

The Land of MILK & MONEY

By Gary Stix

The first drug from
a transgenic animal may be nearing approval

Proteins are biotechnology's raw crude. For much of its 30-year history, the industry has struggled to come up with a steady source of supply, squeezing the maximum out of these large-molecule commodities from cell lines isolated from hamster ovaries and the like. In the late 1990s—with the advent of a new class of protein-based drugs, monoclonal antibodies—demand sometimes outstripped supply. For decades, the scientists who created recombinant erythropoietin to rejuvenate red blood cells and monoclonal antibodies to combat cancer have sought out alternative forms of manufacture.

A new bioreactor—an animal genetically engineered to produce a therapeutic protein in its milk—may finally be ready to fulfill its long-awaited promise. The European Medicines Evaluation Agency (EMA) may decide early next year on approval of an anticoagulant

protein, human antithrombin, that is produced in goat's milk to treat a hereditary disorder. If the drug, ATryn, finally gets a nod from regulators, its approval will mark the culmination of a meandering 15-year journey for GTC Biotherapeutics, a Framingham, Mass., spin-off of the biotech giant Genzyme.

The idea of making transgenic drugs occurred to a number of scientists during the mid-1980s, when the new industry began to wrestle with the challenge of making complex proteins: ensuring that these big molecules were folded into the proper shape and that they had all their sugars in the right places on the surface of the proteins' amino acids. Chinese hamster ovary cells do the job, but getting enough product has been a constant frustration and one reason why biotech drugs today cost so much. In addition, mammalian cell cultures are not always an ideal medium: at times, it is simply too hard to produce proteins in this manner.

In their quest for greater efficiencies, researchers noticed that the mammary glands of cows, rabbits and goats, among others, are capable of becoming ideal protein manufacturing plants because of their ability to make high volumes of complex proteins. Milk glands, moreover, do not need the constant coddling required for cell cultures.

Genzyme got involved after its purchase in 1989 of Integrated Genetics, which had a portfolio of drugs and diagnostics products. To head up its program, Genzyme recruited one of the pioneers in this technology from another company, Biogen. Harry Meade, along with Nils Lonberg, had patented a method of extracting therapeutic proteins from mice.

In the early 1990s Genzyme's program was targeted at producing drugs in goat's milk. Genzyme, though, was not focusing on transgenics and decided to spin off its operation into a separate entity, Genzyme Transgenics (later re-



TRANSGENIC GOAT gets milked at a farm owned by GTC Biotherapeutics, headquartered in Framingham, Mass. The animal secretes a valuable pharmaceutical protein in its milk.

named GTC Biotherapeutics), in which the parent still holds an equity interest. The new company could thus produce its drugs for other firms without the inevitable conflicts of interest that would have arisen had it remained within the bosom of a large drugmaker.

