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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