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MOLECULAR FARMING MAY BE NEXT WAVE FOR BIOTECH DRUG MANUFACTURERS

It sounds like a science-fiction utopia: renewable, sustainable, cost- and energy-efficient "molecular farms," vast fields of genetically engineered crops bathing in the sun, churning out valuable pharmaceuticals and industrial enzymes. But for an increasing number of major drug companies, "pharming" with transgenic plants is becoming an essential component of their business models.

Facing a looming crisis in production capacity for monoclonal antibodies and other protein-based therapeutics, the industry is taking a serious look at molecular farming as a solution for bringing products to market.

"Plant production [of biologics] is emerging and we believe it is going to be an important methodology for the future," said Caroline Fritz, global business director of industrial biotechnology and biopharmaceutical manufacturing at Dow Chemical. The company makes human therapeutics through its subsidiary, Dow AgroSciences.

"Plants will have significant advantage in [producing] oral or topically delivered pharmaceuticals of the future," agreed Charles Arntzen, director of the Arizona Biodesign Institute. Arntzen engineered edible hepatitis B vaccines from potatoes and tomatoes for Third World nations.

Several therapeutics derived from genetically engineered plants are in late-stage clinical trials in the U.S., and the pharma community is watching closely as the first new drug applications for transgenic plant-derived products come under FDA review in the coming months.

Monoclonal Antibody Crunch

Demand for biological drugs has increased dramatically over the past decade (*see table, Page 7*). The advent of recombinant DNA technology has led to such breakthrough products as monoclonal antibodies, vaccines and blood-clotting factors that are free of disease-causing viruses. Other biotech products include growth factors and treatments for cancer, autoimmune disorders and cardiovascular disease.

Biotechnological innovation also has led to drugs like reverse transcriptase and protease inhibitors to treat HIV infection. Blockbusters like Amgen's Epogen (epoetin alfa) and Genentech's Herceptin (trastuzumab) are proving the value of biotech and capturing the attention of drug company executives.

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Among the leading biotechnology drugs approved in recent years are Enbrel (etanercept), marketed by Wyeth and Amgen for rheumatoid arthritis, and Genentech's Rituxan (rituximab) for B-cell non-Hodgkin's lymphoma. Both drugs are protein products that gained rapid market acceptance and generate sales in excess of $400 million annually.

The FDA has granted 91 approvals or new indications for biotech products and vaccines since 2000, with 35 in 2002 alone. The biotech R&D pipeline has been so robust in recent years that demand is exceeding the capacity to produce monoclonal antibodies and other protein-based therapeutics.

According to data from the Biotechnology Industry Organization (BIO), 14 percent of treatments now undergoing clinical trials are monoclonal antibodies. More than 1,000 protein-based therapeutics are at various stages of development, with 150 to 200 in late-stage clinical trials. Experts forecast that the FDA will approve 20 to 30 new monoclonal antibodies by 2010.

"If many of the drugs in development now are approved, we're going to have a capacity shortage," said BIO spokeswoman Lisa Dry.

The rapid market acceptance of monoclonal antibodies and similar biotech products and their potential moneymaking ability are pushing drugmakers to look seriously at less-costly, higher-volume methods of producing proteins for biological drugs.

Manufacturing Capacity

Existing manufacturing capacity is already inadequate to meet the requirements of products now on the market. According to BIO, 75 percent of the U.S. biologics capacity is occupied producing just four molecules.

Production shortages have far-reaching impact on patients and drugmakers. When Enbrel was approved as a first-line treatment for rheumatoid arthritis in 1998, the demand for the drug quickly outstripped supply, causing a severe shortage. Prior to its acquisition by Amgen in 2002, Enbrel manufacturer Immunex signed an agreement to examine the feasibility of producing proteins in genetically engineered tobacco.

A recent J. P. Morgan Securities analysis said that as biotech products are approved, the shortage of manufacturing capacity for certain protein-based therapeutics will grow more severe. By 2005, demand for manufacturing will be two to four times greater than existing production capacity, the report said.

"We don't have enough capacity in this country to produce the drugs that are in the pipeline," said Dow's Fritz. "[Molecular farming] will be a very important tool for pharmaceutical companies to produce their materials."

