PPL floats IPO as companies consider transgenic switch

PPL Therapeutics's (Edinburgh, UK) initial public offering (IPO) on the London Stock Exchange in early June signals the next phase in the history of transgenic production of protein agents. The flotation, which the company hopes will raise £25–30 million ($38–46 million), comes as Genzyme Transgenics (Framingham, MA) is reaching the final planning stages for human clinical trials of the first transgenic-produced compound, antithrombin III, in the second half of 1996. But, despite these milestones, the biggest hurdle for transgenics companies will continue to be convincing their client companies to switch to transgenic-production systems. Moreover, with increasing diversity in the types of transgenic system available, the chances of selecting a particular transgenic system are reduced.

At the beginning of May, for instance, PPL Therapeutics had restructured its collaborations in preparation for the IPO. On the one hand, PPL has now regained the rights to α-1-antitrypsin (AAT) from its erstwhile partner, Bayer (Leverkusen, Germany), for the treatment of emphysema; on the other hand, it has extended its collaboration with Novo Nordisk (Bagsvaerd, Denmark) on factor VIIa. Novo, which has just launched NovoSeven—produced in yeast—to treat hemophiliacs who do not respond to conventional treatments, bought an extra £3.3 million ($4.5 million) worth of PPL stock, and now holds 13% of the company. Thus, while Novo can still switch to transgenics, Bayer already appears to have decided against it.

The great lure of transgenic methods is the reduced costs of therapeutic protein production: They can be cheaper than microbial or mammalian cell culture by an order of magnitude or more. As recombinant proteins such as insulin and human growth hormone come off-patent, transgenic production may well emerge as a cost-effective alternative production system. "We are interested in any potential reduction in production costs at each step, which is why we are pursuing transgenics for our drug development," says Perry Fell, director of molecular immunology at Bristol-Myers Squibb (BMS, Princeton, NJ). Indeed, companies like BMS, with proteins to produce, can now consider several distinct transgenic production systems.

As a result of a deal signed in May 1995, for instance, the antibody fragment for BMS's doxorubicin-conjugate, BR-96, will be produced by Genzyme's new goat, Grace, in about six months time when she begins to lactate. The compound is currently in phase II trials for breast, colon and lung cancer using an antibody produced in mammalian-cell culture. But BMS also has an agreement with Agracetus (Middleton, WI) to produce BR-96 in its "plant bioreactors"—plants (usually corn) or plant cell cultures genetically modified with Agracetus's Accell gene-gun delivery system. "We are evaluating the optimal methods to produce a variety of proteins. Depending on the molecule, different expression systems or media may work better than others," says Fell.

Agracetus also has a research collaboration with Protein Design Labs (Mountain View, CA) to produce a herpes simplex virus monoclonal antibody (Mab) therapeutic. Not surprisingly, Agracetus vice president of R&D, Ken Barton, reckons it is cheaper to grow drugs in plants than in animals: "Raw materials are inexpensive, and purification costs comparable. . ." But other factors, beside cost, influence the choice of production method. Proteins that require glycosylation or other posttranslational modifications may necessitate transgenic animal or mammalian cell systems, whereas other proteins—like CTLA4-Ig, which does not require glycosylation for activity—may be produced in microbial or plant systems, Fell explained. Conversely, IL-2 would ideally be produced in bacteria, he says, as it could be toxic in animal or plant cells.

NeoRx (Seattle, WA) is also hedging its bets with multiple deals to evaluate both plant-transgenic and animal-transgenic production of its humanized anticancer Mabs, including the antibody part of Avicidin, the company's pretargeted streptavidin-biotin-Mab-isotope construct. Like BMS, NeoRx signed on last June with Genzyme Transgenics. It followed up in November with a deal with biosys (Columbia, MD), a company that grows recombinant baculoviruses in cabbage looper larvae. biosys estimates that the yield of antibody per larva can reach 250 μg and that its current production facility can produce over 200 g antibody per day.

In the intermediate term, the question is not whether production using transgenic animals and plants is more cost effective, but whether the cost of switching from another production method to transgenics can be justified. "Animals' products may be easier to purify," said James Cornett at PDL, "but we must weigh the cost of making the switch."

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Genzyme leads transgenics pack

With 11 transgenic drugs in the pipeline and 6 of them partnered, Genzyme Transgenics is probably the current leader in the transgenics field. Sumitomo (Osaka, Japan) is its licensee for Asian rights to antithrombin III (for anticancer monoclonal antibodies); Genzyme also has deals with Pharmacia & Upjohn for a receptor protein, and with Genzyme Corporation (Cambridge, MA) for a cystic fibrosis transmembrane-conductance regulator. The development of transgenic production for insulin, CD4, glutamic acid decarboxylase, long-acting tPA, and human serum albumin are self funded. The company has two research agreements with AutoImmune (Lexington, MA): The first, agreed in May 1995, is to develop and conduct preclinical testing with type II collagen for Colloral, AutoImmune's rheumatoid arthritis therapeutic, currently derived from chicken sterna and now in phase II trials; the second, agreed to a month later, concerns Myloral, a multiple sclerosis compound.

Holland Labs of the American Red Cross (Rockville, MD) is developing another unusual transgenic system—the pig. But unlike Somatogen (Boulder, CO), which produces human hemoglobin in pigs, Holland plans to produce its plasma products in pig milk. Henryk Lubon, director of Holland's transgenic program, explains that pigs have some advantages—larger litters (easy to expand production quickly) and a better safety profile than cows and goats: "No prions or viruses that can be transmitted to humans via milk have been found in pigs," he notes. But getting enough milk from them is a problem that Holland Labs (and PPL Therapeutics, too) is still working on.

For large-volume proteins, the cow may be the "bioreactor" of choice. In March 1996, Pharming (Leiden, the Netherlands) began preclinical studies with human lactoferrin produced in cows under an agreement with the Dutch food company, Nutricia (Zoetermeer, the Netherlands). The product is intended as a hospital-food supplement for immunocompromised patients. And in April, Collagen Corporation (Palo Alto, CA) made an equity investment in Pharming of Dfl7.3 million ($5.0 million) as part of an agreement under which Pharming will develop production methods for type 1 collagen in cows. Collagen will be happy if the transgenic methods work out: Increased yields would mean that Collagen's current method of obtaining the protein—extracting it from cowhide—would be superseded. The product would be human collagen, less immunogenic and more resistant to degradation by human collagenase, according to Collagen's chief financial officer, David Foster. *V.B.*