UCSD Scientists to study protein "motors" under three-year, $1.2 million NSF grant

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Tiny protein "motors" that transport vital biological cargo needed to sustain cell life will be studied by a multidisciplinary team of scientists from the University of California, San Diego under a new $1.2 million grant from the National Science Foundation (NSF).

During the three-year project, the UCSD scientists hope to better understand the internal structure and activities of this family of protein motors, known as kinesins, with the potential goal of devising new therapies for a variety of disorders including certain birth defects, neurodegenerative diseases, and cardiac abnormalities.

"I suspect these studies will turn out to be very useful for human health," said Lawrence S. Goldstein, a professor of cellular and molecular medicine, and an investigator at the Howard Hughes Medical Institute at the UCSD School of Medicine.

The UCSD project is one of 18 awarded by the NSF under a one-time, multi-disciplinary initiative in optical science and engineering. The winners, who were awarded a total of $13.5 million in grants, were selected from 76 proposals and 627 pre- proposals.

Optical science and engineering, the study of how light interacts with matter, is an "enabling" technology--one that can be applied to diverse fields of research and education, from information infrastructure, advanced manufacturing, and remote sensing, to devising new optical tools for biotechnology and medicine.

Among other things, the UCSD project builds on recent efforts to image individual molecules under conditions resembling the inside of a living cell.

In an article published earlier this month in the journal Science, UCSD chemists described a new way of trapping such molecules with the help of a porous gel whose matrix is bathed in water at room temperature. Once isolated and contained inside this framework, individual light-emitting dyes and fluorescently labeled protein molecules are imaged, allowing scientists to follow the activities of the protein under a microscope.

"What we are doing with these techniques is to put fluorescent molecules on selected proteins and use them as light sources to tell us something about how the protein functions," said W. E. Moerner, professor of chemistry and biochemistry at UCSD.

"We are doing this in an environment which allows the protein to retain its native structure and its function to remain intact."

The technique is a variation of a method called single- molecule spectroscopy, developed in 1991 at IBM by Moerner and colleagues. Here, a single molecule is trapped inside a crystal lattice which is cooled to extremely low temperatures near absolute zero. A laser tuned to a specific wavelength then causes the molecule to fluoresce, emitting light. By carefully monitoring the light given off by the trapped molecule, the researchers are

able to make direct observations of sometimes extremely subtle and sometimes bizarre motions of the molecule within the crystal.

The method was a vast improvement over conventional spectroscopic techniques which washed out subtle, but sometimes significant actions of individual molecules. For studying protein function, however, it proved virtually useless since very low temperatures, rigid crystals, and dry polymers are incompatible with observations of the motions necessary for biological function.

What was needed was a different way of confining fluorescent molecules, one that was water-based, could work at room temperature, and would allow proteins some motion--although limited enough so they could be studied.

Robert M. Dickson, a postdoctoral researcher in Moerner's lab, quickly homed in on a porous gel called polyacrylamide (PAA), routinely used as a sieve in the laboratory to separate proteins by molecular weight. The biologically friendly gel also is transparent to visible and ultraviolet light (useful for microscopic studies), contains tiny pores filled with water, and forms a generally useful media for the study of single biomolecules.

In recent months, Moerner has begun to apply this and other techniques to kinesins, a protein family of interest to Goldstein and many other research labs around the world.

Essentially, kinesins are types of cellular motors that transport vital molecular packages from one part of a cell to another. Working somewhat like molecular trolley cars, kinesins shuttle their precious cargo along networks of hollow tracks called microtubules that guide their intracellular travels. Such activity is generally believed to be essential for how chromosomes align during mitosis, or cell division; the positioning of structures called organelles within the cell's cytoplasm; and the transport of packets of material to the ends of nerve cells.

When proteins such as kinesin go awry, it may lead to severe disease. For example, familial hypertrophic cardiomyopathy, which can trigger heart attacks in young adults (the disease that killed basketball star Hank Gathers) results from defects in myosin, a protein motor related to kinesin. Certain neurodegenerative diseases also may be related to interference with kinesin-driven transport in nerve cells.

The UCSD researchers will use fluorescent probes and other emerging imaging techniques to trace structural changes and manipulate the actions of single kinesin molecules. In this manner, they hope to find precisely how different members of the kinesin family move along these molecular tracks to their destinations.

"We'll try to test all the various hypotheses using novel optical systems," said Goldstein, also a professor of pharmacology at the UCSD School of Medicine. "In so doing, we hope this will help us explain how motor proteins work, and how they function. Perhaps this work will tell us something surprising about these and other proteins."

Also participating in the study are Sheldon Schultz, UCSD professor of physics and director of the Center for Magnetic Recording Research; and Mark Ellisman, professor of neuroscience and director of the National Center for Microscopy and Imaging Research at the UCSD School of Medicine.

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