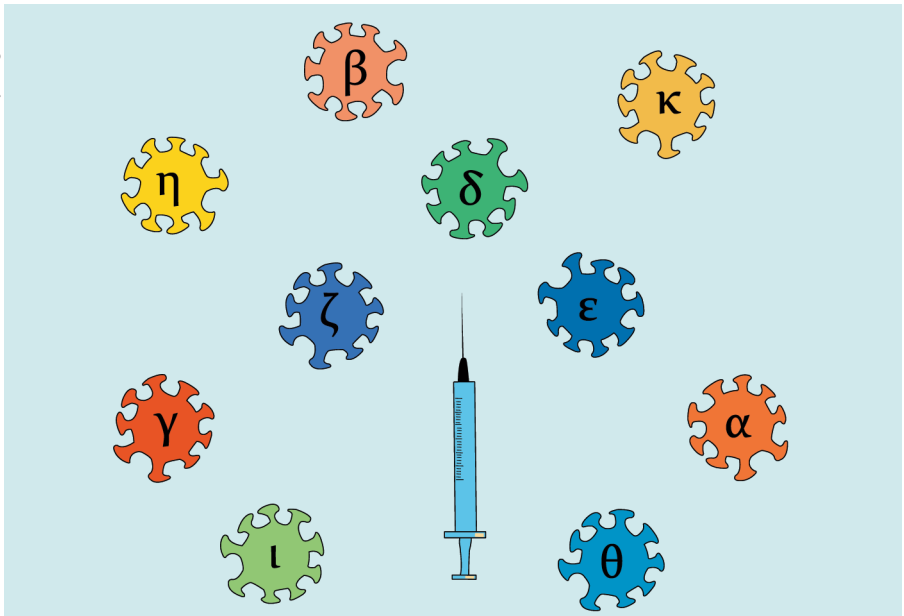

Credit: Nanzeeba Ibnat/iStock/Getty Images Plus

Pan-coronavirus vaccine pipeline takes form

Dozens of 'universal' coronavirus vaccines are in development. But will new technology platforms be able to overcome immunological unknowns?

Elie Dolgin

As debates over additional booster shots for COVID-19 intensify, many public health researchers are looking to the influenza model of vaccination as a guide for how to handle the lasting threat of SARS-CoV-2. That could mean annual shots, as is routine today with seasonal flu prophylaxis. But just as scientists have long sought a universal flu jab that can provide lasting protection against multiple subtypes of that respiratory virus, so too the field is on the hunt for pan-coronavirus vaccines that can ward off future variants of SARS-CoV-2 and preempt the next pandemic.

Dozens of non-profits, government agencies and vaccine makers have made these candidates a top research priority (TABLE 1). Leading the charge, the Coalition for Epidemic Preparedness Innovations (CEPI) and the US National Institute of Allergy and Infectious Diseases (NIAID) have earmarked US$200 million and $43 million, respectively, for R&D into all-in-one coronavirus shots.

Each organization's focus is different. CEPI, with an eye to near-term product development, is primarily backing platform development at small biotech companies. The NIAID is supporting more basic immunology discovery efforts in academia. But their shared overall objective prompted the two organizations to team up. In March, CEPI and the NIAID announced the creation of a joint scientific forum for their funded researchers to discuss their progress and work together toward safe and broadly protective jabs. Its first meeting is scheduled for 25 April.

The vaccine design and delivery strategies under consideration are diverse. They include mRNA- and protein nanoparticle-based technologies. Some vaccine candidates target only the spike protein that enables coronaviruses to enter host cells, while others are directed against additional parts of the viral proteome as well. Some aim to raise only antibody responses, others focus on cellular immunity, too.

"We have quite a nice mix of technologies and antigen designs," says CEPI programme leader Christopher da Costa, who oversees the organization's future-looking coronavirus vaccine portfolio. "It is about getting several shots on goal," he adds. "I'm hoping within that pool, we have some success."

But many researchers think that there are still too many immunological unknowns about how to keep the virus at bay to put much stock in the lead pan-coronavirus vaccines. Decades of failed attempts to develop universal vaccines for influenza and HIV — two other highly mutable viral foes — point to the challenges ahead.

"We have a pretty good sense that what we want to generate is broadly protective immunity that is durable, ideally for life," says Wayne Koff, CEO of the non-profit Human Vaccines Project. There's just one problem: "We don't know how to do that."

Panning for gold

The term "pan-coronavirus" gets bandied about to describe many ongoing vaccine development efforts, but the meaning of that phrase is fuzzy.

