Prepandemic Preparedness under the Spotlight at ASGCT’s COVID-19 Symposium

Elie Dolgin

The coronavirus’ genome sequence appeared online on January 10. Within weeks, scientists had determined the structures of several key viral proteins. Within months, drug makers had begun clinical trials of experimental vaccines and novel therapeutics. Within half a year, federal regulators had authorized well over 100 diagnostic and serological tests for coronavirus disease 2019 (COVID-19). “The speed at which everything is moving is quite staggering,” said Mayo Clinic virologist Stephen Russell, president of the American Society of Gene and Cell Therapy (ASGCT).

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Such a breathtaking speed has only been possible, however, because of decades of slow and steady progress made by pioneering coronavirus researchers. This community of dedicated scientists started small after the discovery of coronaviruses responsible for the common cold in the 1960s, later growing rapidly following outbreaks of more deadly strains responsible for epidemics in the 21st century. And although scientific interest in the topic waned after the severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS) epidemics both petered out, the research that had gone into tackling those lethal coronaviruses proved critical to the fight against the latest coronavirus, SARS-CoV-2.

Thus, an editorial about the then-dwindling SARS epidemic that appeared in the June 2003 issue of Molecular Therapy seems almost prescient today: “Epidemics come and go,” it read, “But from every epidemic we can learn lessons.”

That historical perspective provided a throughline linking the diverse research projects presented at the ASGCT COVID-19 Symposium in mid-September. The online forum, convened virtually over 2 days, featured seasoned coronavirologists and recent contributors alike, with various speakers all collectively drawing a straight line from insights made into coronaviruses of yore to the field’s current understanding of SARS-CoV-2—with a focus on ongoing efforts to control the contagion.

Take vaccines, for example. “Vaccine development for COVID-19 is proceeding faster than for any pathogen in history,” said Dan Barouch, a virologist at the Beth Israel Deaconess Medical Center. And “the reason,” noted viral immunologist Kizzmekia Corbett, who leads the Coronavirus Vaccines & Immunopathogenesis Team at the US National Institute of Allergy and Infectious Diseases (NIAID), “is because of the extensive work that was done previously” on SARS and MERS.

Therapeutics and diagnostics are no different either. From drugs like remdesivir—originally discovered in a screen for molecules with protective effects against a panel of RNA viruses, including the original SARS-CoV-1—to diagnostic algorithms developed for interpreting the results of RT-PCR tests on MERS-CoV, the speedy development of many tools in the anti-COVID-19 toolbox has been made possible because of prior legwork in the coronavirus arena.

Meaningful Progress

The symposium kicked off with a general overview of research progress on COVID-19 from NIAID director Anthony Fauci, in which the government’s top infectious disease expert said he was “cautiously optimistic” that distribution of one or more vaccines could begin next year “in a meaningful way.” Leading virologists then examined what is known about the structure and pathogenesis of SARS-CoV-2: epidemiologists explored global patterns of disease spread, immunologists discussed the nature of our bodies’ responses to infection, and everybody touched upon how insights into both host and viral biology are shaping the design of vaccines, treatments, diagnostics, and more.

Susan Weiss, a virologist at the University of Pennsylvania who has studied coronaviruses for more than 40 years, set the scene with a brief primer on the family of enveloped RNA viruses and how their conserved non-structural proteins allow most coronaviruses to evade host antiviral pathways.

With SARS-CoV-2, Weiss and her colleagues showed that the virus readily infects cells of the nose, lungs, and heart, including those with low expression levels of the ACE2 receptor, which serves as a portal of viral entry. Once inside the cell, however, the innate immune response provoked is much milder than that elicited by related viruses with pandemic potential, comparable to MERS-CoV only if two proteins involved in antagonizing host defenses are genetically disabled.2 According to Weiss, the weaker induction of host immunity could explain why SARS-CoV-2 is less virulent, yet more contagious than the coronaviruses behind SARS and MERS.

Other longtime coronavirologists who presented work at the symposium included Tom Gallagher and Stanley Perlman, both of whom discussed how interrogations of virus-host interactions are informing drug development.

