Nobelförsamlingen
The Nobel Assembly at Karolinska Institutet

October 2, 2023

The Nobel Assembly at the Karolinska Institutet

has today decided to award

the 2023 Nobel Prize in Physiology or Medicine

jointly to

Katalin Karikó and Drew Weissman

for their discoveries concerning nucleoside base modifications that enabled the development of effective mRNA vaccines against COVID-19

The discoveries by the two Nobel Laureates were critical for developing effective mRNA vaccines against COVID-19 during the pandemic that began in early 2020. Through their groundbreaking findings, which have fundamentally changed our understanding of how mRNA interacts with our immune system, the laureates contributed to the unprecedented rate of vaccine development during one of the greatest threats to human health in modern times.

Vaccines before the pandemic
Vaccination stimulates the formation of an immune response to a particular pathogen. This gives the body a head start in the fight against disease in the event of a later exposure. Vaccines based on killed or weakened viruses have long been available, exemplified by the vaccines against polio, measles, and yellow fever. In 1951, Max Theiler was awarded the Nobel Prize in Physiology or Medicine for developing the yellow fever vaccine.

Thanks to the progress in molecular biology in recent decades, vaccines based on individual viral components, rather than whole viruses, have been developed. Parts of the viral genetic code, usually encoding proteins found on the virus surface, are used to make proteins that stimulate the formation of virus-blocking antibodies. Examples are the vaccines against the hepatitis B virus and human papillomavirus. Alternatively, parts of the viral genetic code can be moved to a harmless carrier virus, a "vector." This method is used in vaccines against the Ebola virus. When vector vaccines are injected, the selected viral protein is produced in our cells, stimulating an immune response against the targeted virus.

Producing whole virus-, protein- and vector-based vaccines requires large-scale cell culture. This resource-intensive process limits the possibilities for rapid vaccine production in response to outbreaks and pandemics. Therefore, researchers have long attempted to develop vaccine technologies independent of cell culture, but this proved challenging.

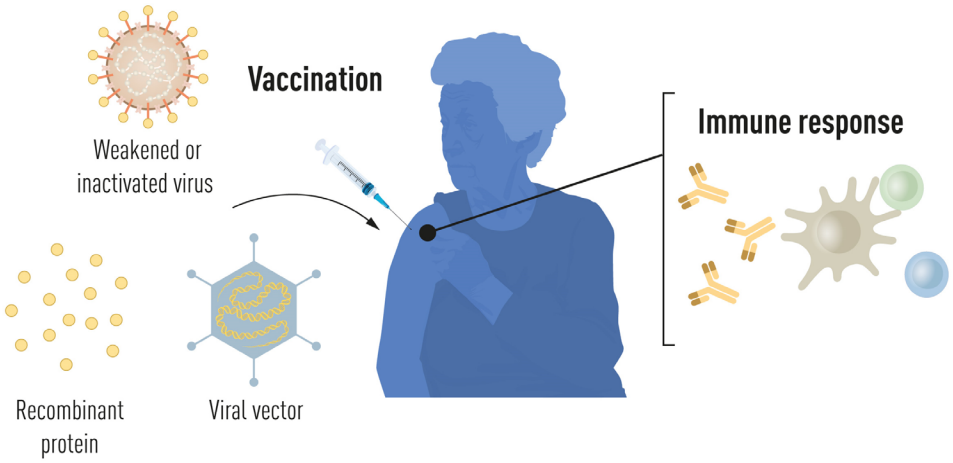

Fig. 1 *Methods for vaccine production before the COVID-19 pandemic.*

mRNA vaccines: A promising idea
In our cells, genetic information encoded in DNA is transferred to messenger RNA (mRNA), which is used as a template for protein production. During the 1980s, efficient methods for producing mRNA without cell culture were introduced, called *in vitro* transcription. This decisive step accelerated the development of molecular biology applications in several fields. Ideas of using mRNA technologies for vaccine and therapeutic purposes also took off, but roadblocks lay ahead. *In vitro* transcribed mRNA was considered unstable and challenging to deliver, requiring the development of sophisticated carrier lipid systems to encapsulate the mRNA. Moreover, *in vitro*-produced mRNA gave rise to inflammatory reactions. Enthusiasm for developing the mRNA technology for clinical purposes was, therefore, initially limited.

