Insect hormone inspires switch for genes

Lights on, lights off. Just the quick flick of a finger on a simple switch brightens or darkens the room.

That power is the envy of geneticists. They long for similar ease in switching genes on and off in cultured cells and transgenic animals. In recent years, these scientists have gained some measure of control by using chemical compounds, including the antibiotic tetracycline, to govern genes in cells and mice (SN: 12/17/94, p. 404).

The insect hormone ecdysone may provide the most effective gene switch yet, suggest investigators from the Howard Hughes Medical Institute at the Salk Institute for Biological Studies in La Jolla, Calif., and the University of California, San Diego (UCSD). To support that contention, the group has made mammalian cells and strains of mice with genes that turn on when ecdysone reaches them.

With such a system, researchers should be able to examine the importance of the timing of gene activity, particularly during an organism's development. Since the hormone has no known effect on mammalian cells, ecdysone-based switches may ultimately provide a nontoxic way to control therapeutic genes inserted into humans.

"It looks pretty promising. It seems to work as well as, if not better than, the tetracycline system," says Janet Rossant, a developmental biologist at the Mount Sinai Hospital in Toronto.

In insects and creatures such as lobsters, ecdysone determines the course of molting, explains UCSD's David No. In the fruit fly, the hormone helps guide the complex metamorphosis of an insect larva into an adult.

The concept of an ecdysone-based gene switch arose a few years ago, when scientists finally found the hormone's receptor, the cellular protein to which it must bind in order to turn genes on. The receptor turned out to be a complex of proteins floating inside the nucleus, the cell's repository of DNA.

To exert its influence, ecdysone enters the cell and travels into the nucleus. There, it binds to one part of the receptor complex, freeing another portion of the complex to attach to a specific control sequence of the cell's DNA. That control sequence governs whether an adjacent gene is on or off.

The apparatus for ecdysone-controlled gene switching can be transferred to mammalian cells, report No and colleagues Tso-Pang Yao and Ronald M. Evans in the April 16 PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES.

To install a switchable gene, they add to the cell's DNA a target gene coupled to a control sequence designed to bind a modified ecdysone receptor. They also add genes for that receptor. The cell manufactures the receptor, and when the hormone reaches the nucleus of the cell, it binds to the receptor; the combination then attaches to the control sequence of the target gene, turning it on.

The new gene switch already works in cultured cells and in selected tissues of genetically engineered mice. The investigators used a synthetic version of ecdysone in mice to turn on a gene only in certain immune cells.

The ecdysone gene switch has some advantages over the tetracycline switch, says No. Ecdysone turns genes on quickly when administered and is cleared from an animal within hours, making possible precise timing of gene activity.

For most tetracycline switches, however, investigators must continuously administer the antibiotic to keep a gene off; withdrawing the drug turns the gene on. Furthermore, since bone stores tetracycline, researchers cannot control exactly when a mouse gene will become active after they stop providing the drug. "It takes a number of days to turn on a gene," says No.

Still, No suggests that switches based on ecdysone, tetracycline, and other compounds may one day be combined to provide investigators with authority over multiple genes. — *J. Travis*

Deep images favor expanding universe

According to the Big Bang theory, the universe began in a giant explosion. Ever since, the cosmos has ballooned in size, carrying galaxies farther apart.

But gravity slows that expansion and determines the fate of the universe. If gravity is weak, the universe will remain open, expanding forever. However, if the universe contains sufficient mass, it will eventually close in on itself: Gravity will halt cosmic expansion, crashing galaxies together in a Big Crunch. In a third scenario, the universe is delicately balanced between expansion and collapse, possessing just enough gravity to halt inflation without contracting.

Although cosmologists have by no means reached a consensus, recent evidence suggests that the cosmos will grow indefinitely. An analysis of some of the deepest cosmic images ever taken supports this idea.

In the new findings, presented last week in Liverpool, England, at the Royal Astronomical Society's National Astronomy Meeting, Thomas Shanks, Nigel Metcalfe, Ana Campos, and their colleagues at the University of Durham in England relied on a standard method. Gravity curves space in such a way that the volume of universe within a given radius from Earth is greater for an open universe than a closed one. The number of galaxies in that volume will therefore also be greater, so counting them could indicate the nature of the universe.

So far so good. But the difference in volume between an open and a closed universe becomes significant only when astronomers consider a chunk of universe containing distant objects. Unfortunately, galaxies located far from Earth are often too dim to detect.

Enter the Hubble Deep Field, a set of Hubble Space Telescope images that provide detailed portraits of galaxies deep in space and far back in time (SN: 1/20/96, p. 36). Armed with these images, as well a smaller set his team took with the William Herschel Telescope in the Canary Islands, Spain, and the United Kingdom Infrared Telescope atop Hawaii's Mauna Kea, Shanks' team found that the number of galaxies increases sharply as their brightness decreases.

Robert E. Williams *et al.*/NASA

Section of the Hubble Deep Field.

In interpreting this finding, the astronomers tried to avoid some well-charted pitfalls. A dim galaxy doesn't necessarily signify a distant galaxy, and as telescopes peer further back into time, the galaxies they detect may differ in size or brightness from galaxies seen today. In particular, if more distant galaxies shine more brightly, astronomers might overestimate their number.

After taking these confounding effects into account, the team still finds a large number of faint galaxies. The count, Shanks says, in most cases falls in the range predicted for an open universe, approximately four times that expected for a cosmos poised between expansion and contraction. He notes, however, that the data from ground-based infrared images don't distinguish between the models.

Mark Dickinson of the Space Telescope Science Institute in Baltimore notes that using the Hubble images to count galaxies is an important step, "and these are the first people to make a careful attempt." — *R. Cowen*