the plasmid DNA injected into the skin collects—it could be in APCs like dendritic cells, in fibroblasts, in dermis or in muscle myocytes, or all of the above. Regardless of their cellular destination, to function, DNA plasmid-based vaccines need to reach the nucleus. There they are transcribed into mRNA, which then exits the nucleus to undergo translation in the cytoplasm. Critics have raised theoretical concerns about the integration of plasmid DNA into the genome of recipient cells, but there has been no experimental evidence of this, despite, as Liu notes in a recent review, extensive testing of the first licensed animal vaccines.

So far, scientists have tested lipid nanoparticles, electroporation, jet injectors and gene guns with varying success, and new delivery technologies continue to emerge. The ZyCoV-D vaccine uses PharmaJet's needle-free Tropis device. It employs a pressurized jet of liquid, powered by a simple spring mechanism, to puncture the skin and deliver the vaccine intradermally. It is already pre-qualified under the WHO's Performance, Quality and Safety assessment process, which means it can be readily deployed by United Nations agencies and WHO member states. At a reported price of $3.57 per dose, the vaccine is not particularly cheap—a full course will cost over $10.

> "My personal opinion is we're never going to get to mass vaccination with DNA until we find a way to deliver it that's less device dependent."

Most of the cost is down to the liquid injection device. Electroporation is another tried and tested way to boost the cellular uptake by applying an electric field to the injection site, causing transient pores to form in the cell membrane and allowing large molecules to pass across. However, progress with this technology has suffered some setbacks. Inovio Pharmaceuticals, a leader in the field, had the phase 3 trial of its DNA-based COVID-19 vaccine INO-4800 put under a partial FDA clinical hold because of outstanding questions about its Cellectra 2000 handheld device, which uses electroporation. The company has since obtained authorizations to conduct the phase 3 portion of its ongoing pivotal trial in Brazil, the Philippines, Mexico and Colombia, but even if the vaccine does reach the market, scaling up could be a challenge. "I think it's always problematic for global distribution when you have a device that's high tech," says Liu. Schmaljohn concurs: "My personal opinion is we're never going to get to mass vaccination with DNA until we find a way to deliver it that's less device dependent," she says. It's the main reason why the US Department of Defense discontinued funding of several DNA vaccine programs. "A lot of places, including the Department of Defense, were very hesitant to be device dependent, whether it be electroporation or gene gun."

An efficient, ultra-low-cost device could help to shift that mindset. A group at the Georgia Institute of Technology, Emory University and Sun-yat Sen University, in Shenzhen, China, has developed an electroporation device for SARS-CoV-2 vaccination that costs less than a dollar to produce. It relies on a piezoelectric element—a thumb-operated trigger like that in a domestic stove lighter—to generate a very short electric pulse of 10 microseconds. "Electroporation is usually done with a much longer pulse," says Georgia Tech's Mark Prausnitz, one of the corresponding authors on a recent publication that describes the device. But the group was able to generate an electric field that was strong enough to ensure efficient gene uptake by designing a tightly spaced array of microneedle electrodes to deliver the current to the skin. In mice, the system was about ten times more efficient than conventional intramuscular or intradermal injection at eliciting a neutralizing antibody response against a SARS-CoV-2 DNA vaccine. It is completely portable, weighing less than 50 grams, and involves none of the cost or power requirements of conventional electroporators. "I think there's a new appreciation that cost matters in healthcare," Prausnitz says. Clinical trials are still some time away, however.

Entos Pharmaceuticals, of Edmonton, Alberta, is starting a phase 2 trial in South Africa of a DNA-based COVID-19 vaccine that employs device-free delivery. Its Fusogenix technology combines naturally occurring lipids with a non-immunogenic membrane fusion protein derived from a reovirus. These proteolipid nanoparticles fuse directly with the recipient cell membrane and deposit their contents directly into the cytoplasm, bypassing the endocytic pathway that lipid nanoparticles use. "For our platform that's a huge distinguishing feature," says CEO and co-founder John Lewis. "We're able to achieve very, very high dosing with great systemic tolerability. They go pretty much everywhere," says Lewis. The Fusogenix technology has the advantage of being fridge stable and, "because of the kinetics of expression, we actually have pretty good data showing it's probably effective after a single dose," Lewis adds. Vaccines based on mRNA

Moderna feud with NIH over COVID vaccine

A disagreement over who owns the patent rights to a landmark COVID-19 vaccine spilled into public view last month as Moderna and the US National Institutes of Health (NIH) pressed their claims. The feud stems from a four-year collaboration on HIV and emerging infectious diseases in which three scientists at NIH's Vaccine Research Center—director John Mascola; Barney Graham, who recently retired; and Kizzmekia Corbett, now at Harvard—worked with Moderna to design the genetic sequence that prompts the vaccine to produce an immune response. Results from this collaboration played "a major role in the development of the vaccine," according to NIH director Francis Collins. "It's not a good idea to file a patent when you leave out important inventors, and so this is going to get sorted as people look harder at this," Collins added. In addition, Moderna received nearly $10 billion in US government funding for large-scale clinical trials and to increase manufacturing and delivery of vaccines. Moderna countered, with a spokesperson saying the company "all along recognized the substantial role that the NIH has played in developing Moderna's COVID-19 vaccine." But in a separate statement, the company said, "We do not agree that NIAID scientists co-invented claims to the mRNA-1273 sequence itself. Only Moderna's scientists came up with the sequence for the mRNA used in our vaccine." While the NIH has traditionally declined to exercise its march-in rights on technology it has funded, co-ownership of the vaccine's patent rights would allow the US government greater say in allowing out-licensing of the technology and manufacturing rights, as well as a piece of the projected $18 billion this year—and $22 billion in 2022—that Moderna stands to earn with its only approved product.

Published online: 8 December 2021
https://doi.org/10.1038/s41587-021-01166-1