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SPECIAL REPORT

Crossing The Gene Barrier

On the frontiers of biotech, two scientists are mingling the genetic materials of man and beast in new ways. The hoped-for outcome: Radical treatments for some of mankind's most intractable ailments

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Goats throughout history have been symbols of vitality and cunning, and treasured for their silky fur and nutrient-rich milk. But Sweetheart, a brown-striped goat with soulful eyes, has a secret that could elevate her far above this illustrious legacy. Named for her laid-back disposition, she has a single human gene in the twined strands of her DNA that enables her to produce a life-saving drug in her milk. It's a protein that's normally found in human blood.

In ancient times, the Greeks revered the god Pan -- part-man, part-goat -- who defended Athens against the Persians. Today, the dash of humanity imbedded in Sweetheart and 59 other goats at a central Massachusetts farm could provide a different but equally vital line of defense. Some people don't make enough of the protein in their livers, explains Harry M. Meade, the chief scientist at the company that created her. That raises the risk they'll suffer fatal blood clots during surgery. Others, such as burn victims and heart surgery patients, need a bit more of the protein to speed their recovery. If regulators in Europe approve Sweetheart's elixir in February, as expected, it's likely to be the first drug on the market derived from the milk of a part-human "chimera" -- a creature that bears the cells of two or more species.

A Tale of Two Scientists

Three thousand miles away, scientist Nils Lonberg reaches into a cage and scoops up a different sort of chimera. It looks like a subway-variety mouse, but its tiny body cradles a partial replica of one of the most intricate systems known to biology: a human immune system. This whiskered fur ball has the extraordinary ability to produce disease-fighting antibodies in its cells that can be harvested and turned into drugs. As the creature sniffs the hand of the scientist that invented her, the 49-year-old Lonberg responds as if he is encountering the animal for the first time. "I find this amazing," he says. The challenge of engineering this rodent is comparable to building a towering skyscraper, he says: "It's amazing that people can create something of this complexity."

This is the story of two scientists, Meade and Lonberg, who are toiling on the fringes of biotechnology. Their paths crossed 20 years ago, setting them on a quest to alter the age-old partnership between man and beast by mixing genes to concoct new medicines. Since then the two have pursued their goal on separate but parallel tracks. Meade, 59, is now chief scientific officer of Framingham (Mass.)-based GTC Biotherapeutics (), which created Sweetheart. Lonberg is scientific director at Medarex Inc. (), which is taking a lead in commercializing transgenic mice.

In the business of biotech, chimeras are about as close to science fiction as you can get. People have been crossing critters for centuries -- yielding everything from mules to labradoodles. But jumping the gene barrier by giving animals copies of human genes is more sensational. These creatures look, act, and smell like animals, yet their cellular machinery conceals unique biochemical capabilities. Already, 50 biotech and pharmaceutical companies are using mice from Medarex to develop treatments for terrible diseases -- from malignant melanoma to lymphoma to lupus. And GTC's goats may become factories for drugs that are too complex to produce any other way.

Yet as promising as these developments are, Meade and Lonberg strive to hold their optimism in check. Both spent years

confronting the skepticism of other scientists, and even derision. Today, GTC and Medarex are burning through cash and investors are getting impatient. Other transgenics companies have shriveled and died. As drug regulators start issuing their rulings in coming months, the two men will learn whether their life's work will enrich mankind's supply of drugs or if their companies will sink into oblivion like so many other promising biotechs.

The saga of the goat and the mouse began in 1984, in a lab at Biogen Inc. in Cambridge, Mass. Meade and Lonberg were brainstorming how to manufacture a human protein that looked promising as a treatment for blood clots. They pulled an all-nighter devising a scheme for slipping human genes into the DNA of animals and then milking them to harvest the drug. The pair thought it was a brilliant idea, but few of their colleagues agreed. When Lonberg described it the next day to then-CEO Walter Gilbert and his management team, they nearly laughed the young scientist out of the room. "Gilbert looked at me and said, 'how about making it in goose eggs? You could have the goose who laid the golden egg,'" recalls Lonberg.

In fact, Meade points out, companies are now trying to do exactly that -- extract drugs from transgenic chicken eggs. "It sounds incredibly simple," Meade says, "but everything's in the details."