Gallagher, who studies the molecular mechanisms of viral entry at Loyola University

1Somerville, MA, USA
Correspondence: Elie Dolgin, PhD, Somerville, MA, USA.
E-mail: elie@eliedolgin.com
Chicago, described a new cell-free assay that recapitulates part of the membrane fusion process by which coronaviruses gain access to human cells. It involves two basic ingredients: virus-like particles containing the four structural proteins of SARS-CoV-2 and extracellular vesicles with ACE2 receptors on their surface. Both also include fragments of luciferase that will glow if the two ingredients fuse, as happens in the presence of protease enzymes added to the mix. When any putative drug gets in the way, however, no such signal is observed. “The assay—which can be performed without cells, in BSL-1 conditions, cheaply and high-throughput—can now serve as a screen for antiviral compounds,” Gallagher said.

With an eye to vaccine deployment, Perlman, who studies the immunopathology of coronavirus infections at the University of Iowa, focused on long-term patterns of immunity following coronavirus exposure. Typically, he noted, antibody responses have waned swiftly among people infected with common-cold coronaviruses or those with mild cases of MERS, which could portend short-lived protection against SARS-CoV-2 as well. There is one notable exception, though: among people infected with SARS-CoV-1, low levels of neutralizing antibodies and memory T cells have been detectable up to 15 years later, in particular among those who develop severe disease.

That mixed picture of immune durability to past coronaviruses means it is still unclear how long defense functions will last among people infected with SARS-CoV-2 or vaccinated against it. Fortunately, on the safety side at least, it does not seem that immunization against SARS-CoV-2 is as dangerous as some feared. “The vaccine—whether it be RNA, DNA, protein subunits, virus-like particles, or viral vectors—that carries some or all of the spike protein.

Many candidates, for example, are built around adenoviruses that normally cause common colds but have been disabled so that they cannot replicate. These include JNJ-78436735, which is based on an engineered version of adenovirus 26, and AZD1222, which takes advantage of a chimpanzee adenovirus to carry DNA for the spike antigen. At the symposium, Barouch and Vincent Munster, chief of the NIAID’s Virus Ecology Unit, each described experiments showing how these two vaccines protect against SARS-CoV-2 in rhesus macaques. Sabine Hauck, head of research and development at Leukocare Biotechnology, also presented data on a novel gorilla-adenoviral vector-based platform from ReiThera in early-stage clinical testing.

Multiple Shots on Goal

Several other immunization approaches were also the focus of short oral presentations. These included viral vector strategies incorporating an adeno-associated virus (Nerea Zabaleta Lasarte and Wenlong Dai, Massachusetts Eye and Ear), a vesicular stomatitis virus (Timothy Carey, Imaris Life Sciences), and a measles virus (Miguel Muñoz-Alía, Mayo Clinic).
Ami Patel and Ebony Gary of the Wistar Institute described a synthetic DNA vaccine from Inovio Pharmaceuticals that induced robust immune responses in both small and large animal models. And Sean Sullivan, executive director of process development at Arcturus Therapeutics, characterized a mRNA vaccine that, like its more clinically advanced mRNA counterparts from Moderna and Pfizer, encodes the full-length spike protein, but also includes genes that allow for self-replication.

Sarah Gilbert, a vaccinologist at the University of Oxford who developed the vector behind AZD1222, welcomed the assortment of competing platforms. “It’s a very good thing that we have multiple different vaccine technologies in development,” she said. “This means that, should multiple vaccines be shown to be safe and effective, there will be multiple manufacturers able to produce the vaccines...in large quantities in order to supply the world.”

But a couple of major criticisms came up. Florian Krammer, an immunologist at the Icahn School of Medicine at Mount Sinai, noted that today’s crop of vaccines only induce serum antibodies without eliciting much in the way of secretory responses. That means the candidates may succeed at protecting vital organs, such as the lungs, but may have a limited impact against viral replication in the nasal epithelium. “For me personally,” he said, “the biggest elephant in the room is mucosal immunity.”

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Gavin MacBeath, chief scientific officer at TScan Therapeutics, also lamented the emphasis on protective antibodies, arguing that more attention should be paid to T cell responses to achieve long-term immunity. And he presented data showing that vaccine designers likely need to start looking beyond spike to the virus’s many other proteins.

