COVID-19: A Wake-up Call for More Fundamental Research in Immunology

Interview with Barney Graham, M.D., Ph.D.
Deputy Director of the Vaccine Research Center,
US National Institute of Allergy and Infectious Diseases (NIAID)

Part of Barney Graham's work focuses on structure-based design of vaccines and monoclonal antibodies against existing and emerging infectious diseases, including Ebola, Zika, HIV, influenza, and now SARS-CoV-2. His team designed a SARS-CoV-2 vaccine antigen that was the first to enter clinical trials in partnership with Moderna, using the company's mRNA technology. Graham and colleagues also discovered a monoclonal antibody to SARS-CoV-2 that was the first to be tested clinically.

HVP editor Kristen Jill Abboud spoke with Graham about the basic research that facilitated the rapid development of COVID-19 vaccine candidates and NIAID's efforts to systematically prepare for future viral pandemic threats. A slightly edited version of the conversation appears below.

How did you develop a COVID-19 vaccine antigen so quickly?

In our case, we had a 10-year plan to try to get to this point. It started with our work on respiratory syncytial virus [RSV]. This work showed that if you stabilized the original, functional structure of the RSV fusion protein it made a much better vaccine immunogen. Our work with RSV happened about the same time as when MERS [Middle East Respiratory Syndrome] started, and we thought that if two coronavirus outbreaks have happened in 10 years, it's going to happen again, and so we started a program to define the structure of the spike protein of a human coronavirus [which is the protein that most current vaccine candidates are based on].

We had been trying to stabilize the spike protein of MERS and SARS and it wasn't working, and then one of the students in my lab got infected with HKU1 [a common-cold causing coronavirus], which was somewhat serendipitous, and so we tried it with that virus. HKU1 was inherently more stable and it allowed us to get the structure of spike. Once we had that structure, we could define stabilizing mutations that would keep the protein fixed. This stabilized version turned out to be much more immunogenic than wild-type spike, and those same stabilizing mutations were transferrable to SARS and MERS and a bunch of other coronavirus spikes, including SARS-CoV-2.

How did the collaboration with Moderna come about?

We started the collaboration with Moderna because we wanted to combine what we call precision vaccinology with platform manufacturing so that you can get both precision and speed.

Between the Ebola outbreak in 2014 and the Zika outbreak in 2016, the WHO [World Health Organization] and CEPI [The Coalition for Epidemic Preparedness Innovations] made lists of priority pathogens for vaccine development. At NIAID, we thought there should really be a systematic approach for all 25 virus families that infect humans—something we call the prototype pathogen approach to pandemic preparedness, which meant developing products for protype pathogens in each of those virus families at least through Phase I trials. So, we did that for paramyxoviruses using Nipah, and for coronaviruses using MERS. That was our initial project with Moderna. We were planning to do a clinical trial for Nipah using mRNA this year, but when SARS-CoV-2 emerged at the beginning of January, we decided to switch our demonstration project to this new coronavirus. As soon as the [SARS-CoV-2] sequence came out, we designed a protein using those stabilizing mutations we had already identified, and it worked. Moderna got off to a very fast start. We designed the protein, they designed the mRNA, and we collaborated on the preclinical work. It's been a good collaboration all the way through.

Are you optimistic about the vaccine candidates in development now, particularly the mRNA candidate?

I think we have several candidates, including this mRNA, that are driving responses into the upper tier of antibody responses that are seen in convalescent sera, and those are people who probably got a pretty good immunization from their infections. I think if we're achieving responses at this level, we'll hopefully at least have lower respiratory tract protection, if not some protection in the upper airway that will reduce viral shedding. I think we're in a reasonable position, but you really need to have the Phase III efficacy data to know.

Do you think it will be necessary to develop a second generation of vaccines that are more immunogenic?

I don't think we could do any better than this. There are ways to stabilize the spike protein even more—we know how to do that now—but this spike is good enough, and I don't think we could make a much better immunogen than we already have. It may be that we have to find better ways to deliver it or to use adjuvants to boost it, but in terms of the antigen itself, we're not going to do much better.

What do you think the situation with SARS-CoV-2 will be like three years from now?

I think it's likely that this will become another endemic coronavirus that will eventually become seasonal. But we need herd immunity to drive it toward that, and, ideally, we could do that with a vaccine instead of so much infection.

What do you think is the biggest gap in our understanding of COVID-19?

