MOUSE ECONOMY
▶ACADEMIC FACILITIES

The Mouse House as a Recruiting Tool

Talent hunters at major research centers are luring scientists by promising to build state-of-the-art animal facilities and reduce cage charges

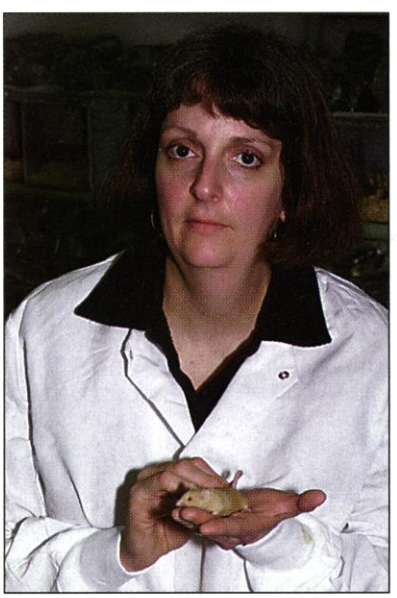
Although several universities have tried to recruit developmental neuroscientist Susan Ackerman, she has rebuffed them all. They've offered her generous salaries and state-of-the-art labs, but they can't match the most important perk: the unusually low cost of caring for mice at her current institution, The Jackson Laboratory (commonly known as "Jax") in Bar Harbor, Maine. The cost of mouse care at one university, she says, "was going to be far more than my salary." This would have limited her ability to create the genetically altered animals she uses to study how the nervous system is wired during development. Having more animals means you can test more ideas, and Ackerman says, "being at Jax allows me to do more risky experiments."

Ackerman is not alone in sizing up jobs according to the mouse factor. Mouse geneticist John Mercer says he made his first job decision almost solely on mouse costs. The two offers he was considering were similar, he says, except for charges at the animal-care facility. The University of Texas Southwestern Medical Center (UT Southwestern) in Dallas charged researchers 48 cents per day per cage (a cage holds up to five mice), whereas the other university charged 26 cents per day per mouse. That made his decision simple: He accepted the job at UT Southwestern.

Within a year, however, Mercer's careful analysis went out the window as UT Southwestern's costs doubled, and he began comparing facilities again. In 1995, Mercer moved to his current job at the McLaughlin Research Institute in Great Falls, Montana, where he pays as little as 18 cents per cage per day. "It's like getting a grant that can never be taken away," he says. The bargain rates have allowed him to try more frequent and more daring experiments, and at McLaughlin he's created several useful knockout mice.

For many scientists, the subject of animal costs may never come up, but for geneticists, developmental biologists, immunologists, neuroscientists, and others who use mice as models, it is a major concern. Indeed, a recent committee at the National Academy of Sciences listed inadequate funding for mouse care as one of the top threats to immunology research in the United States.

Developmental biologist Brigid Hogan of Vanderbilt University in Nashville, Tennessee, says she uses the bulk of her Howard Hughes Medical Institute funding to pay for animal care. For her, a generous animal budget is essential. To help colleagues track the issue, she set up a Web site that compares mouse-care costs at several institutions,* as reported by researchers. But some have done more than report on their troubles.



Empowered. Low-cost animal care allows Susan Ackerman to try experiments at Jax she couldn't afford elsewhere.

CREDITS: (TOP) S. SHORT/THE JACKSON LABORATORY

At several universities, frustrated scientists whose mouse-care bills have skyrocketed have banded together to demand that administrators give an explanation. Some found that they were subsidizing research on larger, more expensive animals, says immunologist Irving Weissman of Stanford University. Several years ago, he and several colleagues asked Stanford to account for the actual costs of keeping each type of animal. Once the results were in, he says, the university lowered mouse charges more than a third and raised charges for other animals.

"Before the rate change at Stanford, I had to raise $800,000 to $1 million a year to keep the 2000 to 3000 cages I believe I need for the research I do," Weissman says. "That meant I was spending most of my time writing grants." Other researchers, he says, had to decide between giving up mouse research or leaving Stanford.

A combination of factors drove animal costs dramatically higher over the last few years, says Linda Cork, head of Stanford's Department of Comparative Medicine, which oversees animal care. The main problem was the federal government's decision to classify animal-care buildings as "specialized facilities," as they were used by only a subset of researchers. This meant that universities could no longer pay for their construction or maintenance with the "indirect cost" allowance that pays for labs, libraries, and infrastructure. Institutions compensated in various ways. Some found the funds in de-

*www.mc.vanderbilt.edu/vumcdept/cellbio/hogan/html/cost.html

1976 Rudolf Jaenisch, now at the Massachusetts Institute of Technology (MIT), uses a virus to transfer DNA to mouse embryos, the first report of success in creating a transgenic mouse.

1978 François Bonhomme in France breeds two species, *Mus spretus* and *Mus musculus*, enabling geneticists to build the first comprehensive linkage map of the mouse genome. This makes the mouse a "formidably efficient system for genome mapping," notes mouse geneticist Phil Avner.

1979 William Russell of Oak Ridge proves that the chemical ethylnitrosourea (ENU) is effective in generating mouse mutations. Oak Ridge and other labs that had been studying radiation effects begin producing ENU mutants.

1979–80 Using microinjection to insert DNA into a mouse egg, six labs independently demonstrate that foreign DNA can be put into the mouse genome.

THE JACKSON LABORATORY

1981 Martin Evans and Matt Kaufman in Cambridge, U.K., isolate mouse embryonic stem cells, which can develop into the full range of tissues.

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

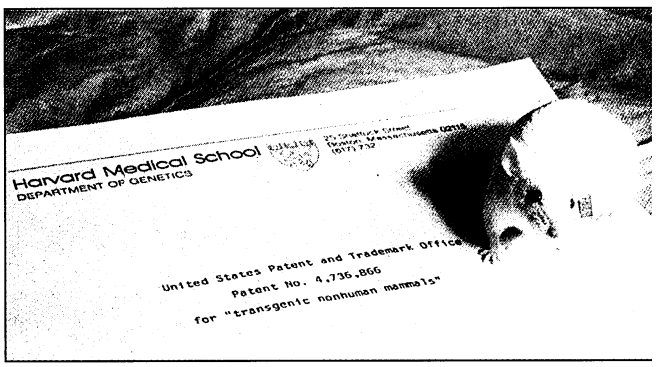
A Deluge of Patents Creates Legal Hassles for Research

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.

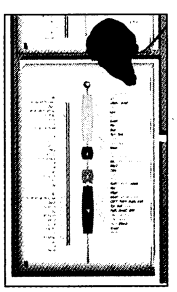


Trendsetter. Harvard's tumor-prone, genetically engineered OncoMouse was the first animal to be patented, in 1988.

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.