

# Sculpting Brain Connections

A SIMPLE AND ELEGANT WAY TO ENABLE THE PROCESS OF LEARNING

Unlike your computer's memory chips, whose circuits are etched into a solid slab of silicon, real brain circuits change shape as they learn. HHMI investigator Michael D. Ehlers and his colleagues at Duke University are themselves learning how neurons remold their connections, and they may have identified the brain's favored sculpting tool.

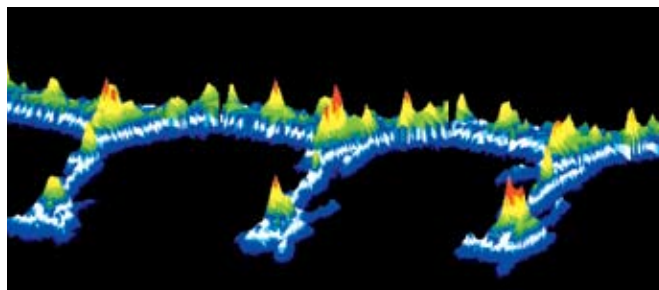
Ehlers' team focuses on dendrites—the neuronal branches that support the nerve cell's connections to other neurons—and in particular on the tiny spines that sprout on dendrites and act as the receiving stations for incoming signals. These dendritic spines, Ehlers explains, are the centers of neuronal rewiring—i.e., learning.

The spines contain receptors for neurotransmitters, notably the AMPA receptor proteins that accumulate in the surrounding membranes. Several years ago, Ehlers' group discovered that these receptors migrate to the membrane by way of tiny vesicles called recycling endosomes. "The way you functionally enhance the synapse (the connection between neighboring neurons) is to get more AMPA receptors there," says Ehlers.

In a paper published in the December 7, 2006, issue of *Neuron*, Ehlers and colleagues extended those earlier findings. Using advanced light- and electron-microscopy techniques, they found that recycling endosomes provide not only the AMPA receptors but also the membrane components neurons need to shape their connections. This discovery, he says, emerged from

no small amount of free thinking. "No one had ever asked 'Where does the membrane come from?'"

The findings are already simplifying the way neuroscientists think about learning and brain circuitry, says Ehlers. "You don't need a hundred different mechanisms to mobilize a hundred different molecules. Maybe you just need one core transport mechanism that delivers a prepackaged set of molecules and membranes to the synapse." He hopes the discovery may lead to new avenues for restoring or augmenting the brain's plasticity—its ability to mobilize healthy nerve cells to compensate for damage caused by disease or injury. ■ -PAUL MUHLRAD



As it develops and stores information, the brain undergoes physical changes in microcircuitry. These three-dimensional profiles show intensity of recycling endosome cargo in a single dendritic spine, with a scale from low (purple) to high (red), as well as long term potentiation of synaptic strength over time (left to right).

## IN BRIEF

### GENES LARGE OR SMALL, P[ACMAN] PLACES THEM ALL

To determine a gene's function, scientists often alter the gene and insert it into the genome of a model organism; larger genes, however, have proven more difficult to insert. Now, HHMI investigator Hugo J. Bellen at the Baylor College of Medicine and colleagues have developed a technique that enables both large and small genes to be inserted into mammalian and fruit fly chromosomes. By applying a method called "recombineering," they retrieved large DNA fragments from fruit flies and inserted them into modified bacterial artificial chromosomes (BACs). They then used an enzyme called phiC31 integrase to integrate the BAC-carried gene fragment into specific docking sites in the fruit fly chromosome, giving rise to the technique's name, "P/phiC31 artificial chromosome for manipulation," or P[acman] for short. Their findings were published November 30, 2006, in *Science Express*.

### GLEEVEC'S GOOD NEWS

In a study of patients with chronic myeloid leukemia (CML), some 95 percent survived the cancer after five years due to treatment with Gleevec, according to results published

in the December 7, 2006, issue of *The New England Journal of Medicine*.

"The lesson from Gleevec for cancer treatment is simple: if you understand what's driving the growth of the cancer and develop a specific drug to target that cause, you can obtain remarkable results," says HHMI investigator Brian J. Druker at the Oregon Health & Science University Cancer Institute, who led the original clinical development of Gleevec (imatinib) as well as this follow-up study.

Gleevec inhibits a biological switch called a tyrosine kinase that is abnormally activated in CML. This activation, triggered by an abnormal breakage and rearrangement of a chromosome, drives uncontrolled proliferation of white blood cells.

The study followed 553 patients who were receiving Gleevec as their primary therapy. Aside from the high survival rate, the report shows that the drug produced few significant side effects, which is important because CML patients need to remain on Gleevec long term.

The researchers are now working on eradicating the reservoir of aberrant cells that cause the disease to reappear if therapy is stopped.

### SEEING THE PATTERN IN HAIR FOLLICLE DEVELOPMENT

Studying the unruly fur that saddles certain mutant mice has provided HHMI investigator Jeremy Nathans at the Johns Hopkins University School of Medicine and his colleagues with a glimpse of how hair follicles communicate their position and orientation to neighboring follicles.

The team studied mice carrying a knockout mutation in the gene called *Frizzled6*. In contrast to the well-organized hair follicles of normal mice, the mutant mice show a complex disruption of hair follicle patterns much like the whorls and waves in fingerprints.

The researchers created mice in which normal hairs were intermingled with mutant hairs and then they created small wounds in the skin of the mice to study how follicle orientation was affected. Using microscopy techniques, they showed that the follicles are mobile in their orientation and that they transmit both global and local signals that can alter that orientation. The normal follicles seem to influence orientation of the mutant follicles, but not vice versa.

"Finding that kind of mobility was quite remarkable, because until now most