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Development of an automated pipeline for enhanced FBDD campaigns at beamline P11

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Fragment-Based Drug Discovery (FBDD) has emerged as a pivotal approach in drug development, offering notable success with the approval of six drugs by the USFDA and over 15 candidates advancing through clinical trials. Compared to traditional high-throughput screening (HTS), FBDD is more efficient, utilizing smaller libraries of low-molecular-weight molecules that enhance chemical space sampling. This method has gained widespread adoption in both academia and industry, becoming a standard practice in major pharmaceutical companies. A crucial element of FBDD is Crystallographic Fragment Screening (CFS), where potential drug fragments are soaked into target protein crystals, followed by X-ray crystallography to elucidate binding poses. This technique, superior to other biophysical approaches, provides essential structural information to guide the chemical optimization of drug candidates. Recent advancements at synchrotron facilities, including automated sample preparation and data collection systems, have transformed crystallography into a high-throughput technique suitable for primary screening. These innovations enable the collection of hundreds of datasets per day and have led to the development of dedicated screening platforms at synchrotrons like Diamond Light Source (DLS), Swiss Light Source (SLS), and BESSY II. Aligned with these advancements, the macromolecular crystallography (MX) P11 beamline at PETRA III, operated by DESY in Hamburg, Germany, has established a fully automated protein-to-structure pipeline. This pipeline integrates cutting-edge technologies such as high-energy beams for superior resolution, automatic crystal mounting robots, and advanced data processing tools. Automated sample preparation and monitoring are facilitated by the Mosquito robot and the Rock Imager at the Sample Preparation Crystallography (SPC) lab, while the Echo acoustic liquid handler and the Shifter robot automate soaking and fishing steps. The P11 pipeline significantly enhances the efficiency of FBDD campaigns, enabling rapid and effective drug discovery processes. This system has been rigorously tested with diverse protein targets, including WD Repeat Domain 5 (WDR5) and the VPS29-COMMD1-BAT3 (VCB) complex, using the Universal F2X fragments library developed by BESSY II. Most FBDD campaigns at P11 are completed within a week, from crystal acquisition to data analysis, although timelines may vary depending on target complexity and fragment library size. In conclusion, the automated pipeline at PETRA III's P11 beamline exemplifies the integration of advanced crystallographic techniques and automation in FBDD, offering a powerful platform for drug discovery and development. This facility continues to contribute to the growing success of FBDD in identifying and optimizing new drug candidates.

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