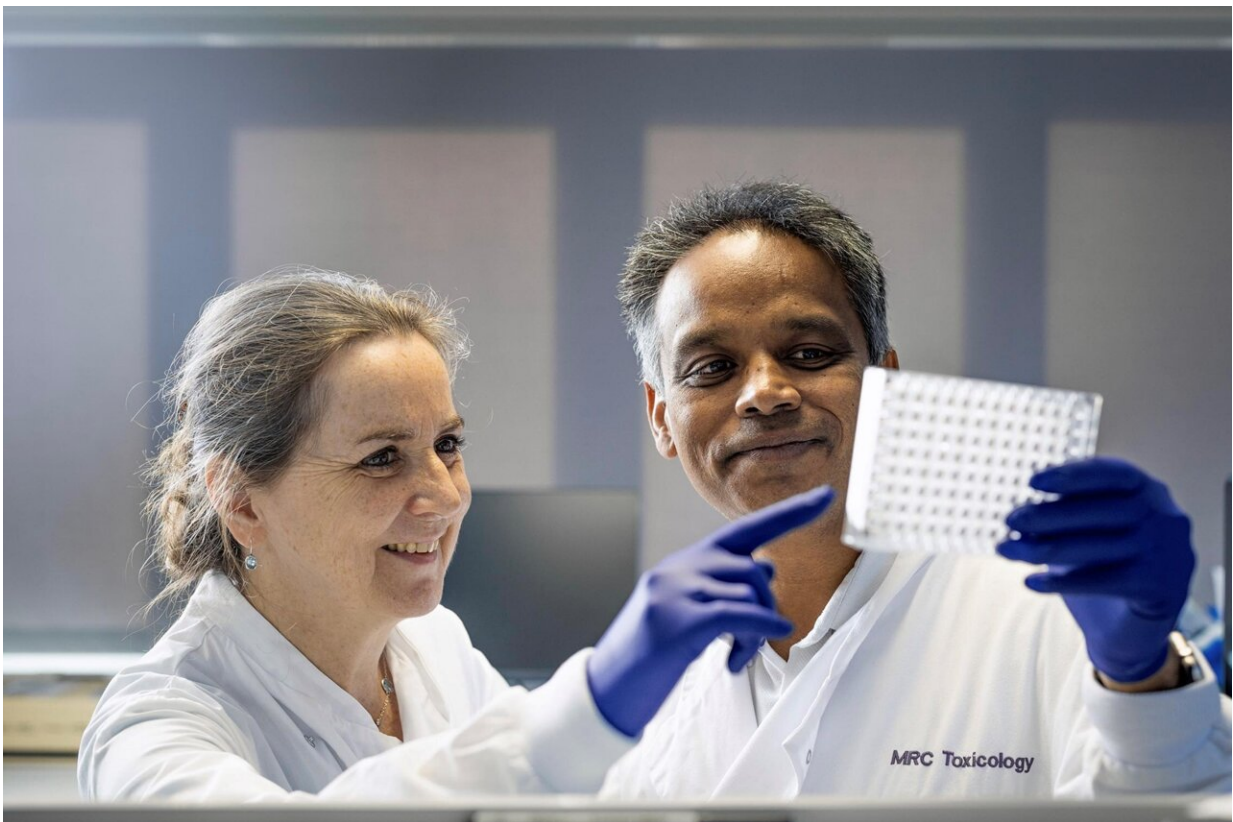


Researchers redesign future mRNA therapeutics to prevent potentially harmful immune responses

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Biochemist Professor Anne Willis and immunologist Dr James Thaventhiran at the MRC Toxicology Unit at the University of Cambridge led this work. Credit: Mike Thornton, Still Vision Photography

Researchers have discovered that misreading of therapeutic mRNAs by the cell's decoding machinery can cause an unintended immune response in the body. They have identified the sequence within the mRNA that causes this to occur and found a way to prevent 'off-target' immune responses to enable the safer design of future mRNA therapeutics.

mRNA—or 'messenger [ribonucleic acid](#)'—is the [genetic material](#) that tells cells in the body how to make a [specific protein](#). Researchers from the Medical Research Council (MRC) Toxicology Unit have discovered that the cellular machinery that 'reads' mRNAs 'slips' when confronted with repeats of a chemical modification commonly found in mRNA therapeutics. In addition to the [target protein](#), these slips lead to the production of 'off-target' proteins triggering an unintended immune response.

mRNA vaccines are considered game-changing. They have been used to control the COVID-19 pandemic and are already proposed to treat various cancers as well as cardiovascular, respiratory, and immunological diseases in the future.

