Novavax's fridge-friendly vaccine impresses

Novavax has unveiled results from a large clinical trial showing that its vaccine is 90.4% effective in preventing symptomatic COVID-19 and 100% protective against moderate and severe disease. Results from the phase 3 PREVENT-19 trial with 30,000 participants across the United States and Mexico had been eagerly awaited for the vaccine's presumed advantages over existing jabs. Unlike the approved Pfizer, Moderna and Oxford/AstraZeneca vaccines, NVX-CoV2373 is a protein-based vaccine that relies on a well-established, traditional approach and is expected to have a benign safety profile. It can also be stored in refrigerators, a practical advantage that could boost distribution to low- and middle-income countries. The Novavax vaccine also appears to protect against escape by variants. The trial data were collected between January and April 2021, when the Alpha (B.1.1.7) variant, first identified in the United Kingdom, became the main strain circulating in the United States. The vaccine proved to be 93% effective in preventing symptomatic disease caused by variants of concern circulating during that period. Against symptomatic disease caused by the Beta mutation, an earlier study conducted in South Africa revealed a lower 51% efficacy among HIV-negative participants. It is unknown whether it can protect against the Delta variant, first identified in India, as that was unlikely to be circulating during the study period. NVX-CoV2373 is a MatrixM-adjuvanted recombinant nanoparticle vaccine engineered from the spike protein genetic sequence of the original SARS-CoV-2 strain. Phase 3 results were announced in a company press release and have yet to be published in a peer-reviewed journal. At the same time, another highly anticipated COVID-19 shot, CureVac's mRNA vaccine CVnCov, failed to meet preset success criteria, delivering only 47% efficacy against symptomatic disease in a phase 2/3 trial, according to an interim analysis released by the company. CureVac says there were at least 13 variants circulating in the study population during the analysis, which may have reduced the vaccine's efficacy. The German biotech still plans to file for European approval.

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or applying some combination of these engineering strategies.

To stay relevant, all mAb developers need to account for the wildcard that is viral evolution, says Jane Osbourn, CSO of Alchemab and former head of the UK BioIndustry Association's antibody taskforce on COVID-19. "A number of the clinical candidates out there are falling over against the [emerging] variants," she says. "So, as a community, we should really be taking the time to think through how you stay ahead of the game in terms of that mutational drift."

In lab studies, sotrovimab seems to maintain its neutralization capacity against all circulating variants of concern, including some of the most worrying versions of the virus, first identified in South Africa, Brazil and India. Several of the leading phase 3 mAb candidates—including Adagio's ADG20, AstraZeneca's AZD7442 and Brii Biosciences' BRII-196 and BRII-198—do as well. But Eli Lilly's two-mAb cocktail is hobbled by escape mutations found in these variants, as is one of the agents, casirivimab, in Regeneron's mAb combination. The other Regeneron agent, imdevimab, retains its activity, in large part because the mAb targets an epitope that does not overlap with that of its cocktail companion.

That non-redundancy offers some degree of protection against variant-mediated resistance, says Aeron Hurt, principal global medical science director for influenza and COVID-19 therapeutics at Roche, which partnered with Regeneron to handle manufacturing and distribution outside of the United States. "Single antibodies are vulnerable to single mutations," Hurt says—whereas a cocktail of antibodies that bind at discrete sites provides "an extra insurance policy."

But an even better variant evasion tactic, asserts Adagio CSO Laura Walker, is what her company and Vir have done: both organizations independently screened for ultra-rare broadly neutralizing mAbs that recognize highly conserved epitopes found across the entire family of SARS-like coronaviruses.

The scarcity of these antibodies limits the evolutionary selection pressure for escape mutations in nature, Walker points out. And because conserved residues typically serve essential protein functions, "the virus often can't mutate those residues without suffering a fitness cost," she says, "which means the barrier to escape is typically higher for these broadly neutralizing antibodies."

"But antibodies are not merely things that bind to and neutralize a viral protein," notes Vir CSO Skip Virgin. Through their Fc domain, mAbs also induce innate and adaptive immune responses that help destroy infected cells—and those Fc-mediated activities, Virgin says, "are fundamentally important for treatment of SARS and COVID-19."

Mouse studies published in *Cell*, in the *Journal of Experimental Medicine* and as a preprint in recent months now support this idea. But last year, as the COVID-19 mAb race was just heating up, many companies—including AstraZeneca, Eli Lilly, Abpro and others—chose instead to dial down effector functions in their mAbs. They wanted to minimize the risk of antibody-dependent enhancement of viral infection, a phenomenon in which virus-specific antibodies can promote, rather than inhibit, disease.

This can be a real problem with certain pathogens, including the respiratory syncytial virus and the dengue virus, but Virgin and his colleagues realized early on that it did not seem to be an issue with SARS-CoV-2. So Vir doubled down on the need for strong Fc receptor binding. Not only did the company leave the effector functions intact for sotrovimab, but it also engineered its successor, the follow-on mAb VIR-7832, to have even greater Fc binding activity.

"The concept is to make the antibody vaccinal," explains Virgin. "We're trying to make the antibody so it not only protects the individual, but it also generates an immune response that outlasts it" through the generation of pathogen-specific $CD4^+$ and $CD8^+$ T cells responses. The Vir team joined forces last year with Jeffrey Ravetch's lab at Rockefeller University in New York City to demonstrate the Fc engineering concept with an anti-influenza mAb tested in mice.

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"These are predicted benefits. They haven't been observed in people," Virgin acknowledges, "but that's why we're taking the antibody forward." VIR-7832 and sotrovimab—both of which possess an Fc mutation that confers extended half-life and enhances drug distribution to the lungs—are now part of a master protocol study taking place in the United Kingdom.

Adagio, for its part, has focused its engineering efforts largely on affinity optimization rather than Fc modifications. Although ADG20, like many other next-generation mAbs, does contain Fc changes that improve its circulation half-life, its most distinguishing selling point is the combination of potency and breadth that it offers.

"We took something from nature that was broad, but not very potent, and then improved the potency while maintaining the