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HVP COVID REPORT

Tracking SARS-CoV-2 Mutation and Neutralization

Interview with David Montefiori, PhD
Professor and Director,
Laboratory for AIDS Vaccine Research & Development,
Duke University Medical Center

David Montefiori studies viral immunology and vaccine development, with a focus on neutralizing antibodies. In his extensive work on HIV vaccines, Montefiori established a set of protocols for conducting assays that allowed the field to characterize antibody responses induced by different candidate vaccines. He is now applying this expertise to SARS-CoV-2. HVP editor Kristen Jill Abboud talked with Montefiori about his efforts to establish, optimize, and standardize assays that will be used to assess the antibody responses induced by COVID-19 vaccine candidates that are being evaluated as part of the laboratory program of the US government's Operation Warp Speed (OWS) Initiative.

An edited version of the conversation appears below.

How quickly has your work on developing neutralizing antibody assays for SARS-CoV-2 progressed?

It has been an enormous undertaking to get the neutralization assays developed, optimized, standardized, qualified, and formally validated by when we expect the first Phase III samples will be ready for testing, which is in about five weeks. This process, which typically takes one to two years, has been condensed down to a few months. And there are no shortcuts—you still have to do everything to satisfy the FDA [US Food and Drug Administration] requirements so that the data could be used to facilitate licensure and implementation of the vaccine—so that means working long hours, very efficiently and effectively.

It took several years for the neutralization assay we use in the HIV vaccine field to be ready and validated, to have standardized reagents, and to have a proficiency testing program for GCLP [good clinical laboratory practices] compliance in place.

Has your work with HIV made the process easier?

Having been through all that is very, very helpful. I know all of the steps and what we need to do and so it's just a matter of doing it as quickly and efficiently as possible. I can't emphasize enough how important it was that we had all of this experience with HIV.

Will the efforts to evaluate candidates in standardized assays make it easier to compare or rank them against each other?

We will be able to rank them much better than people can now based on neutralizing antibody titers because that data was generated using different assays in different labs, and there isn't enough standardization involved to do a formal comparison. For the Phase III trials, all the evaluations will be performed using the same validated, highly reliable assays. But keep in mind that although there may be differences in the titers of neutralizing antibodies that vaccine candidates generate, we don't know what magnitude is going to be needed to protect. That information will come from the immune correlates analysis. There might be two different vaccines that generate two different antibody titers, but as long as they are generating a high enough titer to protect people, that's what you want. We just need to know what that protective titer is, and the correlates analysis will be enabled by having validated and standardized assays.

Without that information, there has been an attempt to evaluate vaccine candidates by comparing the neutralizing antibody titers they induce to those seen in samples from recovering COVID-19 patients. Is that a reasonable approach?

There is quite a range of neutralizing antibody titers that you see in infected individuals, and the more severe the disease they experience, the higher the neutralizing titers tend to be. Given that range, which is orders of magnitude, you can't just randomly select convalescent serum samples and use that as your bar. It has to be standardized—everybody has to be comparing the results they get to the same convalescent sera samples—and there's been no standardization of that whatsoever, so it's been very difficult to really draw any conclusions based on these comparisons.

You also have been involved in tracking the mutation of SARS-CoV-2. How have the dominant mutations that have occurred affected the transmissibility or pathology of the virus?

Bette Korber started very early analyzing the sequences of the viruses that were coming in from investigators around the world and what she was interested in were any mutations that were occurring in the Spike protein, given that this is the protein in many of the vaccine candidates and is also the target of neutralizing antibodies. There were a lot of mutations that were occurring in Spike, which you would expect, but they're really not a concern unless you see that mutation in a lot of isolates because that is an indication that it is spreading. This was what happened with the D614G mutation, which spread rapidly and has been the dominant form of the virus for several months. The rate of spread and the way it spread indicated that this mutation was giving the virus a transmission advantage, which was what we eventually published in *Cell*.

And what was the reaction to this publication?

People wanted to discount this initially and attribute it to a founder effect, but Bette knows more than anybody else the importance of considering founder effect. We showed that this D614G mutation makes the virus more infectious *in vitro*, and many other groups are finding that now.

This mutation actually has been an advantage for us in setting up the assays. One of the things we struggle with the most with the neutralization assay is being able to produce a pseudovirus that is adequately infectious to do a neutralization assay. We struggled a lot with the original form of the virus, but when we started working with the mutated form, we were able to routinely produce infectious virus stocks, so it offered a technical advantage for those of us working on the assays.

