

BioCentury

Technology Briefing

Biopharming LEXicon

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Production of proteins in plants or animals each provides advantages over protein production in mammalian cells or E. coli, including the capacity to economically scale up and express complex proteins. However, no products produced this way have yet made it to the market.

In February, Biolex Inc. joined a cluster of transgenic pharmaceutical manufacturers with products in the clinic. But it is also accumulating a roster of development collaborations for its plant-based system, which the company is selling as a highly efficient solution for expressing hard-to-make proteins.

The deal flow was topped up in March with the expansion of a 2003 partnership with Centocor Inc. The new deal added scale-up and manufacturing of up to 10 proteins on top of the six Biolex was already working on.

"Centocor was interested in Biolex because the technology has the potential to improve efficiency and reduce costs," said Denise McGinn, vice president of business development at Centocor, a subsidiary of Johnson & Johnson (JNJ, New Brunswick, N.J.). "While the technology is not yet proven, it has the potential to decrease complexity and capital investment relative to the technology used to manufacture today's marketed biologic products."

Centocor evaluated a variety of transgenic plant systems, including corn and tobacco, McGinn said. "We chose Lemna because of its simplicity and ability to be contained."

Biolex's Lemna Expression (LEX) System employs a tiny, free-floating aquatic plant called lemna, or duckweed, which is a clonal plant that is known to be genetically stable. The method involves introducing a particular gene sequence into the cells of the plant, which serve as the template for constructing a target protein. The recombinant protein is then secreted out into the media where it is purified and collected.

"Systems that use E. coli or yeast are good for producing simple proteins but run into problems with more complex proteins because of folding difficulties and low yield," said Jan

Turek, president and CEO of Biolex (Pittsboro, N.C.). By contrast, he said, lemna is able to express hard-to-make proteins like cytokines and monoclonal antibodies.

It remains to be seen whether LEX will be able to handle the
See next page

Growing a lemna portfolio

Selected Biolex deals.		
Date	Company	Deal
Mar-05	Centocor	Producing up to 10 additional proteins for Centocor
Feb-05	OctoPlus	Partnered to develop a controlled-release formulation of Biolex's BLX-883 recombinant alfa interferon using PolyActive delivery technology from OctoPlus
Feb-05	Medarex	Partnered to research feasibility of using LEX System to produce undisclosed monoclonal antibody from MEDX
Oct-04	Centocor	Further expanded Centocor deal to include two additional proteins, bringing total to six
Jun-04	Centocor	Expanded 2003 deal with Centocor to scale up production of the three proteins from 2003 deal, and added a fourth protein
May-04	Epicyte	Acquired antibody company Epicyte
Jun-03	Centocor	Agreed to use LEX System to express three therapeutic proteins from Centocor
Oct-02	Bayer	Partnered to research the feasibility of using the LEX System to produce human plasminogen and an undisclosed protein from BAYG
Sep-02	Debiopharm	Partnered to research the feasibility of using the LEX System to produce an undisclosed recombinant protein from Debiopharm

Biolex,
from previous page

humanized glycosylation patterns necessary for some proteins. "We have not observed any immunogenicity issues so far," said Turek, adding that ongoing studies should provide results in the next couple of years.

In the meantime, he said, "I believe Biolex can generate commercial value with or without proving the LEX System can handle humanized glycosylation patterns. There are a lot of proteins that either don't have glycosylation or where it is not necessary for proper activity."

On the efficiency side, Turek said a LEX facility can be built for \$50 million in three years, while mammalian manufacturing plants can cost as much as \$400 million, because of the control systems needed to prevent contamination, and take up to five years. The LEX timeframe allows a potential partner to wait for Phase II efficacy data before having to invest in a commercial facility.

Turek also said a LEX System can be developed more rapidly than the equivalent transgenic animal system. GTC Biotherapeutics Inc. (GTCB, Framingham, Mass.) has developed a method of producing target proteins in the milk of transgenic goats, while companies such as AviGenics Inc. (Athens, Ga.) and Viragen Inc. (VRA, Plantation, Fla.) are independently developing chickens that synthesize human proteins in the whites of their eggs.

These systems also can make complex proteins. But, according to Turek, "the cross-breeding needed to generate the founder line of animals can take two or three years. We can go from gene to IND in 18 months with the LEX System, and can double our biomass every 36 hours."

Turek also argued that proteins produced in animal systems are harder to purify because "it is difficult to differentiate between the target protein and other similar proteins that occur naturally in the animal's milk."

Turek said LEX provides advantages over other plant-based transgenic models, typically crops such as tobacco and corn, as the Biolex system is fully contained inside a manufacturing facility.

Biolex is using the revenue and investments from its string of recent partnerships to advance its own products (see "Growing a Lemna Portfolio," previous page). In February, the company started a

Phase I trial of its lead BLX-883, a recombinant alfa interferon to treat HCV. The candidate was formulated using the LEX System.

Safety results are expected mid-year. But the company already has decided to pursue development of a controlled-release formulation of BLX-883 called Locteron, which is being co-developed with OctoPlus Technologies BV (Leiden, the Netherlands). The candidate will be produced in the LEX System before being formulated using OctoPlus' PolyActive drug delivery technology. Phase I testing of Locteron will begin this year, said Turek.

Biolex is far from the first transgenic manufacturer to enter the clinic with its own product. Furthest along is GTCB, which is developing ATryn recombinant antithrombin to treat hereditary antithrombin deficiency in patients undergoing high-risk procedures such as surgery and childbirth.

ATryn, which is manufactured in the milk of goats, is under review in Europe. GTCB plans to respond by July 8 to a list of questions the EMEA has raised about the MAA, which would allow for a decision from the agency by October. In the meantime, GTCB plans to start a U.S. Phase III trial of the recombinant protein this quarter.

GTCB is developing a number of models for producing recombinant proteins in the milk of transgenic animals, said spokesperson Tom Newberry. The company has expressed more than 80 proteins using a variety of animal platforms including goats, mice and cattle, he said.

Another transgenic biomanufacturer making headway in the clinic is Meristem Therapeutics SA (Clermont-Ferrand, France), which is using a corn-based system to produce Merispase, a recombinant gastric lipase protein.

After completing two Phase II trials of the candidate to treat pancreatic insufficiency associated with cystic fibrosis (CF), the company is working to develop a slow-release formulation in collaboration with SkyePharma plc (LSE:SKP; SKYE, London, U.K.) and West Pharmaceutical Services Inc., now part of Archimedes Pharma Ltd. (Reading, U.K.).

CEO Jean-Paul Rohmer said Meristem will begin optimization studies of a new formulation of Merispase in animals within two months, which will allow it to start another Phase II trial by the end of this year. Assuming the European agricultural authorities sign off on the company's plans, he hopes to start a Phase III trial in September 2006 and be prepared to submit a marketing application for Merispase by late 2007 or early 2008.