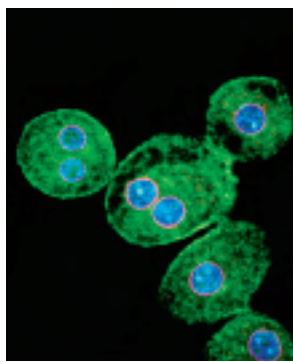


# Turning Growth On and Off, One Cell at a Time

OSCILLATING CALCIUM CONCENTRATIONS IN THE NUCLEI OF LIVER CELLS  
TRANSLATE INSULIN'S SIGNALS INTO OPERATING INSTRUCTIONS.

How does your body regulate its 50 trillion cells? The short answer is that it sends chemical messages to tiny subassemblies operating inside each one of them. Despite decades of study, however, intracellular communications are only dimly understood. Now a team led by HHMI international research scholar Maria de Fátima Leite has discovered an elegantly simple explanation for one of these command mechanisms.

In the November 2008 issue of *Hepatology*, the researchers describe for the first time the transfer of information from insulin to calcium



Insulin receptors, shown in green, coat liver cells.

ions in liver cell nuclei. Because it regenerates even after severe damage, the liver could be a key to explaining both normal cell growth and cancer. And calcium is a known “second messenger,” decoding commands like “Die!” or “Grow!”—carried through the bloodstream by hormones such as insulin—into language that the cell’s subsystems understand.

“We’ve known for a long time that insulin affects regen-

eration,” Leite says. “We’ve also known that insulin changes calcium concentrations in the cytoplasm, the part of the cell surrounding the nucleus. But we’d never seen insulin receptor in the nucleus itself.”

Detecting insulin receptors in the same places and at the same times as rising and falling calcium concentrations told the researchers they had made two discoveries, says Leite: “One, insulin causes calcium oscillations in the nucleus; and two, receptors translocate from the cell wall to the nucleus, traveling much deeper than we had thought.”

Although a receptor is submicroscopic, Leite says, at the cellular scale its dive to the nucleus is an epic one. “If you imagine a receptor molecule as a two-meter-tall lifeguard, the distance would be something like swimming the length of Lake Titicaca.”

Both discoveries are far more than just scientific curiosities, she says. “These are very important clues to specific problems. If we can learn to stimulate calcium oscillations in the nucleus, in a way that switches on regeneration or inhibits tumor growth, we may be able to design finely targeted medications with fewer side effects.

“And the beauty here is that the explanation is so simple. In science, the simplest explanation tends to be the right explanation.” ■

—GEORGE HEIDEKAT

## IN BRIEF

has now discovered one gene that’s necessary for normal fly sleep. She and her colleagues at the University of Pennsylvania School of Medicine sorted through more than 3,500 lines of fruit flies searching for the one that slept the least each day.

The line they found—with a mutation in a gene dubbed SLEEPLESS—slept 80 percent less than most flies, and 9 percent of flies with the mutation didn’t sleep at all.

The SLEEPLESS gene, the researchers discovered, codes for a small protein that likely regulates potassium ion channels. Sehgal thinks it might regulate channels in neurons involved in arousal—these neurons have to be silenced for sleep to occur.

SLEEPLESS flies not only had shorter and fewer sleep episodes, but also shorter life spans compared to flies without the mutation. “Even the SLEEPLESS animals need sleep,” says Sehgal. “That’s probably why they are so short-lived.”

The details on SLEEPLESS were published in the July 18, 2008, issue of *Science*.

### SCIENTISTS SPOT CAUSE OF EYE DISORDER

A common eye movement disorder is caused by a mutation in a signaling molecule that normally allows developing nerves to

reach eye muscles, HHMI researchers have discovered. Individuals with the disorder—Duane syndrome—can’t move one or both of their eyes outward toward their ears. And when they look inward toward their nose, the eye is pulled back into the socket.

Scientists once thought that muscle defects caused these symptoms, says HHMI investigator Elizabeth C. Engle of Children’s Hospital Boston and Harvard Medical School, who led the latest study. Engle’s long-standing hypothesis, though, has been that Duane syndrome—and other congenital eye movement disorders—results from improper nerve development.

An earlier study had identified a mutation within a large chromosome region in individuals with Duane syndrome. To zero in on the mutation, Engle and her colleagues screened DNA isolated from patients and their family members and discovered mutations in *CHN1*—a gene that encodes alpha 2-chimerin, a signaling molecule known to be essential in mice for guiding neurons during development. The team showed that in chicks the Duane syndrome mutations cause neurons to stall while they’re growing, so they never reach the correct eye muscles. The results were published August 8, 2008, in *Science*.

Engle next hopes to learn why the muta-

tions she’s found cause the symptoms they do. “We’re very interested in why these mutations in this ubiquitously expressed molecule affect the development of just this circuit,” she says.

### EXERCISE IN A PILL?

It’s a couch potato’s dream: a pill that offers all the benefits of an afternoon run. HHMI investigator Ronald M. Evans has discovered two compounds that increase the ability of cells to burn fat, enhance exercise endurance, and genetically reprogram muscle fibers to use energy better.

In 2004, Evans and his colleagues at the Salk Institute engineered mice that could run twice as far as normal mice and were resistant to weight gain, even when fed high-fat diets. The researchers wondered whether they could mimic the genetic effects through drugs and began testing compounds.

One drug they’ve found—called AICAR—allows mice to run 44 percent longer than untreated mice. Another drug, GW1516, has even more pronounced effects, but only if it’s combined with regular physical activity. Both drugs cause shifts in muscle composition and blood flow, and enhance fat metabolism. The results were published July 31, 2008, in an advance online edition of *Cell*.