# Tetracycline Turns Genes On and Off

Again tapping the genetic reservoir of simple organisms, biologists have developed another way to fine-tune gene expression in transgenic animals.

In July, a multinational team got rid of a gene in certain immune cells of mice, for the first time deleting DNA after the animals' birth. With this well-timed, tissue-specific genetic manipulation, they studied how the loss of the gene affected the mice (SN: 7/9/94, p.20).

The new approach goes a step further. It uses a common antibiotic, tetracycline, to switch gene activity on and off throughout the life of the organism, says Glenn I. Fishman, a molecular cardiologist at Albert Einstein College of Medicine in New York. And it, too, can target specific tissues. The researchers control gene activity by altering the amount of tetracycline in the transgenic animal's drinking water.

Genetic on-off switches — along with other advances in genetics, immunology, and cell biology — may greatly increase the utility of gene therapy, says Helen M. Blau, a molecular pharmacologist at Stanford University School of Medicine.

For several years, she has been investigating the potential of muscle cells to become generic drug factories. These cellular shops would not only replace proteins missing or defective in genetic diseases, but replenish proteins depleted by other disease processes.

Toward that end, Blau and her colleagues have harnessed tetracycline to control gene activity in rodent leg muscle, they reported this week in San Francisco at a meeting of the Society for Cell Biology. They use the antibiotic to halt production of a particular protein; they restore production by withdrawing the drug.

Hermann Bujard of the University of Heidelberg in Germany developed this tetracycline-based switch in cultured cells in 1992. It involves a bacterial protein that stops doing its job — activating a particular gene — when tetracycline binds to it.

"Everybody who is working on genes needs this system or one like it," comments Lothar G. Hennighausen of the National Institute of Diabetes and Digestive and Kidney Diseases in Bethesda, Md. "You can keep the transgene silent until you want to turn it on."

His group is creating a mouse model for breast cancer and will use the tetracycline switch to learn when breast tissue becomes vulnerable to carcinogenesis. Since September, more than 80 researchers have requested copies of the DNA Hennighausen made that incorporates this genetic switch.

At the cell biology meeting, Fishman described his plans to use this procedure to study how cells maintain ties, called gap junctions, to one another. His group has put the tetracycline switch into cells grown in the laboratory. With it, the group controls production of a protein essential to maintaining some junctions, he reports.

In addition, Fishman and his colleagues have created two new strains of mice and bred them to make animals well suited for studying how heart muscle develops. The first strain carries the gene for the tetracycline-sensitive protein and links activation of the gene to DNA that works only in heart tissue. The second strain has the sensitive protein's target gene plus a gene called Id1, which helps in cell differentiation.

Fishman wants to understand Id1's role in forming the heart. In the resulting offspring, altering the dose of tetracycline influences how fast the gene turns on and off, Fishman and Einstein colleague Rod S. Passman report in the December 1994 JOURNAL OF CLINICAL INVESTIGATION. "It's reversible and controllable," Fishman says.

Such precise regulation means that researchers can begin to figure out exactly what substances like the Id1 protein do during different stages of an animal's life. Fishman hopes to use tetracycline to cause these mice and other transgenic mice to develop hearts with the same characteristics that lead to heart disease in humans.

Other researchers are perfecting different genetic switches, but thus far, none offers the promise of being as innocuous and specific as the tetracycline-based system, Fishman says. — *E. Pennisi*

# Gamma-ray bursts: The mystery deepens

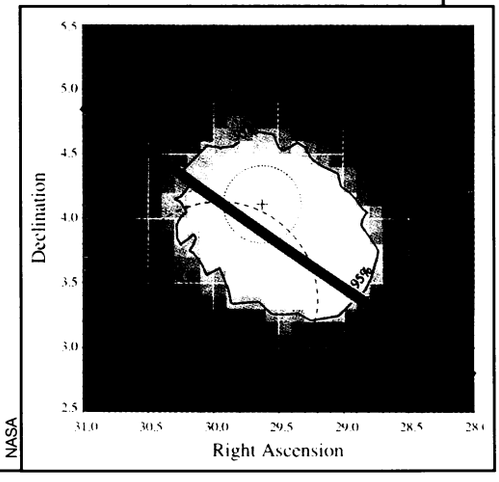
Some call it the greatest fireworks show never seen. Nearly once a day, a burst of gamma rays explodes somewhere in the universe, emitting high-energy photons and then disappearing — usually within seconds. The short duration of the bursts has made studying this phenomenon extremely difficult.

Last February, however, NASA's Compton Gamma Ray Observatory (GRO) spotted a gamma-ray burst that appeared to last 90 minutes. Because Earth slid in front of the orbiting GRO's view, the craft detected only the opening and the finale of the light show, leading astronomers to infer that the burst lasted a full hour and a half. What's more, the burst contained delayed gamma rays with many times the energy of those previously detected.

"Although some scientists had theorized about the presence of [such] delayed high-energy gamma rays, this was the first time we actually observed them," says Kevin Hurley, an astrophysicist at the University of California, Berkeley. Hurley and his colleagues report their findings in the Dec. 15 NATURE.

These observations add to the continuing mystery about the sources of gamma-ray bursts (SN: 2/5/94, p.85). A number of scientists have suggested that the bursts originate from colliding comets within the Milky Way; others maintain that the bursts come from merging neutron stars in a distant cosmos billions of light-years away.

"This observation doesn't necessarily fit one model or the other," Hurley cautions. "The fact that there were delayed high-energy gamma rays is the significant part, but we don't yet know what to make of it." — *A. C. Brooks*




NASA

*Burst seen by GRO instruments on Feb. 17. Green line indicates position plotted by the Burst and Transient Source Experiment (in conjunction with readings from the Ulysses spacecraft). The Energetic Gamma-Ray Experiment Telescope localized the burst to the area inside the jagged contour line. The Compton Telescope revealed that the burst lies within the larger dotted circle. The location of the highest-energy photon recorded by GRO lies within the small dotted circle.*