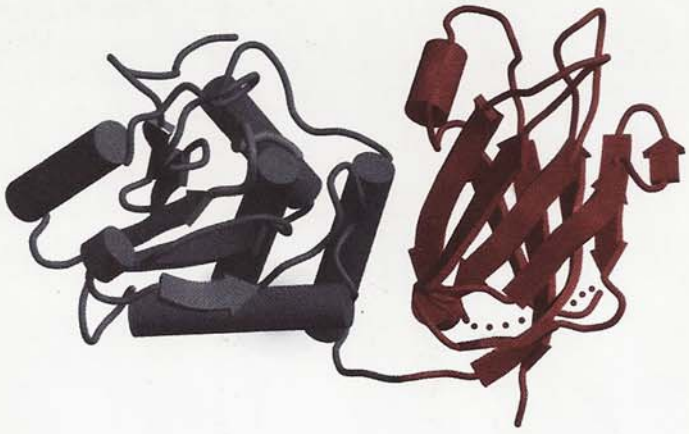
MEMORIAL SLOAN-KETTERING CANCER CENTER • JUNE 2001

Center News

Structural Biology: Understanding Proteins to Write a Repair Manual for the Cell

Now that scientists have essentially determined the complete sequence of human DNA — the primary goal of the Human Genome Project — their next big task is getting underway. It promises to be equally ambitious and arduous, but it also is expected to be a boon to medical research and drug development. This new endeavor focuses on identifying the structure and function of the tens of thousands of human proteins whose instructions are written in the genetic code.



Nikola P. Pavletich and colleagues determined the crystal structure of the PTEN tumor suppressor protein, illustrated above in a ribbon diagram created with computer modeling. The protein has two distinct domains, shown here in red and blue. The red portion binds to cell membranes, and mutations in that area can change the way the protein binds, affecting its ability to suppress tumor-cell growth. PTEN mutations have been linked to several cancers, including prostate tumors and glioblastoma, a brain tumor.

Structural biologists at MSK will play an important role in characterizing many of these proteins. Their work is important because it is proteins that make up the cells in the body and carry out their specific functions, and when they're defective it can lead to disease. In several laboratories, Center researchers already are using a variety of techniques to determine how proteins operate normally and how they go awry in disorders such as cancer. Their efforts will dramatically improve scientists' understanding of disease and make it easier to design drugs that specifically target defective proteins.

Structural biology is the study of the three-dimensional shapes and interactions of biological molecules — including proteins — to determine how those molecules function within the cell. Identifying the shape of a protein is important because proteins interact with other molecules based on their three-dimensional configuration, much like puzzle pieces fitting together.

"Almost all biological processes are controlled by protein molecules doing what they do," said Jonathan D. Goldberg, Head of the Laboratory of Protein Structure and Biophysics, "which is interacting with each other, undergoing changes

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Writing a Repair Manual

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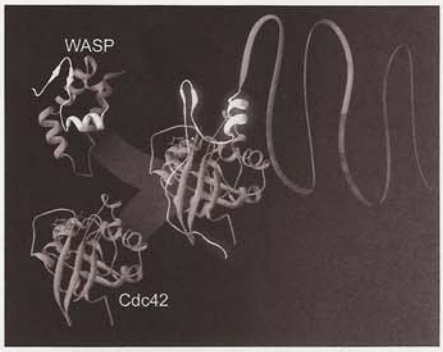
in shape, or bringing about chemical reactions. Modern biology over the past 20 years has benefited tremendously from structural insights, and this has really opened up our understanding of how cells work." Dr. Goldberg's research focuses on the structure of proteins related to cell transport.



Michael K. Rosen's laboratory delineated the structure of part of the Wiskott-Aldrich syndrome protein (WASP), which can cause altered immune function when mutated. This illustration shows how WASP interacts with a molecule that activates it, called Cdc42.

James E. Rothman, Chairman of the Cellular Biochemistry and Biophysics Program, likens basic structural and cellular biology research to writing a repair manual for the cell. "Developing that manual is what basic scientific research is striving to do," he said. "If you don't understand how a cell works, there's less hope of fixing it when it's 'broken.' And this is true of most diseases, not just cancer."

Already, the progress that scientists have achieved in understanding cell growth and signaling and the proteins that regulate them is leading to the development of novel cancer drugs. For example, monoclonal antibodies such as Herceptin® and IMC-C225 slow cancer growth by targeting specific receptors in cancer cells that receive signals to grow and divide. Herceptin is beneficial in some patients whose breast tumors have the HER-2 protein; IMC-C225 is being evaluated for the treatment of head-and-neck, colorectal, and lung cancers. Small-molecule drugs such as Iressa™ (which is useful against non-small-cell lung cancer) target another protein involved in cell growth, the tyrosine kinase enzyme.

"Structures further our understanding of the many different processes that occur in cancer," said Nikola P. Pavletich, Head of the Laboratory of Structural Biology of Oncogenes and Tumor Suppressors, "including tumor formation, metastases, and response to chemotherapy." And knowledge of how proteins are shaped provides opportunities for developing better drugs. "Studying what these molecules look like, the properties of their shapes, and how those shapes might fit together with other molecules is extremely valuable for identifying potential drugs," said Dr. Pavletich, who has spent his career determining the structures of several important cancer-related proteins called tumor suppressors.

The efforts of structural biologists will improve scientists' understanding of disease.

In the past, basic scientists have not been involved in drug discovery, Dr. Pavletich explained. But things are changing, largely because of computer modeling programs. The methods used by structural biologists also have been improved substantially in recent years. Having DNA sequences for proteins of interest has made it easier to manufacture them in large quantities. Computer programs that build and compare molecular models make it easier to study the bends and twists of the chains of amino acids that string together to form proteins, once the shapes have been determined using the techniques x-ray crystallography and nuclear magnetic resonance spectroscopy.

Michael K. Rosen, Head of the Laboratory of Structural Biology and Signal Transduction, also noted that basic research is crucial to the drug-discovery process. For example, his work studying proteins involved in cell movement and structure has implications for the development of anti-metastatic agents — through understanding the movement and migration of cells — and drug-delivery agents — through understanding cell signaling. "I'm interested in the fundamental processes that control the way cells function," he said. "But the things I work on have a strong tie-in to cancer."

PTEN figure on page 1 adapted from *Cell*; vol. 99; Lee, et al; "Crystal Structure of the PTEN Tumor Suppressor"; pp 323-334; 1999; with permission from Elsevier Science. Figure below courtesy of John Kuriyan and Bhusnan Nagar.