

Reversing Evolution

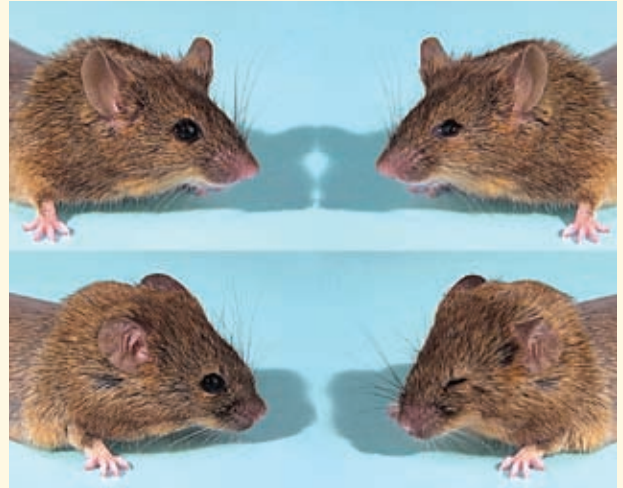
University researchers gained new insight into evolution by reversing the process. They reconstructed a 530 million-year-old gene by combining key portions of two modern mouse genes that descended from the archaic gene.

Mario R. Capecchi, Ph.D., distinguished professor of human genetics and biology, and co-chair of the U Department of Human Genetics, said the work “provides further evidence at the molecular level of how evolution has occurred and is occurring.”

The study by Capecchi and postdoctoral fellow Petr Tvrdik, Ph.D., was published in the August 2006 issue of *Developmental Cell*.

Capecchi and Tvrdik focused on the coding regions and regulatory sequences of two Hox genes—*Hoxa1* and *Hoxb1*—that direct the actions of other genes during the development of an animal embryo. They switched the coding regions of the two genes, so each gene produced the other’s protein. Then they replaced a portion of *Hoxa1*’s regulatory sequence with that of *Hoxb1*. The hybrid gene performed the function of both individual genes.

The ability to reconstruct a gene from its descendants has implications for new types of gene therapy. The study suggests it might be possible to insert a portion of a related gene into a disease-causing mutant gene to restore its normal function and cure the disease.



At top and bottom left are two mice in which the gene *Hoxb1* has been disabled. The gene controls the development of nerves needed for facial expressions. When a puff of air was blown into the face of the first mouse (top right), it was unable to blink its eyes, wiggle its whiskers or pull back its ears due to facial paralysis caused by the lack of the *Hoxb1* gene. But in the mouse on the bottom, a key piece of the *Hoxb1* gene was inserted into the gene *Hoxa1*, in effect recreating an ancient gene that once did the job of both *Hoxb1* and *Hoxa1*. When a puff of air was blown in the face of that mouse (bottom right), it was able to blink its eyes, wiggle its whiskers, and fold back its ears.

Potential Anticancer Drugs

Sponges, sea squirts, and other small ocean creatures contain symbiotic bacteria that produce chemicals with anticancer properties. Harvesting the chemicals for large-scale testing has proved impractical. In a study published in the Nov. 5 on-line issue of *Nature Chemical Biology*, however, U College of Pharmacy researchers used genetic pathways within the bacteria to increase chemical production and investigate the potential for new drugs to fight cancer, HIV, and other diseases.

Eric W. Schmidt, Ph.D., the study’s senior author and assistant professor of medicinal chemistry, examined the chemical and genetic diversity of bacteria in sea creatures and identified individual mutations that change one compound into another. He said that, by mimicking the natural process, he and colleagues synthesized a new compound and paved the way for the creation of large chemical libraries for testing against human disease.

Blood Work In a surprising discovery, U researchers identified an unsuspected mechanism that causes blood cells to form clots. By examining human platelets, they found cells make a protein important to clot formation called tissue factor (TF). The process is regulated by an enzyme found in platelets called cdc2-like kinase 1 (Clk1).

