including the use of sweat lodges, guided visions, and massage therapy. A retired computer engineer, E. Patrick Curry, got so upset when he learned that the nearby university was supporting someone who wrote that he had treated cancer with massage that he went on the offensive, writing a scathing critique in Sampson's journal. In response, the university began an investigation; Mehl-Madrona agreed to resign last year. This year, he accepted a new medical director position—at the Center for Health and Healing at the Beth Israel Medical Center in New York City.

The struggle for control of the medical school agenda isn't going away. It surfaced again recently in Washington, D.C., where both the traditionalists and the new alternative medicine practitioners have allies. The Senate appropriations subcommittee that funds the National Institutes of Health (NIH), chaired by Senator Arlen Specter (R–PA), invited Weil to testify on 28 March about the need to increase funding for programs like his. Weil praised the chair and ranking member, Tom Harkin (D–IA), for instructing the NIH to pay more attention to training physicians in integrative medicine. Noting that NIH had "refused to respond" to the Senate's encouragement, Weil requested that the senators appropriate "specific funds ... to achieve this education and clinical training objective."

–ELIOT MARSHALL

MOUSE GENETICS

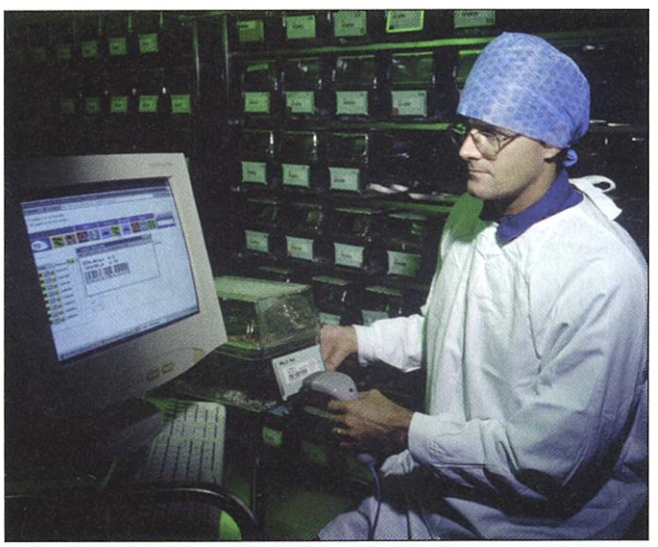
Australian 'Ranch' Gears Up to Mass-Produce Mutant Mice

Chris Goodnow uses the latest technology and sequencing data to advance research on recessive mutations that cause adult-onset diseases

CANBERRA, AUSTRALIA—The overpowering smell of mouse is a sure sign that all is well at the mouse ranch here at the Australian National University (ANU). The aroma means that the state-of-the-art ventilation system is working, protecting the animals from infection by vigilantly flushing would-be mouse germs out of the 20 small rooms where they are caged. Back in the airlock, a cadre of 30 attendants are in various stages of showering, gowning, masking, and slippering as they prepare to care for the 30,000 animals housed on the floor. And while the researchers at the John Curtin School of Medical Research swelter as they toil in aging labs, the mice live in air-conditioned luxury, snug in the Kleenex nests they build to soften their wire cages.

Kid-glove treatment, to be sure, but understandable given the expectations placed on them by their keeper, Chris Goodnow. Goodnow, an ANU immunologist, sees the mice as the key to relieving one of the greatest bottlenecks facing biologists: how to assign functions to the glut of human genes about to appear on computer screens around the world as the Human Genome Project nears completion. The plan is to generate mutants on a massive scale—10,000 mice in 6-month batches for the next 5 years—at an estimated cost of $500,000 a year. "This is big science," says University of California, San Francisco (UCSF), cancer biologist Doug Hanahan. Among the 30,000 are mice with cancer, heart defects, dwarfism, obesity, and immune defects, all resulting from random mutations introduced into their genes. Isolating the responsible genes may allow researchers to find their function. And because mouse genes are thought to do the same thing as their human counterparts, scientists hope to translate the knowledge into clinical studies.

Defying dire predictions from respected colleagues, Goodnow's operation is moving ahead and winning plaudits. "Biology's great strength is science of this sort; it will bring tremendous riches," says Yale University geneticist Richard Flavell. "It's the wave of the future," declares Hanahan.



Chief mouseketeer. Chris Goodnow uses bar codes and specialized software to track his 30,000 mice.

CREDIT: JOHN CURTIN SCHOOL OF MEDICAL RESEARCH/ANU

Goodnow, 40, has been a mouse maître d' for a long time, although not until recently on such a grand scale. Raised in the United States, he migrated to Australia with his family at the age of 12. During graduate study at Sydney University, he developed a strain of transgenic mice whose antibody-secreting B cells, rather than producing a repertoire of millions, were all tricked into producing a single self-reactive antibody. Immunologists used transgenic mice like these to see, for the first time, how self-reactive B cells were either culled or frozen into inactivity at various points of their life cycle.

After arriving at Stanford in 1990, Goodnow used the mice as a microscope to see what goes wrong in mouse mutants that are models of autoimmune diseases. "It's only by understanding things at the level of which cells, what stage, and what biochemical pathway that we can figure out why some people are predisposed to making antibodies that attack their own cells," explains Goodnow. But by 1996, Goodnow had run out of mutants. "The key question was, 'How were we going to move forward?' "

The answer, he concluded, was to delay his research on autoimmunity and instead set up a large-scale operation to create new mutant mice, much like those that fruit fly geneticists have used for decades to identify new genes. Indeed, mouse geneticists have long dreamt of having that capability, but some formidable obstacles stood in the way. Producing the mutations was easy. The chemical, ethylnitrosourea (ENU), has shown phenomenal mutation rates in mouse sperm cells, some 10-fold over what had been achieved in flies. Even so, tens of thousands of mice would be needed to ensure that the random mutations would eventually cover every gene. And housing and caring for that many mice would require a new lab and lots of steady funding.

