partmental budgets, Cork says, but many others decided to pass costs along to the researchers who used the buildings.

At the same time, managed care began to squeeze medical school budgets, drying up funds—including money for animal care—that had helped underwrite research. All the while, scientists were producing new and intriguing animal models, driving up the demand for transgenic mice. The result: Animal-care costs rose across the board.

But there is some relief in sight. The National Institutes of Health decided last year to return to an earlier policy and allow universities to include animal research facilities in the indirect cost rate. Cork believes the change will enable many institutions to significantly lower the daily charges for keeping mice. It will take time to reach some researchers, however, because universities renegotiate their indirect cost rate only every 5 years.

Universities are also responding on their own. Nearly 40% of those in a recent Yale survey said they were planning new animal facilities. Baylor College of Medicine in Houston, Texas, for example, is in the final stages of constructing a building designed to house 45,000 mouse cages. The project includes several cost-cutting innovations, says Bob Faith, director of Baylor's Center for Comparative Medicine. For example, Baylor hopes to save on labor costs by using conveyor belts and robots to clean cages. And each cage will have a constant stream of fresh air, which will not only help prevent disease but also reduce the need for fresh bedding. When the new facility is completed, he says, the university will actually lower its daily cage rates, from 31 cents to 26 cents per cage.

It's a step in the right direction, says Weissman, but he thinks more universities need to follow suit. "As long as artificially high prices for mouse care exist," he says, this obstacle, "not the right-to-life or animal-rights [movements], will be the major stumbling block for the transfer of molecular biology to humans."

–GRETCHEN VOGEL

CREDITS: (TOP) J. WYMAN/SYGMA

MOUSE ECONOMY
▶ PROPERTY CLAIMS

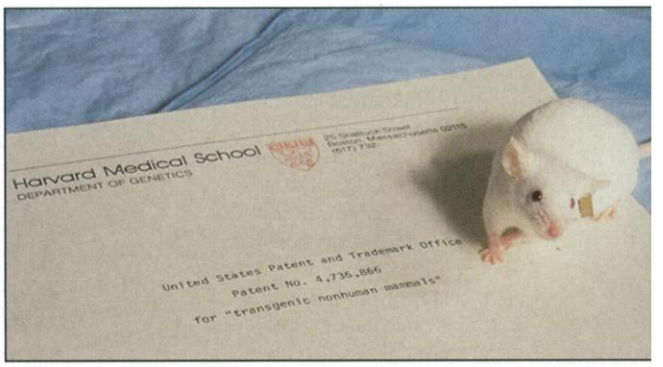
A Deluge of Patents Creates Legal Hassles for Research

Scores of animals have been patented since Harvard claimed the OncoMouse in 1988, but now Merck and NIH are funding patent-free mice

Tom Doetschman, a geneticist who creates exotic strains of mice, says he's beginning to feel "old-fashioned." It's not that his methods are antique; far from it. The animals he breeds for genetic research are in high demand, and his lab at the University of Cincinnati (UCI) has a hard time keeping up with requests. Doetschman has created over 120 knockout (gene-deleted) mice in the past decade, he says, and given them away at cost. Unlike peers who have patented mice with ailments that mimic everything from AIDS to bovine spongiform encephalopathy or "mad cow disease," he has never patented an animal. "I make the mice available to anyone who wants them—no questions asked, no restrictions, nothing," he says. It is this noncommercial attitude that makes Doetschman feel that he's in "an incredible minority."

To Doetschman, the mice are tools to be shared. But to UCI's technology transfer chief, Norman Pollack, they are university property. Pollack understands Doetschman's view: "In practice I don't have a problem with it," he says, partly because engineered mice are not great moneymakers. But in principle, Pollack cannot agree that a faculty member "has the right to give that stuff away." Recently, UCI warned Doetschman that he may be giving away mouse technology patented by others.

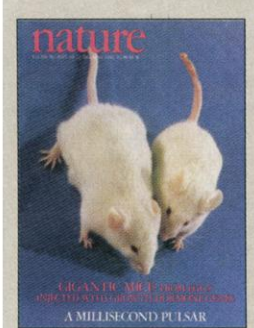
This tension between the creators and the controllers of knockout mice is indicative of a tension throughout the research world. Pollack is one of thousands of university officials empowered under federal law—the Bayh-Dole Act of 1980—to capitalize on federally funded research. Many have leapt at the chance, even if it has meant selling inventions to other researchers. And a new generation of scientists assumes that research tools will be marketed.



