Dankesrede

von

Prof. Dr. Uğur Şahin

anlässlich der Verleihung

des Paul Ehrlich- und Ludwig Darmstaedter- Preises

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Es gilt das gesprochene Wort!

Distinguished Guests, Ladies and Gentlemen,

On behalf of my esteemed colleagues Katalin Kariko and Özlem Türeci, I would like to express our sincere gratitude to the members of the Scientific Council of the Paul Ehrlich Foundation, to Prof. Sir John Walker and to Prof. Thomas Boehm.

We are deeply honored to receive the Paul Ehrlich and Ludwig Darmstädter Prize. We are humbled to be among the renowned scientists who have received this award in the past. We believe that this is not only a recognition of our own work, but also a recognition of the efforts of many scientists who helped to establish mRNA as a powerful new drug class.

We also are honored to receive this recognition at such a historic site, an important place in German democracy where civil rights were first anchored in law. In times like these, it is important to stand on the side of democracy, freedom and solidarity.

The history of messenger RNA as we know it today began more than 60 years ago. After the structure of DNA was described in 1953 by Watson and Crick, DNA became broadly recognized as the carrier of genetic information. What remained unclear was how this genetic information was translated into protein. In 1961 two studies published side by side in Nature showed that an unstable ribonucleic acid is transcribed from DNA as a copy and carries the information from genes to ribosomes for protein synthesis. Both studies used the term messenger RNA (or mRNA) for this new form of carrier, a term which had been coined by Jacob and Monod in a seminal review in the same year.

The next 2 decades of research focused on the enzymes involved in mRNA biology, its structural elements, the function and regulation of mRNA in cells. Researchers isolated mRNA from cells and transfected them into other cells confirming that mRNA introduced from the outside is capable of instructing the synthesis of proteins. Various reagents were discovered that facilitated the procedure of “transfection”; and the first lipid transfections were published in the mid-1970s.

In 1984 the first detailed description of synthesis of molecularly defined mRNA by in vitro transcription from a DNA plasmid template using phage RNA polymerases was reported. Starting 1990 mRNA was injected into animals and by 1993, for the first time, mRNA was used to vaccinate mice against influenza.

As young scientists in the 1990s, on different sides of the Atlantic, Katalin, Özlem and I became very interested in mRNA. We believed that it is ideally suited to deliver therapeutic proteins to the human body. Unlike DNA, which carries the risk of mutagenicity, mRNA is not prone to being integrated into the genome of the target cell. We believed that this instability was actually a useful feature of mRNA. Because mRNA is degraded rapidly, its temporal effects can be well controlled.

We recognized its potential, but also understood the challenges we needed to solve: How to prevent degradation of mRNA before it could even take action? How to deliver mRNA to the right cells in the body? And how to achieve efficient translation into functional protein to mediate the intended biological effect?

Our work over three decades generated solutions to overcome these problems and formed the basis for the development and successful use of mRNA medicines in humans. This required the discoveries of several puzzle pieces.

One puzzle piece was to improve mRNA’s tolerance in the body and to increase their translational performance. Our colleague Katalin Kariko began her work at the University of Pennsylvania with the goal of introducing mRNA into living cells to replace missing or defective proteins in patients with inherited diseases such as cystic fibrosis. She found that externally delivered mRNA is sensed by three Toll-like receptors that activate the innate immune system, thereby limiting protein production in the host cells.

She found that replacing the uridine building block in mRNA with the corresponding naturally occurring modified nucleoside prevents recognition by Toll-like receptors and immune activation. This discovery provided a solution to attenuate the endogenous defence response against synthetic mRNA, improve tolerance, and consequently significantly increase translational performance. This finding is particularly important if mRNA encodes proteins for which an immune response is not intended or is even harmful. Both approved COVID-19 mRNA vaccines carry this modification.