First, there are the improved COVID-19 vaccines that were designed to protect against any mutant forms that the SARS-CoV-2 virus could plausibly adopt. These might be better called pan-variant COVID-19 vaccines. But when lab tests reveal some degree of cross-protection against SARS-CoV-1 — the virus behind the 2002–2003 severe acute respiratory syndrome outbreak — some vaccine developers are quick to adopt the more expansive pan-coronavirus label.

Among shots purposely designed to be more inclusive, the pan-coronavirus moniker takes on different meanings. Few, if any, scientists are developing truly universal candidates that would protect against all four major lineages of coronavirus. Most are instead taking aim either at sarbecoviruses, the subgenus that includes all the SARS-like viruses, or betacoronaviruses, the larger branch of the family tree that also counts the pathogen responsible for Middle East respiratory syndrome (MERS) and some seasonal coronaviruses that cause the common cold.

Moderna's 'pan human coronavirus' vaccine falls into a category of its own. Unveiled in March, the preclinical-stage candidate mRNA-1287 is designed to protect against endemic human-infecting coronaviruses — two alphacoronaviruses and two betacoronaviruses — that collectively cause 10–30% of all common colds in adults. According to Raffael Nachbagauer, head of infectious disease development at Moderna, this programme is not intended to prevent the next pandemic, but rather to "decrease the currently unaddressed disease burden from seasonal coronaviruses in the population."

The vagueness of language around cross-clade coronavirus protection has led to "a lot of painful discussion" at CEPI about the best terms to use, da Costa says. The organization ultimately settled on "broadly protective" to describe any vaccine directed at multiple coronaviruses, and "variant-proof" or "variant-targeted" to describe next-generation COVID-19 jabs. It is supporting both types of development efforts. "The vision is that we would have a limited number of variant-targeted vaccines

and a more substantial number of broadly protective vaccines going forward," says da Costa.

CEPI has announced funding for eight projects to date, with more expected to come. Three take aim at emerging forms of SARS-CoV-2. All of these take advantage of novel protein subunit technologies to deliver parts of the spike protein containing mutations from variants of concern. One, from MigVax, is orally administered with a bacterial toxin serving as a mucosal adjuvant. Another, from Affinivax, is built around an antigen–polysaccharide conjugate platform. The third, from the University of Saskatchewan's Vaccine and Infectious Disease Organization, will use a proprietary matrix to present antigens in a structured fashion.

The other five CEPI-backed efforts are geared toward deflecting a broader range of coronavirus threats. Three — from BioNet, DIOSynVax and NEC Corporation — will rely on computational modelling to identify novel vaccine antigens that can be used in mRNA delivery systems. The other two — one from India's Translational Health Science and Technology Institute in collaboration with Panacea Biotec, the other from SK bioscience — are for multi-epitope, nanoparticle-based, protein subunit vaccines.

Mosaic approach

Among the five broadly protective vaccines in the CEPI portfolio, the SK candidate received the largest chunk of change. It looks to be closest to clinical evaluation as well.

Backed by up to $50 million from CEPI, the vaccine — named GBP511 — builds on the progress made with SK's experimental COVID-19 jab GBP510, now in phase III testing. Both are adjuvanted products based on a two-part nanoparticle system developed at the University of Washington's Institute for Protein Design. It displays 60 copies of the spike protein's receptor-binding domain (RBD) in a trimeric form to induce potent immune responses.

But whereas GBP510 includes only RBDs from the original strain of SARS-CoV-2, GBP511 takes a mosaic approach to present more antigens. It displays three or four RBDs from human- and bat-infecting viruses — from all three clades of the sarbecovirus phylogeny — to generate cross-reactive B cells that will bind to conserved epitopes shared by different RBDs. This multivalent antigen presentation, the thinking goes, should lead to selective activation and expansion of immune cells with broadly protective capabilities.

SK's academic collaborators demonstrated as much last September in proof-of-concept experiments in mice and monkeys. The South Korean biotech is gearing up to launch a first-in-human study by the end of 2023.

Structural biologist Pamela Bjorkman from the California Institute of Technology has developed a similar mosaic RBD nanoparticle construct, first described in January 2021. It uses the same icosahedral nanoparticle at its core, but is decorated with RBDs from eight sarbecoviruses — six of these infect bats, one infects pangolins and one comes from the Beta variant of SARS-CoV-2.

In Bjorkman's vaccine, the RBDs are arranged by chance, with a low probability of identical antigens landing next to each other. SK's self-assembling nanoparticles, by contrast, use RBDs organized non-randomly in groups of three — a structural difference that may impact the likelihood of stimulating cross-reactive antibody responses. "If they're randomly distributed," Bjorkman says, "you should activate B cells that bind to regions of the receptor-binding domain that are more conserved."

