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# Plant-Based Vaccines Challenge Big Pharma for $3Bn Flu Market

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New York: Two tiny companies are preparing to challenge some of the world's largest drugmakers in the battle for dominance in the $3-billion global market for influenza vaccines, armed with little more than tiny tobacco plants.

The use of plants to produce life-saving pharmaceuticals captured global attention when it was revealed that the Ebola drug ZMapp is produced in the leaves of tobacco plants.

Even as Ebola cases multiply in West Africa, a far greater market for plant-based biopharmaceuticals will likely be influenza vaccines used to fight pandemics, industry experts said. Making vaccines from plants may turn out to be faster and cheaper than current methods which use chicken eggs to grow the virus needed to make the vaccines.

Leading producers such as GlaxoSmithKline and Sanofi need six months to produce flu vaccine once scientists identify the dominant virus expected to circulate during flu season. Vaccine production from tobacco plants by Quebec City-based Medicago or Bryan, Texas-based Caliber Biotherapeutics could do it in weeks.

"Seven to 10 years from now, plants might be the dominant vaccine-production system," said Brett Giroir, an MD and CEO of Texas A&M Health Science Center in Bryan. Texas A&M has one of three US facilities tasked by the government with being ready to produce and deliver 50 million doses of flu vaccine in just 12 weeks. It is working with Caliber toward that goal.

If the upstarts succeed, they will make little difference to the tobacco industry, which regards even a $3-billion market as marginal. But they could threaten the pharma giants that dominate flu vaccine production — or be gobbled up by them.

Medicago is now testing its flu vaccine in elderly people, who are most at risk, and plans to launch a large human trial in 2016. "We hope to hit the market in 2019," said Jean-Luc Martre, director of government affairs.

Tobacco plants could be enlisted in the fight against flu even sooner if a pandemic hit. The 50 million doses that labs like Texas A&M's pledged they'd be able to produce in a few months can't be manufactured in today's egg-based systems.

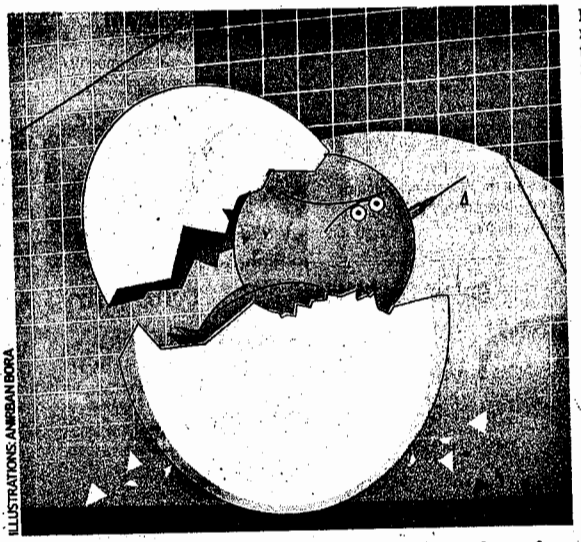

ILLUSTRATION: ANIRBAN BORA

"If there is a need for it that requires plant-based production, we'd turn to Caliber," said Giroir, referring to an accelerated vaccine-production schedule to counter a flu pandemic.

### WAITING FOR CHICKEN EGGS

Each year, manufacturers including Sanofi, Novartis, the Medimmune unit of AstraZeneca and GSK make about 155 million doses of flu vaccine for the US market alone, growing the virus in chicken eggs. Usually the doses, which protect against strains that experts predicted the previous February, are ready in time and in sufficient quantity.

But if the strain that appears during flu season was not the one experts forecast, the vaccines might not work. The appearance of H1N1 swine flu in 2009-2010 took experts by surprise, and the flu was already on its second wave before a vaccine was ready; an estimated 61 million people in the US got swine flu and 12,500 died.

Failures such as that led the US government to award $400 million in start-up funding to three Centers for Innovation in Advanced Development and Manufacturing (CIADMs) to boost biodefense and preparedness for pandemic flu.

"There's no way you can produce 50 million doses in 12 weeks" with current production technology, said Giroir. "But plant-based production could."

While one chicken egg can produce one or two doses of flu vaccine, one tobacco plant can produce 50 at a fraction of the cost.

The Defense Advanced Research Projects Agency (DARPA), an arm of the defence department that funds cutting-edge research, is impressed enough with the potential of tobacco-plant production systems to have awarded multi-million-dollar grants to both Medicago and Caliber, and so far the support has paid off.

In a 2012 DARPA challenge, Medicago, jointly owned by Philip Morris International and Mitsubishi Tanabe Pharma Corp, produced 10 million doses of H1N1 flu vaccine in just a month in tobacco plants inside its sprawling North Carolina greenhouses. In animal tests, the experimental vaccine successfully triggered the production of protective antibodies against H1N1.

### HURDLES AHEAD

All the company had to go on was part of the virus' genetic sequence. But while in egg-based production whole flu viruses are injected into the eggs, where they replicate and form the basis for the vaccine, all that's really needed to trigger immunity are the proteins that stud the virus's coat.

Those proteins, called hemagglutinins, are what the immune system attacks. They can be produced by splicing the hemagglutinin gene into almost any kind of cell; Medicago uses harmless bacteria to carry the hemagglutinin genes into the tobacco plant leaves.

Technicians at the greenhouses in North Carolina then soak 36-day-old Nicotiana benthamiana plants (cousins of those used for cigarettes) upside down in a liquid containing the Trojan Horse bacteria, explained chief scientist Marc-Andre D'Aoust. Through a process called vacuum infiltration, air is drawn out of the leaves and they suck up the bacteria.

After growing in special chambers for a week, the leaf cells are churning out hemagglutinins. Extracted, purified, and combined with other bits of the virus, they form the basis for a vaccine.

To succeed, the companies will have to persuade the US Food and Drug Administration not only that the vaccine is safe and effective, as clinical trials are designed to show, but also that the hemagglutinin or other proteins can be extracted from the leaves cleanly and that the largely-untested manufacturing process yields a uniform, reliable product.

Major vaccine makers are cautious about the new technology. "We tend to avoid publicly speculating on what future technologies we might embrace," said Robert Perry, a Glaxo spokesman said.

"Today, all of our flu-vaccine production is in (chicken) eggs," said Rene Labutat, vice-president of manufacturing for Sanofi. "But we are looking at the recombinant approach, including in mammalian cells, algae, fungi and plants." Reuters

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