These obstacles did not discourage the Hungarian biochemist Katalin Karikó, who was devoted to developing methods to use mRNA for therapy. During the early 1990s, when she was an assistant professor at the University of Pennsylvania, she remained true to her vision of realizing mRNA as a therapeutic despite encountering difficulties in convincing research funders of the significance of her project. A new colleague of Karikó at her

university was the immunologist Drew Weissman. He was interested in dendritic cells, which have important functions in immune surveillance and the activation of vaccine-induced immune responses. Spurred by new ideas, a fruitful collaboration between the two soon began, focusing on how different RNA types interact with the immune system.

The breakthrough

Karikó and Weissman noticed that dendritic cells recognize *in vitro* transcribed mRNA as a foreign substance, which leads to their activation and the release of inflammatory signaling molecules. They wondered why the *in vitro* transcribed mRNA was recognized as foreign while mRNA from mammalian cells did not give rise to the same reaction. Karikó and Weissman realized that some critical properties must distinguish the different types of mRNA.

RNA contains four bases, abbreviated A, U, G, and C, corresponding to A, T, G, and C in DNA, the letters of the genetic code. Karikó and Weissman knew that nucleoside bases in RNA from mammalian cells are frequently chemically modified, while *in vitro* transcribed mRNA is not. They wondered if the absence of altered bases in the *in vitro* transcribed RNA could explain the unwanted inflammatory reaction. To investigate this, they produced different variants of mRNA, each with unique chemical alterations in their bases, which they delivered to dendritic cells. The results were striking: The inflammatory response was almost abolished when base modifications were included in the mRNA. This was a paradigm change in our understanding of how cells recognize and respond to different forms of mRNA. Karikó and Weissman immediately understood that their discovery had profound significance for using mRNA as therapy. These seminal results were published in 2005, fifteen years before the
COVID-19 pandemic.

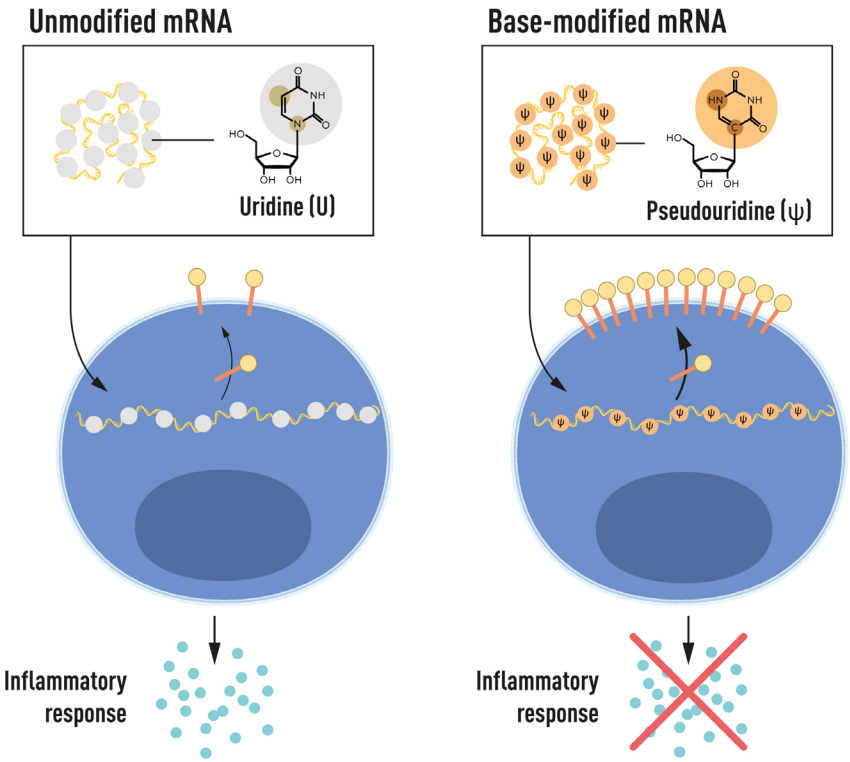

Figure 2 *mRNA contains four different bases, abbreviated A, U, G, and C. The Nobel laureates discovered that nucleoside base-modified mRNA can be used to block activation of inflammatory reactions (secretion of signaling molecules) and increase protein production when mRNA is delivered to cells.*