When Meade and Lonberg first began to tackle those details, they found themselves cast in the role of mad scientists. Having left Biogen in 1985, Lonberg was studying transgenics at Memorial Sloan-Kettering Cancer Center in New York. With the help of Meade, who often visited the lab, he succeeded in rejiggering the DNA of mice so they could produce human proteins in their milk. The scientists then rented a woman's breast pump from a pharmacy in New York and rigged it up to fit their tiny research subjects. "I remember them using this pipetting apparatus and applying it to the mouse nipples," laughs Elizabeth Lacy, Lonberg's former adviser at the cancer center. When Meade tried to return the borrowed breast pump a year later, the pharmacist was so shocked to hear what it had been used for that he refused to take it back.

Meade and Lonberg seemed like biotech's version of the Odd Couple. Meade, a jock who sometimes bikes 26 miles to work, once attracted a crowd at Biogen by demonstrating the moves he had learned in a break-dancing class. He wore his bike helmet to protect his head as he spun on the floor. The display startled Lonberg, who once ditched a required physical education credit at Reed College. It cost him his bachelor's degree, but it was a satisfying "act of defiance," Lonberg says. Having already been admitted to Harvard's PhD program in molecular biology, Lonberg called the head of the department to make sure the missing degree wouldn't matter.

Differences aside, Meade and Lonberg played off each other's strengths. Meade, the elder, passed on his knowledge of biochemistry and genetics to the young student. And as Lonberg focused his postgraduate studies on the then-embryonic field of transgenics, he taught Meade the intricacies of stitching human genes into animals. Together they co-authored the first issued patent on extracting drugs from milk in 1989.

Contemplating the gallons of milk necessary to make a drug, Meade planned to apply the technology to cows. Having grown up on a dairy farm outside Pittsburgh, he knew his research subject intimately. When the young Meade didn't have his nose buried in a science textbook, he was milking the family's herd and hanging out with the 4-H Club and the Future Farmers of America. "I was probably the only person who figured out butterfat content using a slide rule," Meade jokes.

At Biogen, Meade wasn't always confident that his bosses supported his plan to marry biotech with bovines. During analyst meetings, he recalls, "I had this feeling they were trotting me out for comic relief." He didn't feel truly in his element until he was managing research at GTC, a company devoted mostly to goat/human chimeras.

The Dolly Difference

In principal, giving Sweetheart and the rest of her herd the machinery to make human proteins is basic college biology. It's a matter of inserting a copy of a single human gene into her DNA and programming it to turn on in her mammary gland. But in the early days, GTC's method for tweaking the goat's DNA was so clumsy that only 5% of the kids were born carrying the human gene. Over the years, a string of scientific breakthroughs enhanced the process. Topping the list was the sheep called Dolly. After the Roslin Institute in Scotland cloned the now-famous sheep, GTC adapted the technology to its newest breeds of drugmaking goats -- boosting the success rate to nearly 100%.

Investors at first went wild over GTC's goats. In the late 1990s demand for biotech drugs was skyrocketing, and drugmakers faced a dire manufacturing crunch. GTC promised virtually unlimited capacity at a fraction of the $500 million it costs to build the typical biotech factory. It made perfect sense: You need more drugs? Breed more goats. Even some majors like Bristol-Myers Squibb () and Johnson & Johnson () began talking with GTC. Investors piled in, pumping GTC's stock up to $50, which gave the unprofitable biotech a market value of more than $1 billion.

This wasn't sustainable. Drugmakers gradually improved the traditional way of making biotech proteins -- in cells housed in giant steel vats. Fears of a biotech manufacturing shortage subsided, and one by one, GTC's deep-pocketed partners pulled out. Investors bailed, too, driving GTC's stock down to single-digit territory. "You don't get many swings at the bat in this business," Meade says. "People lost faith."

But Meade himself remained steadfast. He was certain that his goats could correct a major shortcoming of steel vats -- the latter are terrible at churning out complex proteins. Sweetheart's protein, called antithrombin, is one such molecule. And to this day it can only be harvested from donated human blood, which is often in short supply. So, armed with $75.7 million from a stock offering GTC pulled off during the 2000 market boom, the company charged ahead on its own. Executives at GTC's former parent Genzyme Corp. () were impressed that Meade and his team never seemed to get discouraged. "There were enormous challenges. Some people thought they were crazy," says James A. Geraghty, senior vice-president at Genzyme, which still owns 9.6% of GTC's stock. "But crazy is not that different from passionate."

