Interview: Prof. Dr. Kremsner evaluates the current situation of the Corona Crisis

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***Abstract*- Over the last months, 24.000.000 people worldwide have been infected with the virus SARS-CoV-2, which is the causative agent of the disease COVID-19. Of those people, 800.000 have lost their lives. As a reaction to this, governments and public as well as private institutions from all over the world established numerous vaccine programs. In Tübingen, the infection biologist and Director of the Institute for Tropical Medicine Tübingen Prof. Dr. Peter Kremsner is the head of a phase 1 clinical trial, testing the mRNA-based vaccine developed by the company CureVac. In this interview, Prof. Dr. Kremsner evaluates the current situation of finding a cure, talks about the different approaches of designing a potential drug and gives personal insight into his academic career.**

***Index Terms*-** COVID-19, vaccine, clinical trial, interview

You are currently involved in three major vaccine studies. One that is an mRNA-based vaccine, another one that is based on the use of viral vectors, and a third one that uses virus-like particles. Could you explain the basic differences between the approaches to us a little more?

The first CVnCoV vaccine study has been in the 1st clinical phase since June 18. It is a so-called mRNA-based vaccine. The sponsor is the Tübingen company CureVac. In contrast to conventional vaccines, in which the patient or the test subject is given the antigen for immunization, this vaccine injects mRNA (the building instructions for a virus protein), in this case for the virus's spike protein. The mRNA then penetrates the cells and is translated by the cell's own translation machinery into a spike protein that the human body recognizes as foreign and then triggers an immune response. This reaction begins as soon as fragments of the S antigen are presented on the MHC complexes of the affected cells. The difficulty with mRNA-based vaccines is that the mRNA is a chemically unstable molecule that can - in vivo - be broken down by RNases. However, CureVac's research has managed to address these issues. At the end of the study, the subjects should show an increased level of nCov spike protein antibodies and nCov neutralizing antibodies.

In autumn, we want to start another vaccine study with Danish colleagues. This is called COUGH-1 and has the EU as a financial sponsor. In this study, our work will be based on a previously researched malaria vaccine. At that time, we incorporated the malaria antigen, which is used for immunization, into virus-like particles. Now for nCov this will be done analogously, using the antigen of the coronavirus. The study will begin with a small phase 1 that will be continued if promising results are shown. In accordance with the mRNA study, the blood concentrations of the nCov-specific antibodies will be examined fourteen days after the first and second vaccination. The third approach is based on Modified-Vaccinia-Ankara (MVA) virus vectors in which the S antigen is incorporated.

Which of the approaches do you think is more promising?

All of these approaches generally have a very high potential. Overall, we receive a large number of international requests for cooperation. Large, medium-sized, and small companies worldwide are currently trying to develop a vaccine. Globally, there are around two hundred vaccine programs right now, most of which are in preclinical studies until further notice. This means that these are still tested in a test tube or animals. There are about 30-40 serious programs at the moment, and 10-20 vaccine candidates that are likely to enter the final testing phase. Of course, we try to work on the most promising approaches, granting us conceptual freedom in our research and testing. For example, in the mRNA study we collaborated with CureVac in developing the clinical protocols.

Have you noticed a difference in working with other scientists since the pandemic has started? Did it bring all of you closer together or are you rather fighting in the search for an active compound?

Especially in times like these, we as scientists have to move closer together. At the same time, we also have to work more ambitiously. We will not be able to succeed if we all work individually. It usually takes 10 or even 20 years before a possible vaccine is designed and approved for selling. Decreasing this time to one to two years is only possible in a very close and well-coordinated cooperation. This is because despite the high-pressure work, no reduction in the very high standards of development, security testing, and especially in the work of the ethics committee can be made. At the moment, many groups are working together in the university area. We are in close contact with colleagues from the University Hospitals in Ghent, Hanover, and Munich when testing the CureVac vaccine. CureVac coordinates who takes which steps and when. But we are also currently in active contact with colleagues from the Netherlands, Denmark, Finland, and France.

Especially with regard to the CureVac vaccine, the work of the groups involved interferes very closely. Therefore, considering the central coordination by CureVac, it is more a friendly cooperation than a reckless conflict. However, you are of course

also happy if, as in our case, you can work on the most promising projects. I am therefore very optimistic that we will find a vaccine soon. However, I also believe that the CureVac vaccine will not be the only one that will soon receive preliminary approval because, as I said, there are numerous companies and working groups that are currently in the running. But that's good, because it means that there will be a wide range of corona vaccines in the future, which can offer more effective protection against COVID-19 in all parts of the world than protective masks and hand hygiene currently do.

When do you think the first COVID-19 vaccine will be available?

The studies are currently running smoothly. Right now, we are in phase 1 of the drug trial which means that we are administering the drug in the lowest dose to 168 healthy human subjects for the first time. The aim is to find out whether the vaccine is safe and does not do any harm. What is pleasing about this study is that we are in the luxurious position of being able to choose our test subjects due to the massive excess of applications, which is not common in many studies. It is not yet possible to make any statements about the concrete results, but the study is running very rapidly, which is promising for a phase 1 study. In fact, we aim to get the first results in the next two months, so that we can move on to phase 2 and, if possible, to phase 3 before the beginning of the next year. In the phase 2 tests, healthy 18 to 60 year olds will be vaccinated, as in the first phase, but risk groups will also be included. In the risk group, mainly those over 65 year of age and those with previous illnesses will be included.

It is then to be examined whether the vaccine still has the desired effect and to determine the amount of the vaccine that needs to be administered for one person to build up an immunity. As of right now, the phase 3 study, aka the approval study, will very likely become a classic placebo-controlled, blinded, randomized, multicentre study, in which, in addition to the safety and tolerability of the vaccine, its effectiveness will also be tested for countries that were heavily affected by the virus. The extension to other countries is important because we can then test the vaccine in many different patient groups and later possibly even offer it worldwide.

I believe that the CureVac vaccine will be approved by the end of next winter, mainly because of the joint efforts, and can then be administered to a broader population. In fact, many companies are already adjusting and increasing their current production of drugs and other vaccines to be able to meet the demand in the following years.

Recently there were news reports that cured COVID-19 patients show a measurable decrease in neutralizing antibodies in the blood. This is seen as an indication that the permanently acquired immunity to SARS-CoV-2 may decrease. Do you see the vaccine effort at risk?

Of course, this is a phenomenon that still needs to be investigated, but the immune system and in particular the acquired immunity cannot simply be characterized by measuring the antibody concentration. The immune system is a very complex system in which cellular components such as lymphocytes play an important role. To evaluate the chances for the effectiveness of an active ingredient, one must examine the dynamics of the entire immune system. There are other viral diseases in which immunity can be acquired that is not necessarily detectable by an increased antibody concentration. Therefore, despite these reports, I do not consider efforts to get a vaccine at risk.

Teams of young students compete against each other at the iGEM competition. In contrast to us, you can look back on a very successful and long scientific career. If you had yourself in front of you as a student, what advice would you want to give him for his career as a scientist?

The most important qualities in my experience are hard work, perseverance, and self-organization. I can remember how I always got up at six a.m. in my first semester to study as much as I could before the lectures started. This made it possible for me to spend my free time however I liked it. For example, I enjoyed going to the opera even when I was still a student. You will not be successful without discipline. But it is also important to specialize in what interests you most as early as possible in your studies. During my studies, I specialized in the field of infectiology as early as I could and worked on corresponding projects. This enabled me to gain experience as a young student and gain insight into current research, which helped me a lot for my future career.

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