Goats as Drug Factories

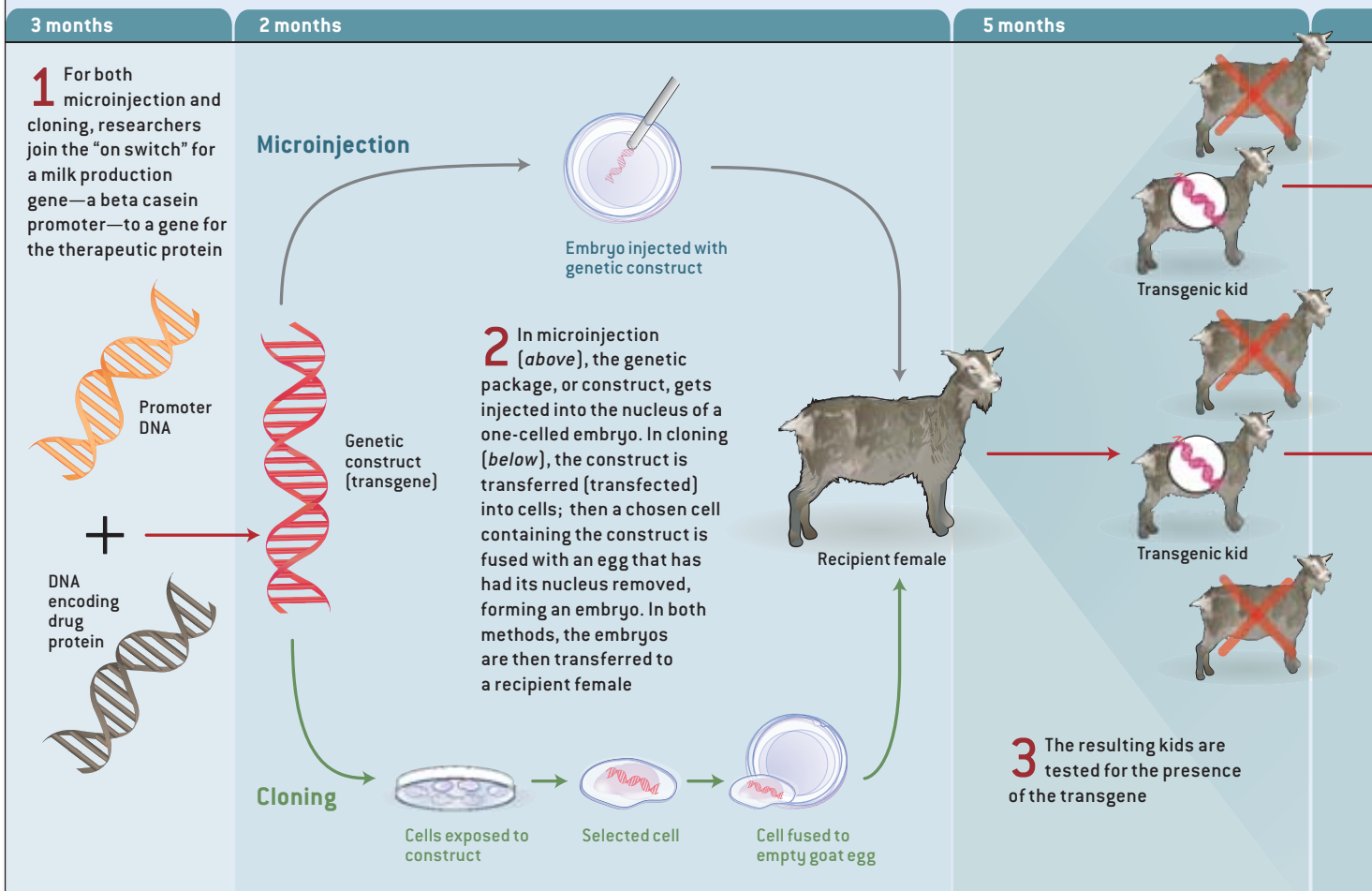
INITIALLY, GTC generated transgenic goats by microinjecting into the developing nucleus of a one-cell embryo a gene encoding the desired human protein (along with DNA that promotes activation of that gene in milk). Such embryos were transferred into female goats, which produced offspring that were then tested for the presence of the newly integrated gene. The milk of these “founder” animals contains the therapeutic protein, which must then undergo a purification process. The mature transgenic animals were bred usually with nontransgenic goats as a first step toward producing a herd [see box on next two pages]. Microinjection, however, is an inefficient process. Only 1 to 5 percent of the embryos result in transgenic animals. For newer drugs in its portfolio, GTC has adopted somatic cell nuclear transfer, a.k.a. cloning, which ensures that an animal will carry the desired transgene. Dolly the sheep was cloned, in fact, with the intention of eventually using this procedure to create transgenic animals having useful properties, not as a means to make carbon copies of baseball legend Ted Williams or a favorite dead pet.

GTC stuck with goats because they reproduce more rapidly than cows and can yield more protein than mice or rabbits. Other efforts, including a more nascent GTC endeavor, have opted for cows. Pharming, a Netherlands-based company, aims to milk both cows and rabbits for drugs. Yet others have pursued distinctive forms of bioreactors: making drugs in chicken eggs, for instance. After undertaking basic development of the technology during the 1990s,



MILKING GOATS FOR DRUGS

GTC Biotherapeutics, which is counting on European approval of an anticlotting drug produced in goats, has used two major approaches to create a transgenic animal. The older technique, microinjection, employed for the drug undergoing regulatory review called ATryn,



GTC hung out a shingle, marketing itself as a technology platform for companies that either wanted to produce difficult-to-make pharmaceutical proteins or needed large quantities at low cost. The one catch was that regulators had never approved a transgenically produced drug, and the more than a dozen partners that GTC took on tended to view the technology as a backup in case other protein-drug development strategies did not work out. They were unwilling to accept the expense and risk of an arduous regulatory process for a pioneering form of drug manufacture.

