The next next-gen vaccines

Spurred by the pandemic response, a new wave of vaccine technologies is poised to expand a menu of prophylactic options.

Mark Zipkin

By all accounts, the pandemic response was remarkable. Hundreds of vaccine candidates based on a wide range of traditional and novel technologies were investigated at exceptional speed, and one of the novel technologies—mRNA vaccines—became established as a key tool to combat COVID-19.

But the approved mRNA vaccines are not without limitations. Last year, the vaccine development foundation Coalition for Epidemic Preparedness Innovations (CEPI) launched a call for proposals seeking innovative RNA platforms that could offer improvements over existing mRNA vaccine technology.

"What we're looking for are high-impact innovations that potentially could be used for next-generation RNA platforms—things that would maybe improve on some of the characteristics of the current RNA vaccines, which obviously made huge strides," said In-Kyu Yoon, CEPI's director and global head of programs and innovative technology. Yoon pointed to a range of characteristics with room for improvement, such as the balance between immunogenicity and reactogenicity, the thermostability profile, and cost.

Then, in April 2023, the Biden administration announced Project Next Gen, the $5 billion successor to Operation Warp Speed, charged with coaxing development of COVID-19 vaccines that would improve on today's approved vaccine in three areas: durability, effectiveness against new variants, and ability to block transmission. It's a clear sign that public health bodies recognize that available vaccines are not optimal, said Ji Li, who is co-founder, president and CEO of vaccine developer Uvax Bio.

A month later, the United States Food and Drug Administration (FDA) approved GSK's Arexvy, the first respiratory syncytial virus (RSV) vaccine. The RSV vaccine relies on advances in structural biology, and adjuvants that took more than three decades to develop, said Philippe Denoël, head of external research and development GSK Vaccines. The various technologies deployed for recently approved vaccines highlight the value of pursuing novel approaches.

mRNA technologies

The relative success of mRNA-based vaccines has energized groups seeking to improve on the technology.

One commonly overlooked distinction between mRNA and more traditional technologies is that mRNA itself is not actually a vaccine—it effectively turns human cells into vaccine factories by inducing them to produce viral antigens. That means it has to be delivered into cells, which to date has been through lipid nanoparticles (LNPs), artificial shells that house the fragile mRNA molecules and transport them across cell membranes.

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LNPs, however, are imperfect taxis. For one, they are suspected to play a role in vaccine reactogenicity, resulting in inflammatory responses that lead to both local side effects like pain or swelling, and systemic side effects including fever.

As such, several groups are developing alternative vehicles that can carry mRNA without the side effects. In January 2023, CEPI announced the first grant from its calls for proposals, choosing Tiba Biotech's polymer nanoparticle technology. Beyond reduced reactogenicity, Yoon cited several potential advantages of polymer nanoparticles over LNPs, including increased RNA payload capacity and even thermostability—"ultra-cold storage is a feature of the currently licensed mRNA vaccines." The $2 million CEPI grant will support preclinical research for Tiba's polymer nanotechnology.

Meanwhile, Moderna announced a partnership in April 2023 with IBM that aims to utilize artificial intelligence and quantum computing to optimize LNPs for both safety and performance.

Denoël also noted that there are opportunities to improve activity once mRNA has reached a cell, using bioinformatics tools. "There are new technologies that allow us to really optimize your mRNA sequence—for higher expression levels, and to lower any undesired natural response of the host cell, such as interferon responses," he said. In addition, synthetic biology companies are developing DNA templates that could make the production of mRNA even faster in response to emerging pathogens.

Another approach to improving intracellular activity is self-amplifying RNA, where a vaccine encodes not only a viral antigen but also the RNA itself. The result is more antigens produced over a longer period, with less vaccine required. A self-replicating mRNA vaccine for COVID-19 from Gennova Biopharmaceuticals has been approved under emergency use authorization in India. And Yoon notes there are groups developing circular RNA, with similarly long-lasting transcription within the cell.

Learning from nature

Beyond mRNA, several novel technologies are seeking to expand what's worked for approved vaccines, often harnessing naturally occurring elements to trigger immune responses.

One new approach that does both is a self-assembling protein nanoparticle platform developed by researchers at the Scripps

Research Institute. In April 2023, researchers led by senior author Jiang Zhu, associate professor in the Department of Integrative Structural and Computational Biology at Scripps, published positive preclinical data in *Nature Communications* (*Nat. Comms.* **14**, 1985; 2023) for a human immunodeficiency virus (HIV) vaccine candidate based on the platform.

Zhu—who spun out the technology to form Uvax Bio—was inspired by the virus-like particle (VLP) vaccine that produced a highly successful human papillomavirus (HPV) vaccine. "Our intention is to mimic the most successful vaccine on the market," said Zhu. He added that protein-based vaccines are known for producing a more robust neutralizing antibody response than nucleic acid-based vaccines. The goal, he said, is "one shot, protection for life."