In further studies published in 2008 and 2010, Karikó and Weissman showed that the delivery of mRNA generated with base modifications markedly increased protein production compared to unmodified mRNA. The effect was due to the reduced activation of an enzyme that regulates protein production. Through their discoveries that base modifications both reduced inflammatory responses and increased protein production, Karikó and Weissman had eliminated critical obstacles on the way to clinical applications of mRNA.

mRNA vaccines realized their potential

Interest in mRNA technology began to pick up, and in 2010, several companies were working on developing the method. Vaccines against Zika virus and MERS-CoV were pursued; the latter is closely related to SARS-CoV-2. After the outbreak of the COVID-19 pandemic, two nucleoside base-modified mRNA vaccines encoding the SARS-CoV-2 surface protein were developed at record speed. Protective effects of around 95% were reported, and both vaccines were approved as early as December 2020.

The impressive flexibility and speed with which mRNA vaccines can be developed pave the way for using the new platform also for vaccines against other infectious diseases. In the future, the technology may also be used to deliver therapeutic proteins and treat some cancer types.

Several other vaccines against SARS-CoV-2, based on different methodologies, were also rapidly introduced, and together, more than 13 billion COVID-19 vaccine doses have been given globally. The vaccines have saved millions of lives and prevented severe disease in many more, allowing societies to open and return to normal conditions. Through their fundamental discoveries of the importance of base modifications in mRNA, this year's Nobel laureates critically contributed to this transformative development during one of the biggest health crises of our time.

Key publications:

Karikó, K., Buckstein, M., Ni, H. and Weissman, D. Suppression of RNA Recognition by Toll-like Receptors: The impact of nucleoside modification and the evolutionary origin of RNA. *Immunity* **23**, 165–175 (2005).

Karikó, K., Muramatsu, H., Welsh, F.A., Ludwig, J., Kato, H., Akira, S. and Weissman, D. Incorporation of pseudouridine into mRNA yields superior nonimmunogenic vector with increased translational capacity and biological stability. *Mol Ther* **16**, 1833–1840 (2008).

Anderson, B.R., Muramatsu, H., Nallagatla, S.R., Bevilacqua, P.C., Sansing, L.H., Weissman, D. and Karikó, K. Incorporation of pseudouridine into mRNA enhances translation by diminishing PKR activation. *Nucleic Acids Res.* **38**, 5884–5892 (2010).

Katalin Karikó was born in 1955 in Szolnok, Hungary. She received her PhD from Szeged's University in 1982 and performed postdoctoral research at the Hungarian Academy of Sciences in Szeged until 1985. She then conducted postdoctoral research at Temple University, Philadelphia, and the University of Health Science, Bethesda. In 1989, she was appointed Assistant Professor at the University of Pennsylvania, where she remained until 2013. After that, she became vice president and later senior vice president at BioNTech RNA Pharmaceuticals. Since 2021, she has been a Professor at Szeged University and an Adjunct Professor at Perelman School of Medicine at the University of Pennsylvania.

Drew Weissman was born in 1959 in Lexington, Massachusetts, USA. He received his MD, PhD degrees from Boston University in 1987. He did his clinical training at Beth Israel Deaconess Medical Center at Harvard Medical School and postdoctoral research at the National Institutes of Health. In 1997, Weissman established his research group at the Perelman School of Medicine at the University of Pennsylvania. He is the Roberts Family Professor in Vaccine Research and Director of the Penn Institute for RNA Innovations.

The Nobel Assembly, consisting of 50 professors at Karolinska Institutet, awards the Nobel Prize in Physiology or Medicine. Its Nobel Committee evaluates the nominations. Since 1901, the Nobel Prize has been awarded to scientists who have made the most important discoveries for the benefit of humankind.