Race against time: The complex task of developing a vaccine against the new coronavirus

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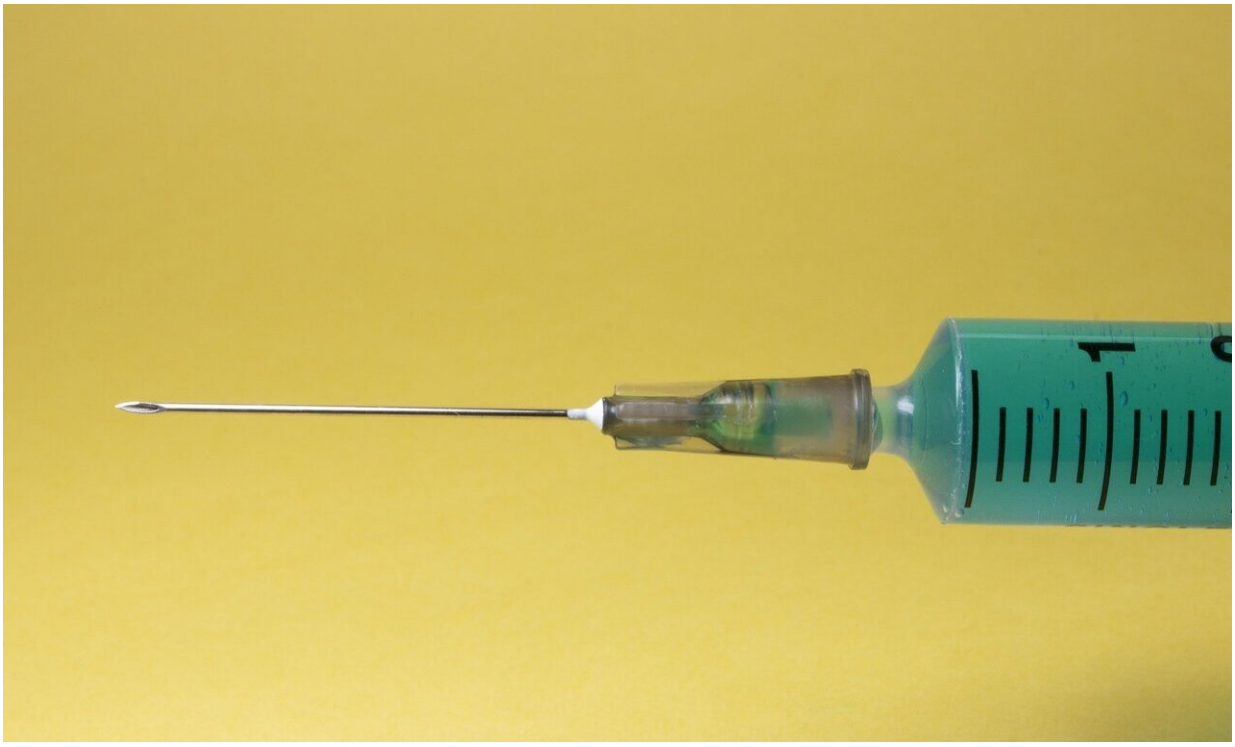

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LMU virologist Gerd Sutter talks about the complex task of developing a vaccine against the new coronavirus—and the approach he has adopted, which is already being tested against the related coronavirus MERS.

The whole world is waiting for a vaccine against the new coronavirus. How is your research progressing?

Sutter: We have essentially completed the gene technological phase of the work, and we are now setting up the first tests. We will, for example, test the genetic stability of our virus construct, and determine whether the desired antigen is expressed in its natural form when the engineered viruses are grown in cell culture. And we will check how well the growth rates of the recombinant viruses under these conditions.

How have you tackled the problem?

Sutter: We are working on what is called a vector-based vaccine. This approach involves the insertion of an innocuous segment of the genetic material of the new coronavirus into the genome of an established virus that can be grown in well characterized cell cultures. This segment of cDNA encodes the information for the synthesis of a specific protein that is found in the surface coat of the new coronavirus. The idea is that this surface protein should be capable of inducing a protective immune response, and can therefore be used as the basis of a vaccine that induces a protective immune response against the new coronavirus. We were very lucky that colleagues in China provided us with the genome sequence of the new virus very early on. This allowed us to modify the sequence obtained for SARS-CoV-2 to make it suitable for use in our virus vector, and ensure that it coded for, and could reliably produce the desired target antigen. The synthesis of the modified gene sequence was carried out by a commercial company that is specialized for the task. This DNA sequence was then inserted into our host virus to enable it to express the desired protein product. The vector system itself is well established and understood.

That's undoubtedly the result of years of basic

research.