I think the durability of immunity and how that's going to play out is a big question and whether you can have waning antibody levels in serum but still have enough memory B cells and T cells to have an anamnestic response in time to be protected are the kinds of things we still have to figure out.

What needs to be done now to prepare for the next pandemic?

I think we need a 20-year plan to prepare for all the different families of viruses that could become pandemics. NIAID adopted the prototype pathogen approach to pandemic preparedness and response, but the price tag for doing it the best possible way is pretty high—it's a couple billion dollars a year. It requires spending a lot of resources on things that may or may not ever happen. But a couple billion dollars a year that could prepare us in a more robust way sounds pretty trivial at this point considering how much we're losing from this pandemic.

To me, the important message is that basic research creates knowledge that puts you in a better position to deal with a crisis like this. All of these findings came through basic research and fundamental science and especially if these vaccines end up working, it is a wake-up call for funders to support more basic, fundamental research, particularly pertaining to viruses and immunology.

Interview by Kristen Jill Abboud

Special Event: Michelson Prize Winners 2020

From left to right: Pulitzer Prize winner and moderator Laurie Garrett, the two 2020 Michelson Prize winners Dr. Danika Hill and Dr. Michael Birnbaum, and our next speaker in the Global COVID Lab Meeting, Harvard professor Dr. Dan Barouch.

Join us for a special two-hour event in our webinar series: On August 13 at 9 am EDT, we will announce the Michelson Prize Winners 2020 and connect the experts of today with the leaders of tomorrow.

Every year, the Michelson Medical Research Foundation and the Human Vaccines Project support the most promising projects from young investigators advancing human immunology, vaccine discovery, and immunotherapy across major global diseases.

This year's winners are Dr. Danika Hill, a research fellow at Monash University and Dr. Michael Birnbaum, assistant professor at MIT. They will be awarded the 2020 Michelson Prize for Human Immunology and Vaccine Research, receiving $150,000 each.

The webinar also features leading voices in the fight against COVID-19: Pulitzer Prize winner Laurie Garrett will introduce the winners and preside over the presentation of awards. After the award ceremony, Harvard Professor Dr. Dan Barouch will present the latest data set published in Nature with his insights on the pandemic in the Global COVID Lab Meeting, at which the Human Vaccines Project connects experts in the field to discuss the latest COVID-19 data. The Global COVID Lab Meeting will comprise a 30-minute presentation from our speaker Dr. Barouch, followed by a moderated Q&A session. Everybody is welcome to join the event.

REGISTER FOR THE WEBINAR HERE

Must Read

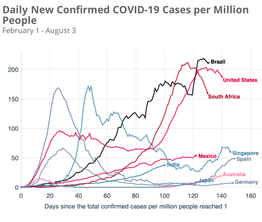
A flurry of recent research spans data on vaccine candidates, studies of immune responses to SARS-CoV-2 infection, and the latest observations on pediatric cases and transmission of the virus.

- Data was recently published for a non-human primate study testing the mRNA vaccine candidate in development by Moderna/NIAID.
- Data suggests that a single dose of an adenovirus serotype 26 vector-based vaccine candidate is sufficient to protect against SARS-CoV-2 infection in non-human primates.
- Phase I clinical trial data was recently reported by Inovio for their SARS-CoV-2 DNA vaccine candidate.
- A recent study indicates that SARS-specific memory T cells are detectable up to 17 years after infection and are cross-reactive to SARS-CoV-2.
- Two studies published recently show that there are several "immunotypes" associated with COVID-19 disease severity and that immune perturbations occur across multiple leukocyte populations in severe infections.
- A recent publication shows that serological signatures track with SARS-CoV-2 survival (see the recording of the last Global COVID lab meeting for more on this study).
- A meta-analysis of nearly 8,000 pediatric COVID-19 cases indicates that coughs and fevers were the most prevalent symptoms and that the majority of children recover from infection.
- A study shows that viral load in children under five can be 10- 100-fold higher than in adults.
- According to a report from the US Centers for Disease Control and Prevention, half of the children ages 6-10 attending a camp in Georgia became infected with SARS-CoV-2.

COVID-19 in Numbers

Daily New Confirmed COVID-19 Cases per Million People

February 1 - August 3



Source: European Centre for Disease Prevention and Control – Situation Update Worldwide – Data last updated 3rd August, 10:32 (London time), Official data collated by Our World in Data

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