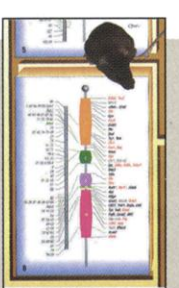
Trendsetter. Harvard's tumor-prone, genetically engineered OncoMouse was the first animal to be patented, in 1988.

But commercialization has brought with it legal problems, including high attorneys' fees. For example, Elan Pharmaceuticals of Dublin, Ireland, is now locked in a bitter fight in U.S. federal court in San Francisco with the Mayo Foundation over rights to a mouse with Alzheimer's symptoms. The tussle has roiled the aging research community for more than a year. And in other fields, scientists seeking custom-engineered mice have complained loudly about the tough licensing conditions and high prices of animals offered by Lexicon Genetics Inc. of

1982 By inserting rat growth hormone gene into a mouse, R. D. Palmiter *et al.* create an extra-large transgenic mouse—and a media splash. The same year, U.S. officials loosen restrictions on DNA cloning in mammals, and the book *Molecular Cloning: A Laboratory Manual* ushers in the era of transgenics.



1983 The SCID mouse, which lacks an immune system, is discovered and becomes a valuable tool for studying human tumors transplanted into mice.



1984 Joseph Nadeau and Ben Taylor's analysis of 83 genes in mice and humans indicates that the mouse genome is an extremely good model for the human genome—but with 150 rearrangements.

1985 Brian Sauer's introduction of the Cre-loxP system for temporal control of transgenic gene expression draws little attention at San Francisco meeting, but 5 years later causes quite a stir when he and DuPont obtain a patent on it.

1985 Harwell's Bruce Cattanach describes genetic imprinting in mice, an epigenetic phenomenon now known to occur in humans as well. Imprinted genes are differentially expressed in the offspring depending on the parental origin of the chromosome.

The Woodlands, Texas. Many scientists, as users of these tools, worry that the tendency to patent every new increment of genetic discovery, including every new mouse, if not resisted, could impede genetic medicine. This has led to a backlash aimed at freeing research tools, especially mice, from commercial red tape. The effort began with individual scientists, was taken up by the National Institutes of Health (NIH), and has been joined by at least one major pharmaceutical company.

Privatizing mammals

Harvard University began the scramble for genetic mouse property in 1988. That's when it obtained the first transgenic animal patent, U.S. patent number 4,736,866, for a "nonhuman eukaryotic animal whose germ cells and somatic cells contain an activated oncogene sequence introduced into the animal, or an ancestor of the animal, at an embryonic stage." Broadly interpreted, the invention by Philip Leder of Harvard and Timothy Stewart of Genentech Inc. in South San Francisco covers any animal genetically engineered to produce tumors. Harvard gave DuPont an exclusive license to distribute the tumor-prone mice but retained the right to use them freely in its own research.

The Harvard mouse fired up a smoldering debate on whether it is right to patent life. The Supreme Court had already ruled in 1980 (*Diamond* v. *Chakrabarty*) that General Electric could patent an oil-digesting bacterium because it had been genetically engineered and was not a product of nature. Church groups and animal rights organizations argued that this policy, if extended, would lead to a devaluation of life. The debate simmered on, and for 4 years, the U.S. Patent and Trademark Office had an unofficial moratorium on animal patents. Then it plunged ahead in 1992, awarding three patents on mice and one on a disease-resistant chicken in a single year. The pace picked up in the 1990s, hitting a peak at 47 patents issued in 1997.

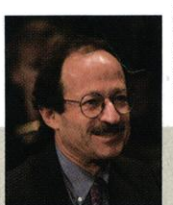
But other patent offices were slow to follow. The European Patent Office (EPO), for example, only received permission in principle to patent animals in 1998, after a 10-year public debate. And in December 1999, an EPO appeals board officially affirmed that patents on plant varieties are permitted—"a beautiful decision," according to assistant U.S. patent commissioner Stephen Kunin. Today, he says, "Europe is operating along U.S. lines," as is Japan. The clear exception is Canada. Its patent office rejected the OncoMouse patent in 1993, and Harvard has been battling ever since to reverse the decision. Harvard, unsuccessful so far, is taking the case to Canada's supreme court this year.

The mouse patenting frenzy didn't upset basic researchers initially. After all, it was they who started it. But many became outraged by the consequences of patenting—particularly by the prices and proprietary restrictions on the use of mice.

One angry response came from a Nobel Prize–winning scientist in oncogene research at the University of California, San Francisco (UCSF): Harold Varmus. He helped organize the mouse malcontents in 1992 and 1993. As Varmus recalls, he and Douglas Hanahan, another UCSF scientist, thought the prices and conditions on use of the *p53* knockout mouse—then supplied by a company called GenPharm, which was acquired by Medarex Inc. in October 1997—were "abhorrent." GenPharm was charging $80 to $150 per mouse and forbidding academics to breed the animals. So, Varmus says, "we went on the warpath." Varmus held an impromptu meeting at the Cold Spring Harbor Laboratory mouse genetics meeting in 1992. About 300 aggrieved scientists showed up and began talking revolution (*Science*, 2 April 1993, p. 23).

