# Reprogramming Cells to Fight Disease

A new approach to treating disease seeks to harness the power of the body's own cells to build and transport healing proteins

October 25, 2014 | By John Jamieson

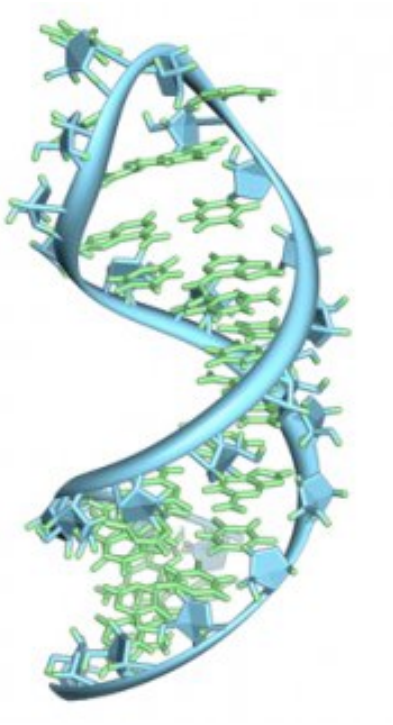


Image credit: Broad Institute

What if instead of being given a drug, you could simply tell your body how to make that drug for itself? That's the idea behind the emerging field of messenger RNA (mRNA) therapeutics, which is changing the way we think about pharmaceuticals. mRNA therapeutics has the potential to treat a host of unmet medical needs that cannot be addressed with current technologies, including cardiovascular disease, cancers, neglected rare diseases, and infectious viruses.

**mRNA is an incredible molecule**

mRNA is naturally found in every cell of your body. Its purpose is to carry building instructions from DNA, your genetic library, to ribosomes, which are cellular factories that produce proteins. You can think of mRNA as a working copy of your DNA, a temporary blueprint that tells your body what proteins to make and when to make them.

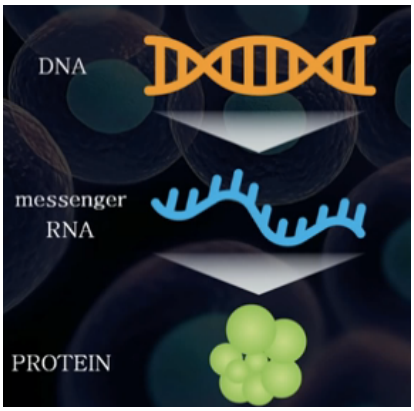
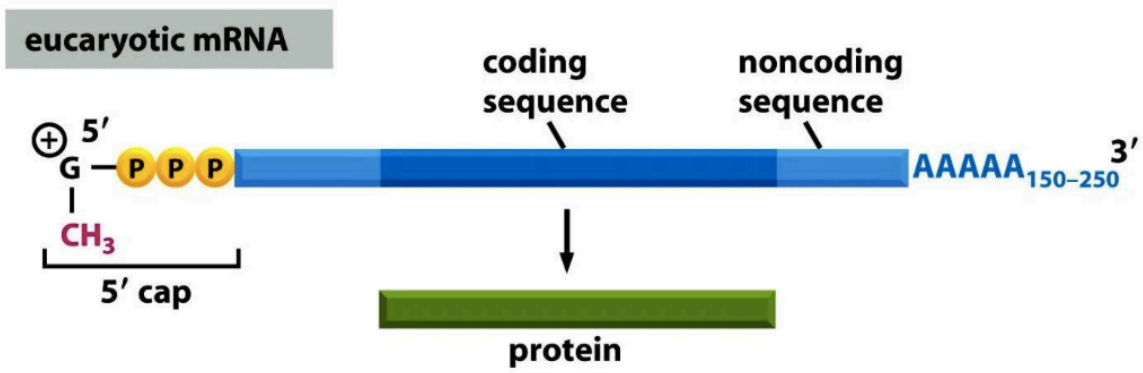



Image credit: mRNA TEDx Talk

Many diseases share a common feature—the failure of the body to produce the correct protein at the correct time. There are 22,000 different proteins that your body can make, and if even one of them isn't being produced as much as it should be, the consequences can be disastrous. By introducing an mRNA that "codes for" the missing protein, scientists can supply the cells with the instructions for the cell to build that protein naturally. For example, by treating a heart attack victim's cardiac cells with an mRNA that promotes new cell growth, heart tissue that was destroyed by the heart attack can be regenerated, restoring the patient's heart function.




