Is X-ray crystallography a viable tool for lead discovery?

Identifying quality lead molecules is a crucial step in bringing new compounds to the clinic. Generally, existing lead discovery strategies fall into three classes: experimental screening of large corporate databases, computational screening and testing of fragment libraries. Crystallographic screening might best be applied in the case of fragment libraries because these are composed of fewer compounds and therefore do not require an ultra-high throughput testing method. Crystallographic screening also detects weaker binding ligands (1mM), and the resolution of the resultant crystal structures can provide clear paths to linking the bound fragments into novel leads.

Although the advantages of screening using X-ray crystallography have been discussed for many years [1,2], the method has not been implemented until recently; it was viewed as impractical because of the time and labor required to acquire and analyze crystallographic data. However, recent technical advances developed to support structural genomics [3] have made high-throughput structure determination feasible and have provided an infrastructure for crystallographic screening. Structural genomics could also provide access to crystallization conditions and crystal structures for many potential drug target macromolecules.

Figure 1 depicts the basic steps of crystallographic screening and the corresponding technical advances that have minimized bottlenecks at each step. These advances have recently been reviewed in the context of crystallographic screening [4]; to implement this, a compound library and crystals that ideally diffract to at least 2.5 Å resolution are required. Technical advances that can be incorporated into the researcher's own laboratory include crystallization and crystal mounting robotics [5], CCD detectors, improved optics and more intense X-ray sources. By contrast, crystal mounting robotics are also being installed at synchrotron sources and should be available to users in the near future, most probably through remote access from the home laboratory. With robotic crystallization and rapid unmanned data collection becoming a more common practice, the current bottleneck is in the analysis and data archiving step of the process. To facilitate analysis, software tools developed for structural genomics have been modified to automate data processing and electron-density map calculation. In addition, ligand identification could be expedited if compounds in the library are grouped into shape-diverse mixtures so that a hit can be identified by the shape of the electron-density map rather than through additional testing [4,6]. Successful implementation of custom automated map interpretation tools that have been developed specifically for crystallographic screening with shape-diverse mixtures has also been reported [6].

To conclude, the field of high-throughput crystallography is at a point where it could be applied routinely in lead discovery. Many drug discovery and genomics companies own, or have access to, the requisite infrastructure, and crystallographic screening has proven successful in the past [4,6]. Analysis of the strengths and weaknesses of the method shows promise and with time and further application its true use might be revealed.

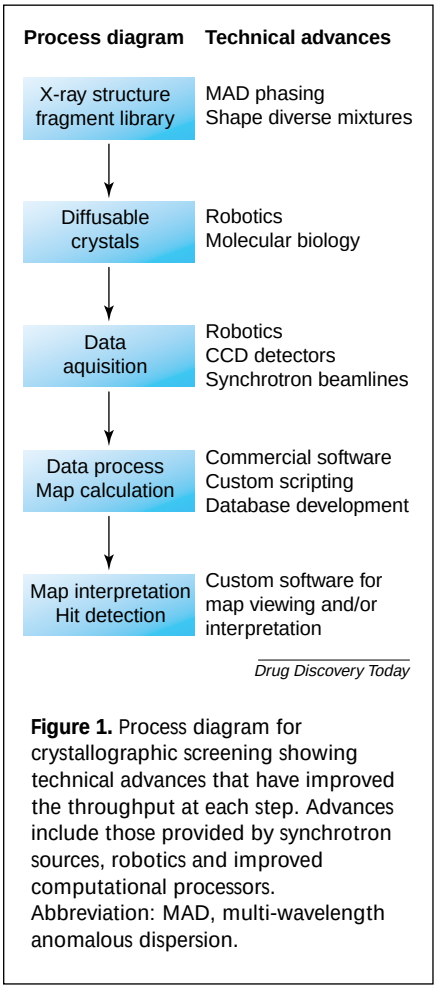

Figure 1. Process diagram for crystallographic screening showing technical advances that have improved the throughput at each step. Advances include those provided by synchrotron sources, robotics and improved computational processors. Abbreviation: MAD, multi-wavelength anomalous dispersion.

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1359-6446/02/$ – see front matter PII: S1359-6446(02)02338-3