Sutter: I have worked with this MVA virus as an immunogen for more than 30 years. MVA stands for "Modified Vaccinia Virus Ankara." This is an attenuated virus—which was developed in Munich—and has been approved as a vaccine against smallpox in Europe, the US and Canada. It provides us with a platform technology that allows us to place foreign genetic material under the control of the MVA's gene expression system.

Which components of the new coronavirus are you using?

Sutter: Coronaviruses got their name because, when viewed in the electron microscope, they look as if they have a halo or a corona—which made up of many copies of a spike-like protein that forms part of the surface of the virus particle. We make use of this spike protein as our antigen. The spike protein is essential for the replication of the virus. They need it to dock onto the surface of their host cell. This in turn causes the virus coat to fuse with the plasma membrane of the target cell, and permits the virus to introduce its genome into the cell. We know from our own studies on a diverse set of coronaviruses that the immune responses provoked by this surface protein are capable of efficiently blocking the infection of host cells.

You already have a great deal of experience with the spike proteins of coronaviruses.

Sutter: That's true. In the course of the last few years, we have made great strides in the development of a vaccine against the MERS coronavirus. This vaccine is based on precisely the same concept, which we are now turning against the new coronavirus. That's why we believe that this strategy is likely to be successful. Like the new virus, MERS

virus causes severe infections of the airways and the lungs, and there were several regional outbreaks of this disease in the years 2013-2015. We have shown that, following vaccination with the MERS antigen, antibodies are produced which inhibit the function of the viral spikes. This has been clearly demonstrated and verified in preclinical models. And there are initial tests in humans.

What do the studies tell you?

Sutter: All data we have collected so far strongly argue that it should be possible to develop a comparable vaccine against the new coronavirus SARS-CoV-2. The studies are carried out in close collaboration with the groups led by Marylyn Addo at the University Hospital in Hamburg-Eppendorf and Stephan Becker at Marburg University. All three institutions involved are also linked via the German Center for Infection Research (DZIF). Let me emphasize here that very few groups have had much experience with coronavirus-specific vaccines in humans. Our MERS vaccine is one of the very first to be tested in humans.

But the vaccine against the MERS virus cannot be used against the new coronavirus?

Sutter: That is the case. The spike proteins of the two viruses differ too much from one another.

And if you use the gene that codes for the spike protein of the new coronavirus, it should work?

Sutter: That is our basic assumption. To the best of my knowledge, all the researchers now working on candidate vaccines have chosen to use the spike protein as the target antigen.

So you have designed a virus that has the potential to induce an immune response against SARS-CoV-2. What happens next? How long is it likely to take to produce the vaccine?

Sutter: Preclinical tests can now begin. As a rule, such tests take 12 to 18 months, because they normally require very painstaking tests on animal models. In the current situation, this stage in the procedure is likely to take less time than that. I am confident that clinical tests of the first vaccine candidates—in humans—can be carried out this year. The aim of these Phase I trials is to characterize the tolerability of the vaccine and its ability to induce a specific immune response.

There have been reports in the media that feature photos showing volunteers being injected with candidate vaccines.

Sutter: Yes, these tests are being done in Seattle. In this case, what is called a messenger-RNA-based vaccine is being used, which was developed by the American biotech company Moderna, in cooperation with the US National Institutes of Health (NIH). This vaccine is made up of a single synthetic RNA sequence, whose protein product is expected to trigger a direct immune response to the virus.

Apparently this substance hasn't even been tested in animal models.

Sutter: I assume that preclinical data are available that justify its use in humans. I would be very surprised otherwise, as that would be incompatible with one of the central elements of the procedures required for the approval of new medicines. But I don't how the authorities are

treating this particular case. The NIH has, however, admitted that, even after first-in-human trials, it will take time to bring such a vaccine onto the market.

According to the World Health Organization (WHO), more than 40 projects are already underway with the aim of producing a vaccine against SARS-CoV-2.

Sutter: Yes, a lot of things are now happening. Among them are projects which, like ours, are inspired by the protective effects of the MERS vaccine, but other vector-based approaches are also being tried. Then there is a whole series of projects that involve the use of nucleic acids, such as those being pursued by Moderna or by CureVac in Tübingen. At this point, it's important to make use of all available technologies. If you asked me a year ago, I would have said that we would be very pleased if it took less than 2 to 3 years to get from the discovery of a new virus to a Phase-I trial of a new vaccine. Now, we can probably reckon with a year or thereabouts.

Phase I trials are designed to test whether the vaccine is well tolerated and whether it induces an appropriate immune response. What happens in the next step?