This gathering led to a review of restrictions on the sharing of research tools at the U.S. National Academy of Sciences in Washington, D.C., in March 1993. The NIH followed up in 1993, just before Varmus was appointed director, with funding for a new shared mouse facility. Together with private donors, NIH backed the Induced Mutant Resource at The Jackson Laboratory (widely known as "Jax") in Bar Harbor, Maine, a repository of genetically altered mouse strains that was meant to give all researchers equal access to new genetic research tools (see main text and www.jax.org/resources/documents/imr).

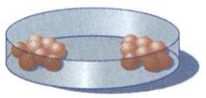
The repository helped. But there were logistical problems—and new legal barriers. Jax couldn't afford to maintain live stocks of all the animals researchers wanted to share; space and resource constraints made it necessary to keep many strains as frozen embryos. The lab began having big headaches over the fine print in conditions that



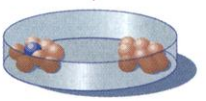
R. KOZAK

CREDITS: (TOP) ILLUSTRATION BY C. CAIN/SOURCE: TACONIC FARMS

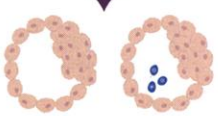
To Make a Knockout Mouse,



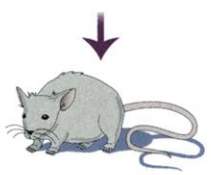
Introduce a designer gene into mouse embryonic stem (ES) cells in culture.



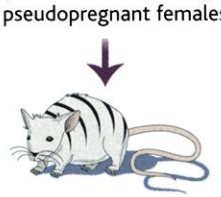
Screen ES cells and select those whose DNA includes the new gene.



Implant selected ES cells into normal mouse embryos, making "chimeras" of mixed heritage.



Implant chimeric embryos in pseudopregnant females.



Females give birth to chimeric offspring, which are bred to verify transmission of the new gene, producing a mutant mouse line.

1987 Mario Capecchi's team at the University of Utah describes a method for making knockout mice, as does Oliver Smithies's group at the University of Wisconsin.

1988 Harvard mouse patented. (See photo, p. 255.)

1990 *Mouse News Letter* becomes a peer-reviewed journal, *Mouse Genome*, marking an increase in formality in the mouse community. In 1997, that journal is folded into *Mammalian Genome*.

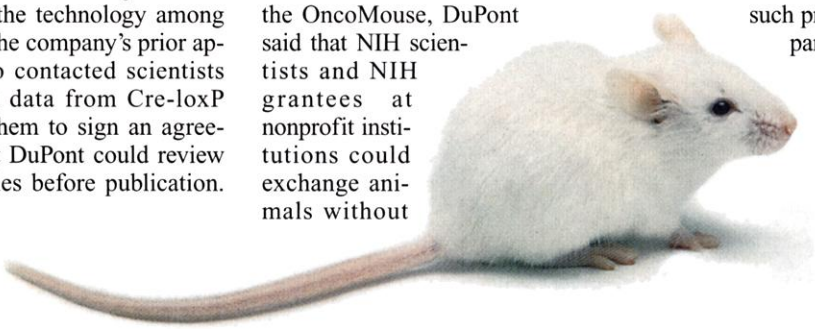
1992 Researchers at MIT and at Baylor College of Medicine in Houston describe a knockout mouse lacking the *p53* tumor-suppressor gene, an instant sensation among researchers.

1992 The U.S. District Court rules that mice, rats, and birds are not excluded from the Animal Welfare Act of 1971. Although the ruling has no immediate impact, activists are now arguing that the decision requires stricter controls on rodent use.

1993 The NIH starts supporting a new repository to make genetically engineered mutant animals widely available to the research community. With molecular geneticist Harold Varmus at the helm, NIH takes even more notice of mice. In 1998, Varmus stimulates a Trans-NIH Mouse Initiative.

were placed on who could or could not receive animals from its repository.

In the mid-1990s, Jax stopped handling mice created with a popular gene-insertion method known as Cre-loxP, which allows the experimenter to set conditions that cause a gene to be turned on or off. In 1990, DuPont had obtained a patent on mice incorporating this method and made itself unpopular by demanding that researchers not share the technology among themselves without the company's prior approval. DuPont also contacted scientists who had published data from Cre-loxP animals and asked them to sign an agreement stipulating that DuPont could review their scientific articles before publication. Furthermore, the company sought "reach-through" rights, or rights to second-generation inventions that might arise from using these animals. "It was a major problem," says David Einhorn, Jax's legal counsel: "Nobody was able to exchange materials" freely any longer.



