The real deal

The human genome fired the public's imagination. But for many geneticists, the genome of their main experimental mammal — the mouse — is even more exciting. *Nature*'s reporters sample the buzz in three leading laboratories.

J. SUMMERS/NCI-FREDERICK

Labour saviour: the mouse genome sequence will allow Neal Copeland and Nancy Jenkins to spend more of their time on functional analysis.

On the double

Nancy Jenkins and Neal Copeland are very much a team. Married for 22 years, they oversee the National Cancer Institute's Mouse Cancer Genetics Program in Frederick, Maryland. They have been co-authors on every paper they have published over the past two decades, many introducing new mouse models for studying cancer and other important human diseases.

Copeland and Jenkins also have a habit of finishing one another's sentences that helps to convey a sense of breathless excitement about the mouse genome. Their interest in mouse genetics began in 1980 when, as young molecular biologists, they joined the world's pre-eminent mouse lab, the Jackson Laboratory in Bar Harbor, Maine. "We decided to go there so that we could fuse molecular biology with mouse genetics to try to answer questions that would not be possible with either technology alone…," Copeland begins, "…and it turned out to be a moment that will never be recaptured," finishes Jenkins.

While Jenkins and Copeland look back fondly on those early days, the mouse genome sequence (see page 520) is accelerating their research in ways that make their past achievements seem pedestrian. Back in the 1980s, if Jenkins and Copeland were interested in investigating a spontaneous mutation presented at the Jackson Lab's weekly 'Mutant Mouse Circus', it was a laborious process. Identifying the gene involved meant crossing about 1,000 mice to map it to a stretch of chromosome bearing about 20 candidate genes. From there, a postdoc would have to sequence all of them in both normal and mutant mice to find out which was mutated.

"It used to be one postdoc project per mutation…," says Jenkins, "…and it was like looking for a needle in a haystack," adds Copeland. But since the mouse genome sequence became available in May (at www.ensembl.org/Mus_musculus), researchers can simply go to the database after the initial breeding experiments and look up all the genes in the relevant chromosomal region. By knowing from their sequences what types of proteins most of them encode, they can choose one or two that look most promising to search for the mutation.

"It took us 15 years to get 10 possible cancer genes before we had the sequence," says Copeland. "And it took us a few months to get 130 genes once we had the sequence." What's more, Jenkins points out, going back and forth between the mouse and human genomes will help to target related human genes that could be candidates for drug development.

The pair's eyes light up at the mention of the companion to the draft mouse genome: the set of full-length mouse complementary DNA (cDNA) sequences, representing an inventory of the sequences of expressed genes, produced by a team at the Institute of Physical and Chemical Research (RIKEN) Genomic Sciences Center in Yokohama, Japan (see page 563). This library of some 61,000 cDNAs gives researchers a functional copy of almost every mouse gene that can be easily manipulated in the lab — making it much easier to create gene-knockout mice, for example.

It will also erase time spent on deciphering gene sequence and structure. "We are skipping to an era that frees us from all the mechanical stuff that took up most of a mouse geneticist's time so that we can go straight to the functional part..." says Copeland, "...and the functional part is truly the fun part!" adds Jenkins. ■

Kendall Powell

http://web.ncifcrf.gov/research/mcgp/default.asp

Talkin' about regeneration

Newts do it, so why don't we? That's the question that dominates the thoughts of Nadia Rosenthal, head of the European Molecular Biology Laboratory (EMBL) Mouse Biology Programme at Monterotondo, near Rome.

A newt can regrow a severed leg in its entirety, whereas mammals can only slowly patch up small-scale damage, with the production of low-quality scar tissue. But Rosenthal suspects that the newt's healing powers also lie hidden in mammalian genomes, and might be reawakened by appropriate tweaking. So for her, the mouse genome offers the promise of contributing to the emerging revolution in regenerative medicine. "My research remains hypothesis-driven," says Rosenthal, "but the sequencing of the mouse genome has opened a new world."

Rosenthal has already generated some intriguing results. She has, for example, shown that transgenic mice that overexpress the growth factor IGF-1 in their muscles develop Arnold Schwarzenegger-style biceps, due in part to an influx of stem cells from bone marrow that develop into new muscle cells. Along with other research groups, she has also found that IGF-1 can slow or reverse muscle loss in mouse models of degenerative diseases such as muscular dystrophy.

