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RESEARCH NEWS

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Sponge Toxin Halts Molecular Motor

An ocean-dwelling sponge may provide a tool for understanding the molecular motors that power cell division and other intracellular transport processes, say researchers at the Howard Hughes Medical Institute at the University of California, San Diego.

A toxin produced by the sponge *Haliclona* is the first chemical to be identified that shuts down the ubiquitous cellular motor proteins known as kinesins, according to Lawrence S. B. Goldstein , a Hughes investigator. Goldstein and colleagues from the Scripps Institute of Oceanography (SIO) published their findings in the April 10 issue of the journal *Science.*

"A molecular model of the motor protein kinesin."

Motor molecules that provide the power for cellular transportation are divided into two superfamilies: dyneins and kinesins. Dyneins move vesicles and organelles from the periphery of the cell into the cell's center. Kinesin motors transport freight from the middle of the cell outward. They also help to separate chromosomes during cell division.

Transportation within a cell is carried out over a grid of tiny track-like structures called microtubules. Each type of motor is composed of two globular domains resembling "feet" that alternately "step" down the microtubule track, some scientists believe. The feet balance on the proteins that compose the track, while the other end of the motor carries the cargo.

The toxin discovered by Goldstein and his colleagues puts a halt to kinesin's life-sustaining transport by clogging the motor. Goldstein theorizes that the small toxin mimics the motor's binding site on a microtubule. The toxin effectively "locks up the motor," he says.

"It's an important proof of principle that the motor can be inhibited," Goldstein said. With engineering and luck, the sponge toxin may lead to compounds as powerful as the anticancer drug Taxol. Derived from the bark of the yew tree, Taxol disrupts deadly cell division in patients with ovarian cancer. Unfortunately, Taxol also perturbs the growth of normal cells. It may be possible, Goldstein says, to design a new drug that is more selective than Taxol based on information gleaned from studying the sponge toxin.

"There's a universe of things in the natural world that might ultimately be used therapeutically," Goldstein said. "It's a numbers game. If you study enough things with odd chemistry, you just might find what you need."

The rope-like, mauve-colored sponge is a member of the species *Haliclona* (also known as *Adocia*). Scientists from SIO plucked the sponge from the sea floor near Palau in the Western Caroline Islands. Soon after returning from Palau, SIO chemist John Faulkner began analyzing the organism's chemical treasure trove. "Marine sponges are an amazing source of biologically active materials," said Faulkner.

Of particular interest to Faulkner are the toxins that these sponges use to defend themselves. While studying *Haliclona,* Faulkner isolated the unusual toxin described in the *Science* article. In search of the toxin's biochemical properties, Faulkner teamed up with Goldstein, an expert in mechanisms involved in intracellular movement. Goldstein's team analyzed the properties of the toxin and noticed to their surprise that the toxin, which they named *adocia* sulfate-2 (AS-2), stopped the kinesin motors.

"It has been a long wait for a specific inhibitor of kinesin. Now the functions of kinesin can be experimentally separated from other motor systems, such as dyneins and myosins," said Thomas Reese of the National Institute of Neurological Disorders and Stroke. "AS-2 is the first of what I am confident will be a family of exquisitely fine tools with which to manipulate cells for therapeutic as well as experimental purposes."

Goldstein says that AS-2 alone will not work as a drug because it cannot permeate a cell's surface. Moreover, it inhibits many kinds of kinesin motors, not just those responsible for movement during cell division. Goldstein and his colleagues hope to refine the toxin to allow inhibition of kinesins with roles in cell division but leave intact those with other cargo transport capabilities.

Whatever the ultimate fate of AS-2, the scientists say that their study highlights the potential of marine biomedicine to unlock the secrets of human physiology.