Cell-based vaccines yield only modest advances for seasonal flu

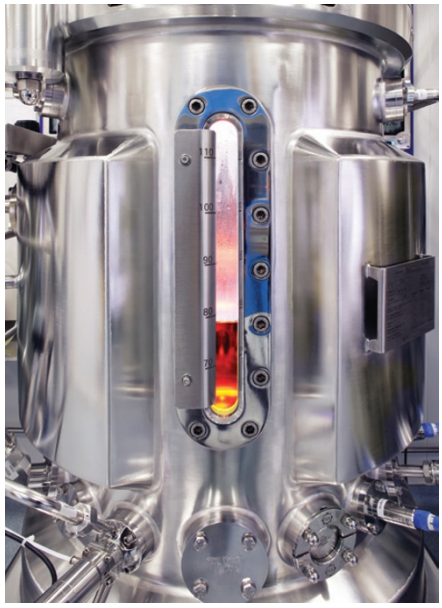
You cannot make an omelet without breaking eggs, and the same could be said about influenza vaccines. Most vaccine makers today grow the influenza virus in fertilized eggs, a manufacturing method that originated in the 1930s. Over the past decade, however, the US government has invested billions of dollars in companies developing new eggless manufacturing techniques designed to produce more vaccine more quickly—and those investments have finally begun to pay off.

In late November, the US Food and Drug Administration approved the first influenza vaccine grown in cell culture in the country: Novartis's Flucelvax, a seasonal flu vaccine that is produced in dog kidney cells. Another company, Protein Sciences of Meriden, Connecticut, expects to receive US approval for its recombinant flu vaccine—Flublok, which uses an engineered virus that expresses flu proteins when it replicates within insect cells—by mid-January. (In Europe, a version of Flucelvax and a vaccine made in monkey kidney cells from Illinois-based Baxter are already available.)

The new production processes hold at least one major advantage over traditional egg-based manufacturing techniques, which typically take about five to six months from identification of the strains until production of the first dose of vaccine. With cell-based approaches, manufacturers don't have to wait for eggs to be delivered or worry about supply shortages. And with recombinant vaccines, manufacturers don't even have to grow the virus at all; they just need to know the nucleotide sequence of the flu protein they want for the vaccine.

This added speed can be crucial during an influenza pandemic, when the ability to vaccinate people quickly can save tens of thousands of lives. It can also provide a first-to-market advantage for manufacturers of all flu vaccines when production schedules are tight. "We save a couple of weeks, at least, with the cell-based vaccines," says Robin Robinson, director of the US Biomedical Advanced Research and Development Authority in Washington, DC. "And recombinant vaccines would probably save you four or five more weeks on top of that."

Philip Dormitzer, a senior project leader for viral vaccine research at Novartis Vaccines and Diagnostics in Cambridge, Massachusetts, points out another potential benefit of the new manufacturing methodology. When scientists adapt the influenza virus to grow in eggs, mutations can occur in the receptor that binds the host's cells. Currently, manufacturers of cell-based vaccines such as Flucelvax use seed virus that has been adapted to grow in eggs and readapt that virus to grow in mammalian cells. If eggs were eliminated from the process, as Dormitzer hopes they will be, "there could be additional advantages of strain match," he says.



Novartis

Cell-ing point: Novartis's flu cell fermenter.

All in good time

For most seasonal flu vaccines, these differences could be largely inconsequential, though. Seed viruses are always tested to ensure they trigger an adequate immune response. And the speedier production process makes little difference to seasonal flu vaccine makers, which typically have seven months or so between the time that the World Health Organization recommends the viral strains to be included in the following season's product and when the vaccines have to be on the pharmacy shelf. Moreover, the cell- and egg-based approaches currently yield essentially the same final product. The manufacturing platforms may have changed, notes Michael Osterholm, head of the University of Minnesota's Center for Infectious Disease Research and Policy in Minneapolis, but the antigen in the vaccine stays the same. "There is no reason to expect or anticipate any improvement in how the vaccine actually protects," he says.

Jeffrey Almond, head of discovery research and external research and development at Sanofi Pasteur in Lyon, France, agrees. In 2005, his company received a $97 million contract from the US government to develop a cell culture–based vaccine—the first such federal contract for commercial scale production of the newer influenza vaccine methodology. However, the parties terminated the contract in 2009 after Sanofi Pasteur concluded that the technology didn't hold significant advantages over egg-based platforms. "We don't want to bring in a new technology that simply substitutes for the eggs and does no better," Almond says.

Swiss drugmaker Novartis, however, has embraced the new cell-based flu vaccine. The US government awarded the company a $220 million development grant in 2006 and another $486 million contract in 2009 to help with the construction of Novartis's $1 billion cell-based manufacturing plant in Holly Springs, North Carolina. That facility has the capacity to produce more than 50 million doses of Flucelvax, and, in the event of a pandemic, it could provide up to 150 million doses of pandemic influenza vaccine within six months of the health emergency's declaration.

Whether these new seasonal flu vaccines will have a market advantage over egg-based products remains to be seen. "I think the major drawback is cost," says Doris Bucher, an immunologist at New York Medical College in Valhalla. "The cell-based vaccines are much more expensive to produce per dose than egg-based."

Novartis declined to provide information on the production costs of Flucelvax, but Dormitzer says the company is "not doing this for cost-savings purposes right now." He anticipates that Flucevax may win over some consumers of seasonal flu immunizations by being free of antibiotics and preservatives. OptaFlu, the European version of Flucelvax, which was approved in 2007, has attracted enough fans to become one of the ten best-selling flu vaccines, bringing in an estimated $71 million last year.

But there's a catch. The new cell-based products, which are all trivalent vaccines, containing two strains of influenza A and one strain of influenza B, will have to compete with newly approved quadrivalent vaccines, which contain a second influenza B strain and may offer better protection (see *Nat. Med.* **18**, 471, 2012). Adding that extra B strain gives vaccine makers a "huge advantage," says Brad Tebbets, an infectious disease analyst at the London-based research firm GlobalData. Cell culture–made seasonal flu vaccines may one day go quadrivalent, but for now consumers are likely to continue to shell out for egg-based products.

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