



CASE STUDY

In crystallo fragment screening

In the past two decades, fragment based drug discovery has emerged as a powerful method to discover and develop new drugs. Such strategy relies on the identification of low molecular weight compounds that bind weakly to a target. The structural information gained on fragment-target complexes provides an excellent starting point for the development of potent and selective drugs.



The Challenge

Most screening efforts rely on a cascade of sensitive biophysical methods to isolate weakly binding compounds. X-ray crystallography is also an excellent, and validated, fragment screening option. The method allows screening of all potential binding locations, including allosteric sites, at once while providing a direct structural feedback on hit-target complexes. However, screening a full library of compounds via crystallography is usually laborious, resource hungry and time consuming.



The Solution

Diamond Light Source, in collaboration with the Structure Genomics Consortium, has developed a streamlined X-ray fragment screening platform. To facilitate and parallelise soaking, compounds are transferred, through an acoustic liquid dispenser, directly to crystals grown in high throughput crystallisation plates. A motorised stage located under a microscope, and associated to a touch screen user interface, significantly speeds up the crystal harvesting step.

Samples are then transferred to I04-1, a fully automated MX beamline, for rapid and unattended X-ray data collection. Benefitting from immediate access to the Diamond data processing pipelines, electron density maps can be readily analysed for the presence of bound ligands.



The Benefits

By seamlessly integrating each step of the process, Diamond has tremendously accelerated the X-ray fragment screening approach, while reducing the experimental overheads. Hundreds of compounds are now routinely screened in a matter of days, with a rapid turnover between projects.



“Access to the fragment soaking platform and automated data collection at Diamond has added a further element on top of our diverse internal portfolio of streamlined biochemical, high-content and biophysical screening capabilities at Evotec. Operating through the facility infrastructure and with supporting expertise of Diamond staff we have added significant value to several collaborations this year alone. Most importantly we are delivering information-rich structures to our clients and internal medicinal chemistry teams in a time and cost-effective manner at a critical early phase in the drug discovery pathway.” **Dr Paul McEwan, Evotec**



For further information

Diamond Industrial Liaison Team

+44 1235 778797

industry@diamond.ac.uk

diamond.ac.uk/industry

@DiamondILO

CS-DDS-EVO-019-2