GTC recognized the need to demonstrate on its own the potential for the technology and, in the late 1990s, began a clinical trial of human antithrom-

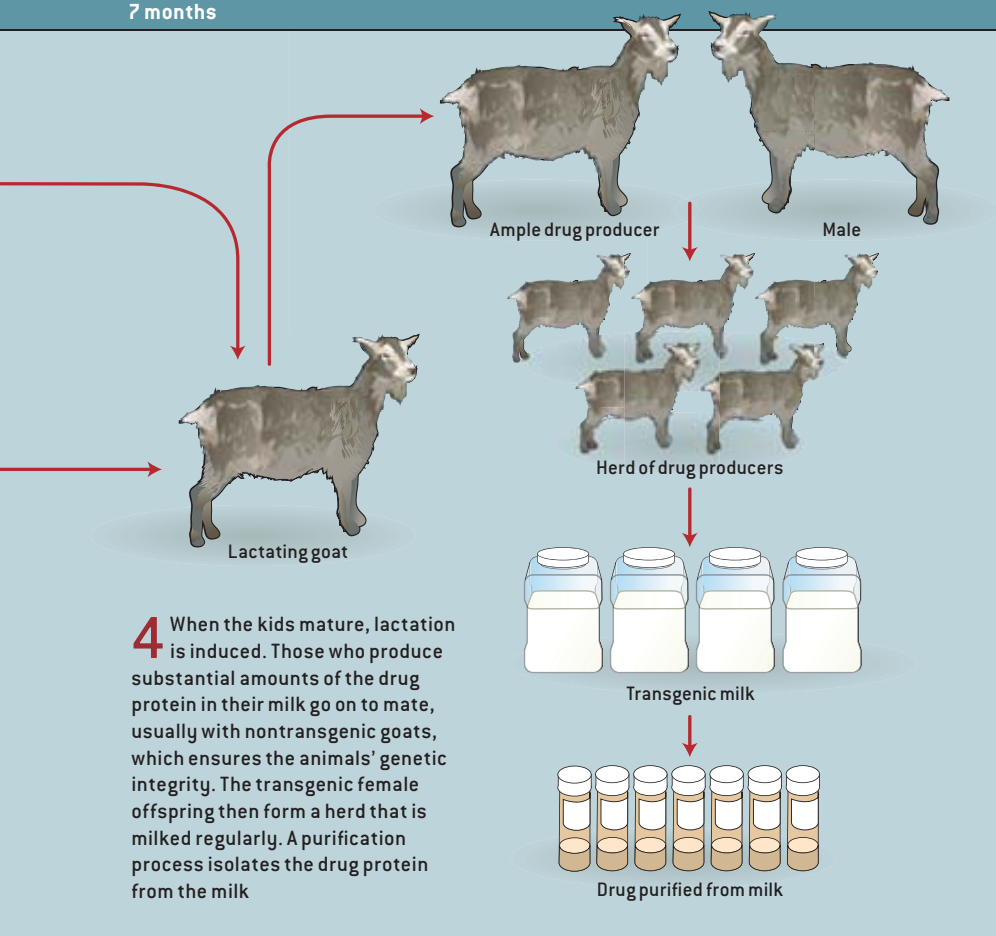
bin for patients undergoing bypass surgery who develop resistance to the anticoagulant drug heparin. Transgenic antithrombin was intended to improve supply and address concerns about pathogens in the form of the drug isolated from human blood. The company completed the required clinical trials. But when the Food and Drug Administration asked for more data in late 2000—which would have necessitated additional testing—then chief executive Sandra Nusinoff Lehrman scrapped the effort. In mid-2001 Nusinoff Lehrman left, and her replacement, Geoffrey Cox, decided to proceed with development of transgenic antithrombin—this time in European clinical trials for patients with inherited antithrombin deficiency. Reg-

ulators there had recently issued guidelines that set out the requirements for getting approval for antithrombin.

