INDUSTRIAL PILOT PROJECT

Fragment-screening by X-ray crystallography at MAX IV on an oncology-related protein from the Sprint Bioscience portfolio

THE INDUSTRIAL CHALLENGE

Sprint Bioscience is a drug-discovery company developing drugs targeting cancer-related proteins. The first step in a fragment based drug discovery process is the identification of small molecules (fragments) able to bind the targeted protein (hits). In this step, the protein is screened using various biophysical methods against a library of fragments, each biophysical method being susceptible to lead to a different set of hits.

WHY USING A LARGE SCALE FACILITY

Fragment screening by X-ray crystallography (XFS) is one of the most powerful methods to perform the screening because it can detect low affinity binders which would have been missed by other techniques. Also, it directly provides a three-dimensional model of the interaction between the fragments and the protein which is essential to develop the fragments into drug candidates. For decades, synchrotrons have developed systems and procedures which increase the productivity of data collection sessions. Due to the large number of crystals which would be tested in an XFS campaign, the use of a synchrotron source is then absolutely essential such a project.

HOW THE WORK WAS DONE

Sprint Bioscience has designed and formulated a fragment-library of 300 members suitable for XFS. This has allowed the screening to be performed at 90 mM fragment concentration, thus enabling the detection of low affinity binders. With the guidance and the support of the FragMAX team from MAX IV, the crystal system corresponding to the protein used in this project was optimized in order to improve its robustness and to determine the optimal conditions to perform the screening. The XFS campaign consisted in growing a large number of crystals, incubating around 300 crystals with one individual fragment using the determined optimal conditions and collecting data for each crystal. All data in this project were collected at BioMAX beamline and processed using FragMAXApp.

THE RESULTS AND EXPECTED IMPACT

In less than one week, 272 datasets were analyzed resulting in the identification of 27 fragments in the electron-density maps. Among these hits, 11 have been previously tested by differential scanning fluorimetry where their interaction with the protein could not be detected. These results clearly confirmed that XFS can lead to a high number of hits, including hits missed by other screening techniques.

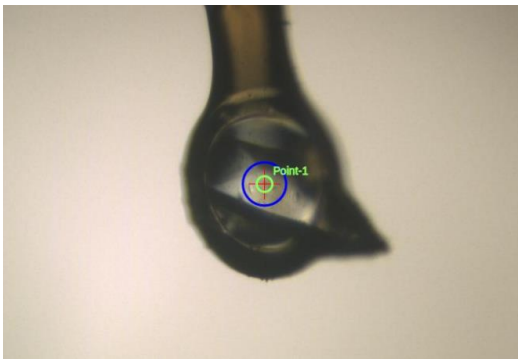

Figure. Crystal incubated with fragment XB00143 mounted on the BioMAX beamline during the XFS campaign.

Through this collaboration, Sprint Bioscience has gained the knowledge on how to bring a crystal system to XFS and to use the state-of-the-art tools and methods developed by FragMAX. By using this opportunity given by XFS in future projects, Sprint Bioscience can progress the projects faster and thereby strengthen the company´s competitiveness in the international landscape.

"Through this project we have added an important tool to our toolbox for lead generation with potential to build value in our drug discovery efforts."
/Jessica Martinsson, CEO Sprint Bioscience

Sprint Bioscience

MAX IV

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