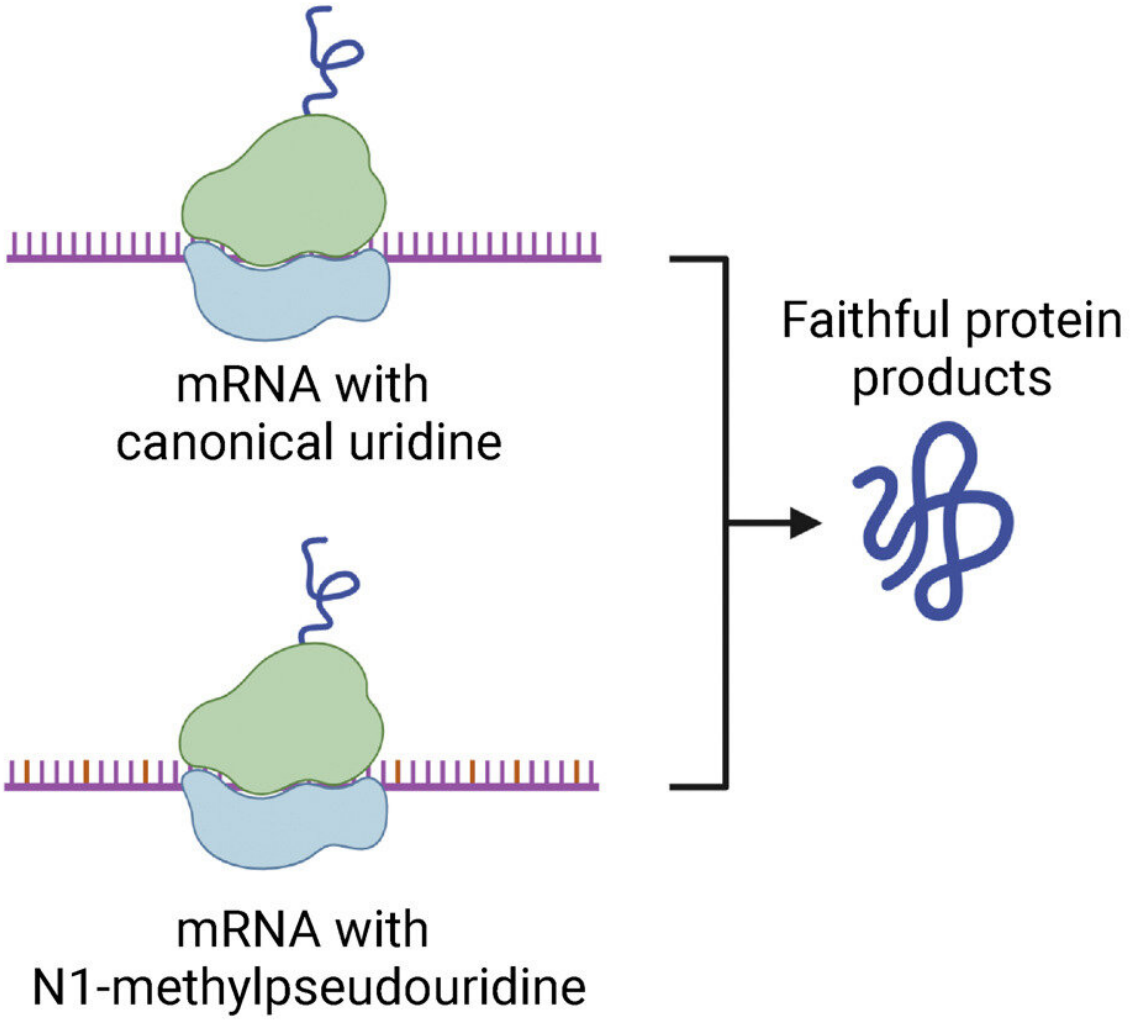
# Modified nucleotides used in COVID-19 vaccines work as designed

August 24 2022, by Talia Ogliore



Graphical abstract. Credit: *Cell Reports* (2022). DOI: 10.1016/j.celrep.2022.111300

The remarkable effectiveness of mRNA vaccines against SARS-CoV-2 has generated much interest in synthetic mRNA therapeutics for treating and preventing disease. But some basic science questions have remained about whether the modified nucleotides used in the vaccines faithfully produce the protein products that they are designed to make.

The synthetic mRNAs used in the COVID-19 vaccines incorporate the modified nucleotide N1-methylpseudouridine to improve stability and reduce unwanted immune responses. Both features are necessary for the vaccine to work properly. Still, incorporating this non-standard nucleotide introduces the possibility that the cellular machinery could misread the genomic information the mRNA encodes—leading to errors during protein translation that might have unintended effects down the line.

Not to worry, as it turns out. A new study from Washington University in St. Louis finds that the N1-methylpseudouridine used in the COVID-19 mRNA vaccines is translated faithfully. The research, published in *Cell Reports*, was led by scientists in the laboratory of Hani Zaher, associate professor of biology in Arts & Sciences.

"Cellular mRNAs don't typically have N1-methylpseudouridine," said Kyusik Kim, a graduate student in the molecular cell biology program, first author of the study. "We found that the presence of N1-methylpseudouridine in mRNAs doesn't seem to lead to increases in the number of mistakes during translation."

"If that's the case," Kim said, "then we can continue to use them in

therapeutics and we won't have to worry as much about them making the wrong protein."

The translation of the genetic code into functional protein is a feat accomplished in all domains of life by the ribosome. The Zaher lab conducts research that expands our understanding of the mechanisms that govern translational fidelity on the ribosome and the impact of these mechanisms on cellular fitness.

In this particular study, the Zaher lab researchers used multiple experimental systems to study the effects of N1-methylpseudouridine on translation. They found that N1-methylpseudouridine is read accurately by the ribosome. They also found that mRNAs containing N1-methylpseudouridine did not appear to make miscoded proteins more frequently than mRNAs containing unmodified nucleotides.

"There's been a huge explosion in interest in the use of therapeutic mRNAs for many different diseases," Kim said. "This paper adds more confidence that therapeutic mRNAs aren't going to make proteins they weren't intended to make."

**More information:** Kyusik Q. Kim et al, N1-methylpseudouridine found within COVID-19 mRNA vaccines produces faithful protein products, *Cell Reports* (2022). DOI: 10.1016/j.celrep.2022.111300

Provided by Washington University in St. Louis