INTELLECTUAL PROPERTY

Researchers Win Decision On Knockout Mouse Pricing

Over the past few years, mice with one or more genes "knocked out" have become one of the hottest commodities in genetics. That's because they provide a relatively easy way to determine the biological function of individual genes: Inactivate the genes and see what happens to the animals. But the mice have also become a visible symbol of a much broader problem that has troubled biology in recent years: the fear that commercialism is impeding the free flow of research materials among scientists. Researchers eager to work with engineered animals, cloned genes (see box), and novel reagents often find themselves confronted by a thicket of patents, high fees, and restrictions on how they can use the materials.

In fact, the whole issue of restrictions on research materials has become so troubling that the National Academy of Sciences (NAS) held a meeting last week to discuss ways to combat it. A partial solution to the knockout mouse problem was announced at the meeting, and a week later the National Institutes of Health (NIH) unveiled a plan that could ease researchers' access to other genetically engineered mice. The broader issue of how to ensure that other such patented research materials are shared freely was, however, far from resolved.

The knockout mouse saga began when some researchers who had bred knockouts were inundated with requests from colleagues eager to work with the animals. Since the researchers were reluctant to get into the mouse breeding business, their universities awarded companies, including GenPharm International, a biotech firm in Mountain View, California, licenses to market the animals. This became a problem, however, when GenPharm announced its pricing policies (*Science*, 5 June 1992, p. 1393).

GENPHARM

Priced to go. GenPharm responded to concerns by cutting the price of its knockout mice.

It was bad enough, researchers complained, that GenPharm charged from $80 to $150 per mouse—as much as 10 times the price charged by nonprofit mouse breeders such as the Jackson Laboratories of Bar Harbor, Maine. But the company also prohibited labs from breeding the mice, which effectively forced researchers to pay GenPharm for every mouse they used. That can quickly amount to thousands of dollars per lab—a lot of money for a resource that researchers are used to getting for free. The grumbling reached insurrection proportions after a meeting at Cold Spring Harbor Laboratory last August, when some 300 researchers stayed for an unscheduled afternoon session on GenPharm's pricing policy led by Harold Varmus, a Nobel Prize–winning virologist at the University of California, San Francisco.

But now the mouse community that roared seems to have won the battle, if not the war. At last week's NAS meeting, GenPharm president David Winter revealed that the company recently decided to allow researchers to breed as many mice as they want for an annual fee of $1,000 and the initial purchase of a breeding pair. One-time breeding, to see if the pups have birth defects, for example, will be free. And that, says Massachusetts Institute of Technology geneticist Tyler Jacks, is a victory, although he'd rather see no breeding fee at all. The community's lobbying on the issue "is a success story, to the extent that it's made an objectionable policy much more palatable," he says. "But I'm still not convinced we've reached the optimal solution."

For most of the NAS meeting, researchers, lawyers, government officials, and industry representatives brainstormed about just what an optimal solution might be. As it turned out, it was easier to define what it is not: the now-notorious policy covering the cancer-susceptible oncomouse patented by Harvard University in 1988 and licensed to Du Pont. Du Pont came up with a pricing policy that contains a "reach-through" clause requiring anyone who develops a product through the use of the mouse, or any derivative strain, to pay royalties to Du Pont. As a result, said Varmus, many scientists now sim-

A New Model for Gene Patents?

When the National Institutes of Health (NIH) filed for patents on thousands of gene fragments in 1991, it created a furor because it was attempting to assert broad rights to sequences whose functions were unknown. The cDNA fragments NIH researchers had discovered were simply short stretches of presumably expressed genes, yet the patent the agency was seeking would give it rights both to the full genes themselves and to all their possible future uses. If NIH prevailed, researchers argued, it would potentially discourage further work on those genes. Now the head of the genome project at the Department of Energy (DOE)—NIH's partner in the program—has proposed an alternative approach to gene patenting.

At a meeting last week of a congressional Office of Technology Assessment panel that is preparing a report on this issue, DOE's David Galas revealed that University of Washington genome researcher Leroy Hood is preparing to file a patent application that could serve as a model for such patents in the future. Hood's team has been sequencing the genes encoding the beta chain of the human T cell receptor. Mutations in the T cell receptor genes may lead to any of a number of autoimmune diseases, including rheumatoid arthritis and multiple sclerosis. A broad patent on the genes could therefore conceivably cover not only techniques for diagnosing autoimmune diseases but also of therapies for the conditions, and indeed anything involving T cell activity.

But Hood's patent application won't make such broad claims. Instead, Hood, with DOE's support, will not seek to patent the genes but will claim only "the specific uses of developing the diagnostic and therapeutic tools for dealing with specific autoimmune diseases," Galas said. By restricting patents just to known uses, Galas argued, the problems of gene "ownership" are neatly avoided.

Reid Adler, the NIH technology transfer director who orchestrated NIH's cDNA patent filing, thinks Galas' proposal "is an interesting idea," even though it would rule out patenting uncharacterized cDNA fragments. To be widely adopted, it would probably need to be made law by Congress, but he notes that there is some precedent for that: "Congress created special rules for the protection of computer chip masks and plant varieties," he says. "Certainly it is worth considering whether gene sequences deserve a special form of protection, too."

–C.A.

ply breed their own oncomice, effectively boycotting the company.