Sutter: An emergency situation, such as the one we are now experiencing, is capable of dramatically accelerating the development process. This was demonstrated, for example, during the 2013-2014 Ebola epidemic. In that case, one candidate vaccine was rapidly approved for a Phase-I study, and the process went from there to a large-scale Phase-III study, which allowed its efficacy to be assessed, within little more than 18 months. – Even so, by that time, the infection rate

had begun to fall off. However, when one considers the current situation with SARS-CoV-2, it must be clearly stated that the outbreak will have to be brought under control by other means than a vaccine—which is not to deny the importance of making an effective and broadly applicable vaccine available as quickly as possible.

In addition, its development should also help us to be better prepared for future cases?

Sutter: That's the avowed aim of alliances like the WHO's Blueprint Activity or the Coalition for Epidemic Preparedness Innovations (CEPI), a worldwide alliance that includes public institutions like the WHO and the EU Commission, research organizations, vaccine manufacturers and private donors. The basic idea is to develop structural frameworks or 'blueprints' for vaccines that can be rapidly repurposed for use against an emerging viral threat. Our MERS vaccine is a good example of this strategy. It's rather unfortunate that—at this stage—we should be confronted with a disease X caused by a previously unknown pathogen which has rapidly spread all around the world.

So far, we have made no mention of money in this context. Developing a vaccine against a new pathogen is a very expensive business. The sum of 2 billion dollars has been mentioned in connection with SARS-CoV-2. Is that a realistic estimate?

Sutter: Yes, the figure is in the right ballpark. Certainly, one must be prepared to invest hundreds of millions of dollars in the development of a vaccine.

US President Donald Trump allegedly offered the

CureVac company in Tübingen one billion dollars to develop their vaccine candidate exclusively for the American market. Is there anything in it?

Sutter: I don't know the details. But I do remember a similar reaction on the part of the American administration when the threat of bioterrorism first emerged. At that time, the American authorities also contacted firms around the world that had developed interesting technologies which might help to combat such a threat, and asked them if they would be willing to work as contractors for the US government. And—as I remember from the smallpox immunization program—these offers are obviously linked to an "America first" clause.

Aren't such incentives essentially immoral?

Sutter: Let me put it this way, in emergency situations like the present crisis, vaccine developers generally take the view that any effective products should be made available to all. CureVac's investors also made that clear.

Is the CureVac approach so very promising?

Sutter: I can't really answer that question because, as far as I know, their clinical data haven't been published yet. The basic concept of using messenger RNA for the direct production of immunogenic antigens is an elegant one. But as yet, we have no idea how these constructs behave in humans, quite apart from the quality control issues that may come up in the course of their large-scale manufacture. And even if the company already has a finished construct, meaningful tests of its efficacy and reliability will take time. We, on the other hand, can make use of a tried and tested vector system, which has already been shown to be compatible with large-scale manufacturing processes. The basic

construct has been characterized, and clinically tested—together with modified variants—in over 12,000 people. We now know how immunogenic the basic construct is, and what sort of side-effects it has. Of course, the new construct is specific for the spike protein of SARS-CoV-2, and the major unknown quantity is how the immune system will react to that. But all the other approaches now being tried also face this problem.

As a non-expert, one is tempted to say that it's already as good as a vaccine.

Sutter: But it isn't. One must remember here that what we now have are laboratory constructs. We still need to go through the various phases of the standard developmental process for vaccines. As far as I am concerned, we will only have a vaccine when our construct has successfully undergone Phase III trials and we have the go-ahead from the appropriate regulatory authorities—in other words, when the vaccine can be sourced from pharmacies. I realize that, in the current situation, this is a message that is difficult to communicate. But we need to rule out all the possible risks involved. The clinical investigations are very, very important, simply because we need to test the vaccine in large numbers of experimental subjects, in order to ensure that we have not just a tolerable, but a reliable means of protection against infection with the virus.

Public expectations that a vaccine should be available sooner rather than later can only grow. How do you, as a vaccine developer cope with this sort of pressure?

Sutter: Clearly, the pressure will continue to rise. Nevertheless, I believe that we must continue to inform the public and to underline the fact that there are no shortcuts. The process of development and testing takes

time—for very good reasons. For 6 years, I headed a department in the Paul Ehrlich Institute, the body responsible for the approval of vaccines in Germany. Of course, there are ways to accelerate the process, but only within certain limits. And I firmly believe that it will take at least 12, and possibly 18 months to produce a vaccine that is ready for use on a large scale. The task just can't be completed quicker than that.

Many politicians have suggested that only the arrival of a vaccine can release us from the present situation of social isolation, which is intended to prevent the deaths of thousands of people. What is your response to such statements.

Sutter: Be assured that all involved are hard at work to ensure that the job is done as fast as humanly possible.

Provided by Ludwig Maximilian University of Munich

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