Genetic Engineering

There are a number of ways to manufacture therapeutic proteins (*see story, Page 8*). The typical recombinant DNA approach involves splicing a gene into a microbial organism, such as a yeast or Escherichia coli bacterium, which is then fermented in closely controlled stainless steel bioreactor vessels. Some proteins require a mammalian system to be structurally correct and are engineered into animal cells, commonly taken from Chinese hamster ovaries.

Once inserted into the host genome, the organisms propagate, churning out proteins that can be extracted, processed and packaged as commercial therapeutic products.

But bioreactor facilities are complex and costly. While a conventional pharmaceutical plant can be built in a year or two, it takes five to seven years to build a biologics facility. A biologics plant can cost $500 million to $700 million, "and you still have limited production," said Dry.

Scaling up production in a traditional biologics facility is no small feat. It requires huge amounts of time and capital investment. Biotech plants also need a large technical staff to monitor and control the

(*See* **TRANSGENIC PLANTS**, *Page 3)*

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temperature and nutrients in the bioreactor vessels, coddling the growth of recombinant cultures.

"People have no idea how much energy it takes to control the fermentation processes, [or] the size of the building you need to make these proteins," said Allan Felsot, an environmental toxicologist at Washington State University.

Meanwhile, progress in agricultural biotechnology has proceeded apace. The first widespread genetic engineering with plants aimed to impart resistance to insects and other pests, such as by splicing in a gene from Bacillus thuringiensis (Bt) that is toxic to insects but harmless to humans. Bt has been engineered into cotton, corn, potatoes and a variety of other crops. The practice has become so common that one-third to one-half of the corn and soy products consumed in the U.S. contain genetically modified ingredients.

Scientists have also engineered corn, rice, barley, alfalfa, tobacco and other plants to produce a range of therapeutic proteins.

"We've demonstrated that plants produce very authentic proteins," said Robert Dose, vice president of business development at ProdiGene. "We've produced everything from monoclonal antibodies to surface antigens."

Scaling and Cost

Manufacturing proteins in transgenic plants offers several advantages over microbial fermentation or mammalian cell culture. "What plants allow us to do is produce [therapeutic proteins] in a way that is more scalable and at lower cost," said Fritz.

The cost of raw materials produced by genetically engineered plants is about one-tenth that of traditional biotech methods, according to Fritz. Processing material is similar, whether the source is a microbial broth, mammalian cell culture or transgenic corn, so the cost savings cancel out for the remainder of the processing stream. Bulk drugs produced by pharming cost about half of mammalian cell culture, Fritz said.

Industry observers suggested that molecular farming could reduce the price of monoclonal antibodies from the current $200 to $2,000 per gram to $10 to $1,000 per gram.

Molecular farming allows drugmakers to scale up production in small increments without a huge capital investment. "You can expand production to meet demand because it's easy to plant another 50 or 100 acres," said Washington State University's Felsot.

With yields of about one kilogram of active material per acre of transgenic corn, a single, modest-sized farm can replace a multimillion-dollar bioreactor facility. "Even if you're talking about 1,000 kilograms of demand a year of active material, that's a relatively small amount of [agricultural] production," said Dose. The total demand for a monoclonal antibody can range from a few dozen to several thousand kilograms.

"If you're looking for small quantities – less than 150 kilograms a year of active material – then plants don't offer a huge competitive advantage," Dose said. "But when you're talking about something needed in hundreds or thousands of kilograms, plants and particularly corn offer rather unique competitive advantages. [Corn is] recognized as a robust, viable system for producing large volumes of recombinant protein."

(*See* **TRANSGENIC PLANTS**, *Page 4)*

Drugs Produced By Transgenic Plants

Genetically engineered plants can produce a variety of protein-based therapeutics. Experts suggest that 300 or more products may be adaptable to a transgenic plant-based system, including:

- Monoclonal antibodies;
- Vaccines;
- Peptides;
- Hormones;
- Enzymes;
- Growth factors; and
- Vitamins and co-factors.

Source: Canadian Food Inspection Service

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However, some technical problems remain with transgenic plants, sources told *F&DL*. Plants like corn currently are unable to produce all proteins, since some molecules require glycolysation for biological activity in humans.

"Plants today, without the human glycolysation technology, address specific products in specific markets," said Fritz. "They don't address all molecules in all markets."

