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OVERVIEW

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The development of science is uninterrupted

Interview with Prof. Katalin Karikó, elaborator of the mRNA-mediated therapy

Abstract

Both Pfizer-BioNTech's and Moderna's corona virus vaccines have been developed on the basis of the mRNA-mediated therapy, discovered by Katalin Karikó, Hungarian-born professor and senior vice president of BioNTech and her co discover, Drew Weissman, professor of the University of Pennsylvania. The greatest scientific achievement of Katalin Karikó's research work over more than two decades is the elaboration of the mRNA-mediated method for therapeutic application. For Professor Karikó the special milestone was the moment when the first

vaccine for COVID-19 was created based on this technology. Her breakthrough discovery has a potent scientific importance in vaccine research, as people are all around the world are hoping for the end of pandemic and lockdown restrictions with arrival of vaccines, wishing that life could finally return to normality. However, we have to remark that several questions emerge concerning the mechanism of action of this new type of vaccines, their side or long-term effects, as well as the duration of immunity or the risk of reinfection. These questions lead to uncertainty in connection with vaccination, therefore clear answers needed. In the fight against the virus, beside healthcare workers, military and police personnel belong to the category of highest risk of infection, therefore, it is crucial to achieve as high vaccination rates in their ranks as possible. To reach this goal, it is important to have authentic information about the vaccine and the indicators of the immune response. As, the unknown always creates fear and uncertainty we intend to put an end to such fears with the help of this interview with Katalin Karikó and to support hesitant colleagues' decision-making process to get themselves vaccinated. We asked Professor Katalin Karikó about vaccine research, the wide area of application of the mRNA-mediated therapy, about skepticism concerning vaccination and about her personal connections to police forces and to scientific research in the field of law enforcement. She was interviewed by Valér Dános and Csaba Szabó.

Keywords: mRNA, science, vaccine, COVID–19

Mrs. Professor, you have been searching mRNA for a long time, while other researchers have preferred gene therapy. The result of your researches – the mRNA-mediated therapy – is the basis of the Pfizer-BioNTech vaccine. When was the moment that you recognised that this technology might be suitable for a vaccine for coronavirus?

To understand this process, we have to go back a bit in time. In 1990 started the Human Genome Project (HGP) in the United States, when gene therapy methods were foregrounded. HGP was a large-size international research cooperation between 1990 and 2003, mapping the total human genome, identifying in this way our complete set of genes and mapping all genes. During this work, function of certain genes were getting known in more and more detail, and recognition of diseases due to these genetic errors were becoming evident. At this time all was about gene therapy. Other researchers and myself dealing with this special area, emphasized frequently that for treating most diseases, gene therapy is not needed. I have then declared dauntlessly and decisively that mRNA offers a much more effective therapeutic opportunity. For example, wound heal-

ing or bone remodelling can be potentiated by temporary proteins produced by the use of this technique. No consideration was then taken into account at that time, of this m RNA therapeutic possibility because gene therapy was dominant then, it was the decade of the human genome.

Besides, we have to consider that the technology needed for research became accessible in the second half of the eighties. The scientific journal Science introduced the title *'The Molecule of the Year'* in 1989 that was awarded the first time to Taq polymerase (Guyer & Koshland, 1989). It made possible the effective formation of appropriately formed DNA sections. The transcription from DNA to RNA was already known that time. Important development was achieved also with the inclusion of nucleic acid into cells as liposomal transfection (lipofection) that was introduced in 1987. It is well perceptible, how much happened at the end of the eighties, practically a scientific revolution was evolving.

The stagnation of the gene technology can be connected to 1999, when Jesse Gelsinger, a voluntary suffering from OTCD disease, was treated with gene therapy method at the Pennsylvania University in Philadelphia. The researchers of the university checked the opportunities how to correct the OTC gene. They tried to achieve production of the deficient enzyme due to the disease to avoid the accumulation of ammonia, responsible for the symptoms. During the therapy, the patient was injected the correct OTC gene built into an adenovirus-vector. The virus (modified to be harmless) infected the liver cells of the patient, getting in this way to the appropriate place and inserted the gene into the chromosomal DNA of the liver cells. Unfortunately, Jesse Gelsinger died four days after the gene therapy (URL1).

