

## Structural Genomics, Round 2

As NIH plans to extend its high-speed structural biology program for another 5 years, researchers remain divided on how to best allocate its shrinking budget

Five years ago, facing some opposition, the U.S. National Institutes of Health (NIH) in Bethesda, Maryland, launched an ambitious effort that some have compared in scale and audacity to the Human Genome Project. Its ultimate goal: to obtain the three-dimensional structures of 10,000 proteins in a decade. Like the genome project, this effort, called the Protein Structure Initiative (PSI), could transform our understanding of a vast range of basic biological processes. And just as the genome project attracted debate and dissent in its early days, the initiative split the structural biology community. The effort is now approaching a critical juncture, and the debate is heating up again.

The project is nearing the end of its pilot phase, a 5-year effort to develop technologies that has begun to transform labor-intensive, step-by-step procedures into a production-line process. Now, the initiative is poised to move into the production phase, dubbed PSI 2. In the next few months, NIH is expected to designate three to five centers, each of which could receive grants of about \$12 million a year to crank out protein structures at an unprecedented clip. It will also pick a handful of smaller labs to work on problems that have so far proven difficult to solve, such as how to obtain the structures of proteins embedded in cell membranes. Officials at the National Institute of General Medical Sciences (NIGMS), which is bankrolling the initiative, are reviewing proposals for the two types of grants, and the winners are expected to be announced this summer.

But, in a debate eerily similar to the one that roiled the genome community a decade ago, structural biologists are divided on how fast to proceed—especially in the light of constraints on NIH's budget. The central issue is whether the technology is far enough along to justify the move to mass production, or whether the emphasis should continue to be on technological development.

Brian Matthews, a physicist at the University of Oregon, Eugene, and chair of PSI's external advisory board, argues that the time is ripe to move ahead in cataloging thousands of new structures. "This information will be broadly applicable to biology and medicine," he says. Raymond Stevens, a structural biologist at the Scripps Research Institute in La Jolla, California, agrees that "the technology that has come out so far has been truly impressive." But he has strong

reservations about PSI 2's planned emphasis on mass-production of structures. "It's premature to start production centers until better technologies are in place," Stevens says.

This is not just an academic debate. The PSI could determine whether a key goal of structural genomics is achievable: the development of computer models to predict the structure of a new protein from its amino acid sequence. The initiative could also provide insights into how proteins interact to choreograph life's most fundamental processes and help researchers identify important new drug targets.

### Picking up the pace

In one respect, the scientists who planned the human genome project had it easy. Gene sequencing relies chiefly on one technology: reading out the string of letters in DNA. By contrast, producing protein structures requires mastering nine separate technological steps: cloning the correct gene,

overexpressing the gene's protein in bacteria, purifying it, coaxing it to form a crystal, screening out the best crystals, bombarding them with x-rays at a synchrotron, collecting the diffraction data as the rays bounce off the protein's atoms, and using those data to work out the protein's precise structure. (Researchers turn out a smaller number of structures using another technique known as nuclear magnetic resonance spectroscopy.)

Initially, the nine centers participating in the pilot phase of PSI had trouble dealing with that complexity (*Science*, 1 November 2002, p. 948). But structural genomics teams have now automated every step. "It took these groups a couple of years to get all the hardware in place," says Matthews. "But I think [the PSI's first phase] has been very successful."

Among the advances is a robot being built at the Joint Center for Structural Genomics (JCSG) in San Diego, California, that can run 400,000 experiments per month to find just the right conditions to coax given proteins to coalesce into high-quality crystals. Synchrotron facilities too have seen vast improvements in robotics. Setting up a crystal for measurement has historically been a cumbersome process, typically



**Pure speed.** Researchers at the Midwest Center for Structural Genomics use robotic gear to speed protein purification.

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