Protein Structure Initiative Advances to Rapid Production Phase

With the announcement of 10 new research centers, the Protein Structure Initiative (PSI) launches the second phase of its national effort to find the three-dimensional shapes of a wide range of proteins. This structural information will help reveal the roles that proteins play in health and disease and will help point the way to designing new medicines.

Selection of the centers, slated to receive about \$300 million over the next five years, marks the second half of the decade-long initiative funded largely by the National Institute of General Medical Sciences (NIGMS), part of the National Institutes of Health.

When the PSI established its pilot centers beginning in 2000, its goal was twofold: to develop innovative approaches and tools, such as robotic instruments, that streamline and speed many steps of generating protein structures, and to incorporate those new methods into pipelines that turn DNA sequence information into protein structures.

Now, the focus shifts to a production phase during which the new centers will use methods developed during the pilot period to rapidly determine thousands of protein structures found in organisms ranging from bacteria to humans. These efforts will facilitate structure determination on a much larger number of proteins through computer modeling.

"The PSI has transformed protein structure determination into a highly automated process, making it possible to go from a selected target to a completed structure much more rapidly than before," said Jeremy M. Berg, Ph.D., director of NIGMS. "Building on these achievements, the new centers will take the PSI to the next level, yielding large numbers of structures and tackling significant new challenges. Importantly, the technology developed as part of the PSI will continue to impact structural studies beyond the PSI."

The PSI production phase includes two types of centers. Four large-scale centers, established during the pilot phase, expect to generate between 3,000 and 4,000 structures. Six specialized centers will develop novel methods for quickly determining the structures of proteins that traditionally have been difficult to study. These include small protein complexes; proteins that attach to a cell's outer envelope, or membrane; and many proteins from higher organisms, including humans.

"We've already made great technological strides that have enabled us to determine more than 1,100 protein structures during the first half of the PSI, and we expect the large-scale centers to extend this progress," said John Norvell, Ph.D., PSI director. "But the fact remains that some proteins are not amenable to high-throughput approaches."

While both sets of centers are charged with developing new methods for handling these more difficult proteins, the specialized centers will focus particularly on this task.

As before, the PSI centers will submit their structures and related findings to the Protein Data Bank (<u>http://www.rcsb.org/pdb/</u>), an NSF- and NIH-supported public repository of three-dimensional biological structure data.

From this repository, researchers can access a wealth of PSI-generated information that may help them better understand the function of proteins, predict the shapes of unknown proteins, identify new targets for drug development, and even compare protein structures from normal and diseased tissues.

"By working cooperatively and in a coordinated manner," said Norvell, "we hope all the centers will advance the goals of the PSI and provide benefits for the entire biomedical research community." The large-scale centers are:

- Joint Center for Structural Genomics (led by Ian Wilson, D.Phil., D.Sc., of the Scripps Research Institute in La Jolla, Calif.)
- **Midwest Center for Structural Genomics** (led by Andrzej Joachimiak, Ph.D., of the Argonne National Laboratory near Chicago, Ill.)
- New York Structural GenomiX Research Consortium (led by Stephen Burley, M.D., D.Phil., of Structural GenomiX, Inc., in San Diego, Calif.)
- Northeast Structural Genomics Consortium (led by Gaetano Montelione, Ph.D., of Rutgers University in New Brunswick, N.J.)

The specialized centers are:

- Accelerated Technologies Center for Gene to 3D Structure (led by Lance Stewart, Ph.D., deCODE biostructures, Bainbridge Island, Wash.)
- Center for Eukaryotic Structural Genomics (led by John Markley, Ph.D., University of Wisconsin-Madison)
- **Center for High-Throughput Structural Biology** (led by George DeTitta, Ph.D., Hauptman-Woodward Medical Research Institute, Buffalo, N.Y.)
- Center for Structures of Membrane Proteins (led by Robert Stroud, Ph.D., University of California, San Francisco)
- Integrated Center for Structure and Function Innovation (led by Thomas Terwilliger, Ph.D., Los Alamos National Laboratory, Los Alamos, N.M.)
- New York Consortium on Membrane Protein Structure (led by Wayne Hendrickson, Ph.D., New York Structural Biology Center, New York City)

In addition to NIGMS, the PSI currently receives funding from the National Center for Research Resources. Both are among the 27 components of NIH, the premier federal agency for biomedical research.

For more information about the PSI, visit <u>http://www.nigms.nih.gov/psi/</u>. A fact sheet about the PSI pilot phase, including its accomplishments, is available at <u>http://www.nigms.nih.gov/psi/facts</u>.

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