Last fall, Dow agreed to team with Plant Research International to enhance transgenic plants' ability to produce proteins with mammalian-like glycan structures. Key to the project are patents covering protein glycolysation in transgenic plants that Dow acquired from Japanese researchers in October 2002.

Dow AgroScience's main competitor, Monsanto Protein Technologies, is involved in a similar corn glycolysation research collaboration with Neose Technologies.

Fritz said research to produce glycosylated proteins in corn is succeeding, and results will be reported at scientific meetings this summer. "Our vision is that we'll be able to produce completely human protein in plants that can then address all disease indications," she said.

Molecular farming has taken root at several large drug and biotech companies, including GlaxoSmithKline, Pfizer, Eli Lilly, Novartis, Bristol-Myers Squibb, Amgen and Centocor.

Two major movers in the emerging pharming industry are Epicyte, which is partnering with Dow AgroSciences, and ProdiGene, which has six products in late-stage development. If transgenic plants pan out, Epicyte and ProdiGene are poised to become dominant players in the field (*see story, Page 9*).

But transgenic plant development leaders did not achieve their places in the market without cost. As with any burgeoning technology, risk management is a key concern for plants that are genetically engineered to produce drugs. Recent incidents in which food crops were contaminated by transgenic plants underscore some of the risks drugmakers must prove they can manage.

The primary concern is that corn or other plants engineered to make proteins for drugs could contaminate food crops. A foreign protein could trigger a potentially severe allergic reaction. This is the primary risk, however remote, drugmakers entering the transgenic plant arena must guard against.

Risk Management

The Starlink fiasco of 2000 illustrated the risks – real and perceived – of genetically modified crops to U.S. food supplies. Made by Aventis Cropscience, Starlink corn contains the Cry9C protein, which is toxic to caterpillars. In 2000, a consumer group found traces of Starlink corn in taco shells and other corn products on supermarket shelves in several U.S. cities.

Although approved as animal feed, Starlink corn had never been OK'd for human consumption. Many observers contended that the risk of a Starlink-like contamination is infinitesimally remote because Cry9C isn't a human protein, and most proteins are quickly broken down in the digestive tract.

Indeed, the Centers for Disease Control and Prevention investigated 28 reported cases of suspected allergic reactions and found no evidence linking complaints to Starlink corn. Nonetheless, Aventis CropScience sustained devastatingly bad press over the incident and withdrew Starlink from the market. A year later, Aventis announced it was getting out of the transgenics business and selling its agricultural unit to Bayer.

"Starlink was sort of like chaos theory in action," said Felsot. "It was people not thinking about the whole system and how it works. The very bad regulatory mistake was thinking that the distribution system in the corn belt can be

(*See* **TRANSGENIC PLANTS**, *Page 5)*

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controlled. Apparently, the people in Washington never went to the corn belt to see what it's actually like out there."

Likewise, ProdiGene learned an expensive lesson last year about what happens when safeguards fail. Although more of a public relations disaster than a public health crisis, ProdiGene's experience with its engineered corn offered a lesson for the whole industry.

In that instance, a few unfertilized stalks of corn from the previous year's crops, engineered to express therapeutic proteins, contaminated soybean fields in Iowa and Nebraska. Although ProdiGene had standard operating procedures and guidelines, farm supervisors under contract to the company stopped inspections a few weeks too early and missed the results of a hailstorm that knocked down fields, allowing residual corn to germinate and poke through the soybean canopy.

The U.S. Department of Agriculture's Animal and Plant Health Inspection Service (APHIS) ordered ProdiGene to burn 155 acres of contaminated crop in Iowa. The company is reimbursing the government for the cost of destroying 500,000 bushels of soybeans in Nebraska, valued at around $5.60 per bushel. The firm also paid a $500,000 fine.

"The incident in Nebraska was most unfortunate," said Dose. "There was never a risk to the food supply. It was a procedural issue." ProdiGene has put "additional safeguards and procedures in place" to prevent a recurrence of problems, he said.

ProdiGene's experience demonstrated that the regulatory system worked, according to Felsot. "The violation of protocol was found out before the stuff went to market," he said. "They got their hand slapped, and they deserved it."

Publicity over the ProdiGene incident appears to have blown over. It never reached the fever-pitch that followed Starlink, perhaps because the problem was caught so early.

"Not that [ProdiGene] caused any damage, but it was stupid," said Arizona Biodesign Institute's Arntzen. "Throw some civil penalties at them so it scares everybody, and it won't happen again."