A preprint that Bjorkman's team posted online in March supports this conclusion. The team's eight-part mosaic nanoparticle vaccine offered broad protection to mice — "as hypothesized," says Bjorkman. She is seeking financial support to advance the candidate into human trials.

Breadth of immunity

Among 'pan-variant' vaccines with some cross-clade potential, a few candidates are farther along. The Walter Reed Army Institute of Research in Silver Spring, Maryland, for example, is developing an adjuvanted nanoparticle vaccine candidate, prepared by conjugating a self-oligomerizing protein called ferritin to prefusion-stabilized versions of the SARS-CoV-2 spike protein. Results from a 29-person phase I study are expected in the coming weeks.

Army researchers call it a pan-coronavirus vaccine because in mouse and monkey studies the shot elicited robust humoral and cell-mediated immune responses against SARS-CoV-2 variants of concern and SARS-CoV-1. When given as a booster after two priming doses of first-generation COVID-19 vaccines, the scope of immunity might be even greater.

Immunologists Barton Haynes and Kevin Saunders from Duke University demonstrated as much last year when they administered their own ferritin nanoparticle shot to monkeys primed with an mRNA vaccine. (Duke's vaccine candidate uses a more modular manufacturing protocol as well as RBD antigens based on an early Washington state isolate instead of full-length spike proteins

Table 1 | **Selected pan-coronavirus vaccines in development**

Vaccine	Sponsor	Properties	Status
Variant-proof COVID-19 vaccines			
SpFN	US Army	Ferritin nanoparticle with prefusion-stabilized spike antigens from the Wuhan strain of SARS-CoV-2	Clinical
RBD–scNP	Duke University	Sortase A-conjugated ferritin nanoparticle with RBD antigens from early WA-1 strain of SARS-CoV-2	Preclinical
GRT-R910	Gritstone bio	Self-amplifying mRNA delivering spike and T cell epitopes	Clinical
hAd5-S+N	ImmunityBio	Spike and nucleocapsid antigens delivered via human adenovirus serotype 5 vector	Clinical
MigVax-101	MigVax	Oral subunit vaccine with RBD and nucleocapsid domains, adjuvanted	Preclinical
Pan-sarbecovirus vaccines			
GBP511	SK bioscience	Mosaic nanoparticle containing RBDs from SARS-CoV-1, SARS-CoV-2 and 1–2 bat coronaviruses	Preclinical
Mosaic-8b	Caltech	Mosaic nanoparticle containing RBDs from SARS-CoV-2 and 7 animal coronaviruses	Preclinical
VBI-2901	VBI Vaccines	Virus-like particles expressing prefusion spike of SARS-CoV-2, SARS-CoV-1 and MERS-CoV	Preclinical
Pan-betacoronavirus vaccines			
DIOS-CoVax	DIOSynVax	Needle-free injection of undisclosed antigens	Clinical
Other			
mRNA-1287	Moderna	mRNA encoding antigens from four human-infecting coronaviruses that cause common colds	Preclinical

derived from the original Wuhan strain, but is otherwise quite similar to the Army's candidate.) "With the boost, you get all this breadth," Haynes says.

"We were hitting bat viruses, pangolin viruses, SARS-CoV-1," he continues. "Not MERS because the RBD is very different, but everything within the sarbecovirus group." As measured by antibody binding titres, the immune responses achieved with a nanoparticle design were greater than those achieved with a soluble RBD vaccine comparator. A recent preprint suggests that the type of adjuvant formulation also matters.

Haynes hopes to move his ferritin nanoparticle vaccine into clinical trials next year — and he received a $17.5 million, 3-year grant from the NIAID's new Pan-Coronavirus Vaccine Development Program to support those efforts. But the money is also meant to underwrite immunogen design efforts. Plus, part of the grant is dedicated to advancing new types of mRNA or self-amplifying RNA constructs that can confer pan-betacoronavirus protection.

Last year, Haynes and his colleagues, led by University of North Carolina virologist Ralph Baric, described one strategy for broadening the benefits of the mRNA platform. They designed sequences coding for a chimeric protein that assembles different parts of spike — the RBD, the N-terminal domain and the S2 subunit — taken from human- and bat-infecting sarbecoviruses. When packaged in lipid nanoparticles (LNPs), these mRNA sequences triggered wide-ranging protection in mice.

"This is an alternative to the mosaic approach to get breadth in the response," Haynes says.

In principle, the same sequences could be encoded in self-amplifying RNAs, which might enable lower dosing regimens and better immune responses. Haynes's team is exploring use of such constructs, which contain both the antigenic sequences and the machinery needed for the RNA to copy itself.

