Toward New and Improved mRNA Vaccines

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Messenger RNA (mRNA) vaccines have been shown to elicit immunity against a number of infectious diseases—including, notably, COVID-19—as well as several types of cancer. Unlike traditional vaccines, which introduce a small amount of the pathogen into the body, mRNA vaccines provide the body with instructions for how to make a specific protein found on the surface of a virus or cancer cell. Once the vaccine is delivered, molecular machines called ribosomes bind to the mRNA, "read" its instructions, and build the protein. This, in turn, prompts the immune system to produce the corresponding antibodies, so that it is ready when it encounters the real virus or cancer cell. Importantly, the mRNA molecules that contain these protein-making instructions are broken down by the cell after they have delivered their "message."

Over the past decade, the field of mRNA therapeutics has advanced rapidly, and scientists are now able to manufacture mRNA in the lab with relative ease. But two significant technical hurdles remain. One is the inherent instability of mRNA molecules, which can cause them to break down before they are turned into proteins. The other is low protein output, as the synthetic mRNA must compete with native mRNA in the cell's protein-making apparatus while avoiding the cell's degradation machinery. Researchers are now trying to figure out how the sequence and structure of mRNA affect its stability and protein output, so as to guide the design of more stable, more "expressive," therapeutic mRNAs.

At Stanford University, former Damon Runyon Fellow Kathrin Leppek, PhD, and her colleagues have risen to this challenge with the help of two RNA-sequencing technologies. The first, a tool called PERSIST-seq, revealed that an mRNA's protein output depends more on its stability than its ribosome load. (This makes sense if you consider that, no matter how many friends gather to help build IKEA furniture, their productivity still depends on the instructions remaining intact.) Excitingly, using another sequencing technology called In-line-seq, the team was able to identify a number of sequence- and structure-related modifications that can improve mRNA stability. For example, substituting the RNA compound uridine for a slightly different compound called psuedouridine makes the molecule less susceptible to degradation.

Together, the team's findings amount to an improved mRNA design strategy that enhances both

the stability and the protein output of these therapeutic molecules. Dr. Leppek and her colleagues have also demonstrated the usefulness of their sequencing tools in the optimization of mRNA drugs. “As mRNA-based medicines are explored for a wide range of human diseases, including cancer therapies,” Dr. Leppek writes, “we hope that these insights and methods can help these medicines become more effective, manufactured at a lower cost per patient, and more accessible and widely distributed to alleviate disease.”

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