Coat of many colors. Coat color can identify mouse strains, but this white mouse might be anything from the best selling BALB/c (from $8) to the hardy Swiss Webster (from $2).

Varmus again intervened, this time from a position of greater influence. As NIH director, he refused in 1997 to sign an agreement with DuPont on the Cre-loxP mouse on behalf of NIH, making it impossible for thousands of intramural staffers at the NIH campus in Bethesda, Maryland, to get access to the technology. It was a nuisance for them and an embarrassment for DuPont, but it produced a change. Varmus wrote to DuPont that the company's restrictive terms could "seriously impede further basic research and thwart the development of future technologies that will benefit the public." After a year of negotiation, DuPont made concessions: The company did away with demands for prepublication review for research-only uses of Cre-loxP mice, loosened up animal sharing provisions, and dropped the reach-through property claims for NIH-based scientists (*Science*, 28 August 1998, p. 1261).

In December 1999, DuPont reached another agreement with NIH on mouse rights—again through the intervention of Varmus. After hearing a plea from Varmus that it relax its rules for use of the OncoMouse, DuPont said that NIH scientists and NIH grantees at nonprofit institutions could exchange animals without directly involving the company (*Science*, 28 January, p. 567).

Other initiatives now in the works could soon make it easier for all researchers to get access to patent-free transgenic mice. The pharmaceutical firm Merck & Co. Inc. of Whitehouse Station, New Jersey, announced plans last year to spend $8 million to have Lexicon Genetics create 150 patent-free transgenic mice to be made available at cost through The Jackson Laboratory. Fourteen of these model transgenics have been created, 61 more are in the pipeline, and the rest will be designated for production soon by a panel of outside experts, says Thomas Caskey, the recently retired chief of Merck's Genome Research Institute who conceived the project. Caskey says the mice will be shared without patent or use restrictions. He explains that Merck wants to give scientists new tools that have no legal hassles attached. But Merck is not motivated entirely by altruism: Minimizing such property claims will benefit the company as well.

In a related effort, NIH has committed itself to a multistage "mouse initiative" that will pay to sequence the mouse genome, develop thousands of new model transgenic animals, and characterize the animals' phenotypes. As a policy matter, NIH leaders will insist that people who accept grants to do this work not file patents. NIH rarely takes this step, says Maria Freire, director of NIH's Office of Technology Transfer, but in this case it will invoke an "exceptional circumstances" clause of the Bayh-Dole Act that allows the government to insist that the animals it produces will be patent-free.

If these new projects pay off, researchers will have access to thousands of new mouse models that have no intellectual property strings attached. And Doetschman may discover that, rather than being old-fashioned, he was ahead of the times.

–ELIOT MARSHALL

Sequencing the Mouse Genome

The United States has awarded $130 million through 2001 to begin sequencing the mouse genome, and 10 U.S. centers have taken on the task of developing maps, generating some whole-genome shotgun sequence data, and sequencing biologically important pieces of DNA. The U.K.'s MRC is providing funds for the sequencing of 50 million bases of the mouse genome. In February, GenBank had about 1.2% of this 3-billion-base genome in-house, more than half of that as a rough draft. The goal is to have a rough draft by 2003 and a finished genome by 2005. (For an update on the sequence, see ray.nlm.nih.gov/genome/seq/MmHome.html) In April, Celera Genomics began sequencing the mouse on its own.

1996 Eric Lander's group at MIT publishes a map of the mouse genome with more than 7000 markers.

1997 Merck Genome Research Institute funds the creation of 150 new mutant mouse types at Lexicon Genetics for restriction-free distribution to the basic research community.

1998 Ryuzo Yanagimachi's team in Hawaii clones mice from somatic cells by using nuclear transfer and discovers how to freeze-dry sperm for future use.

1998 Researchers in Munich, the United Kingdom, and, later, Australia, launch large-scale ENU mutagenesis projects to provide the research community with thousands of new mutants by 2001.

1999 In Japan, Yoshihide Hayashizaki's group determines the first set of full-length mouse complementary DNAs, 20,000 of which have been put on microarrays for analyses of gene expression. NIH eventually gains access to the full database for intramural scientists; others hope to do the same.

2000 Mouse genomics takes off.

–ELIZABETH PENNISI

CREDIT: (TOP) TACONIC FARMS