Underlying the overall problem, researchers at the conference complained, is the fact that eager university technology-transfer offices seek to patent mice and collect royalties on them. Even though the market for genetically altered research mice is often just a few hundred animals and few of the animals make money today, universities aren't willing to forego full patent protections on what may turn out to be the breakthrough mouse of tomorrow. But Jackson Laboratory's Kenneth Paigen disagrees with this policy. "I think the concept that we have to always protect intellectual property rights is mistaken," he said at the meeting.

Some of the other meeting participants agreed, suggesting that there should be a special clause in NIH grants requiring NIH-funded scientists to share the fruits of their research labors freely with other federally funded labs. Others proposed that Congress should pass a "research exemption" to the U.S. patent law, much like the exemption that exists in European patent law. But by far the most popular suggestion was for the creation of a federally funded transgenic mouse repository, preferably at a nonprofit institution such as Jackson Lab, which has strong ties with the research community. Such a facility could both maintain strains that are only occasionally used, and sell mice at cost without burdensome licensing requirements. One of the reasons such a facility doesn't exist now is that Jackson Lab is reluctant to accept mice with restrictions on commercial use and will not accept mice at all if they have any restrictions on research use. That rules out many transgenics.

Varmus and others suggested a possible way around this problem, however: NIH could award a special federal contract for a repository, so that mice sent to it would be essentially donated to the government, to be distributed freely. And, indeed, that appears to be just what will happen. As *Science* went to press, NIH was preparing to release a request for proposals for a transgenic rodent and rabbit facility that would distribute frozen embryos to researchers at far less than cost. Start-up grants for the facility will total $1 million and will be awarded by 30 September.

NIH deputy director Lance Liotta warned that there is one hitch to such a facility: It hinges on the mouse patent holders' willingness to relinquish control of their mice, at least within the research community. With the transgenic research market as small as it is, that may not be a problem for most patent holders today. But when the next breakthrough research tool is developed, depending on the good will of the patent holder to share the resource with other researchers may not be enough.

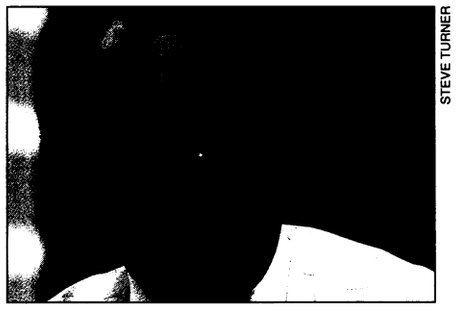
–Christopher Anderson

SCIENCE FUNDING

NSF Wins, NIH Loses in Clinton's 1994 Budget

Next week President Clinton will ask Congress to give the National Science Foundation (NSF) one of the biggest 1-year increases in its history—a $446 million, 16% increase over this year's congressional appropriation. If Congress goes along—a big "if" in a year in which legislators are obsessed with the deficit—NSF's budget would climb to $3.18 billion in fiscal year 1994. But, while NSF officials are jubilant, you won't see many smiles at the National Institutes of Health (NIH). Documents obtained by *Science* indicate that Clinton will ask for only a 3.3% cost-of-living increase for the agency. And most of the additional money is earmarked for AIDS, breast cancer, and research on the health problems of women and minorities. Most of NIH's other programs, including nine of 16 institutes, would be cut—even before inflation is taken into account.

The Clinton Administration's complete budget request will not be released until next week, but NSF went public with its figures on 29 March to allow director Walter Massey to appear at appropriations hearings before he leaves to become provost of the University of California late this week. Massey faced few hard questions, but it may be a little early to start celebrating. In February, Clinton asked for a $207 million supplement to NSF's 1993 funding, and that surprise request may work against the agency in Congress. Representative Louis Stokes (D–OH), the new chairman of the appropriations committee that sets NSF's funding, told Massey last week that those agencies that did the best in 1993 supplemental funding would be the first to face cuts in 1994. "That suggests we're going to have a tough time," in the upcoming appropriations process, says Ray Bye, NSF's legislative affairs director.



STEVE TURNER

Swan song. Walter Massey is departing after requesting a 16% increase for NSF.

NIH can expect rough going, too. Officials estimate that the 1994 request, if enacted unchanged, would mean that NIH would fund about 500 fewer grants in 1994 than this year. And this year's total—5634 new and competing grants—was some 1100 grants fewer than 1992. "It's clear that the Administration has left biomedical research out of the equation of reinvesting in America," says Richard Fuller of the Am-

NATIONAL INSTITUTES OF HEALTH

Institute	1993 Appropriated	1994 Request	Percent Change
Cancer	1961	2142	8.1
Heart, Lung, and Blood	1215	1198	-1.3
Dental	161	163	1.1
Diabetes, Digestive & Kidney Disease	681	677	-0.6
Alcohol Abuse and Alcoholism	177	174	-1.7
Drug Abuse	404	407	0.8
Mental Health	584	576	-1.3
Neurological Disorders and Stroke	600	590	-1.7
Allergy and Infectious Diseases	979	1066	8.8
General Medical Science	833	833	0.0
Child Health and Development	528	542	2.8
Eye	276	272	-1.4
Environmental Health Science	251	261	4.0
Aging	400	394	-1.4
Arthritis, Musculoskeletal & Skin Diseases	212	210	-1.0
Deafness & Other Communications Disorders	155	153	-1.1
Center for Research Resources	312	328	4.9
Center for Nursing Research	48	49	1.8
Center for Human Genome Research	106	135	26.6
Fogarty International Center	20	20	0.0
Library of Medicine	104	133	26.7
Office of the Director	190	235	23.4
Buildings and Facilities	109	109	0.0
Total NIH	**10,327**	**10,668**	**3.3**