Growing and handling transgenic crops demands "a zero tolerance for the escape of DNA," he said. "I can live with those rules. If any company wants to get into the business, they're going to have to live with those rules too."

Experts claim drugmakers are up to the task of managing transgenic crops appropriately to manufacture proteins. "The pharmaceutical industry is used to working under good manufacturing practices, a cradle-to-grave tracking system, following protocols, individuals signing off for what they do, auditing and inspections," Felsot said. "I'm optimistic about the future of the technology. But I'm making the big assumption that everybody is going to pay attention and manage the technology responsibly and do what they're supposed to do."

"With pharmaceutical proteins, every seed is worth a lot of money, so you have an incentive to make sure you control it," he added.

Containment and Segregation

Control hinges on two strategies: containment and segregation. Containment means growing a crop in a greenhouse or in a field far enough away from other crops to prevent the incidental drift of genetically modified pollen, typically a mile-wide buffer zone around fields.

Many companies working with transgenic corn are going to great lengths to stay out of the corn belt. "We have designed a containment program to grow the crops in isolated areas of the southwest U.S.," said Fritz.

"Everybody realizes you have to have very tight confinement," BIO's Dry said. "There have to be special measures. This technology in no way mimics traditional agriculture."

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The other option is segregation, or avoiding prime food crop-producing areas. To avoid the possibility of contaminating food crops, members of BIO agreed in October 2002 to refrain from planting corn engineered to produce therapeutics or industrial materials in the corn belt – an announcement that did not sit well in corn-growing states. The prospect of a value-added crop like transgenic corn is attractive to many farmers struggling with low prices and markets glutted with surplus grain.

"This new area of value-added crops is a tremendous financial incentive for farmers, a new economic opportunity," Dry said.

Concerned that his state may be cut out of a potentially lucrative market, Sen. Charles Grassley (R-Iowa) pressured BIO to capitulate, which it did in December 2002. In a letter to Grassley, BIO President Carl Feldbaum agreed that the position "requires revision," and resolved that his organization would "encourage and invite alternative approaches … that would deliver at least equivalent assurances for the integrity of the food supply and export market."

Some observers estimated that 300 or more protein-based products could eventually be made via molecular farming. However, even when fully deployed years from now, molecular farming will remain a minuscule proportion of the 450 million acres of agricultural production in the U.S.

"It doesn't take a lot of acreage to grow these [therapeutic proteins]," said Fritz. "As we're continuing to work on things like expression levels, we anticipate that as these products go commercial a few thousand acres maximum will be required."

Farmers aspiring to grow transgenic crops must invest substantial time and capital, and meet high production standards. Transgenic crops must be harvested with dedicated equipment to prevent cross-contamination and kept segregated in secured storage facilities.

"Not every Joe Blow farmer is going to be allowed to grow these crops," said Felsot. "They're going to have to be trained, they're going to have to sign off on every step of the process under their control, and they're going to have inspections from beginning to end."

This means that drugmakers seeking to move transgenic plant production to commercial scale will have to be careful about picking farming operations to produce their drugs.

But careful procedures are no guarantee against problems. Dose noted that ProdiGene has a highly selective process of identifying producers. "We have a set of standard operating procedures and training sessions that producers have to go through, very much like an ISO 9000-type approach," Dose said.

FDA Guidance

The pharmaceutical and biotech industries are awaiting final guidance from the FDA. The agency issued draft guidance – *Drugs, Biologics and Medical Devices Derived from Bioengineered Plants for Use in Humans and Animals* – Sept. 6, 2002. The final document is set to come out as early as February, informed sources told *F&DL*. The agency developed the draft with APHIS, which has jurisdiction over field tests of genetically engineered plants.

Adherence to the new transgenic plant guidelines, along with additional measures taken by the major companies in the area, may help avoid repeated problems and foster the field of plant-produced drugs as it comes to fruition.

Those who work in the transgenic plant field welcome the pending final guidance from the FDA. "We do not have a regulatory system in place yet for plant-based pharmaceuticals," said Arntzen. "It's been a challenge for us doing research in this area, because we didn't know what regulation we're going to have to deal with. The draft guidance is a step in the right direction. Let's get on with it."