“The study could be important therapeutically. Current anticoagulant drugs do not

target the Clk1 pathway,” said senior author Andrew S. Weyrich, Ph.D., associate professor of internal medicine. Having identified the role of Clk1, it is possible to develop drugs to prevent the enzyme from making TF and inducing clots.

The study, led by Hansjorg Schwertz, M.D., postdoctoral fellow at the U Eccles Institute of Human Genetics, was published in the Oct. 23 on-line edition of the *Journal of Experimental Medicine*.

Knocking Out Colon Cancer The C-Terminal Binding Protein (CTBP) molecule is implicated in 85 percent of colon cancer cases. Researchers from the University’s Huntsman Cancer Institute (HCI) found that “knocking out” or disabling the molecule in zebrafish protected them from the effects of a mutation in the *adenomatous polyposis coli* (*APC*) gene. Results of the study were published in the Oct. 6 on-line issue of the *Journal of Biological Chemistry*.

APC mutations are known to initiate events that cause potentially cancerous colon polyps in humans. In zebrafish, they prevent the intestine from developing properly. David A. Jones, Ph.D., U associate professor of oncological sciences and study leader, said, “Genetically disabling CTBP promotes normal development of the intestine in zebrafish carrying the *APC* mutation.”

The findings have implications for new colon cancer treatments. CTBP is a new “target” and researchers plan to find potential chemical agents to block its action.

Additional HCI researchers include: Lincoln D. Nadauld and Reid Phelps, both M.D., Ph.D., candidates; postdoctoral fellows Brent C. Moore, Ph.D., Annie Eisinger, Ph.D., and Imelda T. Sandoval, Ph.D.; Stephanie Chidester, lab technician; Peter Peterson, Ph.D., senior research specialist; Elizabeth Manos, M.S., senior lab specialist; Bradford Sklow, M.D., U assistant professor of surgery; and Randall W. Burt, M.D., U professor of internal medicine and HCI senior director of prevention and outreach.

Netrins and Diabetes Dean Y. Li, M.D., Ph.D., U cardiologist and associate professor of internal medicine, found that netrins—a family of proteins that promote nerve development—not only accelerated blood vessel growth in ischemic mice, but also restored blood vessel and nerve growth in diabetic mice.

The study, published on-line in the June issue of *Science Express*, has important implications for the estimated 21 million Americans with diabetes, a disease that damages both nerves and blood vessels. Li, the study’s corresponding author, said, “We now have a growth factor that attracts both blood vessels and nerves. That’s why it’s unique for diabetes.”

Li conducted the research in collaboration with the laboratories of Chi Bin Chien, Ph.D., U associate professor of neurobiology and anatomy, and Douglas W. Losordo, M.D., from the Division of Cardiovascular Research at Tufts University. First co-authors include Brent D. Wilson, M.D., postdoctoral fellow, and graduate students Kye Won Park and Arminda Suli.

Double Exposure from Fallout

Residents who lived downwind from nuclear testing conducted in Nevada between 1951 and 1962 suffered more thyroid damage than once believed, according to a U of U epidemiologist who has been researching the issue for more than 20 years.

In a study published in the November issue of *Epidemiology*, lead author, Joseph Lyon, M.D., M.P.H., U professor of family and preventive medicine, and colleagues reexamined Lyon's 1993 study of 2,497 residents in which he'd found a correlation between exposure to radiation and thyroid tumors. The new study reevaluated the association between dose estimates and disease outcomes.

"What we came up with was a much stronger association for thyroid growths: it more than doubled," said Lyon. "This is the first time a clear link has been established."

Radioactive iodine entered the food chain through the milk of cows that ate contaminated grain and accumulated in the thyroid glands of residents. Children were particularly vulnerable. The study concluded that children exposed to radiation had an increased risk of thyroid neoplasms, a precursor for cancerous lesions, and autoimmune thyroiditis for up to 30 years.

For those with the highest exposure, the risk of neoplasms and thyroid tumors rose from 3.4 times in the earlier evaluation to 7.5 times. The former study suggested residents with high exposure were 1.1 times more likely to develop thyroiditis. The new study found the risk ratio was as high as 2.7 times.

The study involved more than 15 collaborators including: Lynn Anspaugh, Ph.D., U research professor of radiology; Mary Bishop Stone, U research associate; the late Alan Scholl, M.Stat., computer professional; Steve Alder, Ph.D., U assistant professor of family and preventive medicine; Ray Carroll, Ph.D., professor of statistics, nutrition, and toxicology; Kurt Hegmann M.D., M.P.H., U associate



professor of family and preventive medicine; Wayne Meikle, M.D., U professor of internal medicine; and George White, Ph.D., M.P.H., U professor of public health.

The second study was funded by the U.S. Centers for Disease Control and Prevention.

Uncrossing Signals U researchers identified a biochemical signaling pathway between human blood platelets that is essential for clotting and monocytes, white blood cells used to fight inflammation and infection. The pathway usually helps regulate inflammation, but when signals get crossed, an overproduction of Cox-2—an enzyme involved in heart attack, stroke, and other inflammatory diseases—can occur.

Discovery of the signaling mechanism will assist researchers in understanding the role of Cox-2 in many common and serious diseases. "This discovery has immediate clinical relevance," said senior author Guy A. Zimmerman, M.D., professor of internal medicine and director of the U medical school's Program in Human Molecular Biology and Genetics. Scientists may be able to prevent or lessen the severity of inflammatory diseases like clogged arteries and heart attack.

The study, reported on-line in the *Journal of Clinical Investigation*, was led by Dan A. Dixon, Ph.D., a former member of Zimmerman's lab now an assistant professor of biological sciences at the University of South Carolina.

Toxic Tools An unusual nerve toxin in an ocean-dwelling snail that may be useful in designing drugs to treat a variety of psychiatric and brain diseases has been isolated by U researchers. The OmlA toxin fits like a key into certain lock-like "nicotinic acetylcholine receptors" found on nerve cells in the brain and the rest of the nervous system.

J. Michael McIntosh, M.D., U professor and research director of psychiatry, research professor of biology, and member of the University's Brain Institute led the study published in the Aug. 25 issue of *The Journal of Biological Chemistry*. He found and analyzed the toxin in partnership with Baldomero Olivera, Ph.D., distinguished professor of biology.

According to McIntosh, different forms of nicotine receptors control the release of different neurotransmitters. "That's important, because if you had the compounds to facilitate the release of one neurotransmitter and not another, that opens up medicinal potential." It may enable scientists to develop medications for a wide range of nervous system disorders, including Alzheimer's and Parkinson's disease.

Resetting the Internal Clock A gene known to influence the internal clock of humans and other mammals functions differently than previously believed, a finding that could improve the design of drugs for circadian rhythm disorders.

Researchers discovered that contrary to general understanding, the tau mutation increases rather than decreases activity of the *CK1* gene. The study was a collaboration between David Virshup M.D., U Huntsman Cancer Institute investigator, and Daniel Forger Ph.D., assistant professor of mathematics at the University of Michigan. Virshup already had established that the depletion

of proteins from cells resets the body's internal clock. Forger's mathematical simulation confirmed the hypothesis that the circadian rhythm within mouse cells sped up, because the mutant *CK1* gene was more active, thus shortening its day by two to four hours.

"The key to developing treatments for problems like depression and insomnia—disorders influenced by circadian rhythm—is being able to predict how the body's internal clock can be controlled," said Virshup. The findings were published in the July 3 on-line edition of *Proceedings of the National Academy of Sciences*.

Detox Switch People and fruit flies share similar biological responses to detect toxins in their bodies. U researchers gave *Drosophila* water laced with phenobarbital and found that the sedative caused hundreds of genes involved in detoxification to switch on and off.

"Environmental toxins are a major public health issue, and that's what interests us," noted lead author Carl S. Thummel, Ph.D., U professor of human genetics and Howard Hughes Medical Institute investigator.

Researchers were able to identify the genes fruit flies use to resist pesticides, poisons, and other toxins. These genes metabolize the myriad toxins that fruit flies and people encounter every day. The findings were published on-line in the July edition of *Cell Metabolism*.