https://doi.org/10.1038/s41563-023-01770-3

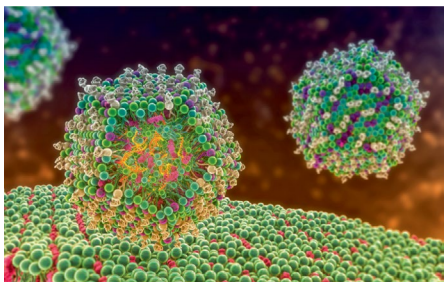
Life-saving vaccines awarded

The fundamental discoveries that enabled the development of effective mRNA vaccines against COVID-19 were awarded with this year's Nobel Prize in Medicine.

The efficacy of mRNA vaccines in providing us with protection against the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus during the COVID-19 pandemic is undoubtedly one of the greatest recent achievements of biotechnology. This would not have been possible without decades of fundamental research on RNA biology and the delivery of nucleic acids into cells. These contributions were recognized by this year's Nobel Prize in Physiology or Medicine awarded to Katalin Karikó and Drew Weissman for their work on how in vitro transcribed mRNA with nucleoside base modifications evades the innate immune system and improves protein expression levels[1].

The concept of using nucleic acids such as DNA and RNA as vaccines emerged during the early 1990s[2,3]. Unlike traditional vaccines that require specialized cell culture facilities and substantial time to optimize them, nucleic acid vaccines encoding for distinct antigens can be easily produced using cell-free systems, allowing for faster screening and development of effective leads. These vaccines also elicit stronger immunity, stimulating potent antigen-specific cellular and humoral immune responses[4]. Initial studies focused mainly on DNA vaccines, owing to RNA's intrinsic instability and innate immunogenicity. But despite early promising results, DNA vaccines showed little effectiveness in human trials.

At the same time, a small set of researchers, including Karikó, continued to work on mRNA and its clinical applications. mRNA was considered promising because it can be produced in high amounts using established in vitro transcription platforms, it does not integrate into the host genome (as can occur with DNA vectors) and is naturally degraded by the host cells after some time. Spurred by the first demonstration where in vitro transcribed mRNA can be translated in vivo[5], Karikó was determined to use mRNA to treat human diseases. She focused on how the different molecular features of in vitro transcribed mRNA affected the expression of proteins in the brain[6]. In the late 1990s, she teamed up with Weissman, who was interested in developing vaccines against human immunodeficiency virus (HIV). Their goal was to use mRNA encoding for an HIV antigen to activate dendritic cells and explore their antigen presentation ability to prime antigen-specific T cells. While doing this, they realized that in vitro transcribed mRNA was recognized by dendritic cells as a foreign molecule, which led to their activation and release of inflammatory cytokines. This outcome is highly undesirable for vaccines, because their goal is to achieve robust antigen-specific immune responses and not to trigger life-threatening systemic inflammatory responses. By studying these responses further, Karikó and Weissman found the solution for the clinical translation of mRNA vaccines and a way out from a future pandemic.



Representation of a lipid nanoparticle mRNA vaccine.

By focusing on how mRNA base modifications affected cytokine production by dendritic cells, they discovered that mRNA without post-translational modifications, namely in vitro transcribed mRNA, activated dendritic cells, whereas eukaryotic mRNA with its abundant post-translationally modified nucleotides did not[7]. Moreover, they showed that only modifications in the nucleotide uridine were required to abolish the non-specific activation of dendritic cells, and in subsequent studies showed that N1-methylpseudouridine modification contributed to a reduced recognition of in vitro transcribed mRNA by the host innate immune system and increased in vivo protein expression[8,9]. Most of the mRNA vaccines used and being developed nowadays incorporate N1-methylpseudouridine in their formulations, including two of the COVID vaccines developed during the COVID-19 pandemic.

Research on the in vivo delivery of nucleic acids was also crucial for the clinical introduction of mRNA vaccines, namely on the precise formulation of lipid nanoparticles that effectively encapsulate mRNA and safely deliver it into living cells[10]. The discovery that in vitro mRNA needs to be purified for potent protein expression and suppressing inflammatory responses further contributed to the translation of mRNA therapeutics.

The recognition of Karikó's and Weissman's contributions has also put a spotlight on the difficulties that researchers working on the fundamental aspects of science are confronted with on a daily basis. At the time when their prized studies were being conducted, both researchers were facing difficulties in securing funding and attaining promotions, and for Karikó, even maintaining her position at the University of Pennsylvania. Despite that, they never gave up and managed to pursue their goals of developing a technology that helps people. At *Nature Materials* we continue to be committed to publishing the most important advances in both fundamental and applied materials research and hope that some of these findings will eventually make our lives better.

Published online: 4 December 2023

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