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RESEARCH NEWS

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HHMI Investigator Mario R. Capecchi Wins 2007 Nobel Prize in Physiology or Medicine

The Nobel Assembly at the Karolinska Institute announced this morning that the 2007 Nobel Prize in Physiology or Medicine was awarded to Mario R. Capecchi, a Howard Hughes Medical Institute investigator at the University of Utah, Martin J. Evans at Cardiff University, and Oliver Smithies at the University of North Carolina at Chapel Hill. The three were honored for "groundbreaking discoveries concerning embryonic stem cells and DNA recombination in mammals." Their research has led to the development of powerful gene-targeting techniques that have provided researchers worldwide with the tools to determine the function of individual genes.

Not too long ago, the notion that scientists could manipulate genes to create animal models of human disease seemed virtually impossible, even to many researchers. Dogged research by Capecchi and others made it a reality. Capecchi is credited with developing a powerful technology known as gene targeting. This technology has allowed scientists to engineer mice with conditions such as cancer, heart disease, Alzheimer's disease, cystic fibrosis, and high blood pressure—a feat that has revolutionized the study of human disease.

Gene targeting allows scientists to manipulate the genetic material of mice with amazing precision to create desired mutations in virtually any gene. By controlling the way a gene's DNA sequence is modified, researchers can completely disrupt—or "knock out"—the function of a gene or modify its activity. Refinements in the technique over the years now enable scientists to restrict a particular genetic modification so that it affects only certain tissues or occurs only during certain stages of life.

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- Mario R. Capecchi

“Gene targeting allows us to genetically dissect the most complex biological problems to create animals that carry specific genetic alterations,” explained Capecchi, “so that we can recreate the underlying cause of a specific disease or study the function of a particular gene of interest.”

Through a series of bold experiments begun in the 1980s, Capecchi demonstrated that he could alter any gene in a mouse cell by replacing it with a modified version. At the time, scientists were skeptical that such altered DNA could be targeted to a particular gene. But Capecchi was not to be deterred. Indeed, his studies demonstrated that it is possible to replace an intact, functional gene with a modified version that can zero in on the corresponding DNA in the chromosome.

Over the years, Capecchi has used gene targeting to systematically knock out genes in the *Hox* family, considered to be the master switches that control the formation of the body plan during development. Doing so produces mice with dramatic developmental defects. When Capecchi and his Utah research team completely disrupted the activity of the *Hox10* and *Hox11* gene families in mice, they found that both families played important roles in orchestrating the construction of the ribs, spine, and limb bones. In another experiment, Capecchi created mice without a functional *Hoxb8* gene, finding that without this gene, animals groomed themselves excessively, creating bald spots and skin wounds. He suspects that defects in Hoxb8 may underlie obsessive-compulsive disorder in humans that involves excessive grooming behavior.

He and his colleagues have also developed the first accurate mouse model of alveolar rhabdomyosarcoma, an aggressive childhood muscle cancer. This new model has improved researchers' understanding of the cause of the disease and may lead to new therapies to treat the disorder.

Capecchi credits the venerable James D. Watson, co-discoverer of the DNA double helix and his Ph.D. advisor at Harvard University, for inspiring his development as a scientist. “He taught me not so much about how to do science but rather provided me with the confidence to tackle any scientific question that fascinated me, regardless of its complexity,” said Capecchi. “He also taught me the importance of communicating your science clearly and to pursue important scientific questions.”

Capecchi's success belies his very difficult upbringing in war-torn Italy during World War II. At the age of four, he was separated from his mother, who was taken by the Gestapo to the Dachau concentration camp. For the next four-and-a half years, he lived on the streets, fending for himself by begging and stealing. The two reunited when Capecchi was nine, and they soon moved to the United States, where he began elementary school without knowing how to read or write or how to speak English.

“It is not clear whether those early childhood experiences contributed to whatever successes I have enjoyed or whether those achievements were attained in spite of those experiences,” he said. His early experiences have also left him acutely aware of the importance of supportive mentors. “When dealing with human life, we cannot do the appropriate controls. In the absence of such wisdom, our only course is to provide all of our children with ample opportunity to pursue their passions and their dreams.”