At the same time in the 1990s, Özlem and I were working on cancer vaccines. We had a vision that was considered fiction at that time. Because every patient's cancer is unique, we wanted to use mRNA for individualized vaccines that would activate the patient's immune system against their own tumor. However, the mRNA vaccine vectors used at that time elicited poor immune responses, 100- to 1,000-fold weaker than required to control established tumors. By systematic research we discovered modifications of mRNA in certain structural elements such as the cap, poly(A), and untranslated regions that increased intracellular stability and cellular translation of mRNA. While each individual modification had a significant effect on mRNA translation or stability, we found that the combination of modifications within the mRNA scaffold exponentially improved the mRNA potency, resulting in transcripts with prolonged and greatly increased translation. This was another puzzle piece to improve mRNA medicines. These systematic principles we introduced for mRNA vaccine design later became the widely used standard for optimizing vector scaffolds for mRNA therapy.

The next piece of the puzzle was to find out how to get the mRNA vaccine to the right cells in the body. In a preclinical experiment in 2004 we made an interesting observation. The direct injection of mRNA vaccine into a lymph node elicited a much stronger immune response than injection of mRNA into the skin or muscle, which are the usual routes of administration. To our surprise, the mRNA in the lymph node was efficiently taken up by the resident dendritic cells. These immune cells are the "high-performance trainers" of the immune system and mediate particularly strong immune responses. We realized that directing mRNA vaccines into dendritic cells in lymph nodes had to become a critical part of the solution.

In the years that followed, we explored various methods of delivering the mRNA to these cells in the body. We discovered lipid nanoparticle mRNA formulations that acted like a zip code: After intravenous administration, the mRNA vaccines encapsulated in this particular lipid nanoparticles were efficiently taken up by dendritic cells in lymphoid tissues throughout the body. Vaccine-induced T-cell responses were extremely strong and eradicated large tumors in mice.

We started human studies and pioneered in 2015 the first systemic delivery of mRNA nanoparticle vaccines to humans. We observed strong immune responses against tumor antigens and shrinkage of metastatic tumors with the vaccine alone or in combination with checkpoint blockade in a proportion of our patients.

Putting the pieces together, these findings provided the blueprint for the development of highly effective mRNA vaccines. As long as the optimized mRNA is introduced into the lymphoid tissue in a suitable nanoparticle formulation, dendritic cells take it up and trigger strong immune responses.

These advances have also allowed us to successfully realize our original concept of cancer vaccines tailored to the unique set of mutations of each patient's tumor. The approach involves genomic analysis of the patient's tumor, design of a vaccine tailored to the patient's individual cancer mutation profile using computerized algorithms, and optimized technical processes for rapid and reliable production and quality control of this novel mRNA vaccine within less than 6 weeks. In our first melanoma clinical trial, all patients developed a T-cell response against multiple mutations encoded in the mRNA vaccine. The T-cells recognized the patients' tumor cells, and the cumulative metastasis rate was greatly reduced in these patients after vaccination was initiated. Human studies are currently underway in patients with various

cancer types. The approach represents a potential paradigm shift as it can be applied to almost any type of cancer.

In 2013 Katalin joined our laboratory at BioNTech. Together, we combined the modifications that we had independently discovered and optimized. In addition, we investigated various lipid formulations suitable for delivery of nucleoside-modified mRNA via different routes of administration. Through our joint efforts, we have advanced mRNA applications for antibody therapy, pioneered the use of mRNA vaccines for tolerance induction, and autoimmune disease treatment.

In January 2020 the world faced an unprecedented new challenge: the SARS-CoV2 pandemic. The rapid release of the sequence of SARS-COV-2 allowed us at BioNTech to initiate a vaccine discovery program. The facile nature of mRNA technology enabled us to engineer, manufacture and test in parallel more than 20 mRNAs vaccine candidates within a few months. We identified BNT162b2 as the candidate that elicited the best immune responses. The safety and strong efficacy in humans of this candidate was demonstrated by collaborative work between BioNTech and Pfizer. BNT162b2 became the first vaccine – and the first mRNA drug – with proven efficacy to prevent COVID-19, and the first authorized for human use. All of this was possible because of the foundational work we and our colleagues had developed over decades of research.

More than one billion individuals have already been vaccinated in more than 170 regions worldwide, and countless lives have been saved.

Finally, on behalf of Özlem and Katalin, I would like to thank all our scientific colleagues, for their immense support.