The company still has a few partnerships. It also has a preliminary program to make other blood proteins, such as alpha-1 antitrypsin, and a clinical trial in the U.S. for ATryn. But its future hinges on the European approval. The company, which went public in 1993, has flirted with penny-stock status (less than \$1 a share), and its cash levels are much depleted from what they were at the start of the decade. It has also experienced “restructurings,” layoffs that occurred in 2003 and 2004. “This is an important moment,” says Cox of the upcoming EMEA decision. “This isn’t a business for the faint of heart.”

involves introducing a gene directly into an embryo. The company has also been a pioneer in producing transgenic drugs through cloning.

7 months



4 When the kids mature, lactation is induced. Those who produce substantial amounts of the drug protein in their milk go on to mate, usually with nontransgenic goats, which ensures the animals' genetic integrity. The transgenic female offspring then form a herd that is milked regularly. A purification process isolates the drug protein from the milk

Bioreactor Blues

OTHER TRANSGENIC companies have also had a rough haul. The Scottish company PPL Therapeutics, which helped to clone Dolly, encountered difficulties and sold its remaining intellectual property to Pharming in 2004. The latter has staged a comeback since filing for protection from creditors in 2001. It hopes to get approval soon for a treatment for hereditary angioedema, a genetic disease that causes swelling from the absence of the C1 inhibitor protein.

If GTC survives, it could become the leader in transgenics. The impetus for starting the company still appears justified. The capital costs for a drug production facility using hamster cells can amount to \$400 million to \$500 million,

Cox says, whereas a herd of goats can produce the comparable amount of drug for \$50 million. "There's still a need for alternative production methodologies," says Philip Nadeau, who tracks GTC as an analyst with S. G. Cowen. "There are still proteins that are difficult to produce using traditional methods, and therefore a company like GTC should certainly have a niche." ATryn's uses could be broadened to encompass an array of treatments—for coronary bypass, burn or sepsis patients—that might, in total, bring in as much as

\$700 million annually, Cox estimates.

The drug appears to have surmounted an important technical hurdle: so far it has not created any adverse immune response in patients. But such events will always remain a worry. Researchers administering inhaled transgenic alpha-1 antitrypsin from sheep bred by PPL discovered that some patients suffered pulmonary symptoms that caused them to leave the trial—a possible immune reaction to residual proteins from the animal that remained after purification of the drug. The PPL drug, given on a longer-term basis than ATryn is, needed to be better purified, notes Meade, GTC's chief scientific officer.

Producing drugs in goats has so far elicited less criticism than the debate over genetically modified plants. Goats cannot drift with the wind like corn pollen, spreading their transgenes to unexpected places. "If it's able to make drugs available that are not otherwise available by other methods and if it would make drugs cheaper, it would be certainly advantageous to consumers," notes Jane Rissler of the Union of Concerned Scientists. "Frankly, consumers have not benefited very much [so far] from biotechnology in the agricultural sector."

At GTC, the scrapie-free goats brought in from New Zealand are penned within a 190-acre enclosure on a 300-acre plot in Charlton, Mass. The animals are fed—and not permitted to graze—to diminish the possibility of contracting disease from contaminants in other animals. Thirty goats are devoted to making ATryn among a transgenic herd of more than 300, and an additional 1,200 nontransgenic animals are kept for breeding. "We have more veterinarians than M.D.s," Cox says. If ATryn finally receives approval, traditional dairy farmers flirting with insolvency may gaze in astonishment at a product made in milk that commands thousands of dollars per gallon. SA

MORE TO EXPLORE

Transgenic Animals: Generation and Use. Edited by Louis Marie Houdebine. CRC Press, 1997.

Production of Goats by Somatic Cell Nuclear Transfer. Alexander Baguisi et al. in *Nature Biotechnology*, Vol. 17, No. 5, pages 456–461; May 1999.

GTC Biotherapeutics: www.transgenics.com