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The Cell's Tiny Motors

A cell's work is never done. Cells must ferry proteins and lipids, separate genetic material, divide in two, and much more. The tiny mechanochemical motors behind these tasks have fascinated scientists since biologists first saw muscles contract and microorganisms swim.

Recent research in the laboratory of Ronald D. Vale, a Hughes investigator at the University of California, San Francisco (UCSF), provides fresh insight into the structure and operation of motor proteins. These enzymes, smaller than one-millionth of an inch, convert chemical energy in the cell into physical movement.

"We still don't have a complete understanding of how proteins generate physical movement," Vale said, "but our research suggests strategies that may be important for movement. The research also reveals a surprising family tree for the motors.

Publishing two papers in the April 11, 1996, issue of *Nature*, Vale and Robert J. Fletterick, a UCSF X-ray crystallographer, reported the atomic structure of two motor proteins: kinesin, which contains the smallest known motor; and *ncd*, which resembles kinesin's general structure but performs different tasks.

Once the researchers created x-ray crystallographic images of the proteins, they compared the proteins to all other known molecular structures. "The big surprise," Vale said, "was that striking similarities were found to other well-known proteins." Kinesins most resembled myosins, the motor proteins responsible for muscle contraction. That result surprised Vale because the two molecules differ in size, amino acid sequence, and movement style.

The results suggest that kinesins and myosins may have diverged long ago during their evolution. They have each retained those features that are "essential to being a motor," Vale said. "It may be that nature found a good solution and kept it." The structural similarity between kinesins and myosins supports the idea that motors may be modular, with a similar fuel-burning domain that is joined to unique regions for carrying cargo.

Motor proteins work hard and fast. Kinesin, for example, moves protein building blocks from their birth sites to far points in the cell. In the case of a nerve cell, this journey may stretch three feet long. Kinesin molecules can move at the blinding rate of 100 body lengths per second. Kinesins travel on

the molecular equivalent of railroad tracks: long-stranded polymers called microtubules. Though kinesin and ncd are highly similar molecules, their small differences direct them along microtubules in opposite directions. Ncd builds the mitotic spindle and segregates chromosomes prior to cell division.

Vale now hopes to describe just how kinesin and ncd move. Lever, coiled spring and "hand-over-hand" actions have been suggested for various motor proteins. Vale also hopes to place high-resolution images of one molecule's structure against the backdrop of that molecule's microtubule movement. His goal: to learn how nature creates motors with very different properties. "If we can understand that, then we'll finally understand how these motors work," he said. In the future, researchers might design motor proteins to deliver medical cargoes. They might also manipulate motors involved in cell division to halt the runaway growth that characterizes cancer.