

Dr. Ruth Adewuya:

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Dr. Ruth Adewuya:

This episode is part of the COVID 19 mini series, and in today's conversation I'm joined by Dr. Robert Shafer. Dr. Robert Shafer is a Professor of Medicine and Pathology in the Infectious Diseases Division at Stanford University. He has more than 25 years of experience, and his expertise reflects the interdisciplinary nature of antiviral drug resistance research. Bob, I'm pleased to be chatting with you today. Thanks for coming on the podcast.

Dr. Robert Shafer:

Thank you, Ruth. I'm very glad to be invited and to have this opportunity to speak with you.

Dr. Ruth Adewuya:

We are recording this on October 10, 2020, and I think this conversation is timely and relevant to the conversations being had nationally on the use of monoclonal antibodies for the treatment of COVID-19. Before we start, just a quick note to our listeners, Dr. Shafer has a more detailed talk on this topic that can be found on our website at med.stanford.edu/CME. So let's jump right into our conversation. I always like to start these conversations with definitions, just to anchor some of our conversation. So maybe we can start with you defining for us what are monoclonal antibodies.

Dr. Robert Shafer:

Yes, well, within our bloodstream we have billions of the lymphocyte cells that are making many, many different types of antibodies, but a monoclonal antibody is essentially just one of those billions of antibodies. When they're used to treat a person, a single antibody is mass produced in large quantities. So it is quite a challenge to find a single antibody with the best properties to use as a treatment for an illness. And sometimes more than one antibody is used, but in combination as we'll see with SARS-CoV-2, but usually it's just one or two or three antibodies that are all exact replicas of each other.

Dr. Ruth Adewuya:

I wanted to dive into why monoclonal antibodies are a hot topic and a trending topic for the treatment of SARS-CoV-2. So we know that monoclonal have been used for treatment of other diseases such as cancer. Why do we think they are useful or they could be useful for the treatment of SARS-CoV-2?

Dr. Robert Shafer:

Well, there's a long history of antibodies being used to treat infections, and that began more than 100 years ago with serum from patients who've recovered from the illness being used to treat other persons with that illness. So that's the convalescent plasma story, and that's been used for many, many different infections. Generally, they haven't done the best randomized control trials to prove that that works in many of these cases, but the observational data has been very, very convincing in many circumstances, so that's one reason to believe that an antibody treatment would be useful.

Dr. Robert Shafer:

There've also been examples of polyclonal antibodies being used. In other words, patients who've recovered from an infection, to harvest multiple antibodies from them and concentrate them. That's been used to treat a number of infections successfully, like hepatitis B, CMV, rabies infection, so we have that experience also.

Dr. Robert Shafer:

Then finally, just within the past 25 years we've begun to use monoclonal antibodies to treat viral infections or to prevent them. So there is a monoclonal antibody to prevent respiratory syncytial virus infection, and perhaps even more convincingly two monoclonal antibody preparations were shown to reduce mortality due to Ebola virus infection. So clearly there's been some hope that antibodies could be a useful treatment for SARS-CoV-2.

Dr. Ruth Adewuya:

The breaking news or the trending topic right now is that there are, I think currently three monoclonal antibodies that have entered phase II, which I suspect is very encouraging, and phase III clinical trials as well. Is that accurate? I know it's in the news a lot lately.

Dr. Robert Shafer:

Yeah. There are three that are in phase II or three trials. Two of them are in phase III trials, and two of them are actually seeking emergency use authorization. So I think those two might become available within the next few weeks.

Dr. Ruth Adewuya:

What do we know about these two, at least? Can you go over maybe at a high level what we know about these two that may be released shortly?

Dr. Robert Shafer:

Yeah, so Lilly, the pharmaceutical company, in collaboration with others has developed a single monoclonal antibody preparation and a combination monoclonal antibody preparation, and both of these have been very, very effective in the laboratory and in animal models. They released preliminary data about three weeks ago, and then again on Monday, and the data showed that these antibodies are safe, that they reduce virus levels, and that among outpatients they appear to reduce the need for hospitalizations and ER visits.

Dr. Robert Shafer:

Unfortunately, the data, the numbers are not too great, basically because I think they released the data as soon as they kind of saw a signal of efficacy. So there definitely is a signal of efficacy and the data is trending in the right direction, and maybe it's understandable that given the urgent need for treatments, that they've gone ahead and released this so quickly and they've also announced that they're seeking approval.