**The structure of mRNA consists of a 5' cap, a poly-A tail, and a coding sequence which contains instructions for protein assembly. Image credit: Galleryhip**

**mRNA could treat diseases that protein replacement and gene therapy cannot**

Since the 1970s, the standard approach for treating protein-related diseases has been to manufacturing a protein in bulk, then directly inject that replacement protein as a drug. While this was effective for some diseases, most notably insulin for treating diabetes and monoclonal antibodies for cancer treatments, only 20 protein replacement drugs have been developed in the last 40 years. This leaves over 6,000 rare diseases left untreated.

As researchers learned more about genetics, they proposed the idea of replacing bad genes with good genes capable of producing the protein a patient is lacking. This idea, known as gene therapy, was pursued heavily in the 1990s, but resulted in only a single approved drug. Although the concept was revolutionary, incorporating good DNA into the right parts of the patient's genome proved to be incredibly difficult. DNA inserted itself haphazardly, and in some cases there was a legitimate risk of causing cancer.

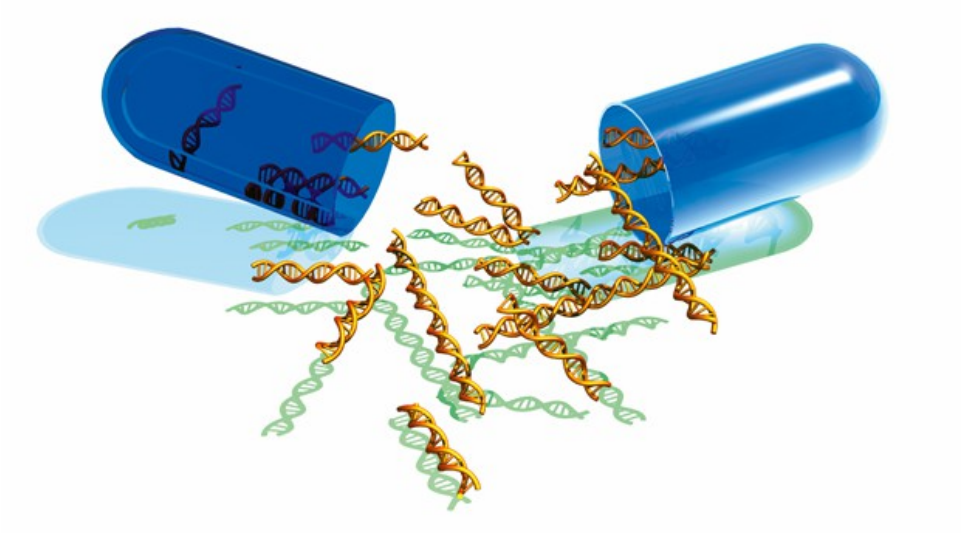


**Image credit: Nordic Life Science**

mRNA therapeutics provide the benefits of gene therapy without the associated risk. mRNA is safer to deliver than DNA, since mRNA does not incorporate itself into the patient's genome. It is also easier to deliver, since it doesn't need to cross into the cell's nucleus. In addition, because the body is making the proteins itself, it knows exactly where in the body to send them, eliminating a costly transport problem faced by protein replacement drugs.

Furthermore, protein replacement drug treatments are restricted to "secreted" proteins, whereas mRNA drugs can also address "intracellular" proteins. "This is really the big breakthrough," says Stéphane Bancel, founding CEO of mRNA pioneer Moderna Therapeutics. "Remember, your body has 22,000 proteins, only 4,000 are secreted. Most of the proteins you need…to live are intracellular. Totally undruggable with any technology available today."

**Stéphane Bancel, founding CEO of Moderna Therapeutics. Image credit: CNBC**

**Development and commercialization**

Bancel's company, Moderna Therapeutics, was recently named #8 on CNBC's Disruptor 50 list, which recognizes companies seen as revolutionaries in their respective industries. Moderna ranked ahead of such renowned disruptors as Spotify, Dropbox, Kickstarter, and Uber, and was the only biotech company to make the list. Founded in 2010, Moderna has rapidly grown to employ over 150 mRNA scientists and engineers seeking to develop and scale up the mRNA production process. They have over $350 million in funding from investors and drug companies with which to work. One reason Moderna has garnered so much attention is that it is a platform company, as opposed to a single drug company. That is to say, the fate of the company is not hinging on the success of any one particular drug, and if Moderna is successful, it could produce tens, hundreds, or even thousands of successful mRNA drugs.

How is Moderna able to develop an entire platform, while protein companies could only develop drugs one at a time? Individual proteins are completely different molecules from each other, and therefore the production and delivery of each is highly specific to that protein. The mRNAs that code for these proteins, however, are remarkably similar to each other, meaning that once the process is optimized for one mRNA drug, others would require mere weeks or months of development time, as compared with years to develop a completely new protein drug.

**Challenges and limitations in the path forward**

It would seem mRNA drugs offer incredible promise and therefore are actively being pursued commercially. This raises some important questions for consumers. First of all, will mRNA drugs be safe for patients? How soon would we see mRNA drugs in the pharmacy? What are the challenges and limitations to developing these drugs?

**Image credit: Genome.gov**

The current status of most mRNA drugs is in the preclinical phase, which occurs prior to human testing. During the preclinical phase, research and development work is performed and animal testing is conducted to ensure that the drug does not pose clear health hazards to mammals like mice and monkeys before testing it on humans. The Food and Drug Administration (FDA) requires three phases of human trials before a new drug can be sold, which can take several years to complete, so don't expect to be taking any mRNA-based drugs for five to ten years at the earliest.

| | Preclinical Testing | | Phase I | Phase II | Phase III | | FDA | | Phase IV |
|---|---|---|---|---|---|---|---|---|---|
| Years | 3.5 | | 1 | 2 | 3 | | 2.5 | 12 Total | |
| Test Population | Laboratory and animal studies | File IND at FDA | 20 to 80 healthy volunteers | 100 to 300 patient volunteers | 1000 to 3000 patient volunteers | File NDA at FDA | Review process / Approval | | Additional Post marketing testing required by FDA |
| Purpose | Assess safety and biological activity | | Determine safety and dosage | Evaluate effectiveness, look for side effects | Verify effectiveness, monitor adverse reactions from long-term use | | | | |
| Success Rate | 5,000 compounds evaluated | | 5 enter trials | | | | 1 approved | | |

**The FDA drug approval process. Image credit: NewDrugApprovals.org**

As with any new treatment type, mRNA has a few roadblocks to overcome. The two main reasons that mRNA was overlooked as a drug until now were stability and immune response. As it turns out, these two issues were related. Cells have the ability to distinguish foreign mRNA from native mRNA, and they destroy foreign mRNA as though it were an attacking virus. The key to using mRNA as a drug is to "camouflage" it so that the cell doesn't "see" it. Breakthroughs in this area have improved the lifetime of mRNA in the body, enabling its use as a drug.

Revolutions in medicine are often viewed with skepticism or distrust, (consider early vaccinations). Genetics in particular, is an area in which many would prefer not to meddle. This is understandable, considering that genetic mutations are responsible for a number of diseases as well as cancers. It is important to note, however, that mRNA therapeutics are not designed to alter your DNA, as gene therapy was. The mRNA delivered into the cell goes directly to the ribosomes to be used for the construction of proteins.

Many of the diseases that could be treated by mRNA therapeutics cannot be addressed by conventional methods, making mRNA drugs a critical development for the treatment of these unmet oncological, cardiovascular, and rare disease needs. Pending the results of their evaluations for safety and efficacy over the next five to ten years, mRNA therapeutics stand poised to change the world.

References

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