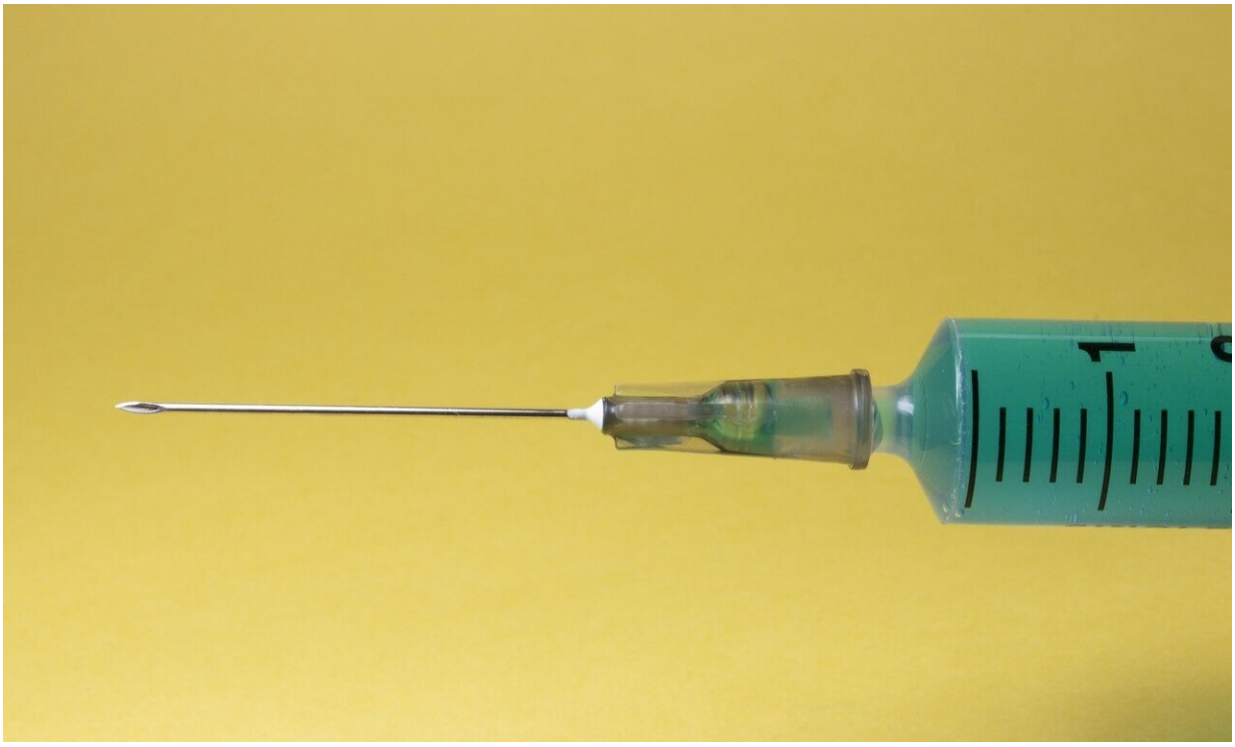
Coronavirus could be the turning point for genetic vaccines, a 30-year-old technology that has not fulfilled its promise

July 1 2020, by Marie McCullough, The Philadelphia Inquirer



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David B. Weiner is known in scientific circles as "the father of DNA vaccines." The tag pays homage to his pioneering work over 30 years, but it's also a reminder that his baby is still aborning.

Not a single human DNA vaccine has made it to market anywhere in the world, and the technology is still rapidly evolving.

The pandemic may be the moment of truth. Genetic code vaccines—built with DNA or RNA—are strong front-runners in the global race to develop an immunization against the coronavirus that has claimed nearly half a million lives worldwide since it emerged in China seven months ago.

Inovio—the Plymouth Meeting biotech that Weiner cofounded, advises, and has financial interests in—was recently dissed as "under-the-radar" in industry press. But in March, the company's DNA vaccine for the coronavirus was featured on TV's "60 Minutes." And last week, the company snagged a $71 million government contract to manufacture the skin-zapping device that is part of its vaccine platform.

Within days, Inovio says, it will announce results of the first small human trial of its coronavirus vaccine, "INO-4800." Initial testing focuses on safety, but that shouldn't be a problem, based on Inovio's other experimental DNA vaccines.

The big question is whether the shots generated signs of a potent immune response. Feeble responses—too wimpy to protect against infection—have been the Achilles' heel of DNA vaccines.

Weiner, 63, is acutely aware that getting a vaccine approved is about managing expectations, cultivating good press, and raising money—as well as solid science. He said that the vaccine race is against the virus, not rival developers. That multiple vaccines using varying strategies are needed. And that perfect is the enemy of the good.

"I think we should set our expectations low," he said. "I really think we're most likely to have several vaccines, and that they will lower

disease severity and prevent some infections. It doesn't have to be 100% effective to have enormous value for the world."

