that are being tracked are MAb-based therapeutics (including single-domain antibody fragments), with the remaining 12% being other targeted therapies such as Fc-fusion proteins, designed ankyrin repeat proteins (DARPin) molecules, and polyclonal antibodies. Anti–SARS-CoV-2 molecules usually are raised against the

virus's spike protein, and they mainly are in early phases of development, with only six candidates having progressed to phase 1 and 2 clinical trials.

Accelerating to Clinical Trials

To reach patients quickly, COVID-19 interventions will need emergency use authorizations (EUAs) from regulatory agencies. Reichert believes that EUAs are possible for 15 to 20 COVID-19 antibody interventions. Some of the anti–SARS-CoV-2 antibodies being tracked could receive EUAs if early clinical study results are positive. Likewise, some of the repurposed MAbs could receive EUAs as early as September 2020.

The current level of activity within the research community developing antibodies to treat infectious disease is without precedent. Reichert believes that it is critical for so many groups and companies to be working in this field because of the scale of the public health problem.

She envisages that companies will seek regulatory approval in their home territories first before seeking approval internationally, if they are able: "I imagine that Celltrion will try to get approval in South Korea in the first instance before trying to get approval in a different territory if it is successful. Likewise, a company in Europe might try to get an approval within the European Union." Such an approach could help alleviate concerns around the availability of manufacturing capacity if different companies can make use of their regional production networks and reduce the pressure on a single company's production capacity and its associated contract manufacturers.

The pandemic has shown how quickly novel antibody candidates can advance to first-in-human (FiH) trials. The conventional drug-development process takes 10 to 15 years and costs between $1 billion and $3 billion. Arguably, that model cannot address the pandemic situation in which the world currently finds itself. Driven by necessity, many companies are finding innovative ways of accelerating the process to enable their products to enter the clinic within six to 12 months.

Thomas Schirrmann (founding chief executive officer of Yumab-spinout Corat Therapeutics and participant in the "Antibodies to Watch in a Pandemic" webinar) points out that multiple publications have demonstrated the effectiveness of antibody therapeutics for treating infectious diseases such as Ebola, Marburg, anthrax, and influenza. However, companies often have found it challenging to develop antibody drugs to combat epidemics because of the unpredictable nature of outbreaks — hence the uncertainty surrounding the potential to generate returns on the investments required to develop and commercialize antibody candidates.

Corat Therapeutics is developing a SARS-CoV-2–neutralizing antibody therapy. Schirrmann has described how the company applied novel techniques to progress from drug target to lead in under four months. He now hopes to advance the candidate to FiH trials by the end of 2020, which would require the company to have submitted an investigational medicinal product dossier to EU regulators within six months of selecting a lead candidate.

Like other companies, Corat Therapeutics is leveraging existing standardized MAb manufacturing platforms and performing some necessary development activities in parallel. Schirrmann believes that some companies may take shortcuts such as performing their first good manufacturing practice (GMP) manufacturing batch with transfectant pools, thereby saving time needed to develop a clonal cell line. He believes that timelines can be shortened further by accelerating preclinical studies and performing ongoing stability studies.

Antibody Research After COVID-19

The COVID-19 Antibody Therapeutics Tracker shows that a large number of organizations have risen to the challenge of developing antibody treatments targeting this deadly infectious disease. It will be interesting to find out whether antibody-discovery companies will continue to invest in infectious disease targets when the COVID-19 pandemic has been brought under control.

Biopharmaceutical companies working with antibodies have long recognized the importance of speed to clinical trials, but the global need to save patients with COVID-19 infections has sharpened those companies' resolve further still. The tools and techniques that innovators are using to accelerate the discovery and development of antibody therapeutics will be retained and are hoped to benefit patients suffering from a range of diseases in the future. The therapeutic-antibody community may yet emerge from this considerable and tragic crisis better equipped to develop life-changing medicines than ever before.

References

1 *COVID-19 Antibody Therapeutics Tracker.* Chinese Antibody Society: Cambridge, MA, 2020; https://chineseantibody.org/covid-19-track.

2 Schirrmann T, Reichert J. *Antibodies to Watch in a Pandemic.* The Antibody Society: Framingham, MA, 30 June 2020; https://webinars-antibodysociety.org/store/seminar/seminar.php?seminar=158390.

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For updated information on clinical studies of anti–SARS-CoV-2 antibodies, please visit https://www.antibodysociety.org/covid-19-biologics-tracker and https://chineseantibody.org/covid-19-track.