Dr. Robert Shafer:

The same applies very much to the antibodies produced by the company, Regeneron. They have a pair of complimentary antibodies. They went into clinical trials about two to three weeks after Lilly in early June. They also issued a press release about two weeks ago, they reported that their antibodies were

safe, they also show that they reduce virus levels in persons who received the antibodies. They also reported the earliest hint of symptomatic improvement and decreased progression to disease. But again, it's really very early data and I hope we see more in the next few weeks.

Dr. Ruth Adewuya:

Are there other antibodies outside of these two companies that are currently under investigation?

Dr. Robert Shafer:

There were about 10 others in clinical trials, but the third one that's furthest along is developed by a company called Vir Biotechnologies. And they're close by in San Francisco. They've entered phase II trials. I think they have a trial of about 800 or so patients. So their program is not as far along as Regeneron's and Lily's.

Dr. Robert Shafer:

And I should say that Regeneron and Lily have a program that has three arms to it. They have an outpatient program, patients who are not that sick, the idea is to keep patients out of the hospital. They have a program for patients who are hospitalized, and they have a program for high risk contacts of persons with the disease. So that would apply for instance, to let's say, family members of somebody who gets ill or persons in a nursing home, probably eventually also healthcare workers who are exposed a lot to infection. So yeah, Vir is probably about two to three months behind. Their product, though is very interesting. They've also presented preclinical data in the scientific literature.

Dr. Ruth Adewuya:

Bob, you had mentioned that at least the two different companies that are moving forward with monoclonal antibodies are showing some efficacy in the treatment of SARS-CoV-2. I'm curious to get your thoughts on what are the implications of this becoming one of our options in terms of treatment?

Dr. Robert Shafer:

Well, first I have to say that it will be a while before they can really produce enough doses to meet the current demand, although they are working hard at this and already have capability, at least Lily does for 1 million doses. I'm not sure about Regeneron at this stage. And when these antibodies are available to the average person who becomes ill or exposed to SARS-CoV-2, I think they will definitely save lives. And they will also, I think reduce some of the fear that we have of what will happen if we become infected.

Dr. Robert Shafer:

I don't think though, they'll change the course of the epidemic as a whole in the United States. We really still need the vaccine to develop herd immunity, to prevent the ongoing circulation of the virus in our communities. In addition, they will not have that much of an impact worldwide, especially in the lower and middle income countries, because these antibodies are quite expensive to manufacture. So I think for the world as a whole, a vaccine is much more important because a vaccine is a much cheaper intervention, but the monoclonal antibodies are a great stop gap measure in the higher income countries. And it's good that they will be there for those persons who don't respond well to a vaccine.

Dr. Ruth Adewuya:

What are your thoughts around the use of monoclonal antibodies in providing us insight to creating the right vaccine for SARS-CoV-2?

Dr. Robert Shafer:

The monoclonal antibodies are useful at doing this because we can find out what they recognize, and if we see the monoclonal antibodies that recognize a certain protein of a virus, or even a certain part of the protein, if they work well at treating infection and at preventing infection, then we know that that's what we would like to see in a vaccine.

Dr. Robert Shafer:

In fact, when monoclonal antibodies are developed they're designed to recognize certain proteins or pieces of proteins, and once you find out that a protein or a piece of protein is very good at being able to fish out the right antibodies from the billions that we have in our circulation, then that is likely to actually be a good immunogen for a vaccine.

Dr. Robert Shafer:

Now, in this situation with SARS-CoV-2, the vaccines and the monoclonal antibodies are running neck and neck, but there has been a head start in the vaccine development because of the research community's experience with the first SARS Coronavirus and with MERS. It was already known that the spike protein is likely to be the best immunogen, and specifically the receptor binding domain. So the vaccine had a headstart because of prior experience with other Coronaviruses.

Dr. Ruth Adewuya:

So again, just a quick note again, a reminder to our listeners that Dr. Shafer dives into more detail on monoclonal antibodies and its potential uses for SARS-CoV-2 in his talk that can be found on med.stanford.edu/CME. So, Bob, thank you so much for just answering a few questions and sharing your insights with us today.

Dr. Robert Shafer:

Thank you so much, Ruth.

Dr. Ruth Adewuya:

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