

Q&A: The engineer who delivers mRNA inside human cells

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Messenger RNA became a household term when it was used as the backbone of the first COVID-19 vaccines, especially after the Nobel Prize was awarded to two mRNA pioneers at the University of

Pennsylvania.

But the fragile genetic molecules would be useless for vaccines and other emerging treatments if they could not be delivered inside the body.

That's where Michael J. Mitchell comes in.

An associate professor of bioengineering at Penn, Mitchell is an expert in lipid nanoparticles, the tiny, fatty droplets that are used to carry mRNA inside [human cells](#).

The vaccines used lipid nanoparticles to deliver mRNA to [immune cells](#) in the arm. That's just the beginning of the potential applications in medicine. Mitchell is now tweaking the chemistry of these lipids to deliver cutting-edge treatments against cancer and other diseases to hard-to-reach organs such as the lungs and brain.

In an interview with The Inquirer, Mitchell described how the nanoparticles are made, how he is designing them to target various organs, and what steps he is taking to improve their efficiency.

This conversation has been edited for length and clarity.

Who came up with the idea of lipid nanoparticles?

The idea of using lipids to encapsulate various types of drugs for delivery has been around for several decades. In the context of mRNA delivery, in the early 2000s, the major discovery was creating what is known as the ionizable lipid nanoparticle [meaning it changes its [electric charge](#) in order to release its medicinal cargo].

Part of the reason they go into cells so well is because cell membranes are made of lipids. Lipid nanoparticles (LNPs) have an affinity for

fusing with those membranes.

Once inside the cell, they are taken up by cellular vessels called endosomes. The pH within these endosomes is more acidic. When the LNP becomes positively charged because of the acidic environment in those compartments, those now positively charged lipids will interact with negatively charged lipids inside, and essentially, it will disrupt that membrane, releasing the mRNA cargo inside the cell.

How do you make lipid nanoparticles?

Our lab uses a technique called microfluidics to make the LNP.

It's a Y-shaped device on a chip. The fluid that flows through one side of the device is a mixture of four lipids dissolved in ethanol. On the other side is the RNA contained in an acidic citrate buffer. As the two fluids collide, they undergo a process known as chaotic mixing.

Because of the ionizable nature of the lipids, when they come into contact with acidic buffer, those lipids become charged. That charge mechanism then binds the RNA to the lipids.

That process is called self-assembly. It's almost like an onion forming.

Were you at Penn when Drew Weissman and Katalin Karikó published their first findings on mRNA in 2005?

I was in high school back then. Unfortunately, I wasn't there for that.

Before I got to Penn, in 2018, I was in Bob Langer's lab at MIT as a research fellow. He's one of the founders of Moderna. He's considered

kind of a father of the drug-delivery field.

Tell me about the study where you improved the efficiency of LNP.

It's believed that only 2% to 5% of all the LNP gets out of the endosomes into the cell to translate the mRNA therapeutic.

We made a new LNP in a way that mimics a [space shuttle](#). You can think of a space shuttle that has rocket boosters that break off over time. These lipid nanoparticles have lipids on the side that almost mimic what happens in the space shuttle. Those lipids can degrade and fall off over time.

As these tails are degrading and falling off, we believe that it's helping to disrupt the endosomes to release the RNA cargo inside the cell more efficiently.

To test it, we fed mice a [high-fat diet](#), then we injected them with this very potent LNP that can induce the secretion of lots of a weight-loss drug. They dramatically lost weight and returned to normal body weight levels.

Those LNPs traveled to the liver. What about targeting other parts of the body?

The RNA technology is now fairly mature. It's now a delivery challenge.

How do we get RNA to other parts of the body? How do we get into the brain? How do we get into the lungs for cystic fibrosis and lung cancer?

My lab has bioengineers, materials scientists, and chemists who are

working on this.

Tell me about that study where you got mRNA into the lungs of mice.

We wanted something that has a positive charge, which would cause the particles to travel to the lungs. But we wanted something that degrades as well. If it's chopped up in the body, it would be safe.

We made a library of variations with different lipids to find a blend of potent delivery to the lungs, but balanced with low toxicity. You want it to be safe.

We tagged the different kinds of [lipid nanoparticles](#) with a bar code of DNA, so we could identify them using next-gen sequencing technology. We can essentially count the number of LNP delivered to specific parts of the body by using those bar codes.

So we could figure out which one was the best out of the pool. We can really iterate and evolve a better technology much more quickly.

Was there one that was the clear winner?

We started out with 180 LNPs. You test those in cells first, because if something doesn't work in a cell, it's not worth testing in an animal.

We had 96 that were promising, then ultimately, we identified four very promising formulations. For targeting the lungs, the best was one called CAD9, which stands for cationic degradable lipid.

There was no LNP delivery to the liver whatsoever. The mRNA only was delivered into the lungs, which is amazing.

Especially for a cancer application, you might not want those

therapeutics going into healthy organs where there's no tumor. This one is very much focused on the lung.

How about getting into the brain?

The brain is very challenging, because you have to cross the blood-brain barrier.

My postdoc was basically able to create a model of the blood-brain barrier on a chip. We developed a type LNP that could cross that barrier on the chip.

We're not at a therapeutic point yet. This is just a fundamental chemistry proof of concept. But we think this is something to build off of that is very exciting.

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