This revolutionary class of therapeutics was made possible in part through the work of biochemist Katalin Karikó and immunologist Drew Weissman. They demonstrated that by adding chemical modifications to the bases—the building blocks of mRNA—the synthetic mRNAs could bypass some of our body's immune defenses allowing a therapeutic to enter the cell and exert its effects. This discovery led to their award of the Nobel Prize in Physiology and Medicine in 2023.

The latest developments, led by biochemist Professor Anne Willis and immunologist Dr. James Thaventhiran from the MRC Toxicology Unit at the University of Cambridge, build upon previous advances to ensure the prevention of any safety issues linked with future mRNA-based therapeutics. Their report is [published](#) in the journal *Nature*.

The researchers identified that bases with a chemical modification called N1-methylpseudouridine—which are currently contained in mRNA therapies—are responsible for the 'slips' along the mRNA sequence.

In collaboration with researchers at the Universities of Kent, Oxford and Liverpool, the MRC Toxicology Unit team tested for evidence of the production of 'off-target' proteins in people who received the mRNA Pfizer vaccine against COVID-19. They found an unintended immune response occurred in one-third of the 21 patients in the study who were vaccinated—but with no ill-effects, in keeping with the extensive safety data available on these COVID-19 vaccines.

The team then redesigned mRNA sequences to avoid these 'off-target' effects, by correcting the error-prone genetic sequences in the synthetic mRNA. This produced the intended [protein](#). Such design modifications can easily be applied to future mRNA vaccines to produce their desired effects while preventing hazardous and unintended immune responses.

"Research has shown beyond doubt that mRNA vaccination against COVID-19 is safe. Billions of doses of the Moderna and Pfizer mRNA vaccines have been safely delivered, saving lives worldwide," said Dr. James Thaventhiran from the MRC Toxicology Unit, joint senior author of the report.

He added, "We need to ensure that mRNA vaccines of the future are as reliable. Our demonstration of 'slip-resistant' mRNAs is a vital contribution to future safety of this medicine platform."

"These new therapeutics hold much promise for the treatment of a wide range of diseases. As billions of pounds flow into the next set of mRNA treatments, it is essential that these therapeutics are designed to be free from unintended side effects," said Professor Anne Willis, Director of the MRC Toxicology Unit and joint senior author of the report.

Thaventhiran, who is also a practicing clinician at Addenbrooke's hospital, said, "We can remove the error-prone code from the mRNA in vaccines so the body will make the proteins we want for an immune response without inadvertently making other proteins as well. The safety concern for future mRNA medicines is that misdirected immunity has huge potential to be harmful, so off-target immune responses should always be avoided."

Willis added, "Our work presents both a concern and a solution for this new type of medicine, and results from crucial collaborations between researchers from different disciplines and backgrounds. These findings can be implemented rapidly to prevent any future safety problems arising and ensure that new mRNA therapies are as safe and effective as the COVID-19 vaccines."

Using synthetic mRNA for therapeutic purposes is attractive because it is cheap to produce, so can address substantial health inequalities across the globe by making these medicines more accessible. Moreover, synthetic mRNAs can be changed rapidly—for example, to create a new COVID-19 variant [vaccine](#).

In the Moderna and Pfizer COVID-19 vaccines, synthetic mRNA is used to enable the body to make the spike protein from SARS-CoV-2. The body recognizes the viral proteins generated by mRNA vaccines as foreign and generates protective immunity. This persists, and if the body is later exposed to the virus its immune cells can neutralize it before it can cause serious illness.

The cell's decoding machinery is called a ribosome. It 'reads' the genetic code of both natural and synthetic mRNAs to produce proteins. The precise positioning of the ribosome on the mRNA is essential to make the right proteins because the ribosome 'reads' the mRNA sequence three bases at a time. Those three bases determine what amino acid is

added next into the protein chain. Therefore, even a tiny shift in the ribosome along the mRNA will massively distort the code and the resulting protein.

When the ribosome is confronted with a string of these modified bases called N1-methylpseudouridine in the mRNA, it slips around 10% of the time causing the mRNA to be misread and unintended proteins to be produced—enough to trigger an immune response. Removing these runs of N1-methylpseudouridine from the mRNAs prevents 'off-target' protein production.

More information: Anne Willis, N1- methylpseudouridylation of mRNA causes +1 ribosomal frameshifting, *Nature* (2023). [DOI: 10.1038/s41586-023-06800-3](https://doi.org/10.1038/s41586-023-06800-3).
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