Europe makes way into structural biology

On June 8, a European research consortium laid the first stone of a new high-throughput structural proteomics platform in Grenoble, France. The platform is designed to help find ways of producing high-quality crystals of poorly expressed proteins—a bottleneck in structural biology—so that their structures can be resolved and used for drug design. With the new platform and the concentration of multidisciplinary expertise in structure resolution in the region, European biotech researchers and companies will be fully equipped to address proteins whose structures are difficult to resolve, once long-term funding has been secured.

Biotech companies have an increasing interest in the determination of protein structures because this approach is becoming a key aspect of targeted drug design. Until now, Europe had only scattered structural biology initiatives. By 2005, biopharmaceutical companies will have more support in determining protein structures, thanks to a new platform set up by a research consortium called the Partnership for Structural Biology (PSB). The platform is backed by research laboratories such as the European Molecular Biology Laboratory (EMBL) outstation in Grenoble, and is "very timely," according to Alberto Podjarny, a structural biologist working on drug design at the Institute of Genetics and Molecular and Cellular Biology (IGBMC) in Strasbourg, France.

The new platform is designed to help to solve the biggest bottleneck in structural biology: protein expression. Many biologically important protein targets, such as membrane proteins, are poorly expressed or have poor solubility and yield, which makes them difficult to crystallize—and their structures therefore difficult to determine. The European approach lays more emphasis on solving difficult protein structure than do structural genomics programs at the US Argonne National Laboratory and at RIKEN's synchotron in Hyogo, Japan, which were set up to find as many protein structures as possible as quickly as possible.

Structures of difficult proteins, such as cell membrane proteins that are often used as drug targets, can now be resolved in Grenoble.

To solve difficult protein structures, the new platform focuses on high-throughput protein expression and crystallization technologies. For example, one PSB team, led by Darren Hart at EMBL, has developed a process by which a problematic protein is fragmented into thousands of possible forms, which are then cloned and tested for expression. Single and multiple domains from the target can then be isolated in a soluble form and taken forward into crystallization trials. "The biological technologies being developed at the PSB are also attracting the interest of companies," adds Hart.

Once PSB has helped them obtain better protein expression and better crystals, companies will then need to determine the structure of their proteins (see **Box 1**). As part of its multidisciplinary approach, the PSB offers access to existing facilities for structure determination provided by its Grenoble-based members, including X-ray crystallography at the European Synchrotron Radiation Facility (ESRF), neutron scattering at the Institut Laue-Langevin (ILL), and high-power NMR, mass spectrometry and electron microscopy facilities at the French Institute of Structural Biology (IBS). In addition, the PSB building will host a deuteration laboratory—unique in the world—that enables isotopic labeling of protein complexes used as a complementary technology to greatly enhance structural information on proteins.

In addition, a number of local biotech startups are already contributing specific technology to the initiative, including the Grenoble-based Protein'eXpert, high-throughput producers of recombinant proteins, whose cofounders were both researchers at the IBS. The PSB partners hope to encourage the creation of spinoff companies in the region as a result of the initiative and also to attract industry-sponsored studentships as a way of enhancing collaboration with industry.

The potential of the PSB might not come to fruition, however, if the partnership fails to secure adequate funding to fully develop its services. The European Union is funding some of the research posts through European research networks such as SPINE (Structural Proteomics in Europe), and additional support has come from a regional genomics initiative. But the PSB is currently looking to the European Commission to provide 10% of its forecasted €17 ($20) million infrastructure budget over the next five years; meanwhile academic partners are being asked to provide the rest.

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Box 1 New synchrotron beamline to determine structures

Among the complementary technologies available at PSB for structure determination, a new, highly automated macromolecular crystallography beamline provided by ESRF has attracted a lot of attention, in part because it is the most powerful synchrotron radiation source in Europe. "We are essentially interested in access to the new beamline," confirms Vincent Mikol, head of structural biology at Aventis Pharma in Paris. Aventis Pharma and four other companies, including Astex Technology, have privileged access to the beamline as associated members of the PSB.

The high level of automation of the new beamline is designed to reduce the amount of time researchers need to spend there, and will completely change the strategy for working with such equipment, according to Sine Larsen, ESRF life sciences director and vice-chair of the PSB. Nonexpert users can have easier access to the technology, thus opening up the spectrum of possible users from industry and academia as researchers increasingly recognize the importance of accurate target protein structure determination in drug design. "The synergy between these techniques and the rapid flow of information between teams working on a single site is very important," says Podjarny. *SG*