Knowledgeable observers said they also expect the FDA to issue draft guidelines governing the production of human therapeutics in transgenic animals during the first quarter of 2003.

SOME APPROVED PROTEIN-BASED DRUGS COULD BE MADE FROM TRANSGENIC PLANTS

With an estimated 750 protein- or antibody-based products in development, and about 200 of those in late-stage clinical trials, industry observers forecast a critical shortage of production capacity for monoclonal antibodies and other protein therapeutics. By 2005, according to experts, the demand for monoclonal antibody production may exceed capacity by two- to fourfold.

Following is a selection of drugs approved within the last five years made with recombinant technology that could be adapted to production in transgenic plants:

Drug	Company	Indication	Approved
Aranesp (darbepoetin alfa)	Amgen	Anemia due to kidney failure, chemotherapy	May 1998
Campath (alemtuzumab)	Ilex Oncology, Millennium, Berlex	B cell chronic lymphocytic leukemia	May 2001
Elitek (rasburicase)	Sanofi-Synthelabo	Pediatric oncology	July 2002
Ebrel (etanercept)	Amgen, Wyeth	Rheumatoid arthritis	November 1998
Forteo (teripratide recombinant)	Eli Lilly	Osteoporosis	November 2002
Herceptin (trastuzumab)	Genentech	Metastatic HER-2 positive breast cancer	September 1998
Humira (adalimumab)	Cambridge Antibody, Abbott	Rheumatoid arthritis	December 2002
Integrilin (eptifabatide)	COR Therapeutics, Schering-Plough	Acute coronary syndrome and angioplasty	May 1998
Kineret (recombinant human interleukin-1 receptor antagonist)	Amgen	Rheumatoid Arthritis	November 2001
Kogenate (recombinant antihemophilic factor)	Bayer	Hemophilia A	June 2000
LYMErix (recombinant OspA)	SmithKline Beecham Biologicals	Lyme disease prevention	December 1998
Myotarg (gemuzumab ozogamicin)	Celltech Chiroscience, Wyeth	Acute myeloid leukemia	May 2000
Natrecor (recombinant human B-type natriuretic peptide)	Scios	Congestive heart failure	August 2001
Neulasta (pegfilgrastim)	Amgen	Preventing infection in chemotherapy patients	August 2001
NovoSeven (recombinant Factor VIIa)	Norvo Nordisk	Bleeding episodes in hemophilia	March 1999
Ovidrel (recombinant human chorionic gonadotropin)	Serono	Infertility	September 2000
Pegasys (peginterferon alfa 2-a)	Roche, Inhale Therapeutics	Chronic hepatitis C	October 2002
PEG-Intron (pegylated recombinant interferon alfa-2b)	Enzon, Schering-Plough	Chronic hepatitis C	January 2001
Procrit (epoetin alfa)	Ortho Biotech	Anemia	February 2000
Rebetron (ribavirin and alpha interferon)	Schering-Plough	Chronic hepatitis C	June 1998
Rebif (interferon beta 1-a)	Serono, Pfizer	Multiple sclerosis	March 2002
ReFacto (antihemophilic factor)	Genetics Institute, American Home Products	Hemophilia A	March 2000
Refluda (lepirudin)	Hoechst Marion Roussel	Anticoagulation	March 1998
Remicade (infliximab)	Centocor	Crohn's disease, rheumatoid arthritis	August 1998
Simulect (basiliximab)	Novartis, Ligand	Rejection of kidney transplant	May 1998
Synagis (palivumab)	MedImmune	Prevention of respiratory syncytial virus	June 1998
TNKase (tenecteplase)	Genentech	Acute myocardial infarction	June 2000
Zevalin (ibritumomab)	IDEC	B-cell non-Hodgkin's lymphoma	February 2002

Source: Biotechnology Industry Organization

PRODUCTION OF THERAPEUTIC PROTEINS POSES CHALLENGES

Unlike traditional small-molecule drugs synthesized by standard chemical methods, therapeutic proteins are produced by living systems. Commercial production of these biological products is more complex – and costly – than traditional chemical drugs. According to a J. P. Morgan analysis, chemical drugs cost about $5 per gram to synthesize, while biologics cost $100 to $1,000 per gram. Following is a look at some common methods for making therapeutic proteins:

- **Microbial culture**. Since the 1980s, recombinant DNA technology has permitted production of therapeutic proteins in large volume through the culturing of bacteria, fungi or other microorganisms. By splicing a gene for blood-clotting factor into Escherichia coli bacteria, quantities of the protein are cultured in huge stainless-steel vats. The first generation of biotech drugs, including human insulin and clotting factors, are produced by recombinant microbial fermentation.

