Streamlining fragment based-drug discovery pipeline at the Australian synchrotron

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The MX beamlines are currently being used by commercial clients for many different purposes including discovery programs, drug and health product development etc. These commercial clients often work on drug/inhibitor/ligand compounds that binds to their target proteins. Their purpose is to screen ligands (inhibitors/drugs/small molecule fragments) to identify which binds strongly to a target protein allowing the researchers to visualise the molecular details of the bound compound. In this process, commercial clients screen a large number of ligands. This requires the collection of multiple datasets (100’s - 1000’s) for each target protein and takes a significant amount of time to analyse each and every dataset to discover if a compound is bound. We, as beamline scientists realised that the automatic-structure determination of such protein-ligand complexes can be undertaken by developing or modifying pre-existing methods as implemented in the Autorickshaw program [1, 2].

We have identified several potentially therapeutic molecular drug targets shown to be ‘essential’ in the bacteria *Streptococcus pneumoniae*. The purified proteins of several of these targets were produced/provided by the New York Structural Genomics Consortium (NYSGC) a subset of these proteins SodA, metF and Thymidine kinase were screened for crystallisation conditions. The structures of these proteins were determined by Se-SAD (unpublished results). To screen the drug targets for crystallisation conditions we have developed a partnership with the Biomolecular Crystallisation and Characterisation facility (BCC) within the Commonwealth Scientific and Industrial Research Organisation (CSIRO), Clayton campus. As part of this project, CSIRO-collaborators have been working on the crystallisation and subsequent optimisation of the original crystallisation conditions of our drug targets. So far, the BCC team have screened three drug targets SodA, metF, and Thymidine kinase for crystallisation conditions. Screening of SodA and metF proteins have produced crystals that result in reproducible diffraction resolution (when screened on the MX2 beamline). BCC team have now produced large numbers of diffraction quality crystals of SodA and metF to allow fragment/drug soaking experiments to be undertaken. Currently, soaking and co-crystallisation of fragments/drugs with SodA and metF crystals is under investigation.

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Figure 1. Fragment based drug discovery pipeline