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A trial volunteer receives a dose of CureVac's vaccine.

COVID VACCINE FLOP SPOTLIGHTS MRNA DESIGN CHALLENGES

Scientists are searching for explanations for CureVac's disappointing final-stage trial results.

By Elie Dolgin

Two vaccines made using messenger RNA (mRNA) have proved spectacularly successful at warding off COVID-19, but a third mRNA-based candidate has flopped in a final-stage trial, according to an initial report. Researchers are now asking why — and some think that the type of mRNA chemistry used might be to blame. Any insight could help to guide the future design of mRNA vaccines against COVID-19 or other diseases.

The company behind the beleaguered trial, CureVac, based in Tübingen, Germany, announced preliminary data on 16 June from a 40,000-person trial. The results showed that the two-dose vaccine was just 47% effective at preventing disease.

CureVac's mRNA vaccine was expected to be cheaper and to last longer in refrigerated storage than the mRNA vaccines made by Pfizer–BioNTech and Moderna. Many had hoped that it could help to expand the reach of mRNA-based vaccines in lower-income countries, and European countries were expecting to order hundreds of millions of doses.

"I'm definitely surprised — and also disappointed," says Philip Santangelo, a biomedical engineer at the Georgia Institute of Technology in Atlanta who has worked with CureVac and many other mRNA-focused companies.

Variant problem

CureVac executives put the poor results down to the high number of coronavirus variants circulating in the ten countries across Europe and Latin America where the company is running its trial. Of 124 COVID-19 cases for which scientists obtained a genetic sequence, only one was caused by the original version of SARS-CoV-2.

But other mRNA vaccines have fared much better in the face of variants, which has led trial investigators and other scientists to suggest that the problem is with the vaccine itself.

"My best take is that the dose is the culprit," says Peter Kremsner, an infectious-disease specialist at Tübingen University Hospital who is leading CureVac's clinical studies.

In phase I testing, Kremsner and his colleagues evaluated doses ranging from 2 to 20 micrograms of mRNA per injection. At the higher doses, the vaccine caused too many side effects, with trial participants frequently complaining of problems such as severe headaches, fatigue, chills and injection-site pain.

At 12 micrograms, the vaccine proved more tolerable, and all recipients developed antibodies that blocked the virus from entering cells (P. Kremsner *et al.* Preprint at medRxiv https://doi.org/ghjkvj; 2020). But the levels of those 'neutralizing' antibodies were relatively low — on a par with the amounts found in people who have recovered from SARS-CoV-2 infections, but well below those seen in recipients of the Moderna and Pfizer–BioNTech vaccines, which are both given at higher doses.

Modified RNA

Others think that the problem might lie in the mRNA sequence. All three mRNA vaccines encode a form of the coronavirus spike protein, which helps virus particles to penetrate human cells. But the Moderna and Pfizer–BioNTech vaccines use modified RNA, incorporating an mRNA nucleotide called pseudouridine — which is similar to uridine but contains a natural modification — in place of uridine itself. This is thought to circumvent the body's inflammatory reactions to foreign mRNA. CureVac's vaccine uses normal uridine and relies on altering the sequence of RNA letters in a way that does not affect the protein it codes for, but helps the vaccine to evade immune detection.

Proponents of modified mRNA have long argued that the chemical adjustment is integral to the success of the vaccine technology. Drew Weissman, an immunologist at the University of Pennsylvania in Philadelphia, describes it as the "best platform for antibody and neutralization levels". In light of the new CureVac data, many scientists who spoke to *Nature* agree.

"Modified mRNA has won this game," says Rein Verbeke, an mRNA-vaccine researcher at Ghent University in Belgium.

There are other possible explanations for CureVac's tolerability problems, so for some scientists it remains too early to draw conclusions. "The jury is still out on which of these is a better technology," says Jeffrey Ulmer, a former pharmaceutical executive who now consults on vaccine research issues. He predicts that modified and unmodified mRNA will be useful in different contexts.

CureVac hopes that its vaccine — or at least its unmodified mRNA technology — might yet deliver. It is continuing its trial and expects a final analysis in the next few weeks. The company, in collaboration with London-based GlaxoSmithKline, has a second-generation COVID-19 vaccine in the works that, like its predecessor, uses unmodified mRNA. However, this one has been fine-tuned so that it elicits higher levels of neutralizing antibodies, according to data from rat and monkey studies. "Our optimization has never stopped," says CureVac's chief technology officer Mariola Fotin-Mleczek. "It's too early to say unmodified, natural messenger RNA is not an option." Human trials are due to launch later this year.