- **Mammalian cell culture**. Some proteins require a mammalian system to create molecules with biological activity in humans, needing essential steps in biosynthesis such as glycolysation or phosphorylation. These proteins can be engineered into mammalian cells cultivated in stainless-steel bioreactor vessels. Although a well-understood technology, cell culture facilities are costly and complex.

- **In Vivo**. Monoclonal antibodies can be produced by the ascites method, in which proteins are derived from fluid in the abdominal cavity of genetically engineered mice. While still used to make small batches of antibodies for research or diagnostic purposes, the ascites method is falling out of favor for commercial applications because of the cost of maintaining animals, public sentiment about animals used in research and the emergence of other technologies.

- **Transgenic animals**. Several academic and private-sector labs have successfully spliced genes into domesticated animals – particularly cows, goats and pigs – so that clinically useful proteins can be harvested from their milk. Because the mammary gland was designed by nature to produce proteins, it is well-suited to this use. An animal mammary gland can make drugs with a rate of productivity 250 to 1,000 times greater than fermentation of recombinant microbes or mammalian cell culture.

  Industry interest in transgenic animals is clear. GTC Biotherapeutics, a unit of Genzyme, collaborated with Tufts University and Louisiana State University to create genetically engineered goats that produce the anticoagulant human antithrombin III, which recently began efficacy clinical trials in Europe. Merrimack is developing goat milk-derived recombinant alpha fetoprotein to treat myasthenia gravis. Genzyme Transgenics is also developing a malaria vaccine and human albumin in goat's milk.

  PPL Therapeutics, famous for cloning Dolly the sheep, has created transgenic sheep that express the alpha-1 antitrypsin protein, a drug intended to

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TRANSGENIC PLANT INDUSTRY LED BY SMALL NUMBER OF FIRMS

The transgenic plant industry – still in its infancy but growing fast – comprises just a few dozen companies, most of which are involved in early research and development. A handful of firms have taken the lead in producing therapeutic proteins in transgenic crops, with various candidate products in the clinical trial pipeline. Several have already partnered with conventional drugmakers in their development efforts. Some major players in molecular farming are:

AltaGen Bioscience. Formed by the merger of PhytaGenics and Sierra BioSource, AltaGen has a transgenic platform to express therapeutic proteins in food crops, primarily potatoes. The company focuses on biopharmaceuticals with proven therapeutic value, including hemoglobin, thrombin, factor XIII, erythropoietin, interferon and growth hormone. AltaGen's collaborators include the U.S. Army and three unidentified biotech companies.

Centocor. Johnson & Johnson subsidiary Centocor makes the monoclonal antibody Remicade (infliximab) to treat Crohn's disease and rheumatoid arthritis, as well as ReoPro (abciximab) and Retavase (reteplase recombinant) in the cardiac care arena. Centocor has teamed with Dow and Epicyte to produce an unidentified monoclonal antibody in transgenic plants.

CropTech. CropTech has developed techniques to produce human therapeutic proteins in tobacco plants. The company is collaborating with several biotech firms, such as Amgen and Immunex, to develop eight product candidates.

Dow AgroSciences. A transgenic plant pioneer with extensive agricultural experience, Dow intends to take genetically modified crops from the field through good manufacturing practice-certified processing facilities to a finished drug. In September 2000, Dow formed a research and licensing pact with Epicyte to produce human monoclonal antibodies in corn, which led to R-19, an antibody for the treatment of respiratory syncytial virus. In 2001, Dow and Epicyte scaled up production of HX8, a treatment for herpes simplex II. Dow also has agreed to produce a monoclonal antibody for Centocor.

Epicyte. In July 2002, Epicyte won a broad patent covering any transgenic plant expressing an antibody, including monoclonal antibodies. The company has a pipeline of monoclonal antibodies focused on treating the herpes simplex virus, the human papilloma virus, HIV, Alzheimer's disease, ulcerative colitis and the hepatitis viruses. Epicyte's lead product, HX8, is the first topical monoclonal antibody and is expected to begin a Phase I clinical trial in 2003. Epicyte partnered with aaiPharma to formulate the topical compound.

