BIOTECHNOLOGY

Drug-making plant blooms

Approval of a 'biologic' manufactured in plant cells may pave the way for similar products.

BY AMY MAXMEN

It was midnight when an anxious Ari Zimran finally got the phone call for which he had been waiting. The news couldn't have been better: the drug he had worked on for nearly a decade had just been approved by the US Food and Drug Administration (FDA).

Zimran, who heads the Gaucher Clinic in Jerusalem and is a member of the scientific advisory board at Protalix Biotherapeutics, a small biotechnology firm in Carmiel, Israel, was not the only one celebrating the company's success last week. Biotechnologists around the world cheered, because Protalix's Elelyso (taliglucerase alfa) is the first biological drug for human use that is manufactured inside modified plant cells.

"It's a great day for plant-made pharmaceuticals," says Scott Deeter, president of Ventria Bioscience, a biotech firm based in Fort Collins, Colorado. "This shows the triumph of innovators over the status quo, and that's really very important."

Drugs that are based on large biological molecules — known as biologics — have been produced inside genetically engineered animal cells, yeast and bacteria for more than two decades. Insulin has been made by genetically modified *Escherichia coli* bacteria since 1982, and by 2010, the global market for such therapies had reached about US$149 billion.

Since the early 1990s, some researchers have been developing plants that could act as cheaper factories for biologics. Plant-cell cultures are also attractive because they require less precise conditions for growth than animal cells. But efforts to exploit plants in this way have lagged, in part because companies and investors were wary of this unfamiliar production method.

Protalix was strategic in targeting a rare heritable disorder called Gaucher's disease, because current means of producing treatments for it have fallen short. The disease is caused by an enzyme malfunction that results in the accumulation of fat in cells and organs, with symptoms ranging from bone deterioration to anaemia. Two existing drugs compensate for the enzyme deficiency, but they can cost up to $300,000 per year in the United States, and drug shortages in recent years have left some patients in need of hospital care.

Structurally, Protalix's Elelyso resembles one of those drugs: Cerezyme, made by Genzyme in Cambridge, Massachusetts. Cerezyme is produced in modified hamster cells, which require regulated temperatures, a complex growth solution and an environment scrubbed free of the viruses that infect hamsters and humans alike. These factors contributed to manufacturing problems that dogged Genzyme last year, limiting supplies of Cerezyme.

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Protalix's solution is to take a normal version of the human gene affected in Gaucher's disease and introduce it into carrot cells, which are more robust than hamster cells, and then extract the enzyme they make. The lower production overheads will allow the company to sell Elelyso for just 75% of the price of Cerezyme, the most popular drug on the market, says David Aviezer, Protalix's president.

Charles Arntzen, a plant biotechnologist at Arizona State University in Tempe, says that Elelyso's approval sends a clear and positive signal to investors and companies that plant-manufactured drugs are worth pursuing (see 'Plants in the pipeline'). When he began working on plant-made vaccines in 1991, he says that he was naive about how long it would take for the technology to blossom. He expected companies and the FDA to embrace the technique, speeding inexpensive products to market.

"Many of us in academia thought that manufacturing costs were a significant part of the entry barrier in making a new product," Arntzen says. But "it's really the regulatory hurdles and costly clinical trials that are a barrier, and big pharmaceutical companies don't want to take this on because they know there is an enormous risk inherent to trying something new".

For those companies trying to produce drugs from whole plants, rather than in cultures of plant cells, Aviezer cautions that Elelyso's approval might not set a precedent. But others in the field are more optimistic. "Even though [Protalix's] technology doesn't use whole plants, it does address many issues of producing proteins in plant cells," says molecular immunologist Julian Ma of St George's, University of London, who is scientific coordinator for Pharma-Planta, a European consortium that is developing plant-derived pharmaceuticals to treat, for example, HIV (see *Nature* **458,** 951; 2009).

Nathalie Charland of Canadian biotech company Medicago, in Quebec City, which is developing vaccines produced in tobacco plants, agrees: "I don't think there will be major differences in how the FDA handles their product and ours." ■

PLANTS IN THE PIPELINE

Manufacturers have begun or completed phase II clinical trials on a handful of biologics made in plants, and hope to follow Elelyso to market.

Drug	Condition	Company	Platform
Locteron (interferon-α)	Hepatitis C	Biolex Therapeutics	Duckweed
H5N1 vaccine	Influenza	Medicago	Tobacco
VEN100	Antibiotic-associated diarrhoea	Ventria Bioscience	Rice
CaroRx	Dental caries	Planet Biotechnology	Tobacco

CORRECTION

The News Feature 'Date with history' (*Nature* **485,** 27–29; 2012) incorrectly located the University of Waikato in Wellington instead of Hamilton.

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