It normally takes a decade or two to get a vaccine from concept to clinic, yet the aim is to start immunizing people against the new coronavirus, SARS-CoV-2, by next summer. More than 120 vaccine candidates using five different strategies are advancing at a breakneck pace, aided by billions of dollars from governments and philanthropies such as the Gates Foundation.

Among the developers already conducting human testing are four with RNA platforms: Moderna, Pfizer, CureVac, and Imperial College London. Inovio is the only front-runner with a DNA-based vaccine.

All vaccine approaches involve teaching the immune system to recognize a virus' unique proteins, or antigens. If the real microbe tries to invade—and viruses have to hijack living cells to replicate—immune cells are primed to attack.

Tried-and-true vaccine technologies involve growing a weakened or inactivated virus in eggs or animal cells, then extracting and purifying the desired antigens. It's an arduous, time-consuming, costly process.

In the early 1990s, Weiner and some others had an idea: Instead of injecting the antigen, why not inject the viral gene that carries instructions—DNA—for making it? DNA would transfer the instructions to RNA in the cell's molecular machinery, which would then produce the antigen to ward off infection.

The beauty of the approach was obvious from the beginning. DNA is a sequence of chemicals, called nucleic acids, that can be rapidly synthesized and fused together in the lab.

Consider that after Chinese researchers published the coronavirus' entire genetic code in January, Inovio scientists "printed" their vaccine in a matter of hours with a DNA synthesizer. Like almost all developers, they used the code for the "spike" protein, which makes the stud-like projections that the coronavirus uses to latch onto and sneak into cells.

But while the advantages of using DNA were clear, so were the challenges.

Weiner was a professor of medicine and a researcher at the University of Pennsylvania in the 1990s when he pioneered the technology for delivering the DNA into cells.

Decades earlier, researchers had discovered that bacteria carried strange little loops of DNA that were separate from their chromosomal DNA and could replicate independently. Some of these "plasmids" were found to help bacteria resist antibiotics.

Weiner's lab synthesized and equipped plasmids to carry viral antigen genes into human cells.

"We look for nature to teach us what to do," said Weiner, who is now emeritus at Penn and vice president of Wistar Institute, which is collaborating on Inovio's vaccine.

In 1997, Weiner's team reported a breakthrough: their novel vaccine had protected two chimpanzees from the virus that causes AIDS. (Fun fact: Weiner and his lab had a cameo in Philadelphia, the 1993 movie about HIV/AIDS and homophobia that earned Tom Hanks an Oscar.)

In humans, however, DNA vaccines simply weren't very effective. At the injection site, uptake of plasmids by skin and muscle cells was nominal and unpredictable. When the cells produced antigen, it triggered

a tepid response by the first line of immune defense—namely, antibodies. But few plasmids found their way into "antigen-presenting cells," which are essential for activating the more powerful second line of defense—T cells. "Killer" T cells can destroy virus inside as well as outside of cells, and "memory " T cells remember the invader to prevent future infections.

By 1999, when Weiner wrote about DNA vaccines in Scientific American, the best he could say was, "Preliminary findings hint that useful immune responses can be achieved."

He soldiered on with a team that included graduate student Joseph Kim, now president, CEO, and cofounder of Inovio.

"A lot of big boys and girls left the field," Kim said, referring to giant pharma companies that abandoned DNA vaccine research. "One who persisted, by conviction or stubbornness or both, was Dave Weiner."

Among the "optimization" measures: The plasmids were engineered to carry additional genes that made cells produce natural immune-boosting substances, including one that stimulated proliferation of the important antigen-presenting cells. To get better uptake of the plasmids, the vaccine was delivered along with electrical charges that briefly opened pores in cell membranes near the injection site.

Manufacture of that handheld "electroporation" device—a proprietary, battery-operated gizmo now named Cellectra—will be scaled up using $71 million from the U.S Department of Defense.

RNA vaccine technology, which is also about 30 years old, has a different set of pros and cons. Messenger RNA doesn't need a plasmid because it doesn't have to get into the cell's nuclear DNA to work. But single-stranded RNA is far less stable than double-stranded DNA.

Enzymes in the body can quickly degrade RNA, which cuts antigen production. The vaccine has to be kept refrigerated or frozen.

The instability problem is like "buying fruit that spoils in a few minutes," said Weiner, adding that he is biased.

Inovio can be seen as a dark horse in the vaccine race—or an odds-on favorite.

None of its prospects has crossed the finish line. Its Ebola and Zika vaccines had to be abandoned because as the outbreaks waned, so did funding and the number of potential clinical trial subjects.

On the other hand, Inovio has 15 vaccines in clinical testing for cancer as well as infectious diseases. The company is expanding human testing of its vaccine for Middle East Respiratory Syndrome (MERS) - caused by another coronavirus—because it generated strong antibody and T-cell responses in most participants in an initial trial.

"It's going to take many technologies crossing the finish line to make an impact in the face of SARS-CoV-2," Weiner said, "and we hope our technology can be part of the solution."