Rosenthal is now probing exactly how IGF-1 promotes regeneration. How does it

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Nadia Rosenthal (above) says the mouse genome has "opened a new world". Monica Justice has already used it to pinpoint recessive mutations.

cause stem cells to settle in muscle, and persuade them to differentiate into muscle cells? What genes are switched on and off as the stem cells evolve through different levels of commitment into muscle? To investigate, Rosenthal is using DNA microarrays to study the expression of hundreds of genes at a time. "But biology is more complicated than just finding out what genes are active at a particular stage," she says. "We want to know all about the genes that regulate the gene, its regulators and their switches — and for this, only full genome information will help."

In future, comparing the mouse genome with those of other species will be revealing, Rosenthal believes. "We can learn a lot by looking at the same genes in genomes of other species that are either bad or good regenerators," she says. She also hopes to work with a remarkable mouse strain called MRL, bred at the Wistar Institute in Philadelphia, which can repair damage to its heart without scarring.

Rosenthal joined EMBL's Italian outpost from Harvard University last year for the opportunity to work with the five other groups applying genetic and genomic approaches to the study of mouse biology. Her colleagues are similarly enthused about the opportunities that the mouse genome offers.

"We've really been waiting for the genome sequence," says neurobiologist Liliana Minichiello, whose team is trying to understand the control mechanisms of the complex cellular signalling pathways triggered by nerve growth factors. "It is so easy now to identify the genes you are interested in from just a scrap of information." ■

Alison Abbott

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All mutants great and small

Hidden beneath a rolling lawn at Baylor College of Medicine in Houston, Texas, lies a subterranean colony of tens of thousands of mutant mice. The mice have been altered by a chemical that mutates their DNA, and their cage labels reflect their respective genetic hiccups. 'Audrey Hepburn' is a charming specimen with a perky, upturned nose. 'Kojak' has a striking pattern of hair loss. And the unfortunate 'Wee Willie' is under-endowed and infertile.

Monica Justice, director of Baylor's Mouse Mutagenesis and Phenotyping Center for Developmental Defects, hopes that her growing menagerie of defective rodents will serve as models of human disease. But without a sequenced mouse genome, her project would be well-nigh impossible.

Take Wee Willie. To create him, a lab technician injected a male mouse with a chemical called *N*-ethyl-*N*-nitrosurea, which causes random, tiny mutations in sperm. The male's offspring were then bred for several generations. Justice noticed that male mice in Wee Willie's lineage sometimes had smaller penises than normal and couldn't make sperm.

Nobody had ever seen a mutant like this, so Justice and her colleague Richard Behringer at the University of Texas MD Anderson Cancer Center in Houston decided to study it with Behringer's postdoctoral fellow Andrew Pask. In the past, pinning down the mutation responsible for Wee Willie's condition might have taken the best part of Pask's career. But thanks to the mouse genome sequence, he and Baylor geneticist David Stockton were soon able to pinpoint the defect to a small region of chromosome 5.

Pask has found that Wee Willie's defects mirror a human disease called idiopathic hypogonadotropic hypogonadism, in which patients fail to develop normal adult sexual characteristics. Wee Willie may become a useful model for studying this distressing disease, and it turns out that he is a type of mutant called a 'hypomorph' — his defective gene still functions, but doesn't do its job well enough.

Established methods for making mutants, such as gene-knockout technology, can't easily be used to make hypomorphs, a fact that vindicates Justice's approach. There were plenty of doubters back in 1998, when she and her former colleague Allan Bradley set up the project. At that point, German and British teams had set up projects to screen for 'dominant' mutants, which disrupt development even if only one of a chromosome pair is affected. Justice's screen is designed to find recessive mutants, which are harder to spot. Already, her project has identified some 200 mutants, and several other labs worldwide are now setting up recessive screens — including the Wellcome Trust Sanger Institute in Hinxton, near Cambridge, UK, now headed by Bradley (see page 512).

For Justice and her colleagues, the publication of the mouse genome is a time to reflect on a job well done — although much work still lies ahead. They are also looking back on a close brush with disaster. In June last year, thousands of mice at Baylor were lost in a catastrophic flood. Luckily, the designers of the new facility occupied by Justice's mutants had the foresight to include watertight doors. ■

Erika Check

www.mousegenome.bcm.tmc.edu/ENU/MutagenesisProj.asp