The first steps for vaccination with mRNA were made by French researchers in 1993, packed into lipid for prevention of flue infection (Martinon and colleagues, 1993). In the course of my researches, I have experienced the first surprise when the examinations proved that the injected RNA triggered an inflammation process in the body. We may ask how RNA can cause an inflammation although it is present in all our cells. The answer is that RNA in our cells is created in the cell nucleus, while in case of RNA therapy or vaccination it is introduced into the cell from outside. In this sense, when RNA is located outside the cell membrane, i.e., outside the cell, it poses a real danger, as it may signal the presence of a virus, or it can also emerge from a damaged cell. The body then tries to fight and protect against this danger.

In the course of my research, I began to think further about how to ensure that RNA delivered from the outside does not cause an inflammatory response. That is when I realized what different changes can be successful. The solution was the modification of a nucleoside - an mRNA building block. We then experimentally

confirmed that after the modification, the modified mRNA introduced from the outside no longer causes inflammation in the body. It was also important to solve another problem: during the production of mRNA, many by-products can be produced, also triggering inflammatory processes, and their identification and removal by a purification process had a crucial importance for applicability. The cleaned and modified mRNA could be transferred into the cell without unexpected, harmful consequences. The technology developed in this way has been tested in the development of vaccines against various viruses since 2017, including Zika virus and influenza virus. Our results indicated that the application of the elaborated method can fight successfully against other viruses, as well.

What is the difference between the mRNA-mediated vaccine and earlier vaccines in your opinion?
For the production of traditional vaccines, protein fragments produced via recombinant DNA technique of attenuated or killed pathogens or strains responsible for the infection have been used. In case of the vaccine developed by us, the mRNA coding the spike protein found on the surface of the coronavirus is vaccinated. The delivered mRNA produces then in our cells the protein and responding to that will develop the suitable protection for our organism. In this way we can obtain the production of the specific antibody that will protect us in case of an infection. The effective immune reaction in case of the mRNA-mediated vaccine is combined with an outstanding safety profile and a flexibility of the change in genetic information. On the contrary, in case of a vaccine containing an attenuated pathogen, which is capable of division, antibodies are produced also against particles almost unnecessary for prevention. Knowing the genetic material of the virus and the way of infection it is possible to select the part of the virus that could be the target of protection and antibody production of the body. The modelling of the appropriate part of the pathogen by the mRNA technology can be planned rapidly and so the human organism will act specifically against this part of the virus.

In which other areas can the mRNA technology patented in 2005 be effectively used? Can this vaccine remain effective against mutations of coronavirus, too?
Among pharmaceutical companies, AstraZeneca was the first to use the mRNA-based technology in human trials. The first trial was conducted enrolling cardiac patients, where the goal was to improve the condition of patients with myocardial infarction by neoangiogenesis. In another study they applied mRNA-mediated therapy for diabetes patients to heal dermal ulcerations by facilitating tissue regeneration. Other pharmaceutical companies have clinical trials in progress

for vaccines against several pathogens and for treatment of deficiency diseases or neoplastic diseases.

In case of infections the mRNA technology is applicable not only for vaccination, but it also can deliver information on antibodies to be produced. When we inject antibody-coding mRNA, 2-3 hours later an amount of protein will be present, i.e in which case an antibody may be produced which provides protection against certain pathogens in humans. The aim of these researches is to develop a special mRNA for persons working in the frontline in case of infections, e.g., policemen, so they can be protected within a few hours against that pathogen. For the treatment of malignant tumour diseases, a similar principle is used, by delivering mRNA coding antibodies. These kinds of research have been conducted since the beginning of year 2000. The great difficulty here is, that the detailed identification of the given medical condition takes a long process. Clinical researches are also in progress for patients with cancer disease, applying this method into the tumour itself. This means in case of tumours, e.g., melanoma, that mRNA can be injected directly into the tumour tissue. It is important to use modified mRNA, otherwise we can get a different immune response, different effect and result. In case of tumours, you have to deal with numerous mutations that make selection of the appropriate antibody more difficult. mRNA-mediated therapy can be used in many specialities and in many researches, I mentioned only the main research areas previously.

In my opinion, in connection with coronavirus mutations the vaccine, developed in common work of Pfizer and BioNTech, most probably will provide protection against more virulent versions of the new coronavirus, as well. It is important to emphasize, that the vaccine needs further development to apply it against newer mutations, when needed. Of course, further research is needed to clarify the question.

How does the scientific society evaluate the importance and effectivity of the Pfizer-BioNTech vaccine? Did not you meet professional envy?

The importance and effectivity of the Pfizer-BioNTech vaccine is – in my opinion – appropriately recognised by the scientific society, achievements are accepted, although there are always sceptics and others calling for fraud. That is true that I am quite resistant against professional envy. I have always visualised what I can do to help science and development. As people cannot be changed, I never deal with the question what others do in the wrong way. What really matters is what I can do to solve a task. Further I will continue my work further in this way. The most important thing is that problems due to professional envy should not infect the way I think. A kind colleague of mine said that you might

meet such opinions at work, but these are only noises and you should not pay attention to them. Otherwise, we are unable to concentrate on our own work. You can image that you cannot go ahead if you constantly listen to not supportive and criticising voices, due to envy.

What do you work on nowadays, Mrs.Professor?
At the present, my main research area is in connection with antibodies, among them we work on several projects in cooperation. I would stress out our common work with the Bill & Melinda Gates Foundation, where we develop effective vaccines in an innovative way to be able to help those who mostly need them (URL3). These researches aim prevention and treatment of most dangerous infectious diseases, our result may offer a solution for them.

What is your message for your Hungarian compatriots, how should they position themselves towards vaccines? And what is your message for vaccine deniers?
Years, even decades were sacrificed every day of our lives together with my fellow researchers to be able to offer an effective answer on the emerged problems We have worked together with colleagues, coming from several countries, for our common goal. Every piece of relevant information was made public to resolve all doubts, doubting voices and thoughts of people. If after that doubts are still remaining, nothing can be done about it. Unfortunately, there are determined people, believing in something that cannot be changed. But on the other side, there are people more open for answers given by science. I believe that in science the opinion of others is important, too. We look at the same problem, but we formulate different opinions regarding the solution. Scientific progress requires professional criticism of others to be heard, as it might be right and then we realize that the specific experiments do not corroborate our hypotheses. We have to be open to receive criticism. In science constructive criticism brings results, which make it more crystal clear, and thus is capable of further development and progress. I would be glad if people in Hungary could hear each other's supportive criticism, because whoever is on one side of a debate often listens and hears the opinion and position of that side. Openness and forming appropriate dialogues are important. Nowadays these attributes are lacking in people. My message to my Hungarian compatriots is to pay attention to what others say and to take care of each other. It is a very typical form of behaviour that while the other is talking, many people start thinking about how to refute what the other is saying. In the development of science constructive professional criticism is relevant. Constructive criticism is the most important for development of science, as it can guide us towards solutions and results.

It is a common interest of the society to get as many people as possible inoculated by the vaccine. In your opinion, might it be possible to force inoculation by law enforcement measures?

In my opinion, nobody in the world should be forced to accept vaccination, neither in Hungary nor in the United States. However, persons who are not vaccinated may be excluded from participation in community life. I am thinking here as an example of the importance of going to school, where it is an essential aspect and a public interest that children receive age-compulsory vaccinations. These vaccinations are required by the state. Children who do not have mandatory vaccinations are not allowed to attend school. On the other hand, shedding light on the issue, two negative coronavirus tests are currently required for travel. I see an opportunity in reducing the power of those who refuse a vaccine, with the help of regulations, which would motivate them to take their own decision of getting vaccinated.

Do you have any family, professional, friendly contacts to police or to law enforcement researches?

My cousin and her husband were police officers in Hungary but that was long time ago and they have not talked very much about their works. I have heard much more from a member of my present research group, Mr. Jonas Reinholz, researcher of BioNTech, who made examinations led by Andreas Hellmann in the topic of trace analysis at the German Federal Criminal Police Office and at the German Forensic Scientific Institute (URL2). The reason of my openness for the criminal branch is that my daughter has a master diploma in criminology.

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Online links in this interview

URL1: *The Death of Jesse Gelsinger, 20 Years Later*. https://www.sciencehistory.org/distillations/the-death-of-jesse-gelsinger-20-years-later
URL2: *CaDNAP group*. https://cadnap.org/cadnap-group/
URL3: *Combat infectious diseases*. https://www.gatesfoundation.org/

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