Game plan

Although the Duke project is heavily geared toward platform development, the other three beneficiaries of the NIAID pan-coronavirus initiative — at Brigham and Women's Hospital, at the University of Wisconsin–Madison and at Rockefeller University — are far more focused on basic immunology questions. "There's still a lot of science that's not known," points out programme officer Jennifer Gordon. The hope is that a better understanding of the natural immune responses to coronavirus infections will ultimately yield better vaccine designs.

"Part of the fundamental discovery is understanding what the trade-offs look like," says grantee Duane Wesemann, an immunologist at Brigham and Women's Hospital. Last year, Wesemann and his colleagues identified a potential antigenic target — the spike protein's conserved stem, or S2, region — that yields antibodies that are associated with reduced mortality from COVID-19, quicker healing and improved immune durability following disease resolution.

Those same antibodies also provide enhanced recognition breadth across betacoronaviruses. But they offer weaker neutralization capacity than antibodies directed at spike's more variable head, the target of all first-generation COVID-19 vaccines. Further work is needed to determine which profile is best for a broadly protective vaccine intended to prevent zoonotic spillovers.

Similar challenges have faced researchers aiming to direct immune responses against the stalk region of haemagglutinin, the main conserved protein target of universal influenza vaccines. Given the many setbacks in that field, Wesemann hopes that coronavirus researchers will have some humility about the immunological obstacles in front of them.

"Everyone wants to go ahead and throw the Hail Mary," he says. With luck, that will work. But a more careful consideration of immunological parameters would increase the odds of success. "We need to learn how to block and tackle to improve our chances in future Super Bowls," Wesemann says.

In particular, more insight is needed into how the quality of T cell immunity impacts protection. Many researchers expect that for pan-coronavirus vaccines to succeed, they will have to provide robust and broad protection via multiple T cell subsets as well as antibody-mediated pathways. "To really have a highly effective vaccine, you're going to need to be able to elicit both neutralizing antibodies and T cells," says Corey Casper, president and CEO of Access to Advanced Health Institute.

Casper is working closely with ImmunityBio, part of Patrick Soon-Shiong's NantWorks portfolio of companies, to develop dual-antigen vaccines that include both spike and nucleocapsid (N) components. Nucleocapsid is an internal RNA-binding protein, and has long been viewed as an important target for T cell responses that might confer broad protection. "Once you have N in your construct, you have a good shot at having this pan-coronavirus [protection]," Soon-Shiong says.

ImmunityBio's first product — built around a human adenovirus serotype 5 (Ad5) platform — is now being trialed as a booster among recipients of Johnson & Johnson's spike-only adenoviral-vectored vaccine. But in addition to thinking beyond spike, the company is also developing a "mix-and-match" delivery strategy to improve outcomes.

In mice, a self-amplifying RNA prime followed by an Ad5 boost seemed to enhance the durability and breadth of both humoral and cellular immunity, the company showed in a pre-print. This mirrors results from people who received heterologous prime–boost immunization regimens of first-generation COVID-19 vaccines, which conferred greater breadth of reactivity against SARS-CoV-2 variants of concern.

Lin-Fa Wang, a virologist at the Duke–National University of Singapore Medical School, is advancing a heterologous vaccination strategy of his own. Last year, Wang and colleagues reported that people with 20-year-old SARS-CoV-1 infections who received an mRNA-based COVID-19 vaccine produced a swathe of pan-sarbecovirus neutralizing antibodies. This observation led Wang's team to engineer a consensus spike protein from a group of SARS-CoV-1-related viruses. He hopes to formulate this either as a protein subunit vaccine or as an mRNA-based shot.

Unpublished mouse studies suggest that priming with a COVID-19 vaccine and then boosting with this experimental shot could promote the same kinds of immune responses as those seen in SARS-CoV-1 survivors. Discussions with potential commercial partners are ongoing, says Wang.

Meanwhile, other companies that are moving beyond spike-only designs include TechImmune, ConserV Bioscience and Gritstone bio. The challenge for any of these firms, as immunologist Gaurav Gaiha from the Ragon Institute sees it, is finding T cell epitopes that are mutationally constrained, to allow for coronavirus-spanning recognition, and highly immunogenic. "That's the optimal sweet spot," Gaiha says.

Without the urgency of a new pandemic threat or the whatever-it-costs budget of an Operation Warp Speed, it is unlikely that pan-coronavirus vaccine development will move at the breakneck speed of the 2020 vaccine race. But all the scientific and technological advances of the past two years has buoyed the field — and researchers are confident that finding a broadly protective shot against coronaviruses will not prove as hard as it has been for HIV or flu. "At the end of the day, we need a vaccine that is not only durable, but has a huge breadth of coverage," Soon-Shiong says. "Can we get there? I truly believe we can."