His company performed an unbiased, genome-wide screen of SARS-CoV-2 epitopes that are recognized by memory CD8+ T cells isolated from survivors of COVID-19. Among the most common 29 shared epitopes, MacBeath’s team found only 3 resided in the spike protein. "So, for us," he said, "the take home message is that if you want to generate a vaccine that is going to elicit long term immunity and elicit a natural CD8 T cell response to the virus, then you need to incorporate epitopes that occur outside the spike protein."

**It Takes a Village**

Clinical trial operations for several of the vaccines in phase 3 development are being run through the NIAID’s COVID-19 Prevention Trials Network. As Larry Corey, a vaccine expert from the Fred Hutchinson Cancer Research Center who is co-leading the network’s vaccine testing, told symposium attendees: “It’s an unbelievable logistic effort.”

“It requires essentially the entire village of academia, the manufacturing capabilities of large pharma, and a system both for running the clinical trials and enhancing administration aspects so you navigate the regulatory agencies and get vaccines into people’s arms as soon as possible,” he said.

Meanwhile, on the therapeutics front, Myron Cohen of the University of North Carolina (UNC) at Chapel Hill, is co-leading the network’s testing of monoclonal antibodies. He outlined efforts to treat people at high risk of SARS-CoV-2 infection with spike-directed antibodies. These include trials of Eli Lilly’s LY-CoV555 in nursing homes with active outbreaks and Regeneron’s two-antibody cocktail REGN-COV2 in family households where only some people are infected.

Those particular antibody candidates might not be the most potent, stable, or easily manufacturable monoclonals, though, which is where the Coronavirus Immunotherapy Consortium comes in. As project leader Erica Ollmann Saphire, a structural virologist at the La Jolla Institute for Immunology, explained, the global consortium is currently evaluating dozens of candidate antibodies side-by-side in blinded, standardized assays.

The goal is to eventually find the best ones, which should likely outperform the only antibody-based therapy that had been approved at the time of the symposium: convalescent plasma. Tens of thousands of COVID-19 patients received infusions of this antibody-rich brew, derived from the blood of disease survivors, under a government-backed “expanded access” program before the Food and Drug Administration issued an emergency use authorization in late August.

Mayo Clinic physiologist Michael Joyner, who led the program, defended that regulatory decision in his symposium talk, noting that the treatment appears safe and has shown the potential to save lives. But the inferences of efficacy “need additional validation” in placebo-controlled randomized trials, he said.

Currently, most such trials designed to determine the efficacy of therapeutics or vaccines rely on clinical endpoints: rates of symptomatic illness in a prevention study, say, or progression of disease in a treatment study. To expedite matters, however, several researchers have begun looking for immune correlates that could serve as biomarkers of likely response.

For example, Galit Alter, an immunologist at the Ragon Institute, took a systems serology approach to analyze the humoral responses of 22 severely ill individuals who were hospitalized for COVID-19. In collaboration with infectious disease specialists at the University of Washington, Alter’s group found that a five-antibody signature could differentiate patients who recovered and those who died, with the balance of antibodies against the SARS-CoV-2 spike (S) and nucleocapsid (N) proteins predicting the likelihood of survival. Now, she said, “we are working with multiple groups around the country and across the world to understand how this S:N ratio could help assist with early clinical triaging.”
Looking farther into the future, some presenters have already begun contemplating the possibility of yet another coronavirus pandemic. Linfa Wang, a virologist at Duke-NUS Medical School in Singapore who has been leading the search for the origins of SARS-CoV-2 in bats across Southeast Asia, is one such watchkeeper. He emphasized the danger posed by the virus “spilling back” from humans into bat populations in other parts of the world, which could create new reservoirs for additional SARS-like coronavirus outbreaks down the line. “That really creates a new threat,” he said.

It also creates the motivation for researchers like Mark Denison, a pediatric infectious disease specialist at Vanderbilt University Medical Center, to continue their search for broad-acting antivirals. At the symposium, Denison, also a veteran of the coronavirus community, described an orally available nucleoside analog drug that he discovered collectively with Timothy Sheahan and Ralph Baric of UNC. In lab experiments, the drug potentially blocked the replication of multiple human and bat coronaviruses. Merck is now testing the agent in COVID-19 patients.

Denison, for his part, is already on to the next thing. As he said at the symposium: “When people ask me what I’m working on now, I say, ‘SARS-CoV-3.’”

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