# After early struggles, ‘biopharming’ poised to make big impact on medicine

In December 2015, the U.S. Food and Drug Administration approved the drug Kanuma for a rare but often fatal cellular disorder. While this was huge news for sufferers of the condition, it made major headlines because of the way the drug is made: a chicken was genetically modified to produce the drug — a human enzyme — in its eggs. But this wasn’t the only recent use of drug producing transgenic organisms ( organisms that has genes from another organism). In 2014, ZMapp, an experimental drug made from antibodies expressed by tobacco plants, saved the lives of aid workers stricken by Ebola.

The two events are significant not just because of their impact on health. Kanuma, is the only treatment for lysosomal acid lipase deficiency and ZMapp remains the only effective treatment for Ebola (and it is still progressing through clinical trials). The even bigger impact is that these two drugs might represent the resurgence of biopharming — the creation of pharmaceuticals grown through plants or farm animals.

**Rosy beginning then smoking tailspin**

Biopharming started in the late 1980s with a lot of promise. Back then, scientists reported that monoclonal antibodies could be made by tobacco plants. That opened the door to a number of drugs to be made in a similar fashion, such as vaccines, antibody-based treatments, and proteins. Scientists saw this as a potential way to treat diseases more cheaply, as these methods are cheaper than using traditional chemical or bio-production methods. At the time, edible vaccines, drugs from corn, rice or any number of crops were seen as close to reality. Hundreds of biotech companies applied to the U.S. Department of Agriculture’s Animal and Plant Health Inspection Service (APHIS) — the bureau charged with approving and monitoring field trials and development of these new drugs — for permission to make ‘farmaceuticals.’

Then the bottom fell out. In 2002, corn plants that were engineered to make a pig vaccine were discovered in a Nebraska soybean field. The USDA fined the company conducting the corn operation, a firm called ProdiGene. While the ProdiGene incident may have shown how quickly and effectively USDA regulators handled growing and isolating genetically modified drugs from plants (such fields were supposed to be fallow for a year after harvesting), it also galvanized the anti-GMO movement. The Center for Food Safety announced that “we don’t think drugs should be in food crops.” The Federation of American Scientists, one of the more even-handed organizations looking at genetic modification, observed that the incident showed that:

> Thus, even if USDA develops stringent regulations for pharma crops, companies may not necessarily follow them. It appears that the potential for a small, but consequential, mistake in such large-scale agricultural productions is high.

As the USDA tightened rules for approval of experimental field trials, investors began to scatter like so much stray corn seed. Monsanto dropped its research programs in plant derived biotechnology, and many companies, including ProdiGene, eventually sold their assets or folded.

**Technical programs showed hope**

In addition to regulatory and public relations problems, “pharming” was also running into some technical walls. Plants didn’t always express enough of the desired protein, and purification of the expressed protein was proving to be a major issue. In addition, plant-expressed (or animal-expressed) proteins often could trigger an immune reaction in humans.

However, scientists eventually we able to find resolutions of these and other technical problems that have brought about biopharming’s resurgance. Since 2002, new methods using the *Agrobacterium* (which is also commonly used to make GMO crops), which can more effectively carry the target gene which has drastically increased the amount of the drug the organisms produce. In addition, new immunology methods have decreased the number of artifact proteins that are carried along from the plant host into human, which will drastically reduce the risks of an immune reaction to the drug.

And finally, the field trials, which were the bone of contention after the ProdiGene incident, have largely been replaced by sealed bioreactors, or by isolated, small plots of land. Both solutions have avoided the problem of “contamination” of food with plants (or animals) bred for drug production, a major regulatory achievement according to both the USDA and FDA.

**New phase of pharma**

And, as ZMapp and Kanuma have shown, some movement in pharming is happening. A number of other plants and animals have been approved for drug production, and the list of permits issued by APHIS has started to surge. Some of these new innovations include:

- Gaucher disease treatment derived from cultured carrot cells, which was approved in 2012. This approval marked the first biological treatment engineered from plants (the only previous approval was for a vaccine to protect chickens from Newcastle virus disease). The new drug promised to be a much cheaper treatment for the rare form of lysosomal storage disorder. It has not been a huge commercial success, due in part to competition with other drugs, and the original manufacturer recently sold it to Pfizer.
- Just last year, Ventria Bioscience, a Colorado firm, received USDA/APHIS approval for a field release of rice in St. Croix, U.S. Virgin Islands. The 31 lines of rice were engineered to express 18 pharmaceutical proteins and marker genes. These proteins include lactoferrin, used to control immune responses in infants, lysozyme, a food additive found normally in breast milk, serum albumin, and transferrin, an iron-binding protein.
- Also in 2015, Kentucky Bioprocessing LLC, a subsidiary of the Reynolds American tobacco company and which manufactures the ZMapp vaccine, received approval for isolated field release in Kentucky of a tobacco plant that expresses bovine lung aprotinin, using expression from the tobacco mosaic virus, a long-studied vector for infection and gene transfer. Aprotinin, the natural form of which already is approved as a drug, is a trypsin inhibitor used to stem bleeding during surgeries.
- A Stanford University team found that biopharming the precursor to the cancer chemotherapy agent etoposide could eliminate the need to harvest an endangered Himalayan plant. Podophyllotoxin is

> now only available from the Mayapple plant, but the Stanford scientists discovered new enzymatic pathways that could be reproduced by splicing the responsible genes into a tobacco plant.

**Future of ‘farmaceuticals’**

While pharming may not be back to its 2002 excitatory levels, it has cleared many of the technical hurdles that were holding it back and today has verifiable successes to point at. Whether opposition from anti-GMO groups mounts, and can influence government policy, is another question. But there remain many advantages of pharming over conventional drug making. As Henry Miller, founder of the FDA’s Office of Biotechnology and a current columnist, wrote on Forbes:

> Biopharming offers tremendous flexibility and economy when adjustments in production are necessary. Another advantage is that it offers great potential for cost cutting: The energy for product synthesis comes from light (sun or artificial) and the primary raw materials are water and carbon dioxide.

Not to mention the pharmaceutical product. And a new wave in pharmaceuticals.

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