An accolade to Nobel Laureates 2023

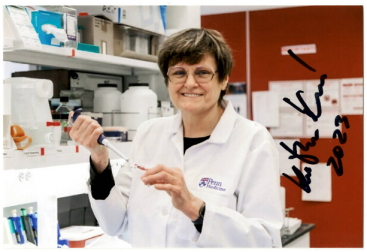
The 2023 Nobel Prize in Physiology or Medicine was jointly awarded to Dr. Katalin Karikó and Dr. Drew Weissman. Their research on the discovery of base pair modifications led to the successful development of mRNA vaccines against COVID-19.

Katalin Karikó was born on 17 January 1955 in Szolnok town in Hungary. She completed her PhD in 1982 from the Biological Research Center at Szeged University. In the subsequent three years, she pursued postdoctoral research in Szeged from the Hungarian Academy of Sciences. She also conducted postdoctoral research at the University of Health Sciences, Bethesda, and Temple University, Philadelphia before joining the University of Pennsylvania as Assistant Professor. In the following years, she became the vice president and then president at BioNTech RNA Pharmaceuticals. In the recent 3-4 years she has been working as an Adjunct Professor at Perelman School of Medicine and a Professor at the Szeged University.

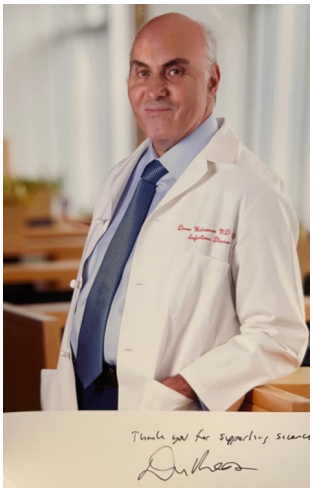
Drew Weissman was born on September 7, 1959, in Lexington, Massachusetts, USA. Dr. Weissman was conferred MD and PhD degrees in the year 1987 from Boston University. His clinical training was at Beth Israel Deaconess Medical Centre in Boston. After his residency, he joined the National Institutes of Health for a postdoctoral fellowship to explore the interactions between human immunodeficiency Virus type 1 and immune cells. Dr. Weissman formed his research group at the Perelman School of Medicine and concentrated his investigations on vaccines and the employment of Dendritic cells (DC) to prime immune responses. He is currently the Director of the Penn Institute for RNA Innovation.

The contributions of the two laureates have been remarkable at a time when the world was looking forward to a vaccine solution for the pandemic. With the spread of SARS-CoV-2, there was a race to develop an effective vaccine as rapidly as possible to tackle the fast-spreading pandemic. The idea of using mRNA platforms for vaccine development and *in-vivo* delivery of therapeutic substances existed for several decades but it could not be utilized clinically. Undesired immune reactions occurring with the existing mRNA and inefficient protein production in cells were considered the primary hurdles to vaccine success. The landmark discovery of nucleoside base modification in the mRNA used for vaccine production enabled everting undesired immune reactions and improved the rate of protein expression. In addition to using the modified bases for mRNA, the stabilization of SARS-CoV-2 spike antigen, usage of an improved system for mRNA delivery, and financial support by the government and industry enabled the application of effective mRNA-based COVID-19 vaccines in the year 2020.

The research done by *Karikó and Weissman was* pivotal in defining the application of the mRNA vaccine platform for clinical use. The use of mRNA for the delivery of therapeutic proteins was a potential area of research among scientists.



Dr. Katalin Karikó in her laboratory.
Picture source: Dr. Katalin Karikó



Dr. Drew Weissman
Picture source: Dr. Drew Weissman

Injections of mRNA for the expression of vasopressin for treating Diabetes in a rat model were tested in 1992. At the same time, Dr. Karikó was testing various forms of RNA suitable for the optimal expression of proteins. She made significant observations during her research that motivated her to pursue the quest for exploring the mRNA platform for therapeutic purposes. While Dr. Karikó was working at the University of Pennsylvania, Dr. Weissman happened to join the same University. She teamed up with Dr. Weissman who had an inclination for immunology. With Dr. Weissman's expertise in immunology and Dr. Karikó's background in RNA biochemistry, they made a complimentary research team that was exploring the therapeutic applications of mRNA. They tested the possibility of delivering in vitro transcribed mRNA to DC that were used subsequently to prime the antigen-specific T cells. The duo successfully demonstrated that DC loaded with mRNA for specific antigenic proteins could stimulate the CD4+ & CD8+ T cells and mRNA loading of DC

leads to the activation and maturation of DC. DC expresses endosomal Toll-like receptors (TLRs). The recognition of specific pathogen-associated molecular patterns (PAMPs) is critical for TLRs. The interaction of TLRs with PAMPs initiates cytokine production through intracellular signaling mechanisms. The contemporary studies demonstrated that unmethylated CpG motifs present in microbial DNA stimulate TLR9. Therefore, next in line was exploring the various ligands for nucleic acids sensing TLRs. Interestingly, Karikó and Weissman demonstrated that there is a dsRNA contaminant in the in vitro transcribed mRNA that is causing the TLR3 activation and cytokine release. The duo continued to look for the effects of mRNA base modification on the release of cytokines by the DC. They found that incorporation of 5-methyluridine or 2-thiouridine, N6-methyladenosine, 5-methylcytidine, and pseudouridine into the mRNA resulted in diminished immune response in the DC and modification of uridines reduced DC activation. Subsequently, it was found that N1-methyl pseudo-uridine with or without 5-methylcytidine further abolishes immune response and enhances protein expression. Currently, N1-methylpseudo-uridine is a widely modified base used in mRNA vaccine development. It was the joint efforts by Karikó and Weissman that helped humankind during the pandemic through effective and safe vaccines and inspired many of us.

Sources

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