Rapid-response technology could produce billions of vaccine doses fast enough to stop the next pandemic

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James Swartz operating a bioreactor that his lab uses to grow cells from which cell extracts used for CFPS are prepared. Credit: Andrew Brodhead

Ever since the COVID-19 pandemic began more than a year ago, public

health officials, scientists and policy leaders have struggled to contain the viral contagion that has claimed more than 2.4 million lives worldwide and caused global economic upheaval.

This should never happen again, says Stanford bioengineer James Swartz, who has spent more than a dozen years laying the groundwork for a novel vaccine technology designed to stop viral outbreaks by inoculating millions, indeed billions, of people within weeks.

Swartz praised the current COVID-19 vaccines as unprecedented scientific and medical achievements, developed as they were with unparalleled haste and global collaboration, but what he's proposing now is even more ambitious: a radically new vaccine design and ultrafast biomanufacturing process so effective that global herd immunity could be established before a pandemic could even start.

To make good on this promise, Swartz envisions a two-stage program. Stage one would involve making bioparticles designed to carry the active ingredient for the new vaccine, testing these delivery agents for safety and then stockpiling the bioparticles without a medical payload until a pandemic threatened. The beginning of stage two would resemble the process used to create current COVID-19 vaccines, with scientists racing to identify unique molecular fingerprints, or antigens, that can be used to target the dangerous virus. Only this time, there will be a rapid-response biomanufacturing system poised to load the antigens onto the bioparticles. That could make all the difference, Swartz said, and allow a rapid-response vaccine to potentially be tested for efficacy and transformed into billions of injection-ready doses within weeks.

But two big obstacles stand in the way. First, Swartz has based his approach on an only partially-proven technology called cell-free protein synthesis that represents a complete break with the bio-processing techniques that have been used to make protein medicines for the last 40

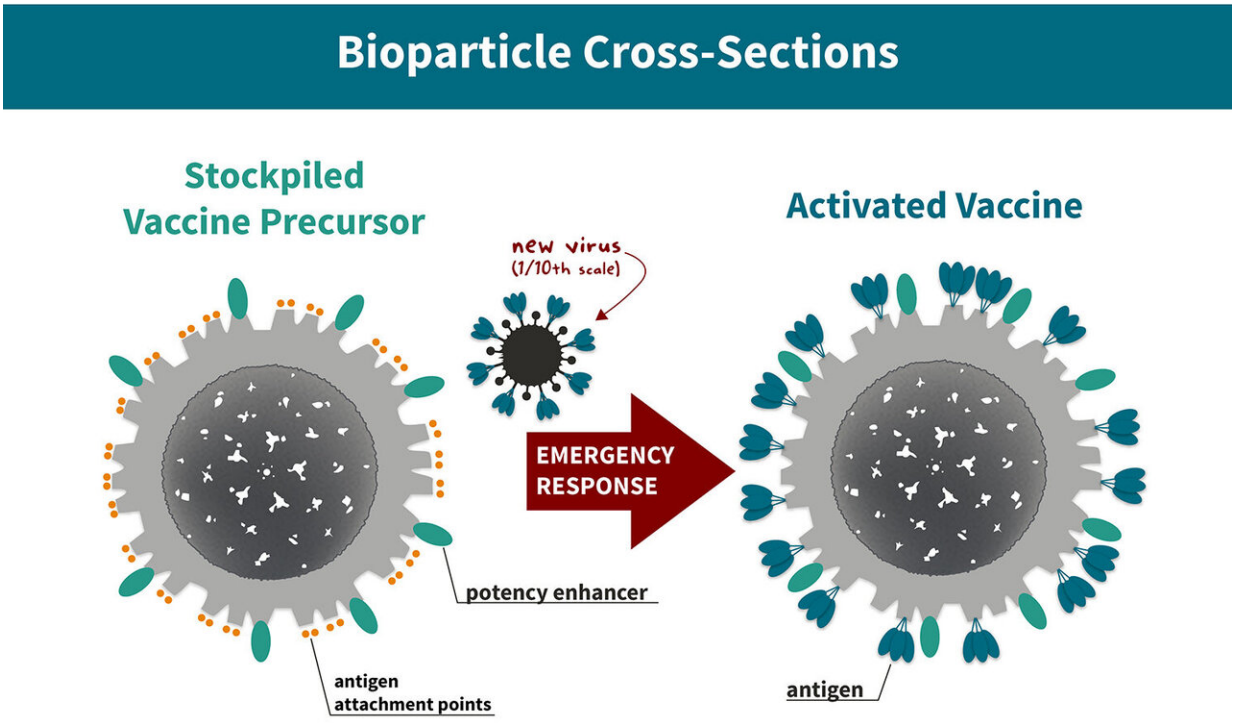
years. Second, his radical idea faces the harsh, economic realities of pharmaceutical development: though the rewards for success could prove extraordinary, the costs of taking the risky project from conception to injection have so far proven insurmountable. Swartz figures he needs $10 million now to fund more extensive animal experiments, that build on the preliminary work he has already done, in order to establish the likelihood of eventual success. Should those animal experiments provide a tentative green light, at least another $30 million would be required to carry out human clinical trials to test the safety and efficacy of trial vaccines. And should all of this go well over the next four or five years, Swartz would then have to convince pharmaceutical manufacturers to invest $250 million or more to build sufficient bio-processing capability to make good his plan to inoculate the world in a hurry when threats emerge.

"I've kept this project alive with my own personal money at times, but I've taken it about as far as I can alone," said Swartz. "I know my proposal is expensive and faces many unknowns, but the question we should ask is what will happen if we don't do this, or something like it, and the next pandemic catches us unprepared?"