For Meade's old partner, Lonberg, passion has always come in a small package: mice. As a boy, in Arlington, Va., he took two gerbils his grandmother gave him and bred them into a colony of 56. And Lonberg met his scientist wife in a lab at Sloan-Kettering. "We literally met in a mouse house," he says. He remembers the two of them attending a transgenics conference in 1989, where a scientist announced a new technique for knocking out certain genes in mice in order to make them more like people. "Everyone got up and applauded," he says.

That same year, Lonberg joined a company with an ambitious plan to make mice more like men. Scientists in the early 1980s had already figured out how to produce human proteins in mice. But there was one snag: Resulting products would have bits of mouse protein in them, which would make people sick with side effects.

Ensconced at his new company, called GenPharm, he created and then bred two different varieties of gene-modified mice. One had a disabled immune system -- it couldn't produce any of its own antibodies. The other bore the genes that are responsible for making human antibodies. Immunologically speaking, the offspring of these two rodents is more human than rodent. Provoked by a disease-causing agent -- bits of a human tumor, for example -- "their cells produce antibodies in exactly the right form to go into humans," Lonberg says. The antibodies can then be mass-produced as drugs.

Triumph to Turmoil

What should have been a triumph led instead to a period of turmoil. After Lonberg trumpeted his mice at a 1993 conference, rival Cell Genesys () filed suit against GenPharm, claiming theft of trade secrets. GenPharm answered with claims of patent infringement. As the battle dragged on, chewing up the company's scarce capital, GenPharm was forced to pare down from 110 employees to seven. Still, amid general despair, Lonberg was determined to keep the technology alive. "We were so sad to see our good team falling apart," says former co-worker Frank Pieper. "One day Nils took us aside and spent a great deal of time explaining why GenPharm was right and how he was going to make sure we came out as winners." Three years later the parties settled. Cell Genesys (now called Abgenix ()) dropped the theft charge and paid GenPharm $40 million to cross-license its patents.

Once the legal hurdles were cleared, other biotechs started approaching Lonberg. One company that was particularly interested was Medarex, which like hundreds of other biotechs was pursuing antibodies, but without a distinctive technology that could quickly identify and generate the most promising molecules. "We needed a tool," recalls Donald L. Drakeman, CEO of Medarex. "Nils's transgenic mice gave us that." Medarex bought GenPharm in 1997 for $62.2 million in stock. Around this time, the stock market once again began to smile on biotech after a long slump. In March, 2000, Medarex made a smart move, just as GTC had done. It raised $388 million in a stock offering. "This changed Medarex," Lonberg says, by allowing it to build a research facility.

As if to remind Lonberg of his ongoing battle to conquer transgenics, a giant framed photo of a mouse stares down at the scientist in his Milpitas (Calif.) lab. Down the hall, more than 6,000 mice live in pathogen-proof rooms, hidden behind double doors. The scientists who wish to enter must first take showers and don cloth gowns from head to toe, to avoid passing along their germs to the valuable and pampered rodents.

But what if the protected mice were the ones that posed the threat? In Greek mythology, the chimera was a hybrid beast that breathed fire and foreshadowed natural disasters. Some experts take that as a metaphor. They worry that transplanted human genes -- particularly in farm animals -- could "leak" into the food supply, say, if a genetically modified critter were to run off and mate with a non-GM cousin. One of the last things you'd want is a bit of human protein -- one that could make healthy people sick -- turning up in the goat cheese that's sprinkled on top of your salad. Some people call this the "ick" factor. "Even when you have an ethical rationale for doing this work, people find it troubling," says Michigan State

University philosophy professor Paul B. Thompson.

It would help if the regulations meant to prevent nightmarish accidents were actually enforced. Critics blast the Food & Drug Administration and U.S. Agriculture Dept. for failing to tighten regulations that will keep transgenic animals used in health care out of the food supply. Lobbying groups such as the Union of Concerned Scientists (UCS) were dismayed in 2002 when the University of Illinois at Urbana-Champaign sent 386 pigs used in transgenic experiments to slaughter. Only one animal had transgenes, but none of the pigs had been approved by the FDA for commercial use. (None ended up in the food supply.)

