



Reaching a Better Understanding of Disease

SUMMARY

With the opening of the Proteomics Research Center in Mayo Clinic Rochester's Medical Sciences Building in October 2002, Mayo Clinic is positioned as a leader among research institutions poised to unravel the complex narrative that proteins have to tell. "This outstanding team we've assembled uniquely positions us to push this field forward toward securing new knowledge of human disease, which I firmly believe will lead to novel diagnostics and innovative therapies," says **John Burnett, M.D.**, chair of Mayo Clinic Rochester's Research Committee, which led the center's development effort.

The Promise of Proteomics

In the book of life, the chapter titles may be made of genes—but the story itself is written in proteins. The study of the array of proteins expressed by a given cell or tissue at a specific time is called proteomics. It's a field so new its name was coined only in 1994, by a graduate student in Australia. It's a field so promising that researchers around the world are rushing to build sophisticated proteomics centers to systematically study proteins. In proteomics, researchers see potential for reaching a better understanding of disease, developing new targeted drugs, and tailoring therapies to a patient's individual needs.

Understanding Proteomics

"Our new facility provides investigators at Mayo Clinic Rochester, Scottsdale and Jacksonville with the necessary tools for understanding the pathogenesis of various diseases, and will lead to the development of new methods for the diagnosis and treatment of human disease," says **Rajiv Kumar, M.D.**, chair of the **Mayo Proteomics Research Center**. "This is important for our mission at Mayo Clinic because of the central role proteins play in diverse biochemical processes and diseases."

Though the term protein is familiar enough as a nutritional element, in the context of 21st century biomedical research, protein refers to the three-dimensional substances that make up the body and carry out its functions. For example, tissues such as bone, blood, muscle, brain and skin are composed of thousands of different proteins. Their behaviors, interactions and communications are all mediated by proteins. In this sense, proteins are the fundamental actors in life processes.

Each protein in the human body consists of a unique sequence of amino acids—its building blocks—arranged like beads on a string. The "code" for how the amino acids are arranged comes from a gene in the form of a three-letter set of instructions, which are called "codons." Simple enough. But the strings of amino acids do things. They fold and change shape to form functional proteins, which do the actual work in the body that the gene has directed it to do.

Think about it this way: a frog egg, a tadpole and an adult frog all have the same number of genes. But both form and function in these three distinct life phases are different. Why? It's not the genes. They remain constant. The difference lies in which proteins are being expressed at different phases of development. It's all in protein expression—folds and functions. These folds and functions are difficult to observe, identify, predict and interpret.

Yet understanding this—how proteins fold; how they function and how they interact with other molecules in the body; how they are modified; when, where, how and why they are expressed—appears to hold the key for creating new approaches to diagnosing and

treating human disease, and designing new drugs to treat disease. For example, knowing the characteristics and shape of a key protein in a given disease could allow researchers to custom-design therapeutic agents. They would be able to create a drug molecule that would bind securely to the protein. This could interrupt the protein's signal, thus stopping, starting or modifying a biologic process. That's the promise of proteomics.

Here's the challenge. There are many more proteins than there are genes in the body—and there are a lot of genes, an estimated 60,000 in a human being. Add to this the fact that proteins can also assume many shapes and are modified while they do their work, and the enormity of the task before researchers emerges. There may be several hundred thousand to more than 1 million proteins in an adult, with their three-dimensional arrangements of amino acids folding, unfolding and changing function. The task is to unscramble these complex patterns of protein expression, interpret them, and then apply these clues or insights to understanding human disease. Proteomics approaches this task through several broad fields. The three major fields are:

- **Expression proteomics**—the study of global changes in protein expression in a cell or tissue.
- **Cell-map or functional proteomics**—the systematic study of protein-to-protein interactions and of protein function in a cell or tissue.
- **Structural proteomics**—the investigation of how shape or structure of a protein affects its function in a cell or tissue.

These sophisticated inquiries into protein expression, interaction, and function are made possible by advanced technology such as automated sample handling, high-resolution mass spectrometry, protein crystallography and powerful computing hardware and software.

Extending Genomics

Two decades of studying genomics provides the intellectual underpinning for proteomics. Proteomics works hand-in-hand with genomics. It does not replace or diminish the genomic revolution's achievements, rather, it extends them.

Here's a simplified way of thinking about the genomics/proteomics relationship: Genes are long strings of DNA building blocks. The genes are found on chromosomes within the nuclei of every cell. DNA is a storage bin of vital information—it encodes the structures of the thousands of different proteins that the cell needs to survive and function. For DNA to be useful to functioning life forms, its information is expressed in another molecule, called messenger RNA, which is used by cells to make proteins. The proteins—thousands of them—are different in amino-acid sequence. This difference specifies how a protein will function in the cell to carry out life processes.

Just as researchers worldwide raced to describe the human genome—the entire set of genes in the human species—a growing number of labs are now pursuing the proteome, the complete set of proteins that humans or any living organism produce.

Mayo's Proteomics Research Center, with 5,500 square feet, more than 20 full-time scientific personnel, several automated protein-handling systems, nine mass spectrometers, and the world's first 12 Tesla magnet which is used for protein identification—is one of the best and most comprehensive centers.— In addition, Mayo's General Clinical Research Center has a 2,500-square-foot facility to measure synthesis rates of several proteins in tissues while measuring functions and gene transcript levels from the same tissues. This facility is exclusively for human-related studies and is

supported by a National Institutes of Health grant.

Although proteomics as a relatively new field, and not yet a part of the popular scientific culture, it soon will be. And the Mayo Proteomics Research Center promises to be on the cutting edge of both this new science and the effort to increase public understanding of its crucial implications in the treatment of human disease. Says the center's director, Dr. Kumar: "The Mayo Proteomics Research Center provides the infrastructure for critical translational research that will be so important for patient care." And in this sense, the Mayo Proteomics Research Center provides an unparalleled research opportunity to help unravel the greatest story ever told: the book of life.

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