Large Scale Biology. Large Scale Biology (LSBC), best known for its work in proteomics, produces patient-specific cancer vaccines in greenhouse-raised transgenic tobacco plants. The plants produce single-chain antibody fragments for patients with B-cell non-Hodgkin's lymphoma. The FDA also granted orphan drug status Jan. 23 to LSBC's plant-produced human alpha-galactosidase A enzyme to treat Fabry's disease. The firm plans to start a Phase I clinical trial later this year. Among LSBC's collaborators and clients are Dow, GlaxoSmithKline, ApoImmune, the U.S. Navy and ProdiGene.

Meristem Therapeutics. The first industrial-scale molecular farming operation in Europe, Meristem was founded in 1997 to develop drugs from genetically modified corn and tobacco. The firm's lead product is recombinant gastric lipase to treat cystic fibrosis, which has been handed over to partner Solvay and is in Phase IIa clinical trials in Germany and France. The gastric lipase product is set to reach the European market in 2004-2005. Meristem has also engineered corn to produce gastric lipase for treating exocrine pancreatic insufficiency. Meristem agreed to produce recombinant proteins in tobacco plants for Eli Lilly. The company also won a patent for the production of hemoglobin in plants.

Monsanto Protein Technologies. Agricultural giant Monsanto has a major stake in the production of therapeutic proteins in transgenic corn. In 2000, the firm entered a research agreement to use Neose Technologies' GlycoAdvance technology to improve the glycolysation of corn plants, enhancing the ability of plant-produced monoclonal antibodies to activate the immune system.

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Phytomedics. Spun off by Rutgers University in 1996, Phytomedics produces therapeutic proteins in genetically modified tobacco plants. The company's pipeline includes drug candidates to treat autoimmune disorders, diabetes, viral infection and cancer. Phytomedics is collaborating with Pfizer to develop PMI-001, a plant-derived drug that has been tested in Phase I/II clinical trials. The company also is collaborating with Bristol-Myers Squibb and DNAX Research.

Plant Research International. Plant Research International (PRI), one of Europe's premiere agricultural research institutions focused on preventing plant disease and improving agricultural stock, has recently begun moving toward commercial development of therapeutic proteins. In 2001, PRI announced a breakthrough in plant biology forged in collaboration with researchers at RIKILT Institute of Food Safety and the University of Rouen, improving the glycolysation of proteins to create more human-like monoclonal antibodies. In November 2002, PRI inked a deal with Dow to collaborate on optimizing protein glycolysation in plants.

ProdiGene. ProdiGene uses genetically modified corn to produce vaccines, antibodies, enzymes and other protein-based therapeutics. In August 2002, the company began a Phase I clinical trial, in cooperation with the National Institutes of Health, of a corn-derived oral vaccine to prevent traveler's diarrhea. The company is also developing a candidate vaccine for HIV. Last year, ProdiGene began commercial scale-up of aprotinin, a protease inhibitor used in cardiac surgery. ProdiGene has collaborations with Eli Lilly, Avant Immunotherapeutics, LSBC and Epicyte.

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treat cystic fibrosis. PPL is developing the drug with Bayer. Clinical trials with recombinant alpha-1 antitrypsin (RecAAT) stalled in Phase II during 2001. Phase III trials have been delayed.

- **Transgenic plants**. The same genetic engineering tools used to splice a gene into E. coli bacteria or a cow can be used on plants. The cost of producing raw drug material from transgenic plants is about one-tenth that of a traditional bioreactor plant for microbial or mammalian cell cultures.

  Transgenic plants offer several advantages over other technologies, including the ability to increase the scale of production affordably. "You can store the grain product for extended periods of time without any loss of active material or risk of contamination," said Robert Dose, vice president of business development at ProdiGene. Producing drugs in plants also avoids the risk of spreading animal viruses or contaminants that may trigger an allergic response.

  However, some technical problems remain to be solved. Plant-produced monoclonal antibodies are different from those made via mammalian cell culture. Antibodies produced in plants have incomplete glycolysation patterns and may not activate the complementary system for full effect. Scientists at Dow AgroSciences and Monsanto Protein Technologies have reported progress in enhancing the glycolysation of corn plants, which could yield a more humanized monoclonal antibody.

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