Every crystal matters

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Here we report on a large fragment screening campaign performed for a global player from pharmaceutical industry. This is a synergistic project involving partners from industry and academia: Protein crystallization, soaking and freezing of 1000 crystals was carried out by NUVISAN ICB where a platform for high-throughput crystallography campaigns was successfully established in order to provide structural biology services for integrated drug discovery programs to clients. MOLOX has a proven track record in data collection and provided this service here. Data processing and structure determination was performed by the client.
To collect high quality diffraction data efficiently, we chose beamline P14 at EMBL Hamburg. While this beamline offers adjustable beam conditions and instrumentation for collecting highest quality data from macromolecular crystals, it has not been optimized for rapid ligand screening. We will describe how in a collaborative effort, hardware and software of P14 were optimized for high quality data collection at high speed.

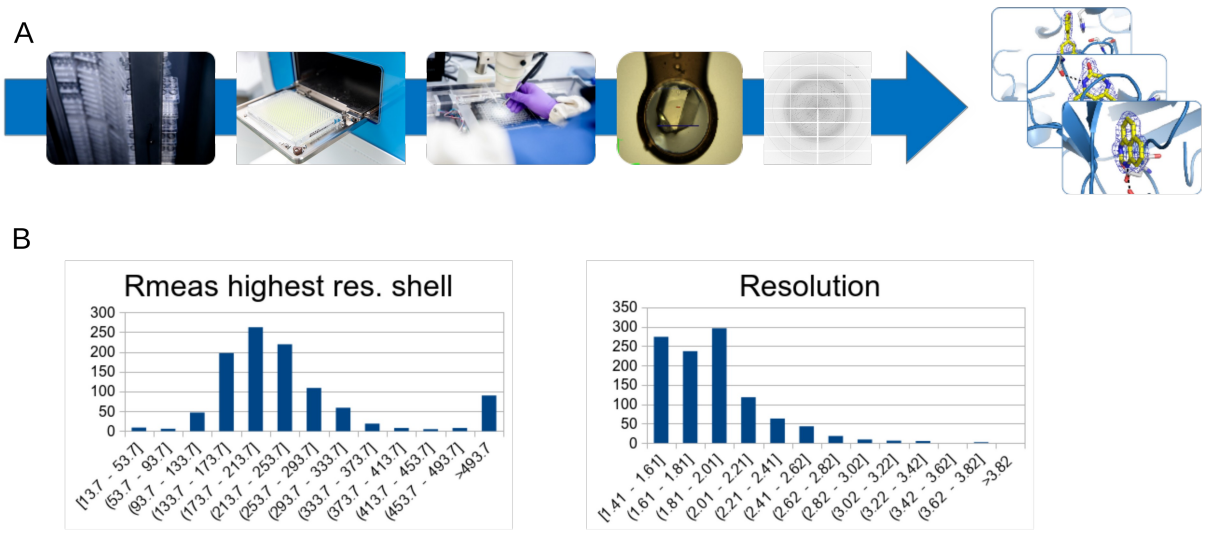

Figure 1: (A) Workflow of the fragment screening campaign, (B) Rmeas and resolution distribution for all crystals.

More than 89 % of all crystals yielded a dataset, for > 97 % of all datasets the resolution was < 2.8 Å, and > 97 % of all datasets had an overall R_{meas} of < 50 %. More than 87 % of the crystals yielded a dataset of sufficient quality for downstream analyses. Overall median resolution over all datasets was 1.84 Å, median R_{meas} was 9 %.
Despite the fact that automation is key to accelerating science, we opted for a non-automated data collection approach here. In many relevant cases protein production and purification consume significant (financial) resources, therefore "every crystal matters" and – once a suitable crystal is available – the best possible data should be collected from it.
Here we demonstrate how the combination of cutting-edge beamline technology with human intervention has created a robust and efficient fragment screening pipeline.