Crystallographic fragment screening for a small cancer target

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Development of small molecule drugs often starts with a 'hit' molecule which is then further optimised. Fragments are low molecular weight chemicals (below 300) and fragment screening is often used to identify for 'hit' molecules that bind the target protein. Various techniques including nuclear magnetic resonance (NMR), isothermal titration calorimetry (ITC), surface plasmon resonance (SPR) and protein crystallography can be used to screen fragments. Fragment screening *in crystallo* allows to identify hits that bind directly at the active site. In addition, the resulting crystal structure provides valuable insight about the binding mode of the 'hit'.

We are running a fragment screening campaign for a small cancer target. Optimisation of expression construct followed by crystal optimisation resulted in reliable formation of crystals diffracting to 1.1 Å. The crystals were tested for soakability and tolerance to DMSO before screening over 150 fragments in collaboration with the fragment screening team at MAX IV. We have and found multiple hits binding at the active site of the target protein. In addition, we have screened the MiniFrags library with the best hits from the FragMAX library.