HiPhaX – A fully automated High-Throughput Pharmaceutical X-ray screening endstation at the PETRA-III synchrotron in Hamburg

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Protein structures are of utmost importance for rational drug design and all major pharmaceutical companies have well developed in-house structure-based drug design capabilities. A highly successful and increasingly popular approach is X-ray screening of fragment libraries and recently also more complex compound libraries to identify compounds that can serve as starting points for drug discovery, as an alternative or complement to purely biochemical and biophysical high-throughput screening approaches [1]. A clear advantage of X-ray screening over other techniques is that it provides 3D structural information about the interaction and binding modes on an atomic level, which allows direct use of the results for subsequent computational fragment extension and compound optimization procedures. There are three major limitations today hindering the full exploitation of X-ray screening in drug discovery; the manual intervention required in the handling of crystals and X-ray data collection procedures which severely limit the throughput, and the challenges associated with expanding initial hits into highly potent and selective lead compounds.

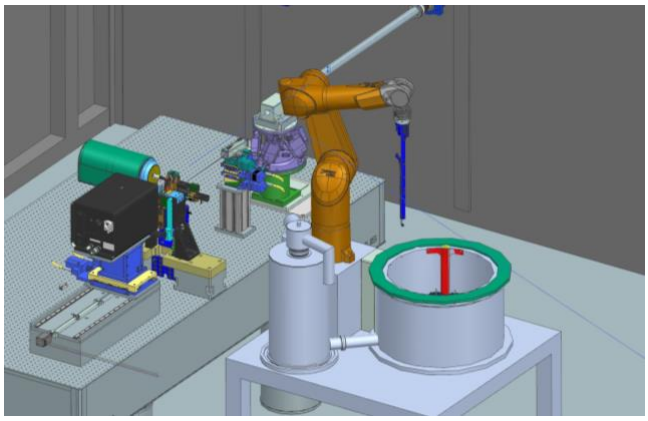

Figure 1: Proposed design of the HiPhaX instrument at beamline P09 at the PETRA-III storage ring in Hamburg.

To overcome these limitations DESY - together with collaboration partners - is building a new instrument for macromolecular crystallography exclusively dedicated to high-throughput X-ray fragment and compound screening. The goal of the project is to develop a fully automated endstation with the capability of determining more than 1000 protein structures per 24 hours. The beamline will operate at a fixed energy of 16 keV and will be equipped with an Eiger 2 4M CdTe detector. Special care will be taken to provide very low background scattering levels. For highest-throughput sample holders with multiple crystals will be supported. The storage Dewar will provide space for more than 500 sample holders. We aim at developing fully autonomous beamline operation, which does not require human intervention. To reach this goal we will implement fully automatic X-ray based crystal identification and centering as well as AI supported data collection and data analysis. The beamline will be open for both academic and industrial users and user operation is expected to commence in 2023.

[1] Günther, S. *et al.* X-ray screening identifies active site and allosteric inhibitors of SARS-CoV-2 main protease. *Science* eabf7945 (2021).