

New, Improved Mini Me

The latest mouse models can mimic human disease with greater precision.

KEVIN P. CAMPBELL USED TO STUDY MUSCULAR DYSTROPHY BY analyzing small pieces of thigh muscle from a child with the disease. Today, there's a better option. Campbell can now mimic the biochemistry of muscular dystrophy and test its effects in mice—rather than children struggling with disease—and evaluate tissues that could never be tested before.

>> “With a patient,” says Campbell, an HHMI investigator at the University of Iowa Roy J. and Lucille A. Carver College of Medicine, “you never biopsy the diaphragm, but it’s a very important muscle because most patients die from respiratory problems. With the mouse,

one can test the diaphragm to study the pathogenesis or the response to particular therapies.”

An astonishing 99 percent of mouse genes have comparable versions in the human genome, and many of them appear in the same order in the two organisms’ chromosomes. “We also have similar reproductive systems, similar physiology, very similar

Mouse models of human cancer help Tyler Jacks explore biochemical pathways regulated by cancer-associated genes.



Flynn Larsen

Researchers

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Mouse models helped Kevin Campbell's team discover that defective sarcoglycan complex causes constriction of smooth muscle in the vessels of the heart. In addition, looking at brain tissue from their mice, they've found that the dystroglycan protein is a "major player" in the abnormalities in neuronal migration and mental retardation associated with muscular dystrophy.

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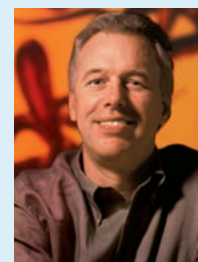
Mario Capecchi has created mouse models to study problems as wide ranging as limb skeletal defects; obsessive-compulsive disorder; and alveolar rhabdomyosarcoma, an aggressive childhood muscle cancer, for which the scientist created the first mouse model.

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Humanized mouse models are getting big support. Richard Flavell received a \$17 million pledge in 2005 from the Bill & Melinda Gates Foundation to develop laboratory mice with immune systems similar enough to humans to allow testing of human vaccines.

NATHANIEL HEINTZ
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To study neurological function, Nathaniel Heintz introduces large pieces of DNA—called bacterial artificial chromosomes, or BACs—into specific brain cell populations in the mouse. Because the BACs contain a gene and all the regulatory information necessary to express that gene, they can be used to introduce human genes into mice.

nervous systems, and so forth," says HHMI investigator Mario R. Capecchi, professor of human genetics at the University of Utah School of Medicine. "For all these reasons, the mouse model is a good representation of human biology."

In the last century, the mouse became the premier mammalian model system for genetic research. Now, the creation of mouse models is "like a cottage industry," says Capecchi. "There are literally thousands of labs all over the world making mutations in mice."

Capecchi pioneered "gene targeting," a technology that has revolutionized scientists' ability to use the mouse to model human disease. This advance of the late 1980s allowed researchers, in their attempts to re-create the possible genetic cause of a specific disease or study the function of a particular gene of interest, to "knock out" the function of that gene or modify its activity.

Since then, researchers have refined gene targeting to create strains of mice with mutations in virtually any gene. They can direct gene mutation so that it occurs in every cell of the body or only in certain tissues or cell populations. And they can control when that mutation occurs—right away, or later in the animal's life span. They can even inactivate combinations of genes, independently of each other, within the same animal.

Mimicking cancer

These advances are critical to faithfully mimic human cancer in the mouse, says Tyler Jacks, an HHMI investigator at the Massachusetts Institute of Technology, because the effects of cancer-associated mutations can depend on the specific type of cell or tissue in which they occur. "Making accurate cancer models requires a good deal of subtlety," says Jacks. "It's important to match the relevant mutations to the appropriate cancer and to pay attention to details ranging from the timing of the mutations to the levels of expression."

"Today, mice
are our test tubes. ”

NATHANIEL HEINTZ

Jacks studies an oncogene called *K-ras* whose activation has been linked to many different cancers. His group recently developed two mouse models of lung cancer involving *K-ras* that come close to mimicking spontaneous human disease. One strain of mice has an inactive *K-ras* gene in its cells; a second strain has an inactive *K-ras* gene plus a tampered-with version of the tumor suppressor gene *p53*. The genes are engineered in such a way that when triggered—by the introduction of a virus, for example—the oncogenes can be turned on or the tumor suppressor can be turned off, thereby tripping the cellular overgrowth characteristic of cancer. This scenario—

mutations in multiple genes, occurring in particular tissues and at particular times in the animal's life span—simulates what we know about cancer initiation in humans.

"That's a powerful tool in the study of lung cancer," says Jacks, "because we are interested in using these models to explore tumor progression, even from the earliest points." In June 2005, his group published a paper in *Cell* identifying a stem cell within the lung as the origin of non-small-cell lung cancers. "We wouldn't have been able to do that without use of sophisticated mouse models to control the initiation of tumor development." —Mary Beth Gardiner ■