HPV vaccines resemble hollowed-out papillomaviruses, sharing a self-assembling protein-based outer capsid but having no genetic information inside. And they are highly immunogenic; 98% of recipients develop antibody responses. But the approach has not been broadly repeatable because, unlike papillomaviruses, many pathogenic viruses are protected by an outer lipid envelope.

Zhu developed protein nanoparticles that resembled the HPV shell and that could display multiple copies of HIV's envelope glycoprotein, inducing a strong immune response in preclinical testing. Because optimized antigens can easily be swapped into the VLP, Uvax Bio has an early pipeline including the HIV program and 11 other enveloped viruses, as well as one for tuberculosis. With backing from the US National Institutes of Health, Uvax is on track to launch its first clinical trial with its HIV vaccine candidate next year.

There's a clear logic to mimicking pathogens in order to trigger immunogenicity. Another such approach is generalized modules for membrane antigens (GMMA), which are modified versions of vesicles naturally produced from the outer membranes of Gram-negative bacteria. "Those vesicles contain surface antigens in a native context," said Denoël. "And they are presented this way to the immune system, like bacteria would present those surface antigens to the immune system."

As with VLPs, the vesicles contain no genetic material. They are produced by bacteria engineered to express a high proportion of multiple selected antigens. "It's really a key technology for bacterial vaccines development," said Denoël.

GSK has three ongoing clinical GMMA programs for vaccines against Shigella, Salmonella and *Neisseria gonorrhoeae*. Denoël said the simplicity of development and relatively low manufacturing costs leave room to grow additional programs for bacterial pathogens with global health implications.

GSK is one of several companies exploring bacterial outer membrane vesicles or other vesicles, such as human cell-based exosomes, as vaccines. Last year, CEPI funded a program to advance the development of vaccines that provide broad protection against SARS-CoV-2 and other coronaviruses using Codiak BioSciences' exosome platform, although the company has since declared bankruptcy. And in April 2023, Capricor Therapeutics published preclinical data in *Microbiology Spectrum* showing promise for its exosome-based approach to a COVID-19 vaccine.

One advantage shared across the variety of novel platform technologies is the ability to display multiple antigens. It reflects a recognition that the focus on just a single antigen—like the spike glycoprotein for COVID-19 vaccines—does not make for an ideal vaccine.

Scratching the surface

A surprising limitation of the traditional vaccine paradigm is the injection, which bypasses several immune functions that could be harnessed to improve efficacy.

In this regard, some groups have explored delivery options to mucosa in the respiratory tract or gut, which are promising approaches given that these are common ports of entry for pathogens. "We believe that it's essential to induce mucosal protective immune response locally, really at the site of the infection or the site of colonization," said Denoël. He added that the industry is beginning to recognize which molecules are likely to induce the right mucosal immune response.

"We are interested in the mucosal approach, especially in terms of its potential for transmission blocking," said Yoon, who added that CEPI's portfolio includes intranasal and orally dissolved vaccine candidates. But these platforms face additional regulatory hurdles: "The usual immune marker correlates that might be relevant for systemically administered vaccines may be less relevant when it comes to the markers for mucosal immunity," he added.

In December 2022, a nasal vaccine against SARS-CoV-2 from Bharat Biotech International received emergency use authorization in India for people aged over 18.

Another often overlooked part of the immune system is the skin, said David Hoey, CEO of vaccine patch-developer Vaxxas. "If they knew at the start of vaccines that most of the immune cells [can be found] in the skin, they would never have wanted to inject."

Vaxxas has developed a needle-free, high-density microarray patch (HD-MAP) platform. The patch is applied to the skin for about ten seconds, delivering vaccine beneath the surface via thousands of coated microprojections. The goal is to reach dendritic cells, which Hoey expects to route the vaccine more directly to the lymphatic system, than intramuscular injections.

One potential advantage is that a lower quantity of vaccine is required—efficiency that could be crucial in a pandemic response. To that end, CEPI announced a $4.3 million partnership with Vaxxas this year, which will determine the potential for delivering heat-stable, dried-formulation mRNA vaccines through the HD-MAP. But unlike mucosa-based approaches, Vaxxas' platform is agnostic to the vaccine type. "If you think of it conceptually as an insulin syringe, it doesn't care what the antigen is," said Hoey. The patch technology has been demonstrated safe in three phase 1 clinical trials, with two more ongoing.

Recent developments in vaccine technology look promising and continue to advance, though it is yet to be seen which novel approach makes its impact globally, as others have before.

Mark Zipkin is a writer for the biotech and pharma industry.