Structural Biology

A healthy mind and body require the coordinated action of billions of tiny molecular workers called proteins. Our genes contain the DNA scripts for manufacturing proteins. Some proteins build our cells and other proteins work like miniature machines to allow us to think, smell, eat and breathe. Proteins are indispensable molecules in our bodies, and each has a unique three-dimensional shape that is well suited for its particular job. And if the shape of even one protein happens to go awry, there can be major consequences for human health. Misshapen proteins are the culprits behind many diseases, including cystic fibrosis, Alzheimer's disease and countless others.

The Structural Biology Roadmap is a strategic effort to create a "picture" gallery of the molecular shapes of proteins in the body. This research investment will involve the development of rapid, efficient, and dependable methods to produce protein samples that scientists can use to determine the three-dimensional structure, or shape, of a protein. The new effort will catalyze what is currently a hit-or-miss process into a streamlined routine, helping researchers clarify the role of protein shape in health and disease.

What will it take to accomplish this task? NIH will begin by funding Centers for Innovation in Membrane Protein Production that will enable interdisciplinary groups of scientists to develop innovative methods for producing large quantities of membrane proteins, those proteins that are wedged tightly within the wrappings of our cells. Scientists currently find it extremely difficult to wrestle these proteins out of cells in a condition suitable for structure-mapping techniques.

NIH anticipates that the development of new, protein-producing methods will enable the creation of specialized facilities that will be capable of quickly and efficiently manufacturing large quantities of research-grade membrane protein samples. Once scientists have access to sufficient quantities of proteins for their experiments, they can determine a protein's shape using standard methods involving X-rays, extremely powerful magnets, or specialized forms of microscopy such as cryoelectron microscopy.

In a technique called X-ray crystallography, researchers aim high-energy X-rays at a very small crystal containing trillions of identical molecules of protein. The crystal scatters the X-rays onto an electronic detector, sort of like a disco ball spraying color across a dance floor. Measurements of the intensity of scattered rays are fed into a computer, which uses a mathematical equation to calculate the exact position of every atom in the protein molecule. The other most widely used technique to solve protein structures is nuclear magnetic resonance spectroscopy. This method, nicknamed NMR, relies on the use of super-strong magnets. In this approach, scientists take advantage of the fact that some atoms in proteins are slightly magnetic. Researchers apply a very

strong magnetic field to a protein sample. Tiny magnetic fields in the protein line up with the NMR magnet just as iron filings align on a toy magnet. The magnetized sample is blasted with a series of computer-generated radio pulses that disrupt the alignment in ways that permit scientists to deduce the protein's three-dimensional shape. Cryoelectron microscopy uses electrons and magnets to magnify frozen protein samples, then combines thousands of images in a computer to generate a three-dimensional model of a protein.

A critical goal of the Structural Biology Roadmap will be the development of a broad inventory of protein structures for research as well as sophisticated new computer-based methods to analyze these data. Scientists will work to streamline methods such that proteins can be produced and analyzed at industrial speed. Large amounts of data will be stored in a format that is easily accessible to researchers working in their own laboratories across the nation.

In later years, efforts will focus on finding ways to deduce the shapes of complicated biological machines consisting of several interlocked proteins working together. To understand how these machines work—and to learn how to fix them when they don't—researchers need to view the protein complexes in several different orientations, mimicking the way these assemblies twist and bend inside living cells. Extremely large amounts of high-quality protein are needed to perform these difficult experiments. NIH anticipates that scientists will require about a decade of intense work to achieve the project's most ambitious goal: the ability to routinely predict the shape and action of a biological machine from its DNA script.

The URL for the NIH Roadmap web site is nihroadmap.nih.gov. For more information on the Structural Biology Roadmap, contact John Norvell, Ph.D., National Institute of General Medical Sciences, (301) 594-0533, norvellj@mail.nih.gov. Further information about NIH can be found at its Web site: www.nih.gov.