Back to the future

Swartz's approach hearkens back to the 1960s when molecular biologists started conducting early DNA experiments to figure out how genes made proteins, the complex biomolecules that perform multiple functions inside cells. The experimental technique they used was a process called cell-free protein synthesis, or CFPS. Scientists identified the basic bio-machinery that cells use to make proteins, extracted these bare-bones components from cells and put them into test tubes. A CFPS system includes three components: a gene to direct the protein-making process; bio-machines called ribosomes and chaperone molecules that have the dual purpose of assembling amino acids, like chains, to form proteins

and then folding these protein chains into whatever shape the gene dictated; and, finally, the CFPS process requires the bio-fuels ATP and GTP to provide power. By the 1970s and 1980s, as CFPS revealed more about how proteins are made, scientists learned how to splice genes into living cells to give their biomachinery the blueprints for making medicinal proteins. CFPS continued as a research tool, and biotech startups focused on turning live cells into medicine-making biofactories.



A cross-sectional illustration of stockpiled bioparticle without a medical payload (left) and a bioparticle that has been “activated” (right) by attaching antigens that mirror parts of a dangerous virus that the vaccine will protect against. Credit: Farrin Abbott

It was at this critical juncture, in 1981, that Swartz joined a fledgling firm called Genentech and learned how to make protein medicines in cells. His first project was helping the then-startup company produce human growth hormone (HGH), a protein secreted by the pituitary gland to stimulate the growth of bone and cartilage. Over the next 17 years, Swartz became adept at cell-based biotechnology, which involved splicing bits of human DNA into fast-growing bacterial or, sometimes, mammalian cells that were grown in large vats. As the gene-spliced cells multiplied, they made copies of medicinal proteins that could be harvested and purified for use. But Swartz also came to learn what could go wrong, particularly with the crucial step of folding proteins, origami style, into the precise shape needed to achieve their therapeutic purpose. "We had to control a chemical assembly process inside cells that weren't built to accommodate what we wanted to make," Swartz said. "If something went wrong in our process, we would end up with a vat of proteins that weren't folded properly and were useless."

He left Genentech to join the Stanford faculty in 1998 to reinvent biomanufacturing by, paradoxically, taking it back to the CFPS style of protein making, by putting the bare-bones protein-making machinery into vats rather than petri dishes. In 2003, Swartz's lab showed how industrial-scale CFPS systems could make and fold proteins more reliably and cost-effectively than prevailing cell-based technologies. He then co-founded a biotech startup that has licensed the CFPS process from Stanford and has used it to make four protein-based, cancer-fighting therapies that are in early-stage human clinical trials. The trials are a partial vindication for CFPS, but still shy of the full validation that would occur if or when the U.S. Food and Drug Administration approves bio-medicines made using his new approach.

To stop a pandemic

Meanwhile, another event in 2003—the first SARS outbreak in

China—got Swartz wondering whether CFPS might be useful for mass-producing vaccines. In 2008, he and former Stanford graduate student Brad Bundy co-authored a paper postulating that CFPS was "well suited for producing versatile protein-based nanoparticles"—VLPs (virus-like particles) for short—providing the intellectual framework for the two-stage, rapid response vaccine technology for which he now hopes to garner support. In a 2015 paper, his lab showed how to remodel and repurpose the inner shell of a common virus; making a VLP that resembles a tiny soccer ball with spikes. The spikes are convenient attachment points for antigens and other molecular bells and whistles, making the VLP so obnoxious that the immune system regards any virus resembling it as an enemy, and creates antibodies to render the infectious invader incapable of attacking our cells.

Swartz has already conducted small-scale animal tests on the rapid response technology and had produced promising results when the new coronavirus caused the COVID-19 pandemic. Now his hope is to get the funding in place to test his approach in more animals, and then in humans, loading the VLPs with antigens to known viral infections for which no vaccine currently exists. One such candidate would be chikungunya, a mosquito-borne viral infection prevalent in Africa, Asia and India that causes fever and joint pain. These human trials would be designed to prove the safety of VLP delivered vaccines for people in general and demonstrate that this approach would be efficacious. Pending a successful outcome, Swartz would still have to persuade pharmaceutical companies to build CFPS production plants to stockpile billions of doses of VLPs ready for activation when it became necessary.

Swartz estimates all of that will take about six years. But with luck, that could still be enough time for his rapid-response technology to be ready before the next pandemic-grade virus hits. Things could proceed swiftly after that: Immunologists could identify an effective antigen within a couple of weeks. Biotech engineers could retrieve the stockpiled VLPs

and hook the newly produced antigens onto the spikes. Since the prior clinical trials would have already proven the safety of VLP vaccines produced by CFPS, the new, pandemic-stopping vaccine could be given on a trial basis to high-risk individuals at the epicenter of the contagion, to further confirm safety and begin testing the efficacy of the antigen. In a best-case scenario, Swartz estimates that billions of doses could be produced within six weeks. Even if the response took twice as long as projected, he says it would still be at least five times faster than current COVID-19 vaccine development and production processes.

Swartz knows it's premature for biotech firms to undertake a project facing so many hurdles, and a stretch even for funding agencies to underwrite the considerable upfront costs of validating or negating his approach. But as he sees it, the current pandemic has proven the need for this new approach. Now is the time for bioengineers to retool the 40-year-old technology for making protein-based therapies. He is eager to complete the mission that brought him to Stanford more than two decades ago.

"If we have the will, this could be how we make sure that the world never has to suffer a pandemic like COVID-19 again," he said.

More information: Bradley C. Bundy et al. Escherichia coli-based cell-free synthesis of virus-like particles, *Biotechnology and Bioengineering* (2007). DOI: 10.1002/bit.21716

Provided by Stanford University

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