Beyond the cost considerations were technical problems. Once an interesting mutation is found in fruit flies, it is mapped to a rough location on the chromosome by crossing the fly to a strain that carries chromosomal markers. But mapping mutations in the mouse is a slow and imperfect art, taking

3 months per cross. And once researchers get the approximate location of their mutant gene, they still have to pinpoint its identity. In the past, that could take 20 people working a year to do. They would have to move incrementally along the chromosome interval where the gene was located, sequencing every adjacent chunk of DNA to see if it differed between mutant and normal animals.

Recent advances in gene mapping and sequencing have made the hunt for mutant genes in mice much simpler. One such development came in 1996, when Eric Lander's group at the Whitehead Institute for Biomedical Research in Cambridge, Massachusetts, provided 7000 new landmarks for the mouse genome. Those landmarks make it possible to map new mutations to within a region of some 50 genes. And the imminent availability of the sequence of the entire human genome means that much of the final work of finding the mutant gene could be done by computer.

Goodnow could also make use of the virtual correspondence over short lengths of the genome between human and mouse genes, which are like a pack of cards that have been shuffled differently. Once a mutation is mapped to within a 50-gene chunk of the mouse chromosome, for example, the researcher need only call up the sequences of these 50 genes from the human database. Within days, all 50 of those genes in normal and mutant mice can be resequenced to see which gene is defective. "I could see that it was no longer going to be necessary to have a big physical mapping lab," he says.

To make full use of these technological advances, Goodnow needed access to a huge mouse-rearing facility. With land and labor costs in Stanford prohibitively expensive, Goodnow realized that he was going to have to look elsewhere. ANU was an attractive choice, especially because the costs of rearing mice are about one-seventh those at Stanford. In addition to offering him a job, ANU's John Curtin School joined with the Australian Cancer Research Foundation to put up $1.5 million for a state-of-the-art screening facility.

After taking 2 years to set up his lab, Goodnow has begun to turn the crank and start churning out mutants. Every 6 months, he injects some 100 males with ENU and screens the offspring for defects. The first two batches have already produced 60 mutants with immune system defects, cancer, skeletal abnormalities, obesity, and dwarfism. Over the next 5 years he hopes to bombard every gene in the mouse.

The results so far have laid to rest some concerns about whether Goodnow's strategy would work. The major concern related to his attempting the most ambitious type of screen, that for recessive mutations affecting adult mice. Goodnow wanted to screen for recessive mutations because these usually mean the gene has lost its activity and, thus, can provide straightforward information about its function. By contrast, dominant mutations often result from a gene gaining a new function that may bear little relation to the gene's normal activity.

Mouse Main Street. A troupe of technicians tends to the needs of the mutant mice housed on the third floor of a screening facility at the Australian National University.

Unfortunately, the logistics of a recessive screen are far more tortuous than those for dominants. Recessive mutations only show up when both paternal and maternal versions of the gene are affected. So rather than being all over in one generation, as in a screen for dominant mutations, Goodnow's screen had to wait for three generations of father-daughter matings just to breed double recessive offspring—in this mating scheme, only one-eighth of the progeny.

In addition, the types of mutations Goodnow was after, those affecting the maturation of the immune system, are best studied in adult mice. Previous attempts to make mice with a double dose of mutant chromosomes had not required the mice to reach adulthood, and skeptics doubted whether such a mouse could survive. But Goodnow has had little trouble producing and breeding mice that carry double copies of mutant chromosomes.

Finally, ENU is such a powerful mutagen that each animal produced from the treated sperm carries numerous mutations. The scientists didn't know if the clustered mutations would interfere with each other and make it impossible to identify the effect of individual mutations. But although each pedigree, by his estimate, carries about 100 mutations, the effects of the mutations appear to be decipherable. "We get simple Mendelian traits almost always," he says. "We can lay to rest the concern of getting horribly complicated mice."

The next big step is to keep the operation humming. In particular, the ANU team has to deal with the logistical nightmare of keeping track of thousands of little black mice for several generations. During the first couple of years of operation, the ANU team used paper records to keep track of all these animals. That was a dangerous situation for Goodnow, a numerical dyslexic. "A typical 3% error could destroy the screen," he says. Now, the researchers have switched to a new automated system, devised by computer programmer Greg Quinn, that uses bar codes on the cages to keep track of the animals in much the way supermarkets keep track of their thousands of products.

Now that Goodnow has proved that a large-scale screening operation can work, other researchers have been quick to share the booty. Hematologists Warren Alexander and Doug Hilton, at the Walter and Eliza Hall Institute in Melbourne, are studying blood cell development using mutants with defects affecting the formation of red blood cells, the clot-forming platelets, and white blood cells known as granulocytes. As part of a project funded by the U.S. National Cancer Institute, UCSF's Hanahan is waiting for delivery of mutants that affect the course of skin and cervical cancers induced in mice by human papilloma virus.

These formal collaborations are only a start, says Goodnow, who plans to make the mutant mice available to the general research community. In an effort to facilitate such collaborations, Goodnow has devised a simple materials transfer agreement that gives ANU 10% of the revenues from any commercially valuable mutant after the recipient university deducts its costs.

With the ANU screen providing a proof of principle, labs all over the world are gearing up to try recessive screens. "This is just what we hoped for," says Goodnow. "People told me I'd end up 2 years down the line with nothing but a lot of mice. Now when anyone [else] encounters resistance, they can point to us!" —ELIZABETH FINKEL

Elizabeth Finkel writes from Melbourne.

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