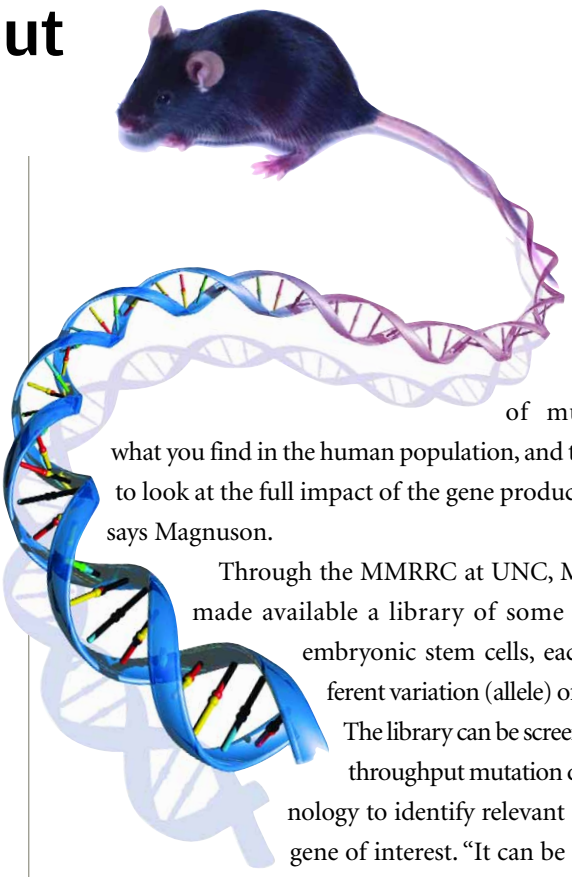
For Understanding Human Disease, the Mouse Is a Knockout



With the human genome fully sequenced, the next big question is "What do all those genes do?" The answers will likely be found in the mouse. "The mouse is the only mammalian species in which we have the ability to specifically delete one gene at a time from the genome, which makes it possible to discover what these genes do in normal physiological processes and in pathology," says Kent Lloyd of the University of California (UC), Davis.

That is why NIH's new Knockout Mouse Project (KOMP) is aiming to eventually disrupt, or "knock out," each of the 20,000 or so genes in the mouse genome. Within the next five years, the effort will create 8,500 to 10,000 new lines of knockout mice, tripling the number currently in existence from all sources.

Although KOMP was officially launched last fall, NCRR-supported researchers have long been laying the groundwork to achieve the project's goals. Since 1999, NCRR has funded a network of public repositories—dubbed the Mutant Mouse Regional Resource Centers (MMRRCs)—that collect, archive, and redistribute mouse strains developed over the years by individual researchers using federal funding.

In June 2006, NCRR expanded this effort by awarding $800,000 to the MMRRCs at UC Davis and the University of Missouri/Harlan in Columbia to develop more lines and to obtain from NIH-funded researchers additional lines that have been created but are not yet widely accessible. With a goal of adding 300 more lines in two years, this effort will significantly augment the public repositories, which already received a boost in October 2005, when NIH purchased 256 lines from two commercial sources.

In addition to providing researchers with mice and embryonic stem cells (from which mice can be generated), the MMRRCs have pioneered new techniques for using knockout mice to investigate normal and disease processes. For example, at the University of North Carolina (UNC) at Chapel Hill, Terry Magnuson has developed a technology to produce mutations in mouse genes that affect proteins in more subtle ways compared to knockouts, in which the protein encoded by the disrupted gene is not produced at all. "These subtle types of mutations are what you find in the human population, and they allow you to look at the full impact of the gene product on biology," says Magnuson.

Through the MMRRC at UNC, Magnuson has made available a library of some 4,000 mouse embryonic stem cells, each with a different variation (allele) of mouse genes. The library can be screened with high-throughput mutation detection technology to identify relevant alleles for any gene of interest. "It can be used to refine the predictions that are being made by proteomics researchers, who use computational methods to try to predict the effect of a given mutation on the protein's structure," Magnuson says. "We can now make the mouse and test the prediction in the actual living system."

The MMRRC at UC Davis, headed by Lloyd, will also play an integral role in the development and cataloging of the new knockout lines targeted by KOMP, as part of a collaboration that also includes the Children's Hospital Oakland Research Institute in California and the Wellcome Trust Sanger Institute in England. Together with Regeneron Pharmaceuticals in Tarrytown, N.Y., the group was awarded $47.2 million by NIH in September 2006 to create the lines. "The effort will contribute enormously, not only to basic science, but also to translational research, by helping us understand the causes so we can find new ways to prevent disease," says Lloyd. **—BRENDA PATOINE**

TO OBTAIN MATERIALS: NCRR funds Mutant Mouse Regional Resource Centers (MMRRCs) at four institutions: the University of California, Davis; the University of Missouri/Harlan; the University of North Carolina at Chapel Hill; and The Jackson Laboratory, which also serves as the Informatics, Coordination, and Service Center for the MMRRC facilities. To learn more, visit www.mmrrc.org/index.html.