But a question that was left unanswered when we published the *Cell* paper, was whether the D614G mutation would have an impact on our vaccines, which are based on the original strain. The question was: did this mutation arise to escape neutralization, and would this form of the virus be less sensitive to neutralization by the antibodies that the vaccines induce? It took me a while to get the relevant samples to do those experiments. I needed serum samples from animals and people that were immunized with the vaccines and serum samples from infected people, for whom we knew what form of the virus they were infected with. I finally got those samples and did the experiments and what we found was that not only was the gene mutation not a neutralization escape mutation, but in fact it actually makes the virus modestly more sensitive to neutralization. The hypothesis is that the virus acquired this mutation to give it a fitness advantage for transmission, but it came at the cost of making it modestly more sensitive to neutralization. It was a very exciting finding and it surprised us.

There have been some reports that the virus spreading in Africa is less pathogenic. Can that be attributed to viral mutation?

It's difficult to know. Those studies are very difficult to do since the original viral strain isn't around much anymore. In some of the studies that have been done there doesn't seem to be any association between the D614G mutated strain and disease severity. But whether or not it is responsible for diminished pathology more recently is very difficult to determine.

Are there any predictions about how the virus may mutate as the pandemic progresses?

Paul Bieniasz and others are generating escape variants of SARS-CoV-2 by culturing the virus in the presence of neutralizing antibodies that have been isolated from infected people and seeing how the virus is capable of mutating. That helps us identify mutations that the virus develops to escape neutralization. Those are valuable data for predicting what might actually happen in the pandemic. Fortunately, those mutations haven't occurred at a level where they spread much so far, but it's very important to keep analyzing the sequences in real time and for people to keep sequencing isolates so we can monitor the emergence of mutations that might actually lead to escape variants that spread enough to become problematic.

Interview by Kristen Jill Abboud

Global COVID Lab Meeting

Join us for the next Global COVID Lab Meeting on September 10th at 10:00 am EDT with Dr. E. John Wherry, Director at the Institute for Immunology and Chair of the Department of Systems Pharmacology and Translational Therapeutics at the University of Pennsylvania. His lab recently published a study in *Science* that uncovered distinct immunotypes in COVID-19 patients, which may have implications for the design of vaccines and therapeutics. Register for the webinar here.

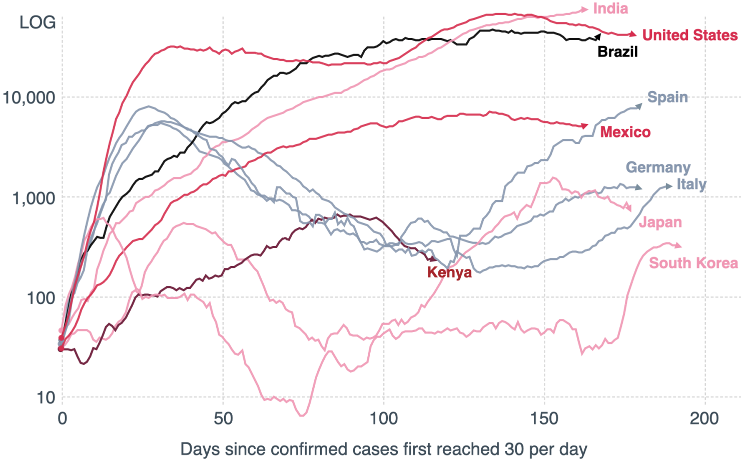
Must Read

More human and animal data on SARS-CoV-2 vaccine candidates were published recently, in addition to studies that are helping to elucidate the mechanisms underlying the variation in immune responses and immune dysfunction that occur in individuals with COVID-19.

- Human immunogenicity data supporting a pivotal efficacy trial of BioNTech's and Pfizer's RNA-based vaccine candidate appear in this preprint publication.
- Data from a study of Novavax's SARS-CoV-2 protein subunit vaccine in cynomologous macaques are available in this preprint publication.
- This preprint publication explores the magnitude and dynamics of T-cell responses to SARS-CoV-2 infection on both the individual and population level.
- This study in *Nature*, and an accompanying editorial, provides more evidence of a severely dysregulated immune system in severe cases of COVID-19.
- A deletion in the SARS-CoV-2 genome appears to be associated with a milder course of COVID-19 disease, according to this article in *The Lancet*.
- Data from a retrospective study of three fishermen with detectable neutralizing and other functional SARS-CoV-2 antibodies who were protected from infection amidst an onboard attack rate of 85.2% (104/122 individuals) are available in this preprint publication.
- This recent study in *Cell* shows that patients who died from COVID-19 showed a marked loss of T follicular helper cells, a lack of germinal center formation, and diminished antibody production.
- Differences in immune responses in men and women may lead to a sex-based approach for treating COVID-19, according to this study published in *Nature*.
- Data published in *Cell* show that a single intranasal administration of a chimpanzee adenovirus SARS-CoV-2 vaccine candidate prevented viral infection in both the upper and lower respiratory tracts of mice.

COVID-19 in Numbers

Daily New Confirmed COVID-19 Cases
January 21 - September 1



Source: European Centre for Disease Prevention and Control – Situation Update Worldwide – Data last updated 1 September, 10:04 (London time), Official data collated by Our World in Data

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