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# A Nobel for Modified mRNA

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This morning's Nobel in Physiology or Medicine should come as no particular surprise - we've been expecting this one for a couple of years now, and I'm glad to see the committee do the right thing with some alacrity. It goes to Katalin Karikó (Karikó Katalin, in the style of her native Hungary) and Drew Weissman, for their discovery that pseudouridine modification of mRNA species enhances their cellular uptake while simultaneously decreasing their immunogenicity and increasing their stability. This is a key discovery in getting mRNA vaccine technology to work, and the research along these lines, which had already been going on for years before the coronavirus pandemic, is absolutely a reason why we had effective vaccines available so quickly.

*Let's get something out of the way right here before going on: I have had very little time and patience for the anti-vaccination crowd over the years. But if I thought my patience with that stuff was low before the pandemic, well, I couldn't imagine how fed up with it I would be by now. As I write this, the Science backstage team is working out a problem with the comments system (should be back shortly!) but maybe at the moment it's a blessing to have it nonfunctional, because I simply do not want to hear about anyone's theories that the mRNA vaccines are a secret depopulation scheme, destroying the bodily systems of billions of people, just about to kick in and cut them down like wheat, totally useless and evil, and on and on and on. Some time back, I finally reached the point of deleting on sight this sort of crap from the comments section, and time has not made me any more forgiving. I am angry that so many people have been deceived by the charlatans who are pushing this bullshit, some of which has come from people who damn well know better. Okay, back to celebrating this Nobel!*

The truth is that the discovery of how to make mRNA more useful as a therapeutic is a straight-up boon to humanity, and Karikó and Weissman absolutely deserve this prize and the gratitude of of the world. It was not easy. And like many such discoveries, it possibly could have been made many years before, but Pasteur knew what he was talking about when he said that "fortune favors the prepared mind". In an interview with *PNAS*, Karikó mentioned that one of her hobbies was reading "really old scientific papers". She had already found that uridine residues seemed to be inducing the immune response to mRNA, and found a 1963 paper where nonimmunogenic RNA species became immunogenic after treatment with nitrous acid (which would have deaminated the cytidines to turn them into uridines!) And it was also known that transfer RNA molecules (tRNA) did not seem to be immunogenic, and that these RNA species contain modified nucleosides such as pseudouridine. Putting such thoughts together led to the breakthrough.

Biologically, the improvement comes from several directions. The immunogenicity of "plain" mRNA species comes from their interaction with TLR (toll-like-receptor) proteins, which are constantly looking for unexpected extracellular DNA and RNA species as signs of infection by foreign pathogens. Pseudouridine-containing mRNAs just don't set them off to anywhere near the same extent. The same modification makes the RNA species more resilient to breaking down, either through plain hydrolysis or through enzyme activity

But no one seemed particularly interested. Karikó and Weissman have told the story many times about how their 2005 paper was rejected by *Nature* within 24 hours (desk rejection, not even going to be sent out to any reviewers, go somewhere else). It was similarly rejected by *Science* and by *Cell*, and the word "incremental" kept cropping up in the editorial staff comments. They had trouble publishing it *anywhere*. Drew Weissman:

> *"...I mean, they were unimpressed. They were uninterested. So we sent it to Immunity, and I think they had four reviewers. One of them liked it, two of them hated it, and one of them was kind of wishy-washy. We kept sending it back to Immunity and saying "You need to ignore these reviewers. They're missing the point of the paper." We kept changing things, we kept adding things, and we finally got it accepted."*

He mentions that a couple of years later he ran into someone who reviewed that paper, who said that he fought with the editors at the journal to get it published, because he thought it was important! Karikó mentions in that same interview that Weissman told her "*You'll see, we'll be invited to give talks, now the phone is going to ring off the hook*". But nothing like that happened. They tried starting their own company, and kept working on RNA modifications and proving their usefulness, and "*...we didn't have to spend time giving interviews and lectures, because there was no interest up until 2010*".

But even at that point, vaccines were not the main focus of the mRNA work. BioNTech and Moderna were both hoping to turn mRNA into a platform that caused particular therapeutic proteins to be produced in the cells, and this is still a very active area of research. But vaccines were taking a back seat to that work, although they (and certainly CureVac, although they held out on the idea of pseudouridine modification) realized that such agents had potential. Some of the earlier work in the field was directed at the high-value high-barrier-to-success targets in potential cancer vaccines, which didn't speed things up, either. But work on things like influenza and RSV vaccines did come along eventually, and it was crucial to the success of the coronavirus vaccines later on.

As was the traditional vaccine development work that had taken place against the earlier SARS coronavirus, of course. We should never forget that as bad as the pandemic was - millions of people around the world meeting an early death, for starters - that it could have been much worse. And we should be glad that we have such a responsive and adaptable technology to deal with the next infectious diseases that come up, because it is a certainty that new ones will. We may well turn mRNA into the new-endogenous-therapeutic-protein platform that people originally pictured, but its utility in vaccines alone is enough for today's Nobel. Congratulations!

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