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The commercial use of structural genomics ▼

There has been a good deal of debate recently about various structural genomics initiatives. It is becoming clear that the goals of these initiatives vary depending upon the nature of the organization(s) involved. From an academic perspective, structural genomics is seen as a way of obtaining the structure of as many novel proteins as possible to fill out further structural-fold space and enable better predictive methods. This is a major goal of the public initiatives funded by the National Institute of General Medical Sciences (Bethesda, MD, USA). For such public domain efforts, it does not really matter whether the proteins are from eukaryotic or prokaryotic sources and pragmatism is generally used to select the proteins.

From a commercial perspective the imperatives are somewhat different. There is an implicit need to concentrate on discovering the structures of proteins involved in specific pathways, or families of proteins believed to be important for drug discovery (for example, proteins involved in bacterial cell-wall biosynthesis, or for eukaryotic cells, the various protein kinases and so on). Once obtained, new crystal structures are used as templates for drug discovery and design by looking at how compounds bind to the proteins and using structural data to guide modification of the compounds for optimized potency, selectivity and, in some cases, reduced toxicity. Several biotechnology companies engaged in structural genomics are building or accessing the means to embark upon programs of structure-enhanced drug discovery. High-performance protein-modeling software can be used to augment structural genomics efforts. Importantly, computational predictions must be subjected to the rigors of experimental testing and methods. There is a great deal of power in being able to check the products of virtual screening by looking at the crystal structures of complexes between the selected compound and the protein. It is this integration of computational and experimental technologies that will be key in fully developing the value of structural genomics for drug discovery.

Access to core technologies that enable structural genomics initiatives is anything but trivial. In the first place, suitable bioinformatics capabilities have to be available to enable selection of the most appealing targets and to choose the most appropriate constructs to make. Most people are now doing structural genomics by using X-ray crystallography as the preferred method for structure determination. Today, NMR is simply not competitive from a high-throughput perspective: 85% of those structures in the Protein Data Bank[1] (PDB; http://rcsb.org/pdb) come from X-ray structure determination.

Crystallography involves setting up rapid and automated crystallization trials. Most structural genomics efforts are using Multiwavelength Anomalous Diffraction (MAD) phasing for crystallography, a technique pioneered by Wayne Hendrickson in which selenomethionine is incorporated into the proteins to enable rapid data-interpretation[2]. Although it is possible to use MAD phasing for data collected at most synchrotron radiation sources, it is becoming widely acknowledged that the best data are being collected from third-generation sources of X-rays, such as the Advanced Photo Source in Chicago (IL, USA), because of the speed and efficiency with which they are obtained. It is now almost routine to collect data at the APS and use automated interpretation methods to go from diffraction pattern to refined novel structures in less than eight hours. Molecular replacement methods are even quicker. The commercial structural-genomics efforts will enable the provision of three-dimensional data on the way compounds bind to their cognate targets to medicinal chemist in real time. This will be important for increasing the efficiency of lead discovery and optimization.

References

1 Berman, H.M. *et al.* (2000) The Protein Data Bank. *Nucleic Acids Res.* 28, 235–242

2 Hendrickson, W.A. (2000) Synchrotron chromatography. *Trends Biochem. Sci.* 25, 637–643

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