To avoid mistakes, GTC has rigorous security protocols. And the farm is hidden on a back road with no signs, to foil animal-rights vigilantes who might want to "liberate" the goats. GTC also designed nibble-proof pens, recognizing that goats have an uncanny ability to open latched doors with their teeth.

Even with such careful measures, there are questions that can't be corralled in electronic fences. As researchers amble further out on biology's frontier, they are forcing society to confront what it means to be human, and to consider whether scientists are changing that very definition by so freely mixing the genes of humans and beasts.

The pioneers of transgenics regard such metaphysical debates as random noise. They argue that a human being isn't defined by individual genes -- most of which are common to all animals. "DNA does not contain the soul or consciousness of a person," Meade declares.

For now, he and Lonberg are focusing on a more urgent matter: persuading regulators that their drugs are safe and effective. Their latest clinical-trial data are compelling, the scientists say, but now they are stuck in a waiting game. In September, European regulators said they needed more time to decide whether to approve goat-made antithrombin -- disappointing investors who had hoped for an October ruling. CEO Geoffrey F. Cox takes the delays in stride. "Making transgenic animals is very clever, but it's not a business," he says. "We've got work to do." If GTC succeeds, he says antithrombin could someday bring in more than $500 million in annual sales.

On a crisp October morning, the normally casual Meade arrives for work dressed in a suit. It's his turn to talk strategy with the board of directors. These days, the discussion is no longer confined to antithrombin. GTC has developed herds to produce other drugs, such as a malaria vaccine and a treatment to shrink solid tumors. Even though Meade is approaching the age when others might prefer golf courses to goat farms, he's too energized by the potential of transgenics to leave it behind. One day, he says, he'd like to make goats that can churn out treatments for infectious diseases such as HIV. "The first 20 years of my life I worked on a farm milking cows," Meade says. "The last 20 years I've spent trying to make [transgenics] work. It all kind of ties in."

As GTC inches toward approval of its first goat-made drug, other companies are showing interest in the technology. In July, Boston-based Merrimack Pharmaceuticals expanded a partnership with GTC, which has developed goats that produce Merrimack's experimental rheumatoid arthritis treatment. "We tried standard production technologies, but they didn't allow us to make it in a commercially viable way," says Robert Mulroy, CEO of Merrimack, who estimates that the drug will address a $4 billion market.

Medarex can also point to some progress. Of the 40 or so experimental drugs that have been derived from humanized mice, 27 come from Medarex' animals and the rest from rival Abgenix. In November, Abgenix announced that a cancer treatment developed with giant Amgen () shrank colon tumors 46% in a late-stage trial. A month later, Amgen scooped up Abgenix for $2.2 billion.

These developments also vindicate Medarex's work in humanized mice -- and it's own close partnership with Amgen. The biotech giant is developing three drugs using Medarex's mice. "It's a highly productive relationship and we anticipate doing further business with Medarex," says Scott Foraker, vice-president of licensing for Amgen. Will Amgen swallow Medarex, too? "We are continually evaluating acquisition and licensing opportunities," he says.

Last September, Pfizer Inc. () took a stake in Medarex and paid $80 million up front for rights to as many as 50 antibodies over the next decade. The deal could ultimately bring Medarex $400 million. And Medarex and Bristol are co-developing a drug to treat metastatic melanoma. To remind himself how far he and his mice have come, Lonberg often pulls up before-and-after X-rays of a patient who received the drug. "He had 31 lung tumors. They're all gone," Lonberg says. The proof won't come until a pivotal, late-stage trial is completed next year, but Bristol is thinking about using the mice on more drugs.

Lonberg and Meade often catch up on the phone and at conferences. The two share a dream of making a drug together -- first generating a life-saving molecule in Lonberg's mice, then mass-producing it in Meade's goats. "Harry and I agree it would be a wonderful collaboration," Lonberg says. And a fitting epilogue to a 20-year history of transgenic beasts and human health care.

By Arlene Weintraub