

**Laudatio
von
Prof. Dr. Sir John Walker**

**anlässlich der Verleihung
des Paul Ehrlich- und Ludwig Darmstaedter-
Preises
2022**

**an
Prof. Dr. Katalin Karikó
Prof. Dr. Özlem Türeci
und Prof. Dr. Uğur Şahin**

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Es gilt das gesprochene Wort!

Anrede,

A little over two years ago, in December 2019, in the city of Wuhan in Hubei province in China, a novel virus was identified from an outbreak of an illness that affected the human respiratory system. This illness is now familiar to us all as coronavirus disease-2019, or COVID-19. Attempts to contain the virus failed, and it spread rapidly across the globe. On 30 January 2020, the World Health Organization (WHO) declared a Public Health Emergency of International Concern, and on 11 March 2020, a pandemic. As we meet here today, this pandemic has caused over 420 million cases and almost 6 million deaths, making it one of the deadliest ever. But for the remarkable story that I am about to relate, the effects of this pandemic would have been unimaginably worse.

In the mid-1960s, scientists in Britain and France proposed, and then showed, that molecules of messenger-RNA (or mRNA) carry genetic information from the DNA in the nucleus of biological cells to cellular machines in the cytoplasm. These machines, known as ribosomes, read the instructions in the mRNA to make proteins from the twenty naturally occurring amino acids. In this process, the genetic information in DNA is translated into the diverse biological functions of proteins.

The idea of injecting mRNA into animals and humans in order to produce a specific protein that would then elicit a beneficial immune response goes back into the late 20th century, but the idea was thwarted by the instability of the mRNA molecules. To make matters worse, our immune system treats injected naked mRNA molecules as undesirable trespassers. Toll-like receptors recognise them, inflammatory signal molecules are released, and the translation of the protein from the mRNA is inhibited. At the end of the 20th century and in the early years of this century, the first of our three Laureates, Katalin Karikó, a Hungarian biochemist working at the University of Pennsylvania in Philadelphia, took the initial significant steps towards solving this conundrum of how to introduce mRNA effectively into living cells. She discovered that by replacing specific ribonucleotides in mRNA with similar, but chemically modified versions, she could stabilise the mRNA, and at the same time weaken the body's defence response to the mRNA, thereby significantly increasing intracellular protein production.

Our two other Laureates, Özlem Türeci and Uğur Şahin, German medical doctors of Turkish origin, are married to each other. Working together with research teams at the Johannes Gutenberg University of Mainz, and encouraged especially by Professor Christophe Huber, they

built on Katalin Karikó's initial breakthrough. They conducted a systematic study of how intracellular protein production is influenced by each of the characteristic features of the injected mRNA molecules: the 5'-cap; the 5'-untranslated region; the codons that specify the amino acids; the 3'-untranslated region; and the 3'-polyA tail. In this way, they optimized and vastly boosted the translation of the mRNA molecules into proteins. They also adopted and improved methods for encapsulating the mRNAs in lipid nano-particles to protect them from degradation. An additional benefit of encapsulation of the mRNA molecules was that it stimulated their uptake into specific dendritic cells located in lymphoid tissues. These particular dendritic cells act as antigen presenting cells, and they are important in evoking specific immunological responses.

From 2005 onwards, Drs Türeci and Şahin focussed on targetting potent vaccines against specific antigens on the surfaces of cancer cells. Their goal was to evoke an immune response in a patient that would recognise the patient's cancer cells and destroy them, and by 2020, they had developed a personalised mRNA therapy against a human melanoma. This extraordinary medical advance has opened the way to a new era of personalised mRNA vaccines, that can be tailored, as required by the tumor mutations in any cancer patient. Remarkably, such specific vaccines can be produced on demand within two weeks. Other scientists in the mRNA vaccine field have benefitted from their methodologies, which were made generally available via prominent publications since 2014.

An important feature of the activities of Drs Türeci and Şahin is that they were not conducted solely in University laboratories, but crucially they extended also into spin-off companies, and especially into BioNTech, which they founded in 2009. The founding and development of BioNTech needed knowledge, vision and technical know-how, plus another vital ingredient, finance. This finance was provided most notably by Thomas and Andreas Strüngmann, and other important funds came from the German Government and the European Union. Another decisive factor in the success of BioNTech has been the close collaborations with Pharma, with Genentech and Pfizer among others.

In January 2020, when Drs Türeci and Şahin read about the emergence and alarming spread of COVID-19 in Wuhan and surrounding regions, they immediately diverted some of the resources of BioNTech towards developing an mRNA vaccine against the coronavirus. They were helped at this point by the release of the sequence of the viral genome, which allowed them to launch a program code-named Lightspeed to develop a new mRNA vaccine against the viral spike protein, which extends from the external coat of the virus.

Today, it is astonishing to relate that in less than 11 months, Drs Türeci and Şahin and colleagues were able to engineer, manufacture and test many mRNA vaccine candidates, leading eventually to BNT162b2, an mRNA lipid nanoparticle vaccine encoding part of the viral spike protein. Here, their collaboration with Pfizer has been crucial. Together with Pfizer, they recruited 44,000 participants of various ethnicities spread around the world into clinical trials of this particular vaccine. These trials established that the vaccine induced a safe and effective immune response in humans, and together with Pfizer they also dealt expeditiously with the various regulatory authorities who authorised the wide-spread use of the vaccine in clinical practice. Thus, BNT162b2 became the first mRNA drug, and, in parallel with the vaccine developed by Moderna, the first vaccine able to prevent COVID-19 to be authorised for human use.

In November 2021, WHO announced the emergence of the omicron variant of the virus, and in a very short time Drs Türeci, Şahin and colleagues, had adapted their procedure to produce a vaccine against this variant. Today, we can envisage that their process for rapid development of mRNA vaccines will be employed against future pandemics and other infectious diseases.

In 1796, Edward Jenner introduced vaccination into medicine when he inoculated his gardener's 8-year son with cowpox lesions taken from the hands of a milk-maid. In the 1880s, Louis Pasteur developed a vaccine against rabies. By the mid-twentieth century, vaccines had been developed as inactivated pathogens, or as modified toxins called toxoids, for treating diphtheria, pertussis and typhoid. It is also worth recalling that Paul Ehrlich himself had the idea of applying vaccination to generate immunity against cancer; his approach was to inject weakened cancer cells.

The novel mRNA vaccines stemming from the work of Katalin Karikó, and developed by Özlem Türeci and Uğur Şahin, usher in a new and exciting era in vaccinology that can be applied to both cancer and infectious diseases, as well as providing the means to treat other diseases by providing missing or corrected proteins.

Katalin Karikó, Özlem Türeci and Uğur Şahin, it is a great honour and a pleasure for me to address these words to you today. Your extraordinary achievements make you to be the most worthy recipients of the 2022 Paul Ehrlich and Ludwig Darmstaedter Prize. You deserve the gratitude of all of us here today, plus countless millions world-wide who have benefitted from your vision and devotion.