The Pfizer–BioNTech vaccine against COVID-19 delivers mRNA in lipid nanoparticles. Credit: BioNTech.

Why drug delivery is the key to new medicines

Designing a new drug is not enough; it has to be delivered to its target, which can be achieved via a cornucopia of vehicles, from nanoparticles and microneedles to red blood cells and microalgae.

Mike May

New drugs are featured daily in the media, but the method of delivery receives scant attention. A new blockbuster drug can work only if it is protected and transported to the right location. Many new approaches to drug delivery have been developed recently, and others are being tested in clinical trials. New methods of drug delivery ultimately aim for increased efficacy, as well as improving the experience for patients — from simplifying the method of taking a drug to improving its safety.

"Drug delivery technologies have enabled the development of many pharmaceutical products that improve patient health by enhancing the delivery of a therapeutic to its target site, minimizing off-target accumulation and facilitating patient compliance," wrote Samir Mitragotri, Hiller Professor of Bioengineering at Harvard University and the Wyss Institute, and his colleagues in a recent review.

A drug and its delivery vehicle must work as a team to accomplish a therapeutic objective. "With some of the advanced delivery systems, it's about getting the right drug to the right part of the body at the right time," says Nicholas Warne, vice president of pharmaceutical research and development at Pfizer.

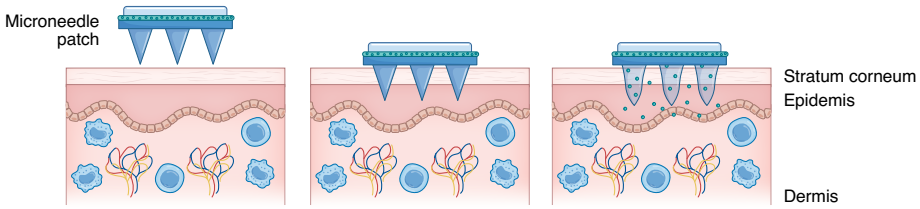
mRNA's unsung partner

During the ongoing COVID-19 pandemic, billions of doses of mRNA vaccines have been delivered that use lipid nanoparticles as the delivery vehicle. mRNA is now rightly famous as a potential cure for many diseases, and this has generated billions of dollars for Moderna, Pfizer and BioNTech, but the design of the lipid nanoparticles was just as important.

Lipid nanoparticles are essential for effective delivery of mRNA. "Nanoparticles are small enough that they can actually get into cells, and the nanoparticles can protect sensitive molecules that would otherwise get destroyed by the body," such as mRNA, says Robert Langer, Institute Professor at the Massachusetts Institute of Technology.

Nanoparticles also help to control the dose. "If you inject a drug directly, it gets into the body at a very high concentration, which could cause various types of toxicity," Langer explains. "When you put the drug in a nanoparticle, you don't get that super-high dose." Instead, the drug is delivered more slowly, which reduces side effects.

Despite the huge benefits of using nanoparticles for drug delivery, there are challenges. Langer mentions safety, efficacy and stability. When a drug is put into a nanoparticle, the safety of the combination



An array of hydrogel microneedles sits below a drug reservoir in a microneedle patch. When pressed to the skin, the microneedles can painlessly deliver a drug into the epidermis. Immune cells, arteries (red), veins (blue) and lymphatic vessels (yellow) are shown in the dermis. Credit: Lalitkumar Vora.

must be determined, as the nanoparticle itself could cause side effects. A nanoparticle vehicle could also reduce a drug's efficacy. Optimization is key, as fixing safety may reduce efficacy, for example. "If you get one to work well, you might run into a problem on another," Langer says.

The lipid nanoparticles in the BNT162b2 (Pfizer–BioNTech) vaccine against COVID-19 include a cationic lipid that binds the mRNA, together with cholesterol and phosphocholine, plus a polyethylene glycol (PEG) lipid for stabilization. "Essentially, we are talking about an emulsion having no or very little aqueous space inside the lipid nanoparticle," says Steffen Panzner, vice president of delivery technologies at BioNTech. That particle is only 70–80 nanometers across.

The lipid-nanoparticle technology, which is in vaccines now used in hundreds of millions of people, was developed over decades, with the levels of each lipid carefully balanced. Alnylam pioneered the medical use of lipid nanoparticles with a drug called Onpattro, which delivers small interfering RNA to treat hereditary transthyretin amyloidosis. "As Onpattro is repeatedly administered into a patient's bloodstream, this has really validated the safety of the new platform," says Panzner. "This gave us a sufficient overview with regards to the safety profile when considering a vaccine that is administered only a few times in small doses into the muscle, not in [the] circulation."

Once the science of lipid nanoparticles was in place, the focus turned to industrial production. "Making the mRNA is well established," Warne says. "People have been doing that for at least 30 years." Getting the RNA in the lipid nanoparticles was also "a pretty simple process, but it has to be done perfectly every time, because we're making billions of doses on an annual basis," he explains.

Although the mRNA vaccines against COVID-19 from Moderna and Pfizer–BioNTech have high efficacy, stability remains an issue. The vaccine is shipped at –70° Celsius and is usable from a refrigerator for about 10 weeks. "It's not the most stable or convenient," Warne says. "So, we're working on that." Through technological improvements, Pfizer and BioNTech have already increased stability at 4° C from 5 days to 1 month.

Organ targeting

Lipid nanoparticles have many potential uses beyond infectious diseases. As Wei Tao, a biomaterials researcher at Brigham and Women's Hospital and Harvard Medical School, says, "Local delivery of mRNA via nanoparticles might also hold promise in the treatment of malignancies."

Tao and his colleagues used nanoparticles to deliver mRNA to the bladder of mice, targeting the lysine-specific demethylase KDM6A, a suppressor of bladder cancer. But the bladder presents challenges for gene therapy, as any treatments tend to be quickly eliminated in urine.

The delivery vehicle developed by Tao's team used nanoparticles made from poly(lactic-co-glycolic acid), which is biodegradable and is approved by the US Food and Drug Administration. But they crucially added an outer coating of PEG, which was molecularly engineered to bind the mucosal surface, with the hope of keeping the mRNA in the bladder longer.

In studies with mice, the mRNA–nanoparticle stuck to the bladder and reduced tumor growth. But without the PEG coating, urine quickly washed the nanoparticles away; this showed proof of principle and paved the way for studies in humans.

Mass manufacturing microneedles

Scientists have been injecting medications since at least the mid-1600s. Over the centuries, technology has understandably improved, with excitement today focused on microneedles. These arrays of tiny projections on a solid support are "minimally invasive devices that painlessly and without drawing blood penetrate the skin's stratum corneum barrier to allow delivery of medicines that ordinarily wouldn't be delivered into or across the skin," according to Ryan Donnelly, Chair of Pharmaceutical Technology at Queen's University Belfast.

The first patent on microneedles was filed in the mid-1970s, but it took until the 1990s for them to be produced in larger quantities. Microneedles are typically less than a millimeter or two tall, are a few hundred micrometers across at the base, and are 10–50 micrometers in diameter at the tip, and can be made from glass, metals or polymers. At present, microneedles are commercially used only for cosmeceutical products, such as Botox, but researchers are exploring how they could be coated with a drug and then dissolve after penetrating the skin, allowing the drug to enter. Alternatively, hollow microneedles could be filled with a drug and could release that drug by swelling when applied to the skin.

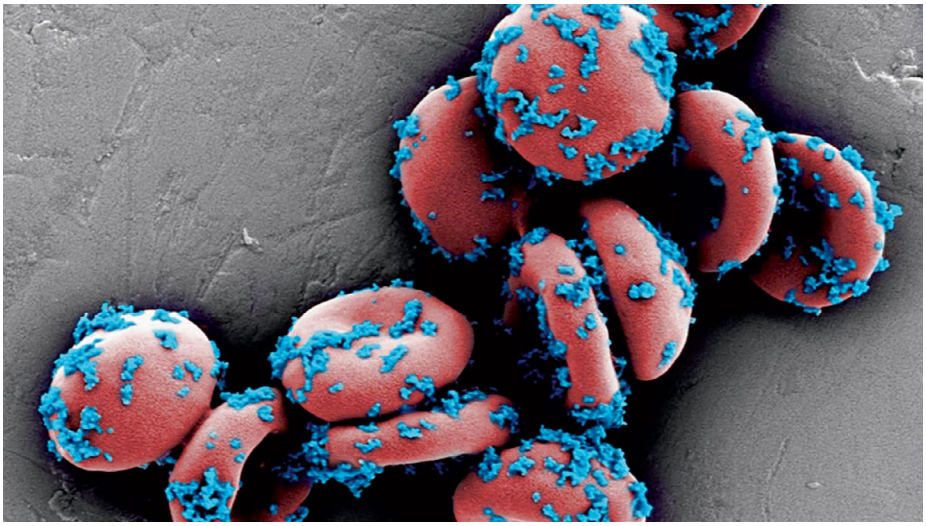
Until recently, manufacturing was a major challenge for microneedles. "It's one thing making something on a small scale by hand in the laboratory, and then there's another thing entirely in making millions of products to high standards that can be reproducibly used by patients, particularly in their own home," Donnelly says. "It's only in recent years that we have seen a number of companies actually working to become manufacturers of microneedles." For example, Kindeva in the United States and Lohmann Therapie-Systeme in Germany manufacture microneedle-based delivery systems.

Microneedles offer benefits beyond being minimally invasive. A dry drug on a polymeric microneedle array would be temperature stable and easy to apply, making it ideal for vaccines against infectious diseases in low-income countries. Donnelly envisions using microneedle arrays for sustained delivery of a drug over time, which could be useful for people infected with human immunodeficiency virus, who currently take daily pills, or people with mental-health conditions, Donnelly notes.

Nanoparticles can also be combined with microneedle technology. "It could be just like a Band-Aid that you could send to the developing world for mRNA therapeutics or mRNA vaccines," Langer explains. In such an application, the simplicity of delivering drugs with microneedles and the potential stability of such a product could make it usable around the world.

Cellular delivery

Intravenously injected drugs travel directly into the bloodstream, where they can be quickly cleared by the liver. By comparison, ingested drugs do not get into the



Polymer nanoparticles are attached to red blood cells for targeted delivery. The nanoparticles shear off into the target organ when the red blood cells pass through the organ's capillaries. Credit: Samir Mitragotri.

bloodstream as quickly. "We are overcoming this hurdle by using red blood cells as a carrier," Mitragotri says. "We reversibly attach therapies to the surface of red blood cells, which shields them from clearance in the liver."

Drugs carried by erythrocytes, or red blood cells, can more easily target tissues. Mitragotri's team is using this method to deliver a variety of therapies, including small molecules, biologics and mRNA. After incorporating the therapeutic with a nanoparticle, the scientists mix that with the erythrocytes. Some of the nanoparticles stick to the outside of the cells, but it is not clear why. It is not a covalent bond, but it could be caused by electrostatic or hydrophobic interactions, or something else.

"This is an orthogonal approach for tissue targeting [that] makes use of the body's own cells to deliver drugs," Mitragotri says. "That's what makes it interesting."

Orally administered medications are usually the most convenient for a patient, but this route requires that the drug make its way through the acidic conditions in the stomach. Stomach acid will denature or degrade many drugs, including those based on nucleic acids or proteins, and even if a drug survives the stomach, it must then cross the mucus barrier in the intestines to reach its target. "Some therapeutics, especially the hydrophobic ones, can be easily blocked by the mucus and thus [are] quickly removed before they can be absorbed by the intestine," says Tao.

If the intestine is the ultimate target for the drug, then there is the opposite challenge: to avoid crossing the mucus membrane and stay in the intestine for as long as possible. "It is also important to increase the intestinal retention time of the drugs, especially in treating different types of intestinal cancers, to reduce the dose or duration of drug administration and reduce side effects," Tao says.

Tao is taking on those challenges in intestinal-disease treatments by delivering drugs such as curcumin, a component of turmeric, with the edible cyanobacterium *Spirulina platensis*, a common dietary supplement. By simply dissolving curcumin in ethanol, diluting it with water, adding that to a suspension on *S. platensis*, and stirring the mixture for 12 hours, he ensures that the bacteria's surface takes up the drug.

Tao says, "Drug carriers based on *Spirulina platensis* possess the properties of easy quantity production and excellent biocompatibility without safety concerns." In 2011, US Pharmacopeia gave this bacterium a high safety rating for human consumption. Plus, the cyanobacterium's spiral structure "enables it to be not only more easily trapped by the intestinal villi but also adhered to the intestinal wall, thereby prolonging the retention time of the drugs in the intestine," says Tao.

Drug delivery via cyanobacteria has already shown promise. In a mouse model of acute colitis, using *S. platensis* to deliver curcumin reduced "the production of proinflammatory cytokines and thereby exerted anti-inflammatory effects against colitis," Tao says. "Our technology may offer safe and innovative means of oral drug administration with clinical potential against various intestinal diseases."

Squeeze to deliver

When cells are used as drug-delivery vehicles, the cell must be 'persuaded' to carry the drug, either on its surface or inside it. Scientists use many methods, such as electricity, to get drugs into cells, but Armon Sharei stumbled across an unexpected approach while working on his PhD at the Massachusetts Institute of Technology.

Sharei found that pushing cells through a constriction — thereby squeezing them — causes transient holes to appear in the outer membrane, which can let in a potential treatment, with the cell membrane resealing afterwards. Sharei spun out this method into SQZBIOTECH, where he is the founder and CEO. SQZBIOTECH already has cell therapies for autoimmune and infectious diseases, such as infection with human papillomavirus, as well as various cancers, in pre-clinical and clinical testing.

Langer, who was one of Sharei's PhD advisors, says, "This was just very unusual." He adds, "You could put almost anything in the cell, and you can do literally billions of cells a minute." It is both surprising and novel. As Langer says, "I've not seen anything like it and certainly didn't expect it."

Perhaps the most exciting advances in drug delivery will arise from other unexpected mechanisms. "That's how science works," Langer says. "Sometimes, you make serendipitous discoveries." ❐

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Published online: 6 June 2022
https://doi.org/10.1038/s41591-022-01826-y