

Sleep-Inducing Monsters

A DRUG FOR TRANSPLANT PATIENTS ALSO KILLS THE PARASITES THAT CAUSE AFRICAN SLEEPING SICKNESS BY GROSSLY DISTORTING THEIR SHAPE AND BLOCKING CELL DIVISION.

A drug that helps transplant patients fight tissue rejection may lead to new therapies for African sleeping sickness. The disease is fatal if left untreated, and current therapies have severe side effects.

HHMI international research scholar Miguel Navarro of the Institute of Parasitology and Biomedicine at the Spanish National Research Council in Granada, Spain, and colleagues have found that the immunosuppressant drug rapamycin kills *Trypanosoma brucei*, the parasite that causes African sleeping sickness. These parasites contain proteins similar to those that rapamycin inhibits in humans.



Trypanosoma brucei infects the tsetse fly, found only in Africa.

Studying how *T. brucei* evades the immune system, Navarro's group realized that four genes of the TOR family enable the parasite to make evasive maneuvers. The genes are called TOR because their protein products are "targets of rapamycin." The researchers wanted to see if rapamycin could inhibit these TOR proteins. To

the team's surprise, it did more than that. Rapamycin-treated parasites enlarged, sprouting multiple nuclei and other cell parts, and then they died. "They look so weird and grotesque we call them monsters," Navarro says.

The drug doesn't cause the same cell deformities in the human immune system. In humans and all other previously studied organisms, rapamycin slows the rate of cell growth. In *T. brucei*, however, the drug inhibits cell division, the team discovered. Their results appeared in the September 23, 2008, issue of *Proceedings of the National Academy of Sciences*.

The different effects come about because humans have one TOR gene and most single-celled organisms have one or two TOR genes, but *T. brucei* have four. Navarro's group found that rapamycin inhibits different TOR proteins in *T. brucei* than in humans. The differences could be exploited to design better drugs to treat African sleeping sickness.

Because it suppresses the immune system, rapamycin could not be used directly to treat sleeping sickness in humans. But rapamycin-derived drugs that ignore immune cells are being tested as anticancer agents in clinical trials, and Navarro plans to test them on *T. brucei*. ■ — OLGA KUCHMENT

IN BRIEF

broken, missing, and overactive genes—some of which were previously unknown. HHMI investigator Bert Vogelstein and colleagues at the Johns Hopkins Kimmel Cancer Center, in collaboration with researchers elsewhere, sequenced 20,661 genes in cells from 24 patients with pancreatic cancer and 22 patients with glioblastoma—the most common form of brain tumors.

The team identified hundreds of gene mutations associated with the cancers. They also found numerous cases where the tumor cells had too many or too few copies of a gene. The typical pancreatic cancer, they discovered, contains 63 genetic alterations and the typical brain tumor contains 60.

The researchers say that the results—which appear in two reports published September 26, 2008, in *Science*—indicate that a small number of commonly mutated genes ("mountains") and a much larger number of rarer gene changes ("hills") cause the cancers.

"If you have 100 patients, you have 100 different diseases," says Vogelstein. The number and variability of tumors poses a challenge to developing drugs. "It's suggesting that maybe we shouldn't be focusing so much on the individual genes that are mutated," Vogelstein says.

"Instead, we should be thinking about the functional pathways in which these genes operate."

MOLECULAR MOTOR FOR MEMORY IDENTIFIED

Building new memories takes raw molecular materials and a cellular vehicle to truck the goods where they're needed within a cell. When new memories are stored, the junctions between neurons in the brain are rapidly reconfigured and rebuilt so they can respond more readily in the future. Researchers led by Michael Ehlers, an HHMI investigator at Duke University Medical Center, have identified the motor protein that carries new receptors and other molecules to the synapse when they're needed.

Scientists had already established that certain myosin proteins haul cargo in the cell. Ehlers' team showed that one specific myosin—myosin Vb—resides within micron-sized dendritic spines of neurons, the sites that respond to memory signals. When neurons receive signals that trigger long-term potentiation—the repeated signaling at a synapse that enhances nerve cell connections during the creation of a memory—myosin Vb attaches itself to cellular containers full of the necessary materials, including new neurotransmitter receptors.

Using fluorescent tracers, the team was able to observe the myosin Vb motor proteins actually carrying the cargo to the tips of the neurons that had been stimulated. When the researchers shut down myosin Vb, the cellular steps of memory formation were blocked, they reported in *Cell* on October 31, 2008.

Scientists suspect that breakdowns in this transport process may contribute to deficits in learning and memory, so understanding their molecular basis could lead to treatments for disorders such as addiction and Alzheimer's disease.

CANCER'S KEEPER

Although many cancer cells remain at their site of origin, some escape to lodge in distant organs, a process called metastasis. These metastases cause most cancer-related deaths. Scientists have found a systematic way to identify genes that might keep cancers from spreading and in the process have identified a gene that suppresses melanoma metastasis in mice.

The team, led by HHMI investigator Michael Green, confined mouse melanoma cells in a matrix that mimics the cells' natural surroundings